CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Randomized, Double-Blind, Parallel Design, Repeat Dose, 2-arm, Multicenter Study Comparing the Efficacy, Safety, Immunogenicity, and Pharmacokinetic Profiles of AVT03 and US-Prolia® in Postmenopausal Women with Osteoporosis, ALVOBOND
STUDY NUMBER:	AVT03-GL-C01
EUDRACT NUMBER:	2021-005071-40
SPONSOR:	Alvotech Swiss AG [redacted]
ORIGINAL PROTOCOL VERSION AND DATE:	Version 1.0, 15 Feb 2022
AMENDED PROTOCOL VERSION AND DATE:	Version 2.0, 03 Mar 2022
AMENDED PROTOCOL VERSION AND DATE:	Version 3.0, 03 Aug 2022
AMENDED PROTOCOL VERSION AND DATE:	Version 4.0 Final, 10 Mar 2023

CONFIDENTIAL

SPONSOR APPROVAL FORM

Protocol Title: A Randomized, Double-Blind, Parallel Design, Repeat Dose, 2-arm, Multicenter Study Comparing the Efficacy, Safety, Immunogenicity, and Pharmacokinetic Profiles of AVT03 and US-Prolia® in Postmenopausal Women with Osteoporosis, ALVOBOND

Study No: AVT03-GL-C01

Original Protocol Version and Date: Version 1.0, 15 Feb 2022

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Amended Protocol Version and Date: Version 3.0, 03 Aug 2022

Amended Protocol Version and Date: Version 4.0 Final, 10 Mar 2023

This study will be conducted in compliance with the clinical study protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and applicable local regulatory requirements.

This study protocol was subject to critical review and has been approved by the relevant members of the Sponsor.

The undersigned have reviewed the content of this protocol and have approved the clinical study protocol. The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the study drug. Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

[redacted]

13 March 2023

Date

Head of Clinical and Medical Affairs
Alvotech Swiss AG

[redacted]

13. März 2023

Date

Head of Clinical Development and Patient Safety
Alvotech Swiss AG

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14 March 2023

Date

Biostatistics Lead
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13 March 2023

Date

President, National Osteoporosis Foundation of South Africa

[redacted]

13 March 2023

Date

Medical & Scientific Consultant

AVT03-GL-C01

A RANDOMIZED, DOUBLE-BLIND, PARALLEL DESIGN, REPEAT DOSE, 2-ARM, MULTICENTER STUDY COMPARING THE EFFICACY, SAFETY, IMMUNOGENICITY, AND PHARMACOKINETIC PROFILES OF AVT03 AND US-PROLIA® IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS, ALVOBOND

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to AVT03 are the confidential and proprietary information of Alvotech Swiss AG, and except as may be required by federal, state, or local laws or regulation, may not be disclosed to others without prior written permission of Alvotech Swiss AG.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and applicable national, state, and local regulations and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Alvotech Swiss AG or specified designees. I will discuss the material with them to ensure that they are fully informed about AVT03 and the study.

Signature	Date
Investigator Name (printed)	Site Number

STUDY SYNOPSIS

Protocol Title: A Randomized, Double-Blind, Parallel Design, Repeat Dose, 2-arm, Multicenter Study Comparing the Efficacy, Safety, Immunogenicity, and Pharmacokinetic Profiles of AVT03 and US-Prolia® in Postmenopausal Women with Osteoporosis, ALVOBOND

Study Number: AVT03-GL-C01

Clinical Phase: 3

Investigator(s)/Study Center(s): This study is planned to be conducted at study centers located in Bulgaria, Czech Republic, Georgia, Poland, and South Africa.

Objectives:

Primary Objectives:

- To demonstrate clinical similarity of AVT03 and United States-licensed Prolia® (US-Prolia, generic name: denosumab, hereafter referred to as Prolia) in terms of percent change from Baseline in bone mineral density (BMD) at 12 months.
- To demonstrate clinical similarity of AVT03 and Prolia in terms of area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1). Note: This objective will be considered as primary for European Medicines Agency (EMA) submission only; for all other agencies, this objective will be considered as secondary.

Secondary Objectives:

- To further compare clinical similarity of AVT03 and Prolia
- To assess and compare the safety of AVT03 with Prolia
- To assess and compare immunogenicity of AVT03 with Prolia
- To compare pharmacokinetic (PK) biosimilarity between AVT03 and Prolia
- To compare pharmacodynamic (PD) parameters between AVT03 and Prolia

Study Design: This is a randomized, double-blind, parallel design, repeat dose, 2-arm, multicenter study comparing the efficacy, safety,

	immunogenicity, and PK profiles of AVT03 and Prolia in postmenopausal women with osteoporosis. After successful completion of the screening activities, eligible subjects will be randomized in a 1:1 ratio to receive either AVT03 60 mg or Prolia 60 mg, administered as a subcutaneous (s.c.) injection on Day 1 and Day 180 (Month 6). At Month 12, subjects in the AVT03 treatment group will receive a third dose of AVT03 60 mg administered s.c. while subjects in the Prolia treatment group will be re-randomized in a 1:1 ratio to receive either Prolia 60 mg or AVT03 60 mg on Day 365 (Month 12), administered s.c. Subject randomization will be stratified by number of years since menopause (≤5 years or >5 years) and prior biologic therapy for osteoporosis (Yes or No). Two weeks after the Month 12 administration, there will be a safety follow-up visit. Afterwards, subjects will be followed until the end of study (EoS) visit at Month 18 (ie, 6 months after the last dose at Month 12).

