CLINICAL STUDY PROTOCOL

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

PROTOCOL NUMBER CT-P41 3.1

EudraCT Number:	2020-005974-91
Investigational Product:	CT-P41 (proposed Prolia biosimilar)
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Version and Date of Protocol	Protocol Version 2.1, including country specific A.0, 18 April 2022

PROTOCOL APPROVAL

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

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled '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' and the accompanying current Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 2.1, including country specific A.0, dated 18 April 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, Declaration of Helsinki (World Medical Association 2013), and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without Independent Ethics Committee (or Institutional Review Board) approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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PROTOCOL SYNOPSIS

Protocol Number: CT-P41 3.1

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

Study Phase: Phase 3

Study Centers: Approximately 20 study centers in 4 countries

Test Drug Formulation, Dose, and Regimen:
CT-P41 will be subcutaneously administered using a prefilled syringe (PFS) of 60 mg/mL solution for injection on Weeks 0 (Day 1), 26, and 52 (6-month interval).
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 end-of-study (EOS) visit.

Reference Drug Formulation, Dose, and Regimen:
United States (US)-licensed Prolia will be subcutaneously administered using a PFS of 60 mg/mL solution for injection Weeks 0 (Day 1), 26, and 52 (6-month interval).
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.

Objectives:
Primary Objective

- To demonstrate the equivalence of CT-P41 to US-licensed Prolia in terms of efficacy in postmenopausal women with osteoporosis as determined by percent change from baseline in bone mineral density (BMD) for lumbar spine (L1 to L4) at Week 52

Secondary Objective

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

Main Selection Criteria:
Postmenopausal women with BMD T-score ≤ -2.5 and ≥ -4.0 at the lumbar spine (L1 to L4) and evaluable region (at least three lumbar spine [L1 to L4] and at least one hip joint) by dual-energy X-ray absorptiometry (DXA) assessment, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:
Each patient must meet all of the following criteria to be randomized in this study:

1. Women, 50 to 80 years of age, both inclusive.
2. Body weight between 40.0 and 99.9 kg, both inclusive, when rounded to the nearest tenth.
3. Postmenopausal, as defined by:
   a) No menstrual period for at least 12 consecutive months prior to the Screening visit with follicle-stimulating hormone (FSH) level $\geq$ 30 mIU/mL assessed by central laboratory at Screening visit, or
   b) Surgical menopause (bilateral oophorectomy with or without hysterectomy) $\geq$ 12 months prior to the Screening visit
4. Bone mineral density T-score ≤ -2.5 and ≥ -4.0 at the lumbar spine (L1 to L4) as assessed by the central imaging vendor based on DXA scan at Screening.
5. Patient must have at least 3 vertebrae considered evaluable at the lumbar spine (L1 to L4) and at least 1 hip considered evaluable by DXA scan assessed by the central imaging vendor at Screening. Patient with unilateral metal in hips that would be allowed for the other side of 1 evaluable hip is included.
6. Patient with albumin-adjusted total serum calcium $\geq$ 8.5 mg/dL ($\geq$ 2.125 mmol/L) at Screening.
7. Patient has adequate hepatic function at Screening as defined by the following clinical chemistry results:
   a) Aspartate aminotransferase and alanine aminotransferase $\leq 3 \times$ upper limit of normal (ULN)
   b) Alkaline phosphatase $\leq 2 \times$ ULN and total bilirubin $\leq 2 \times$ ULN

8. In good general health as determined by medical history, physical examination, and laboratory tests and able to walk without assistance, at the Investigator's discretion.
9. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks, side effects and requirements for supplementation, and must sign the informed consent form before any study specific procedures.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Patient who has previously received denosumab (Prolia, Xgeva, or biosimilar denosumab), any other monoclonal antibodies (e.g., romosozumab), or biologic agents for osteoporosis.
2. Patient with a hypersensitivity to any component of denosumab or dry natural rubber (a derivative of latex).
3. Patient who is confirmed or suspected with infection of coronavirus disease 2019 (COVID-19) at Screening, or has contact with COVID-19 patient within 14 days from Screening.
4. Patient who currently has, or has a history of, any of the following infections:
   a) A known infection with active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). A patient with past hepatitis B virus is allowed if resolved
   b) Any severe or active infection or history of any infection requiring hospitalization, parenteral antibiotics within 4 weeks prior to the first administration of the study drug, or oral antibiotics within 2 weeks prior to the first administration of the study drug
5. Patient who has a medical history of and/or current disease including any of the following(s):
   a) One severe or > 2 moderate vertebral fractures (severe fracture is defined as > 40% vertebral height loss and moderate fracture is defined as 25% to 40% vertebral height loss [Genant *et al., 1993*]) as determined by central reading of lateral spine X-ray
   b) Hip fracture
   c) Hyperparathyroidism or hypoparathyroidism, irrespective of current controlled or uncontrolled status
   d) Current hyperthyroidism (unless well controlled on stable antithyroid therapy)
   e) Current hypothyroidism (unless well controlled on stable thyroid replacement therapy)
   f) Bone disease and metabolic disease (except for osteoporosis) that may interfere with the interpretation of the results including osteomalacia, osteogenesis imperfecta, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteopetrosis, fibrous dysplasia, an elevation of alkaline phosphatase at the Investigator's discretion, Cushing's disease, hyperprolactinemia, malabsorption syndrome, advanced scoliosis or extensive lumbar fusion
   g) History of severe skeletal pain with bisphosphonates
   h) History and/or current oral or dental conditions including osteomyelitis or osteonecrosis of the jaw; active dental or jaw condition which requires oral surgery; planned invasive dental procedure (e.g., tooth extraction, dental implants, oral surgery); unhealed dental oral surgery
   i) History of any malignancy within 5 years prior to the first administration of the study drug except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ. Any history of bone metastases, implant radiation involving the skeleton, or skeletal malignancies are exclusionary
   j) New York Heart Association (NYHA) Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease, or electrocardiogram abnormalities which can be judged as clinically significant at the Investigator's discretion
6. Patient has one of the following laboratory test results at Screening:
   a) Serum 25-OH vitamin D < 20 ng/mL (if vitamin D deficiency has been supplemented at the Investigator's discretion, and retest result shows the level above 20 ng/mL within the Screening period, the patient can be enrolled in the study. The retest is limited up to twice within the Screening period.)
   b) Estimated glomerular filtration rate < 30 mL/min/1.73 m^2
   c) Hemoglobin < 10 g/dL
7. Patient who has a history of and/or concurrent use of medications including any of the following:
   a) Receipt of intravenous bisphosphonates, fluoride, and strontium for osteoporosis within the last

5 years prior to the first administration of the study drug
b) Receipt of oral bisphosphonates ≥ 3 years cumulatively prior to Screening or receipt of any dose of oral bisphosphonates within 12 months prior to Screening
c) Use of parathyroid hormone or its derivatives, systemic hormone-replacement therapy (estrogen with or without progestogen), selective estrogen-receptor modulator, tibolone, calcitonin, or calcitriol within 12 months prior to the first administration of the study drug
d) Use of other bone active drugs including heparin, anticonvulsive (except benzodiazepines), systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists within 3 months prior to the first administration of the study drug
e) Use of oral or parenteral glucocorticosteroids (> 5 mg/prednisone daily or equivalent for > 10 days) within 3 months prior to the first administration of the study drug
f) Receipt of any investigational drug within 4 weeks or five half-lives (whichever is longer) prior to the first administration of the study drug
g) Receipt of any authorized COVID-19 vaccines within 2 weeks prior and after the first administration of the study drug (total of 4 weeks)

8. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 12 months prior to the first administration of the study drug.
9. Patient who has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product or could have interfere with the interpretation of study results, or patient is at high risk for treatment complication in the opinion of the Investigator.

Study Design:
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. 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 and the data will be collected via patient's diary.

A schematic of the study design is presented in Figure S1.

Screening Period (From Day − 28 to Day − 1)
Screening evaluations will be completed within 28 days prior to the randomization.

Treatment Period I (From Week 0 [Day 1] to Week 52 Predose)
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 the 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 randomization will be balanced by using permuted blocks. The randomization will be stratified by age (< 65 *versus* ≥ 65), baseline BMD T-score at the lumbar spine (≤ − 3.0 *versus* > − 3.0) and prior bisphosphonates therapy (Yes *versus* No).
The primary efficacy endpoint of percent change from baseline in BMD for lumbar spine will be measured at Week 52. Efficacy, PK, PD, and safety including immunogenicity data will be collected.

Treatment Period II (From Week 52 to Prior to Week 78 [EOS Visit])
All patients who completed the Treatment Period I will undergo the second randomization process prior to the study drug administration at Week 52 to ensure blinding and will enter the Treatment Period II to receive an additional 1 dose of study drug.
The second randomization 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). 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

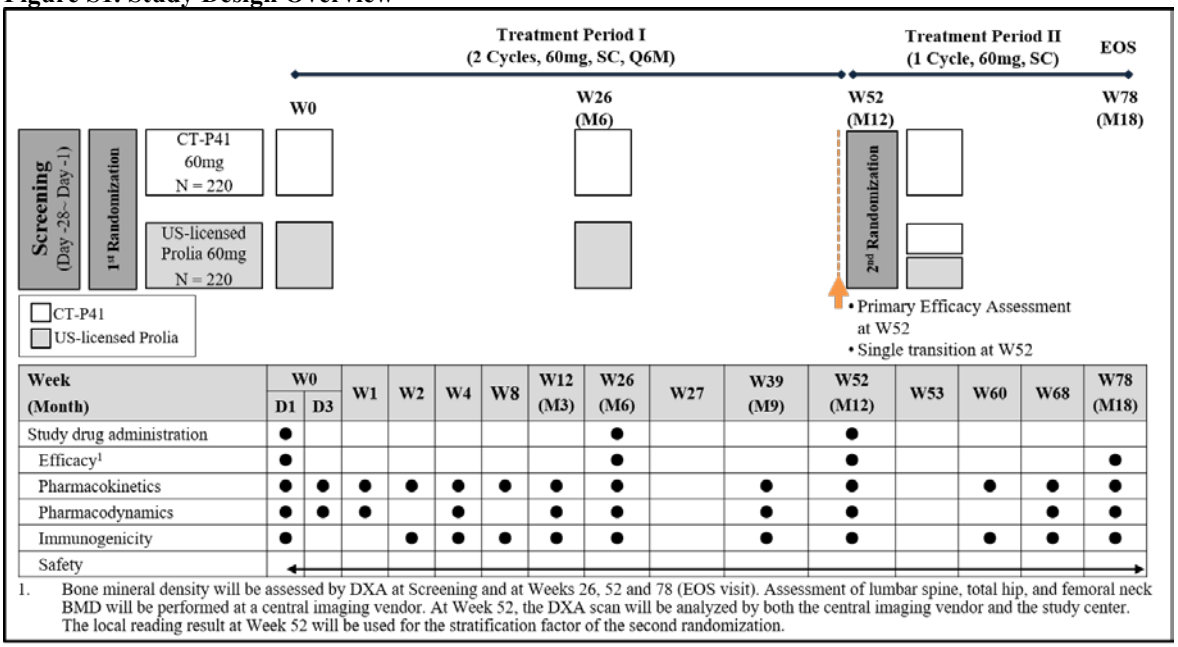
arm (CT-P41) or non-switching arm (US-licensed Prolia). The study drug during the Treatment Period II will be given at Week 52 study visit. All assessments including efficacy, PK, PD, and safety including immunogenicity will be performed.

End-of-Study Visit (Week 78)

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 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, 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 will be conducted by telephone according to the study visit schedule.

Figure S1. 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.

The study will be performed in a double-blind manner. To minimize the risk of unblinding, the study drug will be administered by unblinded healthcare professional. The unblinded healthcare professionals who are responsible for administering study drugs will not be permitted to conduct any patient assessments.

Efficacy Assessments:

Bone mineral density as evaluated on DXA will be measured at scheduled time points. Bone images will be assessed at the central imaging vendor.

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

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

- The incidences of new vertebral, nonvertebral, and hip fractures during the study
- Change from baseline in health-related quality of life at Weeks 26, 52, and 78

Pharmacokinetic Assessments:

Secondary PK Endpoints

- Serum concentration of denosumab (up to Week 78)
- 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)

Pharmacodynamic Assessments:
Serum concentrations of bone turnover markers will be measured in the morning after fasting overnight for 8 hours prior to the assessment at the scheduled time points.