Duration of Treatment:	Subjects will participate in the study for up to 19 months:
	• Screening: Day -28 to -1
	• Active Period: Day 1 to Month 18
	  o Treatment on Day 1, Day 180 (Month 6), and Day 365 (Month 12)
	  o Safety Follow-up
	  ▪ Safety Follow-up visit 2 weeks after Month 12 administration (Month 12 [+ 2 weeks])
	  ▪ Safety Follow-up visit 3 months after Month 12 administration (Month 15)
	  ▪ Safety Follow-up/EoS visit 6 months after Month 12 administration (Month 18)

Planned Sample Size and Treatment Group(s):	Approximately 476 subjects will be randomly assigned in a 1:1 ratio to AVT03 and Prolia treatment arms.
Target Population:	Postmenopausal women with osteoporosis
Eligibility Criteria:	**Inclusion Criteria:** To be enrolled in the study, subjects must meet the following criteria:

1. Postmenopausal women with osteoporosis willing to sign an informed consent form and able to undergo protocol related procedures.

2. Age: ≥50 years.

3. Female subject is postmenopausal according to 1 of the following criteria:

   a. Spontaneous amenorrhea for ≥12 consecutive months

   b. Biochemical criteria of menopause, follicle-stimulating hormone, >40 IU/L except surgically sterile

   c. Having had bilateral oophorectomy ≥6 weeks prior to Screening

4. Body Mass Index: 18.5-32.0 kg/m^2

5. A baseline dual-energy x-ray absorptiometry scan with a T score ≤ -2.5 and ≥ -4.0 at the lumbar spine (LS) (L1 to L4) and/or total hip and/or femoral neck.

   A subject must have a T score within the stated range of ≤ -2.5 and ≥ -4.0 in at least 1 of the 3 areas: - lumbar spine (L1 to L4) - total hip - femoral neck. On the contrary, subjects will be excluded from the trial if the T score is less than -4.0 in at least 1 of the 3 areas (ie, at the LS [L1 to L4], or total hip, or femoral neck).

   Note: The left hip should be scanned for the calculation of total hip T score. If the left hip cannot be scanned (eg, due to left hip replacement, etc), the right hip can be scanned instead. The same hip should be used for all dual-energy x-ray absorptiometry scans.

6. At least 2 consecutive evaluable lumbar vertebrae and at least 1 evaluable hip.

7. Willing to receive calcium plus vitamin D supplements.

8. No history or evidence of a clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to subject safety.

9. Resting supine systolic blood pressure of ≤150 mmHg and diastolic blood pressure of ≤90 mmHg. Other vital signs showing

no clinically relevant deviations according to the Investigator's judgment.

10. 12-lead electrocardiogram (ECG) recording without signs of clinically relevant pathology or showing no clinically relevant deviations as judged by the Investigator.

11. Subject smokes <10 cigarettes per day within 3 months of Screening. Note: It is strongly recommended that subjects do not smoke during their participation in the study.

12. Recommended to abstain from alcohol from 48 hours prior to study drug administration, and 24 hours prior to study visits.

Exclusion Criteria:

Subjects will be ineligible for the study if any of the following criteria apply:

1. Evidence of clinically relevant pathology, especially prior diagnosis of bone disease, or any uncontrolled condition that will affect bone metabolism such as, but not limited to: osteogenesis imperfecta, hyperparathyroidism, non-controlled hyperthyroidism (thyroid stimulating hormone (TSH) <0.5 mIU/L), non-controlled hypothyroidism (TSH ≥5.0 mIU/L), osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as creatinine clearance <50 mL/min as calculated by Cockcroft-Gault formula), Paget's disease of the bone, recent bone fracture (within 6 months), and malabsorption syndrome.

2. History and/or presence of 1 severe or more than 1 moderate vertebral fractures confirmed by x-ray (according to Genant semiquantitative method).

3. History of hip fracture.

4. Presence of active healing fractures.

5. Previous treatment with denosumab and previous use of the following medications:

    a. Intravenous bisphosphonates, fluoride, or strontium ranelate at any dose within 5 years prior to Screening

    b. Oral bisphosphonates used for >3 years cumulative use, and any dose within 12 months of Screening

c. Parathyroid hormone (PTH) or PTH derivatives (eg, teriparatide, abaloparatide), and selective estrogen receptor modulators (eg, raloxifene), within 1 year of Screening

d. Romozosumab within 30 days prior to Screening

e. Calcitonin within 6 months of Screening

f. Other bone metabolism drugs: administration of any of the following treatments within the last 3 months,

   i. anabolic steroids or testosterone

   ii. glucocorticoids (>5 mg/day prednisone or equivalent for >10 days)

   iii. systemic hormone replacement therapy

   iv. tibolone

   v. calcitriol

   vi. anticonvulsants (except benzodiazepines and pregabalin)

   vii. heparin

   viii. systemic use of ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet or any cathepsin K inhibitor (eg, odanacatib), aluminium, lithium, protease inhibitors, methotrexate, gonadotropin-releasing hormone agonists

6. Osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (eg, tooth extraction, dental implants, oral surgery in the past 6 months), periodontal, and/or pre-existing dental disease requiring therapy.

7. Evidence of hypo/hypercalcemia at Screening defined as <8.6 or >10.5 mg/dL.

   Note: If hypocalcaemia can be excluded based on calcium, corrected calcium, albumin, PTH, vitamin D3 values but ionized calcium is pending, the subject may be randomized, as per Investigator assessment and confirmation that exclusion criterion 7 has not been met. This needs to be recorded on source documents.

8. Known vitamin D deficiency (25-hydroxy vitamin D level <20 ng/mL [50 nmol/L]) after supplementation at Screening.

9. Known intolerance to calcium or vitamin D supplement.

10. Any current active infections, including localized infections, or any recent history (within 1 week prior to study drug administration) of active infections or a history of recurrent or chronic infections.

11. Presence of known current infection with hepatitis B or presence of positive serology – ie, hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (anti HBc), hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) at Screening.

    Note: Any subject with positive anti-HBc at Screening should be reviewed and evaluated by the Investigator to exclude active infection. It is at the Investigator's discretion whether to extend diagnostics to exclude current infection of hepatitis B. A local HBV quantitative DNA by PCR test may be performed within the screening window visit.

12. Hematology and chemistry laboratory results outside the reference ranges, which are clinically significant, and, in the opinion of the Investigator or designee, could cause this study to be detrimental to the subject.

13. Donation of more than 500 mL of blood within the 8 weeks prior to study drug administration.

14. Hypersensitivity to denosumab or its constituents.

15. A recent history of major surgery including spine surgery due to disc herniation, spinal stenosis, or similar condition within 3 months prior to randomization.

16. History or presence of malignancy within 5 years (with the exception of successfully treated basal cell carcinoma).

17. Inability to communicate or cooperate with the Investigator because of language difficulties or poor mental development or incapacitation.

18. A history (within the previous 3 years) or evidence of alcohol or drug abuse (including soft drugs like cannabis products).

19. Vaccination with a live vaccine with the exception of flu vaccine within the previous month. Coronavirus disease 2019 vaccination is not considered an exclusion criterion.

20. Any other condition which in the view of the Investigator is likely to interfere with the study or put the subject at risk.

21. Current participation or history of participation in an investigational trial in the last 30 days or period less than 5 half-lives of the medicinal product under investigation - whichever is longer. For investigational products or drugs for which PD effect lasts longer than 5 half-lives, the wash-out period may be extended.

22. A compromised immune system or treatment with immunosuppressants.

Study Drug(s):

Investigational Product: AVT03 60 mg given as a s.c. injection on Day 1, Day 180 (Month 6), and Day 365 (Month 12)

Reference Product: Prolia 60 mg given as a s.c. injection on Day 1, Day 180 (Month 6), and Day 365 (Month 12)

Primary Endpoint(s):

Percent change from Baseline in LS BMD at 12 months

Area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1). Note: This endpoint will be considered as primary for EMA submission only; for all other agencies, this endpoint will be considered as secondary.

Secondary Endpoint(s):

Efficacy endpoint

- Percent change from Baseline in LS BMD at 6 and 18 months
- Percent change from Baseline in hip and femoral neck BMD at 6, 12, and 18 months
- Incidence of new morphometric vertebral fractures at 12 and 18 months

Pharmacodynamic endpoints

- Percent change from Baseline in sCTX-1 at 3, 6, 9, 12, and 18 months

Safety endpoints

- Incidence, nature, and severity of adverse events including adverse drug reactions
- Frequency and severity of injection site reactions
- Frequency and severity of findings in routine safety parameters, including clinical laboratory assessments (hematology, clinical biochemistry, coagulation, urinalysis, and urine microscopy), vital signs, ECG, and physical examination

Immunogenicity endpoint

- Frequency and titer of anti-drug antibodies and frequency of neutralizing antibodies against AVT03 and Prolia at predose and Day 1, Day 2, Day 12, Day 30, Day 60, Day 90, Day 180, Day 270, Day 365 (Month 12), Day 365 (Month 12) +2 weeks, Month 15, and Month 18 (EoS) after treatment.

Pharmacokinetic endpoint

- Serum trough concentration of AVT03 and Prolia

Statistical Procedures:

The percent change from Baseline in LS BMD at 6 and 12 months will be analyzed using mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables and the baseline BMD and number of years since menopause as continuous covariates. The least square mean estimates will be provided for each treatment group at each visit with their standard errors (SE). The difference of least square means between the treatment groups and associated SE, 2-sided 95% confidence interval (CI) (as required by EMA) and 2-sided 90% CI (as required by Food and Drug Administration) will be provided for 12 months. At 12 months, if the 95%/90% CIs are completely contained within the pre-specified equivalence margin of [-1.45%, 1.45%], a clinical similarity will be demonstrated respectively.