Secondary PD Endpoints

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

Safety Assessments:
Safety assessments will be performed on adverse events (AEs), serious adverse events, AEs of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reactions), hypersensitivity/allergic reaction assessment by vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), local site pain using 100 mm visual analog scale, vital sign, weight, height, body mass index measurement, physical examination (including oral examination), clinical laboratory analyses, 12-lead electrocardiogram, prior and concomitant medication, and immunogenicity (incidence of antidrug antibody and neutralizing antibody). Hepatitis B, C, HIV, and FSH testing and NYHA functional classification will be assessed to determine patients' eligibility.

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 standard deviation (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%.

Statistical Methods:
Data Analyses:
The study will be double-blinded. The study will be unblinded for the reporting purposes after database lock for data up to Week 52 or Week 78 for all patients. The second randomization process will be conducted in all treatment groups to maintain the study blind. The study will remain blinded to the Investigators, patients, and predefined blinded personnel from the Sponsor and contract research organization until all patients complete the study and the database is finalized for study termination.

Statistical Analysis:
All statistical analyses will be conducted [redacted] The statistical methods for this study will be described in detail in a Statistical Analysis Plan (SAP), which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.
Continuous variables will be summarized by reporting the number of observations (n), mean, SD, median, minimum, maximum, unless otherwise indicated. Categorical variables will be summarized using frequency

tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

Definition of Analysis Set:

- **Intent-to-Treat (ITT) 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.
- **ITT – 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.
- **Full Analysis Set (FAS):** The FAS is defined as all randomly assigned patients who receive at least 1 full dose of study drug (CT-P41 or US-licensed Prolia).
- **FAS – Treatment Period II subset**: The FAS – Treatment Period II subset is defined as all patients in FAS who are randomly assigned at Week 52 prior to dosing and receive 1 full dose of study drug (CT-P41 or US-licensed Prolia) at Week 52.
- **Per-Protocol Set (PPS):** The PPS is defined as all randomly assigned patients who receive all 2 doses (full) of study drug (CT-P41 or US-licensed Prolia) at Weeks 0 (Day 1) and 26, and have BMD assessments from lumbar spine at baseline and Week 52. Patients with a 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 data review meeting (DRM) before unblinding.
- **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 result.
- **PK – Treatment Period II subset**: The PK – Treatment Period II subset will consist of all patients in PK Set who receive 1 full dose of either of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PK result at or after Week 52.
- **Pharmacodynamic Set:** The PD 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 PD result.
- **PD – Treatment Period II subset**: The PD – Treatment Period II subset will consist of all patients in PD Set who receive 1 full dose of either of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PD result at or after Week 52.
- **Safety Set**: The Safety Set will consist of all patients who receive at least 1 dose (full or partial) of study drug (CT-P41 or US-licensed Prolia).
- **Safety – Treatment Period II subset**: The Safety – Treatment Period II subset will consist of all patients in Safety Set who receive 1 dose (full or partial) of study drug (CT-P41 or US-licensed Prolia) at Week 52.

Efficacy Analysis:

- **Primary Endpoint:** To evaluate the difference between 2 treatment groups in the primary efficacy endpoint, percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 will be analyzed using an analysis of covariance (ANCOVA) model coupled with multiple imputation assuming the data to be missing at random. 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. Statistical equivalence will be declared if the 90% confidence interval (CI) of the difference in the mean of the primary efficacy endpoint between treatment groups falls entirely within an equivalence margin, [− 1.45, + 1.45]. The primary analysis will be performed using the FAS. A supportive analysis will be performed using the PPS. Sensitivity analysis will be conducted in the FAS to examine the impact of missing data on primary analysis result by imputing missing data over a range of possible scenarios for the treatment effect. Subgroup analysis by race and age will be performed in FAS.
- **Secondary Endpoints:** Percent change from baseline in BMD for lumbar spine, total hip, and femoral neck by DXA, incidences of new vertebral, nonvertebral, and hip fractures, and change from baseline in health-related quality of life will be assessed as secondary efficacy endpoints. The secondary efficacy endpoints will be summarized by descriptive statistics or frequency tables using the FAS and PPS and

data for Treatment Period II will be summarized on the FAS – Treatment Period II subset, unless otherwise specified.

Pharmacokinetic Analysis:
The serum concentration and PK parameters of C_{max} and C_{trough} will be summarized by treatment group using descriptive statistics including geometric mean and coefficient of variation (CV), as appropriate. Pharmacokinetic analysis for Treatment Period I will be summarized using the PK Set and that for Treatment Period II will be summarized on the PK – Treatment Period II subset, unless otherwise specified.

Pharmacodynamic Analysis:
The AUEC of s-CTX and P1NP over the initial 6 months (from Day 1 predose to Week 26 predose) and percent change from baseline of s-CTX and P1NP at Weeks 26, 52, and 78 will be assessed as secondary PD endpoints. Serum concentration and percent change from baseline of s-CTX and P1NP will be summarized using descriptive statistics (including geometric mean and CV, as appropriate). Pharmacodynamic analysis for Treatment Period I will be summarized on the PD Set and that for Treatment Period II will be summarized on the PD – Treatment Period II subset, unless otherwise specified.

Safety Analysis:
Adverse events will be coded to system organ class and preferred term according to Medical Dictionary for Regulatory Activities and severity grading of AEs will be recorded according to the Common Terminology Criteria for Adverse Events Version 5.0. Prior and concomitant medications will be coded to drug class and preferred term using the World Health Organization drug dictionary. All safety data including immunogenicity for Treatment Period I will be summarized for the Safety Set and that for Treatment Period II will be summarized for the Safety – Treatment Period II subset, unless otherwise specified.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUEC	area under the effect curve
BMD	bone mineral density
BMI	body mass index
CFR	code of federal regulation
CI	confidence interval
C_{max}	maximum serum concentration
COVID-19	Coronavirus disease 2019
CRO	contract research organization
C_{trough}	trough serum concentration
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DNA	deoxyribonucleic acid
DRM	data review meeting
DSMB	data safety monitoring board
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
EQ-5D-5L	EuroQol-5 Dimention-5 Levels Health Survey
EOS	end-of-study
EU	European Union
eCRF	electronic case report form
FAS	full analysis set
FDA	food and drug administration
FSH	follicle stimulating hormone
GCP	good clinical practice
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator’s brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin

IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IU	international unit
IWRS	interactive web response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NAb	neutralizing antibody
NI	non-inferiority
NYHA	New York Heart Association
PD	pharmacodynamics(s)
PFS	prefilled syringe
P1NP	procollagen type 1 N-terminal propeptide
PK	Pharmacokinetic(s)
PPS	per-protocol set
PT	preferred term
PTH	parathyroid hormone
PVG	pharmacovigilance
QoL	quality of life
RANK	receptor activator of NF-κB
RANKL	receptor activator of NF-κB ligand
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
s-CTX	serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ONJ	osteonecrosis of the jaw
OPAQ-SV	osteoporosis assessment questionnaire-short version
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analog assessment
WHO	World Health Organization

1 Introduction

1.1 Background

1.1.1 Osteoporosis

Osteoporosis is a systemic skeletal disease that is characterized by low bone mass and micro-architectural deterioration of bone tissue, with a low bone mineral density (BMD) and consequent increase in bone fragility and susceptibility to fracture. The incidence of fractures varies greatly by country, but on average up to 50% of women > 50 years of age are at risk of fractures. Fractures severely affect the quality of life of an individual and are a major public health problem owing to the aging population. Postmenopausal osteoporosis, resulting from estrogen deficiency, is the most common type of osteoporosis. The estrogen deficiency results in an increase in bone turnover owing to effects on all types of bone cells (Eastell *et al*., 2016).

According to World Health Organizations (WHO) criteria, osteoporosis is defined as the T-score of ≤ − 2.5 standard deviation (SD) and osteopenia as the T-score between − 1.0 SD and − 2.5 SD. The femoral neck and lumbar spine are recommended as the anatomic region of interest (Ji *et al*., 2015).

Osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells) are 2 kinds of cells that essentially form the bone multi-cellular unit, coordinating well to regulate the balance of bone resorption and bone formation. The enhanced expression of cytokines known to stimulate osteoclastogenesis, such as interleukin (IL)-1, IL-6, and tumor necrosis factor, or enhanced expression of macrophage colony-stimulating factor and receptor activator of NF-κB ligand (RANKL) in osteoblasts/stromal cells may also play an important role (Ji et al., 2015).

Receptor activator of NF-κB ligand is released by bone forming cells known as osteoblasts and stimulates receptor activator of NF-κB (RANK) on the surface of stem cells to form osteoclasts, which are cells that mediate bone resorption. The same pair of proteins can also signal in reverse. In this case, RANK is released from osteoclasts in vesicles, and clusters of membrane-bound RANK activate signaling by RANKL molecules on the surface of osteoblasts to promote bone formation. Separating these 2 signals could prove beneficial to combat the excessive bone resorption that occurs during osteoporosis (Ray 2018).

Receptor activator of NF-κB ligand/RANK plays an important role in the pathway modulated by osteoblasts which affect bone mass density via the regulation of osteoblast and osteoclast

functions. In the RANKL/RANK pathway, RANKL binds to RANK as its receptor and eventually leads to osteoclast precursor maturation (Tobeiha *et al*., 2020).

RANKL inhibition blocks osteoclast maturation, function and survival, thus reducing bone resorption. With reduced RANK–RANKL binding, osteoclast formation, function and survival, and bone resorption decreases and bone mass increases (Hanley *et al*., 2012).

1.1.2 Denosumab

Denosumab, is a fully human monoclonal antibody that binds the cytokine RANKL which is an essential factor initiating bone turnover (Hanley *et al*., 2012). Denosumab binds to and neutralizes the activity of human RANKL, preventing RANKL from activating RANK, its receptor on the osteoclast surface.

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant deoxyribonucleic acid (DNA) technology.

Denosumab has been licensed for the treatment of postmenopausal women with osteoporosis at high risk for fracture and to increase bone mass in men with osteoporosis at high risk for fracture in the United States (US) (Prolia United States Prescribing Information [USPI] 2020). In Europe, it is approved for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures (Prolia Summary of Product Characteristics [SmPC] 2021). It is also approved in both the US and European Union (EU) for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

1.2 CT-P41

CT-P41 is a human monoclonal IgG2 antibody that is being developed and manufactured as a proposed biosimilar to Prolia (denosumab) by CELLTRION, Inc. CT-P41 is identical to Prolia with respect to concentration, formulation, and presentation.

The 60 mg of drug product (CT-P41) will have the same pharmaceutical form and strength as 60 mg Prolia (subcutaneous [SC] injection) and is intended to have a similar quality profile compared with Prolia. CELLTRION, Inc. plans to seek approval for all indications for which the innovator product has been approved by demonstrating similarity of CT-P41 with the

reference product through an extensive array of quality, nonclinical, and clinical comparability assessments.

1.2.1 Nonclinical Studies

The nonclinical program for CT-P41 has been designed to support clinical studies and to demonstrate similarity in binding profiles and functional activities between CT-P41 and Prolia. CT-P41 was evaluated in nonclinical *in vitro* and *in vivo* studies in order to demonstrate comparability of CT-P41 and Prolia. The *in vivo* study was conducted in accordance to Good Laboratory Practice standards.

Detailed information regarding the nonclinical pharmacology and toxicology of CT-P41 can be found in the Investigator's Brochure (IB).

1.2.2 Clinical Studies

Clinical data on Prolia has been published in scientific literature, regulatory submissions, and approved product information (Prolia USPI 2020; Prolia SmPC 2021). As CT-P41 is developed as a proposed biosimilar to Prolia, the clinical findings for CT-P41 are expected to be in line with those of Prolia in terms of safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy.

Study CT-P41 1.1 is a Pilot Phase I, randomized, double-blind, two-arm, parallel group, single-dose study to evaluate the safety and PK of CT-P41 and EU-approved Prolia in healthy male subjects. This study is performed to evaluate the safety of a single 60 mg SC injection and to evaluate the additional safety, immunogenicity, PK, and PD of CT-P41 and EU-approved Prolia in healthy male subjects. Study CT-P41 1.2 is a randomized, double-blind, two-arm, parallel group, single-dose, Phase I study to compare the PK, PD, and safety of CT-P41 and US-licensed Prolia in healthy male subjects.

The current Phase 3 study, CT-P41 3.1, is a double-blind, randomized, active-controlled study to compare efficacy, PK, PD, and safety including immunogenicity of CT-P41 and US-licensed Prolia in patients with postmenopausal women with osteoporosis.