The primary efficacy endpoint analysis will be based on the Full Analysis Set (FAS) which includes all randomized subjects who received at least 1 dose of randomized study treatment. Subjects will be analyzed according to the study treatment arm they were randomized to. For the primary endpoint analysis, in order to provide the most sensitive analysis set to detect potential differences between AVT03 and Prolia, the intercurrent events (ICEs) that can lead to

attenuation of treatment differences are defined, the subjects with any of those ICEs will be excluded from the analysis of primary endpoint. As a sensitivity analysis, the primary endpoint analysis will be repeated based on the FAS without exclusion of any subjects due to the ICEs specified for the main estimator.

For the primary efficacy analysis and sensitivity analysis of the primary efficacy endpoint, the missing values of percent change from Baseline in LS BMD at 12 months may be handled using multiple imputation as needed, details will be provided in the statistical analysis plan. PD endpoints will also be analyzed descriptively. If the normality assumption is not met, then other methods may be utilized, such as log-transformation or use of geometric means.

In addition, for the submission to EMA, the area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1) will be analyzed as primary PD endpoint. The log transformed PD data ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1) will then be analyzed using an analysis of covariance (ANCOVA) model including the treatment as factor and the baseline sCTX-1 as continuous covariate. The 95% CI for the geometric mean ratio (GMR) between treatment groups will be calculated. The PD similarity will be demonstrated if the 95% CIs of GMR lie entirely within the pre-specified margin of (0.80, 1.25). The analysis of the PD endpoint will be based on the PD Analysis Set.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESIs	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	Hepatitis B core antibody
AST	aspartate aminotransferase
$AUEC_{0\text{-}6months}$	area under the effect curve
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
Cfb	change from Baseline
COVID-19	coronavirus disease 2019
CI	confidence interval
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EoS	end of study
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Definition
FSH	follicle-stimulating hormone
GMR	geometric mean ratio
H	heavy
HBsAg	hepatitis B surface antigen
HCO_3	bicarbonate
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICEs	intercurrent events
IEC	Independent Ethics Committee
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IRT	Interactive Response Technology
ISRs	injection site reactions
LDH	lactate dehydrogenase
LS	lumbar spine
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MVF	multiple vertebral fractures
ONJ	osteonecrosis of the jaw
PD	pharmacodynamic
PTH	Parathyroid hormone
PK	pharmacokinetic
RANKL	receptor activator of nuclear factor kappa B ligand
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SAS	Safety Analysis Set
sCTX-1	serum C-terminal telopeptide of type 1 collagen
s.c.	subcutaneous

Abbreviation	Definition
SD	standard deviation
SE	standard error
SERMs	selective estrogen receptor modulators
SoA	Schedule of Assessments
SOP	standard operating procedure
TEAE	treatment-emergence adverse event
TSH	thyroid stimulating hormone
US	United States
WHO	World Health Organization
[redacted]	

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Background Disease Review

Osteoporosis is a systemic skeletal disease characterized by microarchitectural deterioration and high fragility of bone tissue, resulting in low bone mineral density (BMD) and poor bone quality, generally ascribable to estrogen deficiency or ageing.[1] One in 2 postmenopausal women will have an osteoporotic fracture in her lifetime.[2] Those who have had a fracture are at high risk of subsequent fractures.[3] It is estimated that the prevalence of osteoporosis rises from 1 in 3 people aged 50 to 60 years old to more than 50% of people aged over 80 years. By 2050, the global number of osteoporosis sufferers will reach 6 million (including both males and females), 3/4 of whom will reside in developing countries.[4,5]

Bone remodeling occurs over several weeks and is performed by clusters of bone-resorbing osteoclasts and bone-forming osteoblasts arranged within temporary anatomical structures known as "basic multicellular units".[6] Receptor activator of nuclear factor kappa B ligand (RANKL), a member of the tumor necrosis factor family of proteins, has been well-documented as an essential factor in the formation, activation, and survival of osteoclasts.[7,8,9] RANKL production is increased when estrogen is decreased (in menopause and with hormone ablation therapy) which leads to an increase in bone resorption, and excessive RANKL has been implicated in bone diseases associated with increased bone resorption.[10,11] Studies on mice revealed that the administration of soluble RANKL results in an increase in the formation and activation of osteoclasts that lead to osteoporosis.[8]

1.1.2 Compound Review

AVT03 (denosumab) is a recombinant fully human IgG2 monoclonal antibody to RANKL that contains 2 kappa light (L) chains, each comprised of 215 amino acids and 2 heavy (H) chains, each comprised of 448 amino acids (excluding the COOH terminal lysine), which are disulfide-bonded to form a 4-chain molecule (H2L2). It contains a single N-linked glycosylation site at Asn298 amino acid residue of each H chain. The N-linked structures consist of biantennal, core-fucosylated species with galactose and sialic acid heterogeneity with the major N-glycan structures being FA2 and FA2G1. It has a total molecular weight of approximately 147 kDa.[12]

The non-clinical development program for AVT03 has been designed in accordance with the current regulatory requirements for the non-clinical development of biosimilar monoclonal antibodies, as published by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).[13,14] For justification of the plan not to conduct further in vivo studies prior to initiating the clinical program and further details regarding non-clinical studies, refer to Section 1.4 of the Investigator Brochure.

- To date, AVT03 has not been tested in humans. As a proposed biosimilar, the safety profile of AVT03 is expected to be similar to the safety profile of Prolia.

This study aims to compare efficacy, safety, immunogenicity, and pharmacokinetics (PK), between the test product AVT03 and reference medicinal product, United States-licensed Prolia® (US-Prolia, generic name: denosumab, hereafter referred as Prolia), as part of a global biosimilar development program.

1.2 Study Rationale

The purpose of the comparative efficacy and safety study in postmenopausal women with osteoporosis is to demonstrate clinical similarity without evidence of meaningful differences between AVT03 and the reference product Prolia after administration of 2 subcutaneous (s.c.) doses of the test or reference drug.

In addition, in order to evaluate safety and immunogenicity after repeated dosing, subjects will receive a third dose in 180 days (6 months) after the second dose.

1.3 Dose Rationale

AVT03 or Prolia (60 mg) will be administered to subjects, per the approved dosing regimen for postmenopausal osteoporosis.[15,16]

1.4 Study Endpoint Rationale

The efficacy and safety endpoints for this study are considered standard endpoints for the indication of postmenopausal osteoporosis as outlined in the EMA/Committee for Medicinal Products for Human Use Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis (EMEA/CPMP/EWP/552/95).[17] Furthermore, in accordance with the above guidelines, the selected endpoints should allow assessment of clinically meaningful differences between AVT03 and Prolia in a comparative equivalence clinical study.

1.5 Risks and Benefits for Subjects

The totality of evidence available to date from an ongoing analytical program suggests that AVT03 is similar to Prolia (US- and European Union [EU]-sourced) with respect to physiochemical and biological activity. The risks and benefits for subjects receiving AVT03 are the same as those established for Prolia. Refer to the Prolia Prescribing Information for further details.[15] Adverse events of special interest (AESIs) encompass all relevant warnings and precautions from the Prolia label (Section 9.1.5).

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To demonstrate clinical similarity of AVT03 and US-licensed Prolia® (US-Prolia, generic name: denosumab, hereafter referred to as Prolia) in terms of percent change from Baseline in BMD at 12 months.

- To demonstrate clinical similarity of AVT03 and Prolia in terms of area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{0\text{-}6months}$ of %Cfb sCTX 1). Note: This objective will be considered as primary for EMA submission only; for all other agencies, this objective will be considered as secondary.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To further compare clinical similarity of AVT03 and Prolia

- To assess and compare the safety of AVT03 with Prolia

- To assess and compare immunogenicity of AVT03 with Prolia

- To compare PK biosimilarity between AVT03 and Prolia

- To compare pharmacodynamic (PD) parameters between AVT03 and Prolia

3 STUDY ENDPOINTS

Similarity of AVT03 (test treatment) compared to Prolia (reference treatment) will be evaluated with regards to efficacy, PD, safety, immunogenicity, and PK using the following endpoints:

3.1 Primary Endpoints

- Percent change from Baseline in lumbar spine (LS) BMD at 12 months
- Area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{06months}$ of %Cfb sCTX1). Note: This endpoint will be considered as primary for EMA submission only; for all other agencies, this endpoint will be considered as secondary.

3.2 Secondary Endpoints

3.2.1 Efficacy Endpoint

- Percent change from Baseline in LS BMD at 6 and 18 months
- Percent change from Baseline in hip and femoral neck BMD at 6, 12, and 18 months
- Incidence of new morphometric vertebral fractures at 12 and 18 months

3.2.2 Pharmacodynamic Endpoints

- Percent change from Baseline in sCTX-1 at 3, 6, 9, 12, and 18 months

3.2.3 Safety Endpoints

- Incidence, nature, and severity of adverse events (AE) including adverse drug reactions (ADRs)
- Frequency and severity of injection site reactions (ISRs)
- Frequency and severity of findings in routine safety parameters, including clinical laboratory assessments (hematology, clinical biochemistry, coagulation, urinalysis, and urine microscopy), vital signs, electrocardiograms (ECG), and physical examination

3.2.4 Immunogenicity Endpoint

- Frequency and titer of anti-drug antibodies (ADA) and frequency of neutralizing antibodies against AVT03 and Prolia at predose and Day 1, Day 2, Day 12, Day 30, Day 60, Day 90, Day 180, Day 270, Day 365 (Month 12), Day 365 (Month 12) + 2 weeks, Month 15, and Month 18 (End of Study [EoS]) after treatment.

3.2.5 Pharmacokinetic Endpoint

- Serum trough concentration of AVT03 and Prolia

4 STUDY PLAN

4.1 Study Design

This is a randomized, double-blind, parallel design, repeat dose, 2-arm, multicenter study comparing the efficacy, safety, immunogenicity, and PK profiles of AVT03 and Prolia in postmenopausal women with osteoporosis.

On Day 1, after successfully completing screening activities, eligible subjects will be randomized into Groups 1 and 2, in a 1:1 ratio (AVT03: Prolia). Subject randomization will be stratified by number of years since menopause (≤5 years or >5 years) and prior biologic therapy (for osteoporosis Yes or No).