1.3 Study Rationale

CT-P41 is currently being developed by CELLTRION, Inc. and is intended to be developed as a proposed biosimilar to Prolia. For a proposed biosimilar to be approved, it must be proven that there are no clinically meaningful differences between the drug products. The safety and PK as well as PD and immunogenicity of CT-P41 and EU-approved Prolia was

compared in a Pilot Phase I study in healthy male subjects (CT-P41 1.1). The PK similarity of CT-P41 and US-licensed Prolia will be compared in a Phase I study in healthy male subjects (CT-P41 1.2). Assessments of the therapeutic equivalence in efficacy of CT-P41 and the US-licensed Prolia will be demonstrated in a Phase III study in postmenopausal women with osteoporosis (CT-P41 3.1). CELLTRION, Inc. considers that the proposed clinical development programs will be sufficient to demonstrate similar profile of safety and PK (Pilot Study CT-P41 1.1 safety and PK similarity healthy volunteer study), PK, PD, and safety (Study CT-P41 1.2 PK similarity healthy volunteer study), and therapeutic equivalence and safety (Study CT-P41 3.1 comparative clinical similarity) of CT-P41 to the reference product.

The design of this study takes into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues (EMA 2012) and the Food and Drug Administration (FDA) Guidance on Scientific Considerations in Demonstrating Biosimilarity to a reference product (FDA 2015).

1.3.1 Rationale for Study Population

International regulations (WHO 2013; EMA 2012; FDA 2015; FDA 2019) suggest that proposed biosimilars should be tested in a population representative of the approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the proposed biosimilar and the reference product.

The study population in this study was selected in order to be representative of the other clinical studies supporting the development and marketing of the reference product (Prolia), and to align with the indications approved for the reference product.

Postmenopausal female patients between the ages of 50 to 80 with BMD T-score at the lumbar spine (L1 to L4) ≤ -2.5 and ≥ -4.0 will be enrolled in this study. The age group has been selected based on the statistics that the mean age of natural menopause is 51 years in industrialized nations, compared with 48 years in poor and nonindustrialized nations. With the average life span extended to 70 years, the upper age limit is selected as 80 years old (Ji *et al*., 2015). The WHO operational definition of osteoporosis is based on the T-score for BMD assessed by dual-energy X-ray absorptiometry (DXA) at the femoral neck or spine and is defined as a value for BMD − 2.5 SD or more below the young female adult mean (Camacho *et al*., 2020; Kanis *et al*., 2019). The BMD T-score inclusion criteria is based on a 3-year, randomized, double-blind, placebo-controlled trial conducted in 7,808 women to evaluate efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis which

had enrolled women with a baseline BMD T-score between − 2.5 and − 4.0 at either the lumbar spine or total hip (Prolia USPI 2020; Prolia SmPC 2021).

1.3.2 Rationale for Dose Selection

The recommended dose of Prolia is 60 mg administered as a single SC injection once every 6 months. The same dose has been selected for CT-P41 to allow comparisons between the reference drug and the proposed biosimilar.

1.4 Benefit and Risk Assessment

CT-P41 will have the same pharmaceutical formulation and strength as Prolia (60 mg). The proposed dosing regimen is in line with the approved labeling for Prolia (Prolia USPI 2020; Prolia SmPC 2021).

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P41 administration. In view of the structural, biological, and toxicological similarity to Prolia, CT-P41 is expected to display a similar safety profile.

Based upon the clinical evidence as well as the proven safety profile of Prolia, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

The benefit and risk assessments and the risk mitigation plans for coronavirus disease 2019 (COVID-19) are specified in Appendix 11.6. Risk assessments will be conducted during the study by the Sponsor through a sufficient discussion with the Investigators and data safety monitoring board (DSMB).

2 Study Objectives

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 BMD for lumbar spine (L1 to L4) at Week 52

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Study Design

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 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.

The study will be performed in a double-blind manner. To minimize the risk of unblinding, the study drug will be administered by unblinded study site personnel. The unblinded personnel who are responsible for administering study drugs will not be involved in any clinical or safety evaluations that are part of the blinded protocol or have other patient contact.

Patients will comply with all appropriate visits and assessments that will be performed at the time points specified in the schedule of assessments (Appendix 11.1).

Screening Period (from Day − 28 to Day − 1)

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

Treatment Period I (from Week 0 [Day 1] to Week 52 Predose)

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 randomization will be balanced by using permuted blocks. The randomization will be stratified by age (< 65 *versus* ≥ 65), baseline BMD T-score at the lumbar spine (≤ -3.0 *versus* > -3.0), and prior bisphosphonates therapy (Yes *versus* No).

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.

Treatment Period II (from Week 52 to Prior to Week 78 [EOS Visit])

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

The second randomization 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). 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.

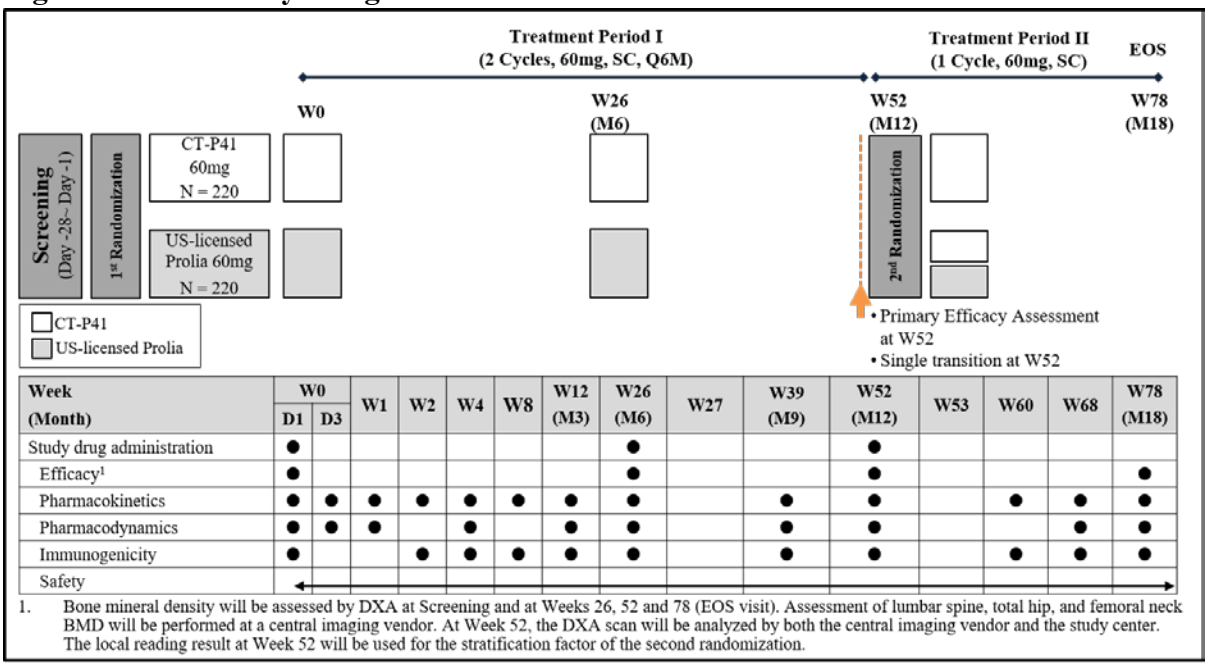
End-of-Study Visit (Week 78)

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 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 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 [AEs], concomitant medication) will be conducted by telephone according to the study visit schedule.

The study design and patient assessment overview is presented in Figure 3-1.

Figure 3-1 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 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 440 patients will be enrolled at approximately 20 study centers in 4 countries. Postmenopausal female patients with osteoporosis will be considered for enrollment in the study if they meet all the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be randomized in this study:

1. Women, 50 to 80 years of age, both inclusive.
2. Body weight between 40.0 and 99.9 kg, both inclusive, when rounded to the nearest tenth.
3. Postmenopausal, as defined by:
    a) No menstrual period for at least 12 consecutive months prior to the Screening visit with follicle-stimulating hormone (FSH) level ≥ 30 mIU/mL assessed by central laboratory at Screening visit, or
    b) Surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥ 12 months prior to the Screening visit
4. Bone mineral density T-score ≤ − 2.5 and ≥ − 4.0 at the lumbar spine (L1 to L4) as assessed by the central imaging vendor based on DXA scan at Screening.
5. Patient must have at least 3 vertebrae considered evaluable at the lumbar spine (L1 to L4) and at least 1 hip considered evaluable by DXA scan assessed by the central imaging vendor at Screening. Patient with unilateral metal in hips that would be allowed for the other side of 1 evaluable hip is included.
6. Patient with albumin-adjusted total serum calcium ≥ 8.5 mg/dL (≥ 2.125 mmol/L) at Screening.
7. Patient has adequate hepatic function at Screening as defined by the following clinical chemistry results:
    a) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN)

b) Alkaline phosphatase (ALP) ≤ 2 × ULN and total bilirubin ≤ 2 × ULN

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

9. Patient and/or their legally authorized representative must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks, side effects and requirements for supplementation, and must sign the informed consent form (ICF) before any study specific procedures.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

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

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

3. Patient who is confirmed or suspected with infection of COVID-19 at Screening, or has contact with COVID-19 patient within 14 days from Screening.

4. Patient who currently has, or has a history of, any of the following infections:

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

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

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

   a) One severe or > 2 moderate vertebral fractures (severe fracture is defined as > 40% vertebral height loss and moderate fracture is defined as 25% to 40% vertebral height loss [Genant *et al*., 1993]) as determined by central reading of lateral spine X-ray

   b) Hip fracture

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

d) Current hyperthyroidism (unless well controlled on stable antithyroid therapy)

e) Current hypothyroidism (unless well controlled on stable thyroid replacement therapy)

f) Bone disease and metabolic disease (except for osteoporosis) that may interfere with the interpretation of the results including osteomalacia, osteogenesis imperfecta, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteopetrosis, fibrous dysplasia, an elevation of ALP at the Investigator's discretion, Cushing's disease, hyperprolactinemia, malabsorption syndrome, advanced scoliosis or extensive lumbar fusion

g) History of severe skeletal pain with bisphosphonates

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

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

j) New York Heart Association (NYHA) Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease or electrocardiogram (ECG) abnormalities which can be judged as clinically significant at the Investigator's discretion

6. Patient has one of the following laboratory test result at Screening:

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

b) Estimated glomerular filtration rate < 30 mL/min/1.73 m^2

c) Hemoglobin < 10 g/dL

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

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

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

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

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

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

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

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

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

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

4.2 Withdrawal of Patients from the Study

Patients have the right to withdraw from the study treatment, procedures/observations, or the study at any time and for any reason. The Investigator and/or CELLTRION, Inc. also can decide to withdraw a patient from the study treatment, procedures/observations, or the study at any time prior to study completion.

Patients who are discontinued from the study treatment or are terminated from the study could be transitioned to another anti-resorptive therapies at the Investigator's discretion.

The primary reason for the discontinuation of the study treatment and study termination must be recorded in the patient's medical record and in the electronic case report form (eCRF) with any comments (spontaneous or elicited) or complaints made by the patient, date of cessation of study treatment, and the total amount of study treatment administered.

As it is vital to obtain follow-up data in all patients, even after study treatment discontinuation or initiation of different osteoporosis medication (including those prohibited by the protocol), the Investigator should attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.

If the patient is lost to follow-up, the Investigator or designee must make every effort to contact the patient (e.g., telephone calls to patient or family members, and if necessary, a letter requesting contact to the last known address).

4.2.1 Discontinuation of Study Treatment

Patients are free to discontinue the study treatment at any time for any reason. The Investigator may also discontinue the study treatment at any time in the interest of patient safety. Study treatment discontinuation should not be considered as study termination.

If necessary, the Investigator may discuss any patient's reason for study treatment discontinuation with CELLTRION, Inc. or its designee. CELLTRION, Inc. may be contacted if clarification is required on a case-by-case basis.

Reasons for study treatment discontinuation include the followings:

- Patient develops signs of disease progression in the judgment of the Investigator
- Patient has any AE that would compromise her safety if she continues to receive the

study treatment

- Patient has a significant protocol deviation(s)
- Investigator's decision
- Patient withdraws consent or refuses treatment
- Patient is lost to follow-up
- Patient dies
- Patient becomes pregnant
- Requirement for alternative therapy: If a patient experiences BMD loss from baseline of 7% or more at lumbar spine or total hip during a 12-month period, decrease in BMD T-score below – 4.0 at lumbar spine or total hip during the study, or osteoporosis-related fracture (e.g., vertebral compression fracture, hip fracture), the Investigator is required to discuss implication for individual fracture risk, alternative treatment options and options for continuing in the study with the patient, and to document that discussion. If a decision is made to begin alternative treatment, the study treatment must be discontinued and every effort should be made to complete all remaining study visits, regardless of any alternative treatment chosen by the patient.

For patients who are discontinued from the study treatment or are initiated 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 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., AEs, concomitant medications) will be conducted by telephone according to the study visit schedule and should be recorded in both the source document and eCRF.

4.2.2 Termination of the Study

Patients are free to withdraw the study at any time for any reason. The Investigator may also decide to terminate the study at any time in the interest of patient safety.

If necessary, the Investigator may discuss any patient's reason for withdrawal from the study with CELLTRION, Inc. or its designee. CELLTRION, Inc. may be contacted if clarification is required on a case-by-case basis. All patients who are terminated from the study will retain their patient identification number.

Reasons for study termination include the followings:

- Patient withdraws consent or refuses to procedures/observations
- Patient is lost to follow-up
- Patient dies
- Investigator's decision
- Study is terminated by the Sponsor

4.3 Replacement and Rescreening of Patients

Patients who receive study drug and discontinue before the study completion will not be replaced.

Patients who are screen failed, for any reason, can be rescreened only once. If there is unusual situation so that additional rescreening should be considered, the Investigator is recommended to discuss with CELLTRION, Inc. Rescreened patient will be assigned with new patient identification number. The following procedures do not need to be repeated during the rescreening if the assessment date for collected samples or performed scans or X-rays under the previous screening number is within 28 days prior to the first study drug administration and the screening results are eligible for the study.

- DXA scan
- Lateral spine X-ray (lumbar and thoracic)
- Laboratory assessments including hepatitis B and C, HIV, FSH, urinalysis, hematology, and clinical chemistry

4.4 Premature Termination of the Study

CELLTRION, Inc. reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is terminated prematurely by CELLTRION, Inc., all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The Investigator will inform the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

An interactive web response system (IWRS) will be used for the randomization. Unblinded biostatisticians will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

First Randomization for Treatment Period I

Approximately 440 patients will be enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (approximately each 220 patients in the CT-P41 and US-licensed Prolia).

During the Treatment Period I, the 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)

Second Randomization for Treatment Period II

Prior to dosing at Week 52, patients in the US-licensed Prolia treatment group will be randomly assigned again in a ratio of 1:1 to either switching arm (CT-P41) or non-switching arm (US-licensed Prolia). All patients who were initially randomly assigned to the CT-P41 on Day 1 (Week 0) will continue their treatment.

The second randomization process will be conducted in all treatment groups to maintain the study blind.

During the Treatment Period II, the randomization 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).

5.2 Identity of Investigational Products

CT-P41 is a monoclonal antibody which is being developed by CELLTRION, Inc. as a proposed biosimilar to US-licensed Prolia. The company code of the product is CT-P41.

The International Nonprioprietary Name of the Commercially available reference material (Prolia) is denosumab and the Anatomical Therapeutic Chemical Classification System code

is M05BX04. Denosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL.

The reference product, US-licensed Prolia, is supplied as sterile, preservative-free, clear, colorless to pale yellow solution for SC administration. Each 1 mL single-dose prefilled syringe (PFS) of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection, and sodium hydroxide to a pH of 5.2 (Prolia USPI 2020).

CT-P41 is supplied as a sterile, preservative-free solution of denosumab for SC administration in a single-use PFS. CT-P41 is a clear to slightly opalescent, colorless to pale yellow solution for injection, with a pH 5.0 – 5.4 and is formulated at 60 mg of denosumab in 1 mL for SC use. Each 1 mL single-dose PFS contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, and Water for Injection. For further details, see the IB.

5.3 Treatment Administered

5.3.1 CT-P41 and US-licensed Prolia

During the Treatment Period I, patients will receive 60 mg of CT-P41 or US-licensed Prolia on Week 0 (Day 1) and Week 26, respectively, as per the first randomization. During the Treatment Period II, patients will receive 60 mg of CT-P41 or US-licensed Prolia at Week 52 as per the second randomization.

The study drug will be administered as a single SC injection in the upper arm, the upper thigh, or the abdomen.

The study drug is required to be administered by the site-qualified and trained clinical staff member(s) (e.g., nurse/physician, etc.), who is designated as an unblinded study site personnel. The people sensitive to latex should not handle the needle cap on the single-dose PFS, which contains dry natural rubber (a derivative of latex). Patients will be blinded through the use of a blindfold, screen, or similar method during the dosing procedure so that the injection syringe will not be visible to the patient. The detail regarding blinding is described in Section 5.7.

5.3.2 Co-administration of Calcium and Vitamin D

Calcium and Vitamin D are co-administered to prevent low serum calcium level while taking study drugs. Therefore, all patients will receive daily supplementation containing at least

1,000 mg of elemental calcium and at least 400 IU vitamin D from randomization to EOS visit. 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.

If a patient becomes hypercalcaemia during the study, the calcium and/or vitamin D supplementation may be discontinued or reduced by Investigator's discretion until the serum calcium concentration has returned to the normal range.

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

If a patient is intolerant of the daily calcium or vitamin D supplementation, the formulation may be changed or the dose could be lowered by Investigator's discretion. The intolerance as well as the resolution (e.g., change in formulation or dosage) should be recorded in both the source documents and the eCRF.

5.4 Prior, Concomitant, and Subsequent Therapy

Information (e.g., drug name, date[s] of administration, etc.) about prior medications taken by the patient within 30 days prior to the signed date of ICF (inclusive of the applicable periods for prohibited medications as defined in Section 5.5) will be recorded until the EOS visit in both the source documents and eCRF. In order to check eligibility, prior medications will be reviewed for the times specified in the related exclusion criteria. This will include all prescription drugs, over-the-counter medicines, vitamins, and herbal supplements.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. All concomitant medications should be reported to the Investigator and recorded on the appropriate eCRF and source document. Any changes in concomitant medications also will be recorded in the source documents and patient's eCRF. All concomitant medications used during the study will be recorded until the EOS visit.

Use of all prior and concomitant medications for the treatment of osteoporosis, from the diagnosis of disease until the EOS visit, will be recorded in the source documents and patient's eCRF.

It is the Investigator's responsibility to ensure that details regarding the medication are adequately recorded in both the source documents and eCRF.

5.5 Prohibited Therapy

The following medications, treatments, or procedures are prohibited during the study (Section 4.1.2). Patients who receive any prohibited therapy during the Screening period should be considered a screen failure. Intake of any of the following prohibited therapy by the patients after randomization will be considered as protocol deviation.

- Denosumab other than study drug or any other monoclonal antibodies (e.g., romosozumab), protein, fusion protein, or other biologic agent targeting IgG
- Treatments for osteoporosis (such as oral/intravenous bisphosphonates, fluoride, strontium, PTH or its derivatives, systemic hormone-replacement therapy [estrogen with or without progestogen], selective estrogen-receptor modulator, tibolone, calcitonin, or calcitriol)
- Treatments that can affect bone metabolism (such as heparin, anticonvulsives [except benzodiazepines], systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists)
- Use of oral or parenteral glucocorticosteriods (> 5 mg/prednisone daily or equivalent for more than 10 days)
- Any other investigational drugs

Patients who completed the study or are permanently discontinued from the study treatment can be transitioned to another anti-resorptive therapies at the Investigator's discretion.

Any authorized COVID-19 vaccines are prohibited for 2 weeks prior and after the study drug administration (total of 4 weeks). During the study, the interval of COVID-19 vaccination schedule would be adjusted to have an interval of at least 2 weeks prior and after the study drug administration scheduled for Weeks 0 (Day 1), 26, and 52.

5.6 Management of Clinical Supplies

5.6.1 Study Drug Package, Labeling, and Storage

The appropriate number of study drug syringes will be allocated to each patient via IWRS system at each visit.

A label will be attached to the outside of each patient kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Patient number/site number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator's name
- Route of administration
- Directions for use
- Storage instructions
- Caution statement (for clinical trial use only)
- Sponsor's contact name and address
- Expiry date

All study drug supplies must be stored in secured area with limited access (e.g., a locked cabinet) and in accordance with the manufacturer's instructions. They will be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study drug from light. The recommended storage conditions, and expiry date where required, are stated in the product label approved by each regulatory authority.

5.6.2 Study Drug Accountability

It is the responsibility of the clinical Investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form will be maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited access area under appropriate environmental conditions.

The Investigator agrees not to supply the study drug to any person other than Sub-Investigators, designated staff, and the patients participating in the study. Study drug may not be relabeled or reassigned for use by other patients unless approved by the Sponsor.

The used syringes can only be destroyed if it is according to local standard operating procedures (SOP) and a specific authorization is given by the Sponsor. Permission will be granted by the Sponsor on a study-center-by-study-center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used syringes immediately after administering the study drug to patients. The list of destroyed syringes must be recorded. The Investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with the Sponsor.

5.7 Blinding

This study will be double-blind until the end of the study. The randomization codes will not be revealed to study patients, Investigators, and study site personnel, except for delegated unblinded staff who will handle the study drug and predefined unblinded personnel in the Sponsor and contract research organization (CRO) until all final clinical data have been entered into the database and the database is locked and released for analysis.

As the presentation of the study drugs are not identical in visual appearance, the trained clinical staff member(s) responsible for drug administration (e.g., nurse/physician, etc.) will be designated as unblinded study site personnel and will not be involved in any clinical or safety evaluations that are part of the blinded protocol or have other patient contact. Patients will be blinded through the use of a blindfold, screen or similar method during the dosing procedure so that the injection syringe will not be visible to patient. Blinded staff will be absent during injection and remain blinded throughout the study.

5.7.1 Breaking the Blind

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 (see IWRS manual, which is provided as a separate document).

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and the medical monitor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medial monitor and the Sponsor. Any patients for whom the blind is broken may continue in the study and receive the study treatment at the Investigator's discretion.

Contract research organization pharmacovigilance (PVG) will have access to the randomization code, if suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities.

The DSMB and the statistical team of CRO who provide the safety analyses for the DSMB will also be unblinded upon the request from DSMB members during closed session.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 52 or Week 78 for all patients. The unblinded personnel will be predefined and documented before breaking the study blind. The study will remain blinded to the Investigators, patients, and predefined blinded personnel from the Sponsor and CRO until all patients have completed the study and the database has been finalized for study closure.

5.8 Treatment Compliance

CT-P41 and US-licensed Prolia will be administered by the unblinded site staff while the patient is at the study center. The date and time of the study drug administration will be recorded in both the source documents and the eCRF. Administration of co-administered treatments (Calcium and Vitamin D) will be recorded throughout the study.

Every effort will be made to encourage patients' compliance with the study visits. 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 follow the original visit date scheduled.

6 Study Assessments and Procedures

Prior to performing any study procedures, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered prior to signing the ICF. The Investigator must address all questions raised by the patient. The Investigator or designee will also sign the ICF.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. Patients will undergo the procedures at the time points specified in the schedule of events (Appendix 11.1).

6.1 Efficacy Assessments

6.1.1 Bone Mineral Density

Bone mineral density will be assessed by DXA at Screening and at Weeks 26, 52, and 78 (EOS visit). Only Hologic or Lunar bone densitometers will be allowed for the study. The same DXA instrument should be used for all study procedures for each patient during the study. If for unforeseeable reasons the same scanner is no longer available, the study site should follow the central imaging provider's guidance on selecting an appropriate replacement scanner and follow a phantom scanning process to quantify any calibration differences. All DXA scans of lumbar spine, total hip, and femoral neck BMD will be submitted to and analyzed by the central imaging vendor.

Primary efficacy assessment will be determined by percent change from baseline in BMD for lumbar spine at Week 52. Secondary efficacy assessments include percent change from baseline in BMD for lumbar spine, total hip and femoral neck at Weeks 26, 52, and 78.

For lumbar spine DXA scan, L1 through L4 should be measured, only excluding vertebrae that are affected by local structural change or artifact, using at least 2 vertebrae for diagnostic classification. Anatomically abnormal vertebrae may be excluded from analysis if they are clearly abnormal and nonassessable within the resolution of the system and using a 1.0 T-score difference between vertebra in question and adjacent vertebrae as a guideline in identifying vertebrae for exclusion (2019 International Society or Clinical Densitometry [ISCD Official Position - Adult).

For femur DXA scan, the left side should be used for all scans at all study visits. If the right side must be used (e.g., due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a patient fractures the hip that has been scanned

during the study up to the time of fracture, no further scans will be obtained for the affected location.

6.1.1.1 Screening Bone Mineral Density Assessment

To determine eligibility based on BMD T-score, lumbar spine DXA scans will be analyzed by the central imaging vendor.