- **Group 1:** Subjects will receive AVT03 60 mg administered s.c. on Days 1 and 180 (Month 6).
- **Group 2:** Subjects will receive Prolia 60 mg administered s.c. on Days 1 and 180 (Month 6).

At Month 12, subjects in the Group 1 (AVT03) will receive a third dose of AVT03 60 mg administered s.c. while subjects in the Group 2 (Prolia) will be re-randomized in a 1:1 ratio to receive either:

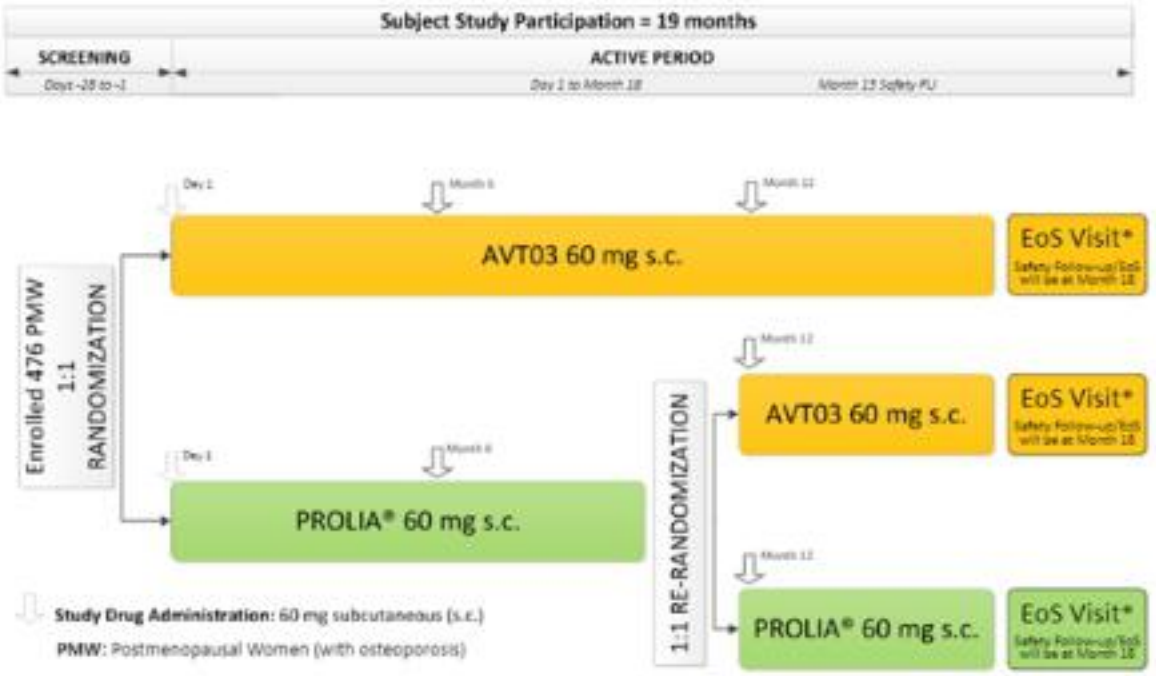
- **Group 2a:** Subjects will receive AVT03 60 mg administered s.c. on Day 365 (Month 12).
- **Group 2b:** Subjects will receive Prolia 60 mg administered s.c. on Day 365 (Month 12).

Two weeks after the Month 12 administration, there will be a safety follow-up visit. Thereafter, subjects will be followed until the EoS visit at Month 18 (ie, 6 months after the last dose at Month 12).

Note: Post trial treatment will be provided to the subject. The Investigator must ensure adequate osteoporosis treatment according to local guidelines is provided for all subjects who have been enrolled into the active period of the study.

The study is summarized graphically in Figure 4.1.

Figure 4.1: Study Schematic



Abbreviations: EoS = End of Study; s.c. = subcutaneous.

4.2 Study Duration

Subjects will participate in the study for up to 19 months:

- Screening: Day -28 to -1
- Active Period: Day 1 to Month 18
  - Treatment on Day 1, Day 180 (Month 6), and Day 365 (Month 12)
  - Safety Follow-up
    - Safety Follow-up visit 2 weeks after Month 12 administration (Month 12 [+ 2 weeks])
    - Safety Follow-up visit 3 months after Month 12 administration (Month 15)
    - Safety Follow-up/EoS visit 6 months after Month 12 administration (Month 18)

5 STUDY POPULATION

Subjects must meet all inclusion criteria and none of the exclusion criteria during the Screening Phase to be enrolled in the study. No deviations will be permitted from the inclusion or exclusion criteria. The Medical Monitor will perform eligibility review for any given subject, before randomization.

Specific entry criteria are detailed in Section 5.1 and Section 5.2.

Any subject designated as a screen failure may be rescreened once after consultation with the Sponsor, or designated representative (see Section 7.2.1).

5.1 Inclusion Criteria

To be enrolled in the study, subjects must meet the following criteria:

1. Postmenopausal women with osteoporosis willing to sign an informed consent form (ICF) and able to undergo protocol related procedures.

2. Age: ≥50 years.

3. Female subject is postmenopausal according to 1 of the following criteria:

   a. Spontaneous amenorrhea for ≥12 consecutive months

   b. Biochemical criteria of menopause follicle-stimulating hormone (FSH) >40 IU/L except surgically sterile

   c. Having had bilateral oophorectomy ≥6 weeks prior to Screening

4. Body Mass Index (BMI): 18.5.0-32.0 kg/m^2

5. A baseline dual-energy x-ray absorptiometry (DXA) scan with a T score ≤ -2.5 and ≥ -4.0 at the LS (L1 to L4) and/or total hip and/or femoral neck.

   A subject must have a T score within the stated range of ≤-2.5 and ≥-4.0 in at least 1 of the 3 areas: - Lumbar spine (L1 to L4) - Total hip - Femoral neck. On the contrary, subjects will be excluded from the trial if the T score is less than -4.0 in at least 1 of the 3 areas (ie, at the LS [L1 to L4], or total hip, or femoral neck).

   Note: The left hip should be scanned for the calculation of total hip T score. If the left hip cannot be scanned (eg, due to left hip replacement, etc), the right hip can be scanned instead. The same hip should be used for all DXA scans.

6. At least 2 consecutive evaluable lumbar vertebrae and at least 1 evaluable hip.

7. Willing to receive calcium plus vitamin D supplements.

8. No history or evidence of a clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to subject safety.

9. Resting supine systolic blood pressure of ≤150 mmHg and diastolic blood pressure of ≤90 mmHg. Other vital signs showing no clinically relevant deviations according to the Investigator's judgment.

10. 12-lead ECG recording without signs of clinically relevant pathology or showing no clinically relevant deviations as judged by the Investigator.

11. Subject smokes <10 cigarettes per day within 3 months of Screening.

    Note: It is strongly recommended that subjects do not smoke during their participation in the study.

12. Recommended to abstain from alcohol from 48 hours prior to drug administration, and 24 hours prior to study visits.

5.2 Exclusion Criteria

Subjects will be ineligible for the study if any of the following criteria apply:

1. Evidence of clinically relevant pathology, especially prior diagnosis of bone disease, or any uncontrolled condition that will affect bone metabolism such as, but not limited to: osteogenesis imperfecta, hyperparathyroidism, non-controlled hyperthyroidism (thyroid stimulating hormone (TSH) <0.5 mIU/L), non-controlled hypothyroidism (TSH ≥5.0 mIU/L), osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as creatinine clearance <50 mL/min as calculated by Cockcroft-Gault formula), Paget's disease of the bone, recent bone fracture (within 6 months), and malabsorption syndrome. For potential causes of secondary osteoporosis, please see Appendix 14.2.
   Note: Appendix 14.2 is a guideline for the Investigators.

2. History and/or presence of 1 severe or more than 1 moderate vertebral fractures confirmed by x-ray (according to Genant semiquantitative method).

3. History of hip fracture

4. Presence of active healing fractures

5. Previous treatment with denosumab and previous use of the following medications:

   a. Intravenous bisphosphonates, fluoride, or strontium ranelate at any dose within 5 years prior to Screening

   b. Oral bisphosphonates used >3 years cumulative use, and any dose within 12 months of Screening

c. Parathyroid hormone (PTH) or PTH derivatives (eg, teriparatide, abaloparatide), and selective estrogen receptor modulators (SERMs) (eg, raloxifene), within 1 year of Screening

d. Romozosumab within 30 days prior to Screening

e. Calcitonin within 6 months of Screening

f. Other bone metabolism drugs: administration of any of the following treatments within the last 3 months,
   i. anabolic steroids or testosterone
   ii. glucocorticoids (>5 mg/day prednisone or equivalent for >10 days)
   iii. systemic hormone replacement therapy
   iv. tibolone
   v. calcitriol
   vi. anticonvulsants (except benzodiazepines and pregabalin)
   vii. heparin
   viii. systemic use of ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet or any cathepsin K inhibitor (eg, odanacatib), aluminium, lithium, protease inhibitors, methotrexate, gonadotropin-releasing hormone agonists

6. Osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (eg, tooth extraction, dental implants, oral surgery in the past 6 months), periodontal, and/or pre-existing dental disease requiring therapy.

7. Evidence of hypo/hypercalcemia at Screening defined as <8.6 or >10.5 mg/dL.

   Note: If hypocalcaemia can be excluded based on calcium, corrected calcium, albumin, PTH, vitamin D3 values but ionized calcium is pending, the subject may be randomized, as per Investigator assessment and confirmation that exclusion criterion 7 has not been met. This needs to be recorded on source documents.

8. Known vitamin D deficiency (25-hydroxy vitamin D level <20 ng/mL [50 nmol/L]) after supplementation at Screening.

9. Known intolerance to calcium or vitamin D supplement.

10. Any current active infections, including localized infections, or any recent history (within 1 week prior to study drug administration) of active infections or a history of recurrent or chronic infections.

11. Presence of known current infection with hepatitis B or presence of positive serology – ie, hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (anti-HBc), hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) at Screening.

Note: Any subject with positive anti-HBc at Screening should be reviewed and evaluated by the Investigator to exclude active infection. It is at the Investigator's discretion whether to extend diagnostics to exclude current infection of hepatitis B. A local HBV quantitative DNA by PCR test may be performed within the screening window visit.