To be eligible for the study, patients must have at least 3 evaluable vertebrae at the lumbar spine (L1 to L4) and at least 1 evaluable hip by DXA scan assessed by the central imaging vendor. Patients with unilateral metal in hips that would be allowed for the other side of 1 evaluable hip are included.

6.1.1.2 On-Study Bone Mineral Density Assessment

Bone mineral density changes for individual patients will be monitored by the central imaging vendor during the study. Investigators will be alerted if a patient experiences a BMD loss from baseline of 7% or more at the lumbar spine or total hip during a 12-month period, or decrease in BMD T-score below – 4.0 at lumbar spine or total hip during the study.

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 administration 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 needed, 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.

6.1.2 Incidences of Fractures

If any fractures occur, the information should be recorded as AE.

6.1.2.1 Vertebral Fractures

Incidences of vertebral fractures which are confirmed radiographically regardless of patient-reported symptoms indicative of a fracture will be reported throughout the study period. A new vertebral fracture is defined as an increase of at least one grade in any vertebra from T4 to L4 that was normal at Screening (Cummings *et al*., 2009).

It is difficult to determine the exact incidence of vertebral fractures due to the absence of specific symptoms in some and the difficulty in determining the cause of possible physical symptoms such as pain and height loss (Mikayel *et al*., 2003). Therefore, to increase the potential of therapeutic intervention to prevent subsequent fractures, the 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. The vertebral fracture will be assessed by semi-quantitative grading at a central imaging vendor (Genant *et al*., 1993):

- 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

If needed, 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 followed by the study drug administration occurring within the same visit window of Week 26 or Week 52 visit.

Information indicative of a vertebral fracture will be recorded. If a patient reports back pain that is considered by the Investigator to be possibly due to a vertebral fracture, a confirmatory lateral spine X-ray will be taken and the back pain (but not a vertebral fracture) will be reported as an AE. The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the patient's individual source documents and will be submitted to the central imaging vendor for confirmation of fracture. The central imaging vendor will inform the sites if a vertebral fracture is identified. If necessary to support the patient's medical care, these X-rays could be read locally. Only fractures confirmed by the central imaging vendor will be included for the efficacy analysis.

6.1.2.2 Nonvertebral Fractures

A nonvertebral fracture 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 (Bone *et al*., 2008; Cummings *et al*., 2009).

Information about nonvertebral fracture (e.g., details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture will be recorded during the study. A copy of radiographs or other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the patient's individual source documents and will be submitted to the central imaging vendor for confirmation of fracture. If the radiograph or diagnostic image is not available, then, at minimum, a copy of the radiology report, surgical report, clinical notes, or discharge summary should be submitted to the central imaging vendor. Only fractures confirmed by the central imaging vendor will be included for the efficacy analysis.

6.1.3 Quality of Life Assessment

Health-related quality of life will be assessed using osteoporosis assessment questionnaire short version (OPAQ-SV) and EuroQoL-5 Dimensions-5 Levels health survey (EQ-5D-5L) at baseline and Weeks 26, 52, and 78.

6.1.3.1 Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV)

The OPAQ-SV is a 34-item osteoporosis-specific health-related questionnaire. The OPAQ-SV evaluates the impact of vertebral and nonvertebral fractures on physical function, emotional status, and symptoms (one question on back pain) (Silverman 2000) (Appendix 11.2). The physical function domain includes questions on walking/bending, transfers, and daily activity, and the emotional status domain includes questions on fear of falling, body image, and independence. Scores for each of the dimensions range from 0 to 100 with higher scores representing better health status. A negative change in score represents a decline in health status, and a positive change in score represents an improvement in health status.

6.1.3.2 EuroQoL-5 Dimensions-5 Levels Health Survey (EQ-5D-5L)

The EQ-5D-5L is a preference-based measurement across 5 attributes (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels (no problem, slight problem, moderate problem, severe problem, and extreme problem) within each attribute (Appendix 11.3). The scale is measured by the visual analog scale (VAS) that requires patients to directly rate their current health. 0 means the worst health and 100 means the best health patients can imagine (Tosteson *et al*., 2002).

6.2 Pharmacokinetic Assessments

Pharmacokinetic blood samples for the determination of serum concentration of study drug will be collected from patients from both treatment groups (CT-P41 and US-licensed Prolia) at the time points specified in the schedule of assessments (Appendix 11.1). Predose samples (Weeks 0 [Day 1], 26 and 52) will be collected up to 30 minutes before the study drug administration. The postdose samples can be taken at any time of the scheduled visit. For patients who early discontinue study treatment, PK samples will be collected until the next study drug administration scheduled visit and further PK sampling is unnecessary. When a patient discontinues study treatment after administration of the study drug at Week 52, the PK samples will be collected until Week 78 visit.

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PD or immunogenicity assessment at the same time point can be used for PK assessment after discussion and agreement from CELLTRION, Inc. Analysis will be performed at the central laboratory.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. Details for PK blood sampling are provided in Section 6.5.1.

6.3 Pharmacodynamic Assessments

Determination of concentration of bone turnover markers will be measured from fasting serum samples at the time point specified in the schedule of assessments (Appendix 11.1). Patients will be required to refrain from intense exercise the day prior to assessment, to fast overnight for 8 hours prior to assessment and to visit the study center in the morning for PD assessment. For patients who early discontinue study treatment, PD samples will be collected until the next study drug administration scheduled visit and further PD sampling is unnecessary. When a patient discontinues study treatment after administration of the study drug at Week 52, the PD samples will be collected until Week 78 visit.

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PK or immunogenicity assessment at the same time point can be used for PD assessment after discussion and agreement from CELLTRION, Inc. Analysis will be performed at the central laboratory.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. Details for PD blood sampling are provided in Section 6.5.2.

6.4 Safety Assessments

Safety assessments will be performed on AEs (including serious AEs [SAEs]), adverse events of special interest (AESI; injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, ONJ, atypical femoral fracture, and dermatologic reactions), immunogenicity including antidrug antibody (ADA) and neutralizing antibody (NAb), hypersensitivity monitoring, vital sign assessments, body weight, height, body mass index (BMI), ECG, physical examination (including oral examination), clinical laboratory analyses, local site pain by VAS, and prior and concomitant medication. Hepatitis B, C, HIV, and FSH testing and NYHA functional classification will be assessed to determine patients' eligibility.

6.4.1 Adverse Events

6.4.1.1 Definitions of Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in any patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after the ICF was signed if any symptoms develop. Any new condition noted at Screening would be regarded as an AE, but not a treatment-emergent adverse event (TEAE).

A 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.

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

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are clinically significant as evaluated by the Investigator

Disease progression of postmenopausal osteoporosis will not be recorded as an AE or SAE.

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.4.1.1.1 Adverse Events of Special Interest

The following AEs are considered as AESIs and will be reported using the same process as for AEs:

- Injection site reaction

Injection site reaction will be observed after study drug administration and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AEs related to injection site reaction including erythema, itching, hemorrhage, pain, and swelling will be reported.

- Drug-related hypersensitivity/allergic reaction

All AEs related to hypersensitivity/allergic reactions including anaphylaxis after study drug administration will be reported. Symptoms include but not limited to hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria will be reported. Diagnosis of anaphylaxis will be based on the anaphylaxis criteria of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (Sampson *et al.,* 2006).

- Infection

All AEs related to infections including but not limited to urinary tract infection, upper respiratory tract infections, skin infections including but not limited to erysipelas and cellulitis, abdomen infection and ear infection will be reported.

- Hypocalcaemia

All AEs related to hypocalcaemia include but not limited to paraesthesia or muscle stiffness, twitching, spasms and muscle cramps, QT interval prolongation, tetany, seizures and altered mental status will be reported.

- Osteonecrosis of the jaw

All AEs related to ONJ include but not limited to jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, and gingival erosion will be reported.

- Atypical femoral fracture

All AEs related to atypical femoral fracture include but not limited to new or unusual thigh, hip, or groin pain will be reported.

- Dermatologic reactions

All AEs related to dermatologic reactions include but not limited to dermatitis, eczema, and rashes will be reported.

6.4.1.1.2 Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- 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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. These should also be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongation of hospitalization are considered as SAEs. Any admission (even if < 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., patient has no place to sleep)
- Purely for convenience (e.g., for easier performance of study assessments)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient
- Hospitalization solely due to disease progression without any other AEs as decided by the Investigator

6.4.1.1.3 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable reference documents (e.g., study drug IB).

6.4.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date patients signs the 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 the CELLTRION, Inc. or its designee.

At every study visit, patient will be asked a standard non-leading question to elicit any medically related changes in their wellbeing. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

6.4.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF and source documents. Information to be collected includes drug treatment, dose, event term, time of onset, Investigator-specified assessment of severity and relationship to study treatment, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent condition, reactions to concurrent condition, or reactions to concurrent medications must also be reported. All AEs will be followed to adequate resolution. Adverse events will be graded for severity according to the CTCAE Version 5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is reported or what is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study treatment in causing or contributing to the AE will be characterized as defined in Section 6.4.1.6 and Section 6.4.1.7, respectively.

6.4.1.4 Reporting Serious Adverse Events

Any AE considered serious by the Investigator or which meets SAE criteria (Section 6.4.1.1.2) must be reported to [redacted] within 24 hours from the time study center staff first learn about the event. The following contact information is to be used for SAE reporting:

[redacted]

Data entry should be completed in the remote data capture system by the Investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax it to [redacted] PVG within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the patient is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be faxed to [redacted] PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the Principal Investigator or Sub-Investigator. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the Principal Investigator or Sub-Investigator deems the event to be chronic or not clinically significant or the patient to be stable.

The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with European Clinical Trials Directive (EMA 2001), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening SUSARs (expedited reports) to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. The Sponsor or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), Investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

6.4.1.5 Suspected Unexpected Serious Adverse Reactions

The Sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the Sponsor will assess the expectedness of these events using the applicable reference documents (e.g., study drug IB).

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6.4.1.6 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE Version 5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[1]

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL[2]

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

1. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2. Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator will assess of the maximum intensity that occurred over the duration of the event. If an AE changes from non-serious to serious, a new SAE needs to be reported.

Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.1.7 Assessment of Causality

As discussed in Section 6.4.1.3, the Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is reported or what is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P41 or US-licensed Prolia in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, e.g., the event follows a reasonable temporal sequence from the time of study drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease states, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.4.2 Other Safety Assessments

6.4.2.1 Medical History, Disease History, and Demographic Information

The medical history (general medical history and medication history), disease history of postmenopausal osteoporosis, fracture history, smoking history, and demographic information including gender, age, ethnicity, race, and BMI (kg/m^2) at Screening will be recorded in the patient's eCRF and the source documents.

6.4.2.2 Immunogenicity Assessment

The immunogenicity of CT-P41 and US-licensed Prolia will be assessed by ADA and NAb test in a validated immunoassay. Blood samples for immunogenicity assessments will be collected at the time points specified in the schedule of assessments (Appendix 11.1). The samples at Weeks 0 (Day 1), 26, and 52 will be collected prior to study drug administration. For patients who early discontinue study 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.

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PK or PD assessments at the same time point can be used for immunogenicity assessment after discussion and agreement from CELLTRION, Inc.

Blood samples for immunogenicity for patients with immune-related AEs will be obtained on onset date of immune-related AEs, if possible, or blood sample can be used if it was obtained at the same date of study drug administration.

Analysis will be performed at the central laboratory.

Details for immunogenicity blood sampling are provided in Section 6.5.3.

6.4.2.3 Injection Site Reaction Monitoring

Injection site reactions will be assessed 30 minutes (± 10 minutes) after the end of the study drug administration, as specified in the schedule of assessments (Appendix 11.1).

For patients who early discontinue study treatment, assessment of injection site reaction is unnecessary after the discontinuation.

Details will be recorded in both the source documents and the eCRF.

6.4.2.4 Hypersensitivity/Allergic Reaction Monitoring

Hypersensitivity/allergic reactions monitoring will be assessed 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, as specified in the schedule of assessments (Appendix 11.1), by additional vital sign measurements including blood pressure, heart and respiratory rates, and body temperature. If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study center or get immediate help.

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 experience or develop life-threatening treatment-related hypersensitivity/allergic reactions, the study drug must be stopped immediately and the patient should be withdrawn from the study.

For patients who early discontinue study treatment, monitoring of hypersensitivity/allergic reactions is unnecessary after the discontinuation.

Details will be recorded in both the source documents and the eCRF.

6.4.2.5 Vital Signs, Weight, Height, and Body Mass Index

Vital signs, weight, height, and BMI measurements will be performed at the time points specified in the schedule of assessments (Appendix 11.1). Vital signs (including blood pressure, heart and respiratory rates, and body temperature) will be measured after 5 minutes of rest (sitting). Body mass index will be calculated by patient's weight in kg divided by patient's height in m^2. All other measurements will be documented at each study center visit. Details will be recorded in both the eCRFs and source documents.

Vital sign measurements will also be monitored before (within 15 minutes) and after the study drug administration (1 hour [± 10 minutes]) as part of the hypersensitivity monitoring (Section 6.4.2.4).

6.4.2.6 Electrocardiogram

All scheduled 12-lead ECGs will be performed at the study center after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of assessments (Appendix 11.1) and if the patient experienced cardiac symptoms during the study drug administration. If following the ECG review by the Investigator there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The Investigator will then report the event in the eCRF and source documents. Regardless of 12-lead ECG result, further evaluation with a cardiologist can be done depending on the Investigator's discretion. In case of hypersensitivity, any type of ECG can be performed (Section 6.4.2.4).

6.4.2.7 New York Heart Association Functional Classification

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 (Appendix 11.5). Patients with congestive heart failure of class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease, or electrocardiogram abnormalities will be excluded from the study. Results will be recorded in both the eCRF and source documents.

6.4.2.8 Physical Examination

Investigators should carefully evaluate patients for any indication of injection site reaction, hypersensitivity/allergic reactions, infection, hypocalcaemia, ONJ, atypical femoral fracture, and dermatologic reactions and treatment should be indicated in accordance with the Investigator's medical judgment. Especially, a thorough oral examination (including mouth, gums, teeth, tongue) with appropriate preventive dentistry should be performed prior to treatment. Physical examination will be performed at the time points specified in the schedule of assessments (Appendix 11.1).

Information about the physical examination will be recorded by the Investigator or designee in the eCRF and source documents. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded in the eCRF and source documents.

6.4.2.9 Osteonecrosis of the Jaw

If a patient has an oral AE which is suspected to be ONJ by the Investigator, the patient should be examined by a dentist or other qualified oral specialist (e.g., oral surgeon), for whom the blind will be maintained until the end of the study, to determine whether it is ONJ based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) ONJ case definition (Ruggiero *et al*., 2014). All available information including age, smoking history, medical history, prior and concomitant medication, physical examination, oral AE, and anatomic location of ONJ lesion will be provided to the dentist or oral specialist. Radiograph could be performed by the dentist or oral specialist's discretion. The Investigator will be notified of the adjudication decision by the dentist or oral specialist whether the oral AE is meeting or not meeting to the ONJ case definition. If the oral AE is adjudicated positively by the dentist or oral specialist, the information including case details (possible inciting event) and AAOMS stage should be provided to the Investigator. The treatment and management plan for the ONJ should be set up in close collaboration between the Investigator and the dentist or oral surgeon.

6.4.2.10 Atypical Femoral Fracture

Patients should be advised to report new or unusual thigh, hip, or groin pain. Radiography should be performed on patients presenting with such symptoms to evaluate the atypical femoral fracture.

The femoral fracture AE or the adverse event which is suspected to be an atypical femoral fracture will be reviewed by a radiologist at the central imaging vendor, for whom the blind will be maintained until the end of the study. All available information surrounding the event will be provided to the radiologist. The radiologist will review the radiograph(s) or other diagnostic image and/or radiology report, surgical report, or discharge summary with reference to the American Society for Bone and Mineral Research (ASBMR) Task Force 2013 Revised Case Definition of atypical femoral fractures (Shane *et al*., 2014). If the event is adjudicated positively for atypical femoral fracture, the Investigator will be notified of the adjudication decision.

6.4.2.11 Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus

At Screening, hepatitis B will be assessed in all patients. Eligibility for Hepatitis B infection will be confirmed according to the Table 6-1.

A patient with past hepatitis B virus is allowed if resolved. If the patient develops hepatitis B

reactivation, the study drug must be stopped.

If a patient has hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb) tests will be performed at Screening. If HBeAg test result is positive, the patient will be excluded from the study. If the patient has HBeAg negative and HBeAb positive test results, hepatitis B virus (HBV) DNA test will be performed; if the HBV DNA test result is low or absent (undetectable) level, the patient can be included in the study.

If a patient has HBsAg negative, hepatitis B surface antibody (HBsAb) negative or positive, and hepatitis B core antibody (HBcAb) (IgM) positive, a HBV DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled based on the HBV DNA test result, testing of HBsAg, HBsAb, HBV DNA, AST, ALT, and total bilirubin will be performed at Weeks 26, 52, and 78 (EOS visit).

If a patient has HBsAg negative, HBsAb negative or positive, and HBcAb (IgM) negative, the patient can be included in the study.

Table 6-1 Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results						Eligibility
HBsAg	**HBsAb**	**HBcAb (IgM)**	**HBeAg**	**HBeAb**	**HBV DNA**	
+	+/-	+	+	+/-	N/A	Not eligible
+	+/-	+	-	+	+/- (low or absent [undetectable] level)	Eligible
-	+/-	+	N/A	N/A	+	Not eligible
-	+/-	+	N/A	N/A	-	Eligible[1]
-	+/-	-	N/A	N/A	N/A	Eligible

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; EOS, end-of-study; 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; IgM, immunoglobulin M; N/A, not applicable.
[1] Testing of HBsAg, HBsAb, HBV DNA, AST, ALT, and total bilirubin will be performed at Weeks 26, 52, and EOS visit.

At Screening, hepatitis C antibody will be assessed in all patients. If the hepatitis C antibody test result is positive, a hepatitis C virus (HCV) RiboNucleic Acid (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 HCV 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.

The HIV test will be assessed in all patients at Screening. If the HIV test result is positive, the patient will be excluded from the study.

Hepatitis B, hepatitis C, and HIV analysis will be performed at the central laboratory.

6.4.2.12 Pregnancy

Women of child-bearing potential will not be eligible for enrollment in this study. However, if a pregnancy is reported from start of the study drug administration through the study period, it should be reported to the Sponsor and [redacted] PVG within 24 hours of the Investigator's knowledge of the event of a pregnancy. The pregnant patient must permanently discontinue the study drug immediately. The study center must complete the supplied pregnancy form and return it to the Sponsor and [redacted] PVG within 24 hours after acquisition of the consent for the pregnancy form.

The pregnancy must be followed up to determine outcome (including premature termination). The pregnant patient will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.4.1.4).

6.4.2.13 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of assessments (Appendix 11.1). Blood samples do not need to be performed in a fasting state unless required in the opinion of the Investigator. Clinical laboratory test samples will be analyzed at the central laboratory.

The following clinical laboratory analyses will be performed.

Clinical chemistry: Albumin, albumin-adjusted total serum calcium, ALP, ALT, 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, phosphates, potassium, sodium, bilirubin (total, direct), total protein, uric acid, Troponin I, serum 25-OH vitamin D, thyroid stimulating hormone, and intact parathyroid hormone.

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelet count.

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

Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D, mineral levels (magnesium, phosphate), and any sign and symptoms of hypocalcaemia will be closely conducted and adequately treated at Investigator's discretion, if occurred. At Weeks 26, and 52, those clinical laboratory tests will be performed to determine the study drug administration. Those clinical laboratory tests will be analyzed at the local laboratory and test results will be recorded in the eCRF and source documents. If abnormal results are reported, patients will be treated accordingly and follow-up actions will be taken at the Investigator's discretion. If needed, those clinical laboratory 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 total serum calcium level could 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]).

6.4.2.14 Patient's Assessment of Local Site Pain

All patients will assess local site pain using 100 mm VAS immediately (not exceeding 15 minutes) after the study drug administration at the time points specified in the schedule of assessments (Appendix 11.1). Patient assessment of pain is measured by the patient indicating the extent of their pain by marking one line (|) through the 100 mm line (Appendix 11.4).

For patients who early discontinue study treatment, assessment of local site pain is unnecessary after the discontinuation.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Appendix 11.1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.2 Pharmacodynamic Blood Sampling

Blood samples for PD assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Appendix 11.1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.3 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained in accordance with the laboratory manual from each patient at the time point specified in the schedule of assessments (Appendix 11.1). All samples should be collected as close as possible to the scheduled time point. The actual sampling date and time will be recorded in both the eCRF and source documents.

6.5.4 Routine Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Appendix 11.1).

An additional blood sample for hepatitis B, hepatitis C, HIV, and FSH testing will also be required at Screening.

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

Each sample tube will be clearly labeled with the following information: study number, patient number, tube identification, and scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, PD, immunogenicity, and safety analyses.

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and backup samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the backup samples.

Additionally, backup samples for PK, PD, and immunogenicity should be retained at the central laboratory as a backup for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK, PD, and immunogenicity is not required, the sample will be stored at the Sponsor or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by the Sponsor to destroy the sample. Additional tests can be conducted at the Sponsor or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Analysis Plan

The statistical analysis will be performed using [redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized before database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report (CSR).

Full details of the statistical methods will be described in the SAP.

7.1 Primary Endpoint

The primary efficacy endpoint will be the following:

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

7.2 Secondary Endpoints

7.2.1 Efficacy Endpoints

The secondary efficacy endpoints will be the following:

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

7.2.2 Pharmacokinetic Endpoints

The secondary PK endpoints will be the following:

- Serum concentration of denosumab (up to Week 78)
- 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)

7.2.3 Pharmacodynamic Endpoints

The secondary PD endpoints will be the following:

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

7.2.4 Safety Endpoints

Safety assessments will occur throughout the study. The following safety parameters are determined as secondary safety endpoints:

- Adverse events (including SAEs)
- Adverse events of special interest (AESI; injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, ONJ, atypical femoral fracture, and dermatologic reactions)
- Hypersensitivity/allergic reaction assessments by vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Local site pain using 100 mm VAS
- Vital sign measurements, weight, height, and BMI
- Physical examination
- Clinical laboratory tests
- 12-lead electrocardiogram
- Prior and concomitant medication
- Immunogenicity (incidence of ADA and NAb)

Hepatitis B, C, HIV, and FSH testing and NYHA functional classification will be assessed to determine patients' eligibility.

7.3 Sample Size Calculation

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%.

7.4 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-Treat (ITT) 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.

ITT – 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.

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

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

Per-Protocol Set (PPS): The PPS is defined as all randomly assigned patients who receive all 2 doses (full) of study drug (CT-P41 or US-licensed Prolia) at Weeks 0 (Day 1) and 26, and have BMD assessments from 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 data review meeting (DRM) before unblinding.

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 result.

PK – Treatment Period II subset: The PK – Treatment Period II subset will consist of all patients in PK Set who receive 1 full dose of either of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PK result at or after Week 52.

Pharmacodynamic Set: The PD 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 PD result.

PD – Treatment Period II subset: The PD – Treatment Period II subset will consist of all patients in PD Set who receive 1 full dose of either of study drug (CT-P41 or US-licensed Prolia) at Week 52 and have at least 1 post-treatment PD result at or after Week 52.

Safety Set: The Safety Set will consist of all patients who receive at least 1 dose (full or partial) of study drug (CT-P41 or US-licensed Prolia).

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

Final determination of the major protocol deviations that can affect the data analysis will be made at the blinded DRM held in accordance with ICH Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E9.

7.5 Description of Subgroups to be Analyzed

Subgroup analysis by race and age will be performed for primary efficacy endpoint in the FAS. Further subgroup analysis could be implemented to reflect medical, regulatory, regional, or ethnic consideration, if required.

7.6 Statistical Analysis Methodology

7.6.1 General Consideration

Continuous variables will be summarized by reporting the following descriptive statistics: the number of observations (n), mean, SD, median, minimum, and maximum, unless otherwise indicated. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

7.6.2 Demographics, Baseline and Background Characteristics

The medical history (general medical history and medication history), demographic (e.g., gender, age, ethnicity, race, and BMI [kg/m^2] at Screening), and baseline characteristics

including disease-related medical history, and medication history will be presented in summary tables (descriptive statistics for quantitative variables, or frequency for qualitative variables). Listings will be provided by treatment group.

Demographics, baseline and background characteristics for Treatment Period I will be summarized using the ITT Set and those for Treatment Period II will be summarized on the ITT – Treatment Period II subset, unless otherwise specified. Listings will be provided by treatment group on the ITT Set. In addition, a listing of patients whose trial participation is impacted by COVID-19 with details of the impact, will be prepared, if applicable.

7.6.3 Efficacy Analyses

7.6.3.1 Primary Efficacy Endpoint

To evaluate the difference between 2 treatment groups in the primary efficacy endpoint, percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 will be analyzed 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. Statistical equivalence will be declared if the 90% confidence interval (CI) of the difference in the mean of the primary efficacy endpoint between treatment groups falls entirely within an equivalence margin, [− 1.45, + 1.45]. The primary analysis will be performed using the FAS. A supportive analysis will be performed using the PPS.

Multiple imputation with the MAR assumption will be applied. The multiple imputed datasets will be generated based on regression model with age, baseline BMD T-score at lumbar spine, prior bisphosphonates therapy (Yes *versus* No), and treatment group as covariates. Ten imputed datasets will be generated and an ANCOVA for the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 will be performed on each of the 10 multiple imputed datasets. The results from each set of imputed datasets will then be aggregated for the final statistical inference using Rubin’s method.

Sensitivity analysis will be conducted in the FAS to examine the impact of missing data on primary analysis result by imputing missing data over a range of possible scenarios for the treatment effect (Section 7.6.3.1.1).

7.6.3.1.1 Sensitivity Analysis of Primary Efficacy Endpoint

In order to evaluate the impact of missing data of BMD at lumbar spine at Week 52 on the primary endpoint results, a tipping point analysis will be conducted for the primary efficacy endpoint in the FAS. Missing data for the percent change from baseline in BMD for lumbar spine by DXA at Week 52 will be imputed by MI and shifted gradually by treatment groups (CT-P41 versus US-licensed Prolia) to assess missing not at random scenarios.

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 missing data imputed by MI will be further adjusted by the NI or non-superiority margin for the CT-P41 treatment group, when testing NI and non-superiority, respectively. For this analysis, missing data due to the situation of Ukraine War will not be imputed under the corresponding null hypothesis thus remain their initial imputed values, and only missing data from outside Ukraine will be adjusted by the margin.

7.6.3.1.2 Subgroup Analysis by Race and Age

To assess the consistency of 2 treatment groups in the primary efficacy endpoint by race and age, 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 and each subgroup in the FAS.

7.6.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarized using descriptive statistics or frequency tables. Data for Treatment Period I will be summarized on the FAS and PPS and data for Treatment Period II will be summarized on the FAS – Treatment Period II subset, unless otherwise specified. Listing will be provided by treatment group on the ITT set.

The following secondary efficacy endpoints will be assessed at the time points specified in the schedule of assessments (Appendix 11.1).

- 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
- Incidence 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

7.6.4 Pharmacokinetic Analyses

The serum concentration and PK parameters of C_{max} and C_{trough} will be summarized using descriptive statistics (including geometric mean and coefficient of variation [CV], as appropriate). Mean serum concentration time profiles of study drugs will be plotted by treatment group on linear and semilogarithmic scales based on scheduled sample times. Individual concentrations and scheduled and actual sample times will be presented in data listings by treatment group.

All PK parameters will be estimated using [redacted]

Pharmacokinetic analysis for Treatment Period I will be summarized using the PK Set and that for Treatment Period II will be summarized on the 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.

7.6.5 Pharmacodynamic Analyses

The AUEC of s-CTX and P1NP over the initial 6 months (from Day 1 predose to Week 26 predose) will be assessed and will be estimated [redacted]

Serum concentration and percent change from baseline of s-CTX and P1NP at Weeks 26, 52 and 78 will also be assessed and summarized using descriptive statistics (including geometric mean and CV, as appropriate). Percent change from baseline versus time profiles of s-CTX and P1NP will be presented graphically on linear scale by treatment group using scheduled sampling times.

Pharmacodynamic analysis for Treatment Period I will be summarized on the PD Set and that for Treatment Period II will be summarized on the PD – Treatment Period II subset, unless otherwise specified. Listings will be provided by treatment group on the ITT set.

7.6.6 Safety Analyses

Safety analyses will be performed at the time points specified in the schedule of assessments (Appendix 11.1) and will be summarized using descriptive or frequency tables. All safety data including immunogenicity for Treatment Period I will be summarized for the Safety Set

and that for Treatment Period II will be summarized for the Safety – Treatment Period II subset, unless otherwise specified. Listings will be provided by treatment group on Safety Set.

7.6.6.1 Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to the MedDRA and severity grading of AEs will be recorded according to the CTCAE Version 5.0. A TEAE is defined as described in Section 6.4.1.1. The following TEAE summaries will be reported by SOC, PT, and treatment group:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 treatment-emergent SAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with TEAEs of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, ONJ, atypical femoral fracture, and dermatologic reactions)

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

7.6.6.2 Immunogenicity

All data will be listed and summarized by treatment group, where appropriate.

7.6.6.3 Electrocardiograms, Physical Examinations, Vital Signs, Weight, Height, and Body Mass Index

Electrocardiograms, physical examinations, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) including hypersensitivity monitoring, and weight, height, and BMI will be summarized and listed by treatment group for each scheduled collection time point. Changes from baseline will also be summarized for all scheduled collection times after the first administration of study drug, if applicable.

7.6.6.4 Clinical Laboratory Analyses

Clinical laboratory tests (clinical chemistry, hematology, urinalysis, and other) will be summarized and listed by treatment group at each scheduled collection time and graded

according to the CTCAE v5.0. For continuous parameters, change from baseline will also be summarized for all scheduled collection times after the first administration of the study drug.

7.6.6.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO drug dictionary. All prior and concomitant medication data will be summarized and listed by treatment group as appropriate.

7.6.6.6 Patient's Assessment of Local Site Pain

Local site pain measurements by VAS (Appendix 11.4) will only be assessed by immediately after the administration of the study drug at each scheduled collection time point and will be summarized and listed by treatment group.

7.6.6.7 Other Safety Analyses

All other safety data will be summarized and listed by treatment group as appropriate.

7.7 Interim Analysis

No interim analyses are planned for this study.

7.8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice (GCP) guidelines on quality and risk management.

Step to be taken to ensure the accuracy and reliability of data includes the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated staff prior to the study, periodic monitoring visits by the Sponsor or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The data will be collected via Electronic Data Capture (EDC) using eCRFs. The study center will be responsible for data entry into the EDC system. The eCRF will be reviewed for accuracy and completeness by the monitor during on-site or remote monitoring visits and after their return to the Sponsor or its designee. In the event of discrepant data, the Sponsor will request data clarification from the study centers, which the study centers will resolve electronically in the EDC system. The Sponsor will be responsible for the data management of this study, including quality checking of the data.

Quality assurance staff from the Sponsor or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The Investigator should immediately notify the Sponsor or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operation procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendment.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the regulatory authorities, or the IRB/IEC.

The Investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the data approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must promptly supply the Sponsor or its designee, the IRB/IEC, and, where

applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form in case new information becomes available that may be relevant to the subject's willingness to continue participation in the clinical study.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate tin the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient's right to withdraw from the clinical study at any time without giving reason and without jeopardizing the patient's further course of medical treatment
- The existence of patient insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions will be given to the patients.

The Investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the Investigator or Sub-Investigator and the patient's legal representatives (according to the local regulations) before the beginning of the study. The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the Investigator's study file. The Investigator will allow inspection of the forms by authorized representatives of the Sponsor, IRB/IEC members, and regulatory authorities. The Investigator will confirm, by signing and dating the eCRFs, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the Principal Investigator or Sub-Investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.4.1.4. In addition, the Principal Investigator or Sub-Investigator agrees to submit annual report to his or her IRB/IEC as appropriate.

8.5 Financial Disclosure and Obligations

CELLTRION, Inc. is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and CRO. The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. The Sponsor will indemnify all Investigators participating in this study against future claims by study patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all study procedures have been carried out according to this protocol.

The Investigator is required to take out liability insurance for all patients included in the study as required by local law and/or regulations and/or ICH guideline for GCP, whichever is applicable.

The Investigator and the Sponsor will sign a clinical study agreement before the start of the study. The agreement will outline overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the costs based on the calculated expenses of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract.

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor its designee is financially responsible for further testing or treatment or any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor its designee is financially responsible for further treatment of the patient's pre-existing disease prior to study participation (Screening).

The Sponsor undertakes to compensate the patient for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

8.6 Investigator Documentation

Before beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulation (CFR) by providing the following essential documents, including but not limited to:

- Independent Ethics Committee/IRB approval
- Original Investigator-signed Investigator agreement page of the protocol
- Curriculum vitae for the Principal Investigator and each Sub-Investigator. Current licensure must be noted in the curriculum vitae. The curriculum vitae will be signed and dated by the Principal Investigators and Sub-Investigators at the study start-up, indicating that they are accurate and current
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- Independent Ethics Committee/IRB-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and

- Laboratory certifications and normal ranges for any local laboratories used by the study center.

8.7 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the Principal Investigator or Sub-Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Principal Investigator or Sub-Investigator agrees to maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc. For data collected using CRO electronic clinical outcome assessment system, data in this system itself will be considered as source document.

The analysis data sets will be combination of these data and data from other sources (e.g., laboratory data).

The eCRF are accessed through the appropriate system, which allows for on-site data entry and data management. Study center users can read from and write to the Sponsor’s database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon account and password that allow for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, Investigators and individuals who have entered or modified records.

8.9 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

8.10 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to the Sponsor and/or IRB/IEC according to the timeline and method outlined in Section 6.4.1.4. In addition, the Investigator agrees to submit annual reports to the study center IRB/IEC as appropriate.

8.11 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide IRB/IEC with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

8.12 Record Retention

All correspondence (e.g., with Sponsor, IRB/IEC, or Clinical Research Associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRFs, and drug inventory sheets pertaining to the study must kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If an Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the Sponsor.

8.13 Patients Identification Register

The Investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and

will be filed by the Investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

8.14 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

CELLTRION, Inc.
23, Academy-ro, Yeonsu-gu, Incheon,
22014, Republic of Korea
Phone: + 82 32 850 5000
Fax: + 82 32 850 5050
E-mail: contact@celltrion.com

9.3 Central Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. Details of analytical facilities will be provided in the ICF.

9.4 Monitoring

9.4.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. The DSMB will review and evaluate accumulating safety data to ensure the safety of study patients and also review study results.

Further details will be provided in the independent DSMB charter.

9.4.2 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. In case where a monitoring visit cannot be made because of the pandemic situation of COVID-19, the monitor will discuss with the Sponsor, CRO, and the Investigator for further plan, which will be specified in the Appendix 11.6.

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) and SOPs.

9.4.3 Inspection of Records

Investigators and institutions involved in the study will permit study related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and CRO of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Substantial amendments to the protocol must be submitted in writing to the applicable IRB/IEC and regulatory authority for approval before patients are enrolled under an amended protocol. This will be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion and agreement from the Sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or Investigator that results in a significant and additional risk to the patient's right, safety and wellbeing. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unblinding. Principal Investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

9.6 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The completion of the study is defined as the date of final database lock with no further database change for the final CSR.

9.7 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the CSR is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the CSR in marketing applications meets the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

CELLTRION, Inc. plans to prepare 1 CSR, including but not limited to the following.

- All data after completion of the study (up to Week 78)

But additional CSRs will be generated upon requirements for regulatory or academic purposes (including all data after completion of the Treatment Period I [Week 52]).

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11 Appendices

11.1 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
Pharmacokinetic Sampling[16]		X	X	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**					
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 follow 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. 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 HCV 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 from 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 at 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 administration 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 needed, 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 needed, 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 followed by the study drug administration occurring within the same visit window of Week 26 or Week 52 visit.
9. Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) 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 occurred.

Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelets count
Clinical chemistry	Albumin, albumin-adjusted total serum calcium, alkaline phosphatase (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 administration 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 total 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 scheduled visit. Additional immunogenicity will be assessed when immune-related AEs occur. Analysis will be performed at the central laboratory. For patients who early discontinue study 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.

11.2 Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV)

Please answer the following questions about your health. Most questions ask about your health during the past two weeks. There are no right or wrong answers to the questions.

	All days	Most days	Some days	Few days	No days
	▼	▼	▼	▼	▼
1. How often were you able to do daily shopping or errands?	□ 1	□ 2	□ 3	□ 4	□ 5
2. How often were you in a bed or chair for most of the day?	□ 1	□ 2	□ 3	□ 4	□ 5
3. How often were you able to do sports and games that you would like to do?	□ 1	□ 2	□ 3	□ 4	□ 5
4. How often were you able to walk as much as you needed to?	□ 1	□ 2	□ 3	□ 4	□ 5
5. How often did you have trouble bending, lifting or stooping?	□ 1	□ 2	□ 3	□ 4	□ 5
6. How often did you have trouble walking a block or climbing one flight of stairs?	□ 1	□ 2	□ 3	□ 4	□ 5
7. How often did you need to use a cane, crutches, walker, or companion while walking?	□ 1	□ 2	□ 3	□ 4	□ 5
8. Could you easily put on or take off a pair of stockings and/or underwear?	□ 1	□ 2	□ 3	□ 4	□ 5
9. Could you easily comb, brush, or style your hair?	□ 1	□ 2	□ 3	□ 4	□ 5
10. Could you easily reach shelves that were above your head?	□ 1	□ 2	□ 3	□ 4	□ 5
	Always	Very Often	Sometimes	Almost Never	Never
	▼	▼	▼	▼	▼
11. Have you had to change the way you bathe yourself?	□ 1	□ 2	□ 3	□ 4	□ 5
12. Have you had to change the types of clothes you wear because of difficulty in dressing?	□ 1	□ 2	□ 3	□ 4	□ 5
13. How often were you able to do	□ 1	□ 2	□ 3	□ 4	□ 5

light housework such as cooking without help?					
14. How often were you able to do heavy housework such as vacuuming without help?	□ 1	□ 2	□ 3	□ 4	□ 5
15. How often were you able to do your daily work, either at home, as a volunteer, at school, or at a paid job?	□ 1	□ 2	□ 3	□ 4	□ 5
	All days	Most days	Some days	Few days	No days
	▼	▼	▼	▼	▼
16. How often do you have trouble getting in or out of bed?	□ 1	□ 2	□ 3	□ 4	□ 5
17. How often do you have trouble getting in or out of a chair?	□ 1	□ 2	□ 3	□ 4	□ 5
18. How often do you have trouble getting on or off the toilet?	□ 1	□ 2	□ 3	□ 4	□ 5
19. How often do you have trouble getting in or out of cars or public transportation?	□ 1	□ 2	□ 3	□ 4	□ 5
	Always	Very Often	Sometimes	Almost Never	Never
	▼	▼	▼	▼	▼
20. How often were you afraid that you would fall?	□ 1	□ 2	□ 3	□ 4	□ 5
21. How often were you afraid that you would accidentally break or fracture a bone?	□ 1	□ 2	□ 3	□ 4	□ 5
22. How often did you feel that you were losing balance?	□ 1	□ 2	□ 3	□ 4	□ 5
23. How often did you use a handrail or other support when walking up or down stairs?	□ 1	□ 2	□ 3	□ 4	□ 5
24. How often did your fear of falling keep you from doing what you want to do?	□ 1	□ 2	□ 3	□ 4	□ 5
	All days	Most days	Some days	Few days	No days
	▼	▼	▼	▼	▼

25. How often did you have any back ache or pain?	□ 1	□ 2	□ 3	□ 4	□ 5
	Severe	Moderate	Mild	Very Mild	None
	▼	▼	▼	▼	▼
26. How would you describe the back ache or pain you usually have?	□ 1	□ 2	□ 3	□ 4	□ 5
	All days	Most days	Some days	Few days	No days
	▼	▼	▼	▼	▼
27. How often did your back feel stiff for more than one hour from the time you woke up?	□ 1	□ 2	□ 3	□ 4	□ 5
28. How often did back ache or pain keep you from doing what you wanted to do?	□ 1	□ 2	□ 3	□ 4	□ 5
	Always	Very Often	Sometimes	Almost Never	Never
	▼	▼	▼	▼	▼
29. How often were you aware of the changes in your body when trying on clothes?	□ 1	□ 2	□ 3	□ 4	□ 5
30. How often were you bothered by the way your back looks?	□ 1	□ 2	□ 3	□ 4	□ 5
31. How often were you concerned by changes in the way your body looks?	□ 1	□ 2	□ 3	□ 4	□ 5
32. How often did you feel confident you could live on your own without assistance?	□ 1	□ 2	□ 3	□ 4	□ 5
33. How often did you have to rely on others for assistance with daily activities?	□ 1	□ 2	□ 3	□ 4	□ 5
34. How often were you worried that you might not be able to take care of yourself in the future?	□ 1	□ 2	□ 3	□ 4	□ 5

11.3 EuroQoL-5D-5L (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

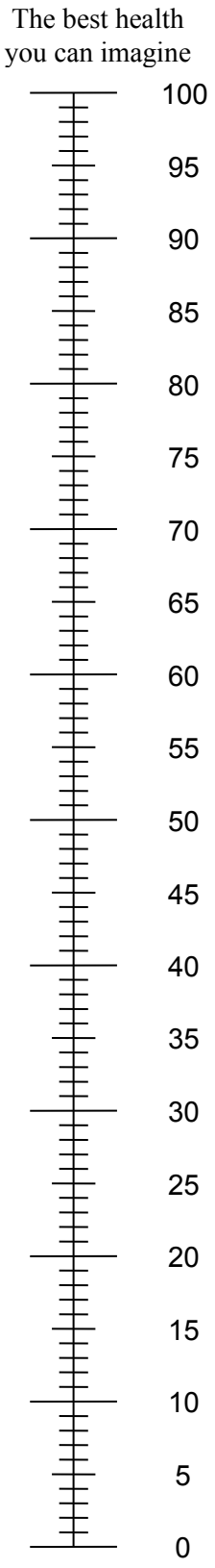
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



11.4 Visual Analog Scale (VAS) Local Site Pain

Patient assessment of local site pain is measured by the patient indicating the extent of their pain by making one line (|) through the 100 mm line (0 mm equals no pain and 100 mm equals most severe pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF.

No pain Most severe pain

Value:_____(mm)

11.5 New York Heart Association Functional Classification

As defined in Zhang *et al*., 2018, the New York Heart Association (NYHA) classification is used in patients with heart failure.

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.

11.6 Risk Assessment and Mitigation Plan due to COVID-19

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as COVID-19. On 11 March 2020, the World Health Organization (WHO) declared the SARS-CoV-2 infection outbreak a global pandemic and to date in excess of 1.6 million deaths have been reported globally (WHO COVID-19 Dashboard 2020).

Due to the global impact of the COVID-19 pandemic, the Sponsor is taking proactive measures to guarantee that all site staff and patients involved in the trial are secure and the patients remain in the study until their last visit, with continuation of treatment during the study period.

1. Benefit and Risk Assessment on Study Population

Considering the most common symptoms of COVID-19 are fever, dry cough, and tiredness (WHO Q&A on COVID-19) and the irrelevance between cause of COVID-19 and osteoporosis disease itself, osteoporosis symptoms and disease itself have a low chance to deteriorate directly due to COVID-19. Furthermore, no high risk was seen for COVID-19 complications in women older than 50 years for postmenopausal or aromatase inhibitor-induced osteoporosis, and the patients are recommended to maintain the denosumab treatment for the management of osteoporosis during the COVID-19 outbreak (Gittoes *et al*., 2020). However, the irrelevance cannot be concluded since no studies have been conducted and there were a few research studies reporting the increased risk for respiratory infections following denosumab treatment (Formenti *et al*., 2020).

Moreover, it has yet to be concluded that calcium and vitamin D, which is a protocol defined co-administration, may have beneficial effects to treat COVID-19. To date, it has been shown that the patients with osteoporosis may be protected from SARS-CoV-2 by vitamin D independently of the pharmacologic antiosteoporotic treatments (Bilezikian *et al*., 2020).

Basically, the quarantine of COVID-19 should be carried out based on the SOP of each site and local regulatory guidelines. Taking all these facts into consideration, the risks of COVID-19 infection for each patient are not expected to increase by participating in this study. Yet due to the possibility of increasing the safety risk by being involved in the study, a systematic risk assessment will be conducted during the study by the Sponsor through a sufficient discussion with the Investigators and DSMB.

2. Mitigation Plans

Investigational Product Management

To cope better with the sudden imposition of movement restriction and/or increased shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient IP will be supplied to cover patient visits for longer periods. Inter-country IP transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, the Sponsor will prepare site-to-site transfer of IP from nearby clinical sites in case an agile resupply is required (e.g., more patients are enrolled at a site than anticipated but additional supplied IP is not sufficient to meet demand).

Rescheduling of Visit and Study Drug Administration Schedule of Patients

The COVID-19 screening tests will be performed locally based on each site and/or local regulatory guidelines upon the Investigator's discretion throughout the study period. If COVID-19 is confirmed positive during the Screening period, the patient should not be enrolled in this study until confirmation of complete recovery from COVID-19 as per site and/or local regulatory guidelines. Although patients can be rescreened only once under normal circumstances as specified in Section 4.3, additional rescreening can be performed only in limited cases considering COVID-19. If COVID-19 is confirmed after randomization, the Investigators will discuss on a case-by-case basis regarding the specific case of the patient with the Sponsor. In the case of a patient who has contact with COVID-19 patients within 14 days from Screening, the patient should not be enrolled in the study. If the patient has contact with COVID-19 patients within 14 days following any site visit, the Investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.

Investigators will promptly notify the Sponsor if any unfavorable situation has occurred in relation to local COVID-19 status (e.g., site shut down, lock down of city, cohort isolation, etc.). For sites where the patients are unable to travel or use public transportation, the Sponsor will support the patients with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can be proceeded at the earliest possible opportunity. Pre-approval is required for reimbursement.

The patients require face-to-face interactions for study drug administration. Therefore, in the event patients cannot visit the study center on the scheduled day for injection, the treatment schedule will be adjusted following Section 5.8. However, if study drug administration cannot be carried out within an allowed visit window or a missed dose is expected, whether

to continue with the subsequent study treatment will be discussed with the Sponsor, ensuring the compliance with the trial protocol to such an extent that an ongoing benefit-risk assessment for the clinical trial and patients is still possible.

Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The Investigator will keep following up with patients regarding any safety issues (AEs, concomitant medication) by telephone call before the patients visit the site.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than under normal circumstances, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed.

DXA scan and X-ray assessments

For BMD assessment, only Hologic or Lunar bone densitometers will be allowed during the study, and the same DXA instrument should be used for all study procedures for each patient during the study. However, in COVID-19 pandemic situation, if the patients are restricted in their ability to travel to the sites and/or the sites ae locked down, the alternative imaging centers can be considered to acquire the DXA scans. The alternative center should follow the central imaging provider's guidance on selecting an appropriate replacement scanner and a phantom scanning process to quantify any calibration differences. All DXA scans will be submitted to and analyzed by the central imaging vendor.

For vertebral fractures, the lateral spine X-ray will be performed throughout the study, and may be performed in the alternative imaging centers in COVID-19 pandemic situation (site shut down, lock down of city etc.). The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and related source documents should be submitted to the central imaging vendor for confirmation of fracture. And, if X-ray is necessary to support the patient's medical care, the X-rays also could be read locally.

The nonvertebral fractures may be assessed by alternative imaging centers in COVID-19 pandemic situation. The information about new nonvertebral fractures (e.g., details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture will be recorded from the alternative centers. A copy of other diagnostic image and/or radiology report, surgical report, or discharge summary will also be included in the patient's individual source documents and should be submitted to the central imaging vendor for confirmation of

fracture. For further details on the source documents for nonvertebral fractures, see Section 6.1.2.2.

Site Monitoring and Audit

In cases where a monitoring visit cannot be performed because of the prevailing COVID-19 situation, centralized monitoring will be performed by the Sponsor and/or CRO as alternatives particularly, for the sites where the first patient is randomized but the first monitoring visit is not performed. Manual data review on the eCRF will be performed and if any mistakes or deviations are observed, proper guidance will be provided to prevent them happening in the future. Sponsor and/or CRO will review the data entered in the eCRF continuously and ensure queries are raised and support the sites as necessary. If necessary, the Sponsor will create and review a report based on the eCRF data to check whether visits, assessments and administrations of study treatment are in progress according to protocol and the same will be shared with CRO for site management.

Audits are required to ensure quality assurance throughout the study period in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. In cases where an audit cannot be performed due to the COVID-19 pandemic situation, the Sponsor will postpone audits or consider performing remote audits after careful consideration of the COVID-19 pandemic situation according to Guidance on the management of clinical trials during the COVID-19 (coronavirus) Pandemic (European Medicines Agency (2020)). Audits will be conducted only when permitted under national, local and/or organizational social distancing restrictions.

Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to Centralized monitoring plan and Risk based monitoring plan. After data collection, missing data on the primary efficacy analysis due to COVID-19 will be analyzed as specified in Section 7.6.3.1.1 with other missing cases. However, if a different approach is required for missing data due to COVID-19, it will be discussed at the blinded data review meeting on a case-by-case basis and the procedure for handling missing data in the statistical analysis will be specified in the SAP.