12. Hematology and chemistry laboratory results outside the reference ranges, which are clinically significant, and, in the opinion of the Investigator or designee, could cause this study to be detrimental to the subject.

13. Donation of more than 500 mL of blood within the 8 weeks prior to study drug administration.

14. Hypersensitivity to denosumab or its constituents.

15. A recent history of major surgery including spine surgery due to disc herniation, spinal stenosis, or similar condition within 3 months prior to randomization.

16. History or presence of malignancy within 5 years (with the exception of successfully treated basal cell carcinoma).

17. Inability to communicate or cooperate with the Investigator because of language difficulties or poor mental development or incapacitation.

18. A history (within the previous 3 years) or evidence of alcohol or drug abuse (including soft drugs like cannabis products).

19. Vaccination with a live vaccine with the exception of flu vaccine within the previous month. Coronavirus disease 2019 (COVID-19) vaccination is not considered an exclusion criterion.

20. Any other condition which in the view of the Investigator is likely to interfere with the study or put the subject at risk.

21. Current participation or history of participation in an investigational trial in the last 30 days or period less than 5 half-lives of the medicinal product under investigation - whichever is longer. For investigational products or drugs for which PD effect lasts longer than 5 half-lives, the wash-out period may be extended.

22. A compromised immune system or treatment with immunosuppressants.

5.3 Subject Withdrawal/Discontinuation Criteria

A subject will be considered to have completed the study when she completes the Month 18 (EoS) Visit. Subjects are considered to have completed the treatment period per protocol if they receive study treatment on Day 1, Day 180, and Day 365 (Month 12). For subjects who complete the treatment period or prematurely discontinue the study treatment for any reason, the end of treatment (EoT) visit must be completed. For these subjects, if the discontinuation

occurred within (or less than) 6 weeks after the last dose of study drug, EoT visit should be conducted as soon as possible. In addition to EoT visit, EoS visit should be conducted at least 6 weeks after the last dose of the study drug. For subjects who discontinue the study treatment prematurely, if the discontinuation occurred in at least 6 weeks after the last dose of the study drug, only EoS visit will be needed as the last study visit. The early EoS Visit will include an evaluation of safety and immunogenicity (formation of ADA).

A termination electronic case report form (eCRF) page should be completed for every subject who receives study drug, whether or not the subject completes the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject discontinuing early should be selected from the following standard categories:

- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the Investigator for the best interest of the subject, are grounds for discontinuation. These events include serious adverse events (SAEs) and nonserious AEs regardless of relation to the study drug.

- *Death:* The subject died. Death report case report form (CRF) to collect Date of Death, Reason (SAE, Other, Unknown).

- *Withdrawal of Consent:* The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.

- *Withdrawal by Subject*: An indication that the subject has removed herself from the study or from one or more segments of the study.

- *Protocol Deviation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits).

- *Lost to Follow-up*: The subject stopped coming for visits and study personnel were unable to contact the subject. If the subject fails to attend a scheduled visit, there will be 2 attempts to contact the subject via telephone and 2 written communications. If these receive no reply, the subject will be considered lost to follow-up.

- *Investigator Decision in the Subject's Best Interest.*

- *Other:* The subject was discontinued for a reason other than those listed above, such as theft, loss of study drug, or termination of study by Sponsor.

Subjects who discontinue early will not be replaced.

6 STUDY TREATMENT AND MANAGEMENT

6.1 Description

Information about the study drugs is provided in Table 6.1.

Table 6.1: Details of Study Drugs

Trade (generic) Name	Preparations to Be Administered	
	AVT03	Prolia (Denosumab)
Strength(s)	60 mg/mL	60 mg/mL
Route	Subcutaneous	Subcutaneous
Formulation	Solution for injection	Solution for injection
Dose(s)	60 mg	60 mg

6.1.1 Formulation and Preparation

AVT03 and Prolia are provided in pre-filled syringes and contain excipients according to the pharmacopeial standards for parenteral drugs.

AVT03 will be formulated at the same concentrations approved for Prolia, using the same excipients qualitatively and quantitatively.

6.1.2 Labeling

Each carton box and syringe will be labeled according to country-specific requirements.

6.1.3 Storage

Study drug must be refrigerated between 2°C and 8°C (36°F and 46°F) in the carton box provided to protect it from exposure to light.

Site storage conditions should be monitored by the site personnel and reviewed by the clinical research associate (CRA) during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor.

Complete instructions for proper study drug storage and handling will be provided in the Study Drug Manual.

6.2 Shipment and Blinding

Both study drugs will be supplied by the Sponsor. No study drug will be shipped to a site until written Independent Ethics Committee (IEC) authorization and regulatory authority approval has been received by the Sponsor or its representative.

Blinding of the study will be achieved by the following measures:

- Prolia and AVT03 pre-filled syringes will be blinded using an appropriate masking method to maintain the study blinding. Additional information on the masking method will be provided in the pharmacy manual.

- Subjects and investigators will remain unaware of the treatment allocation until study completion.

- Dedicated blinded and unblinded teams will be implemented within the Sponsor and contract research organization (CRO) before the Month 12 (+ 2 weeks) Data Unblinding. After the Month 12 (+ 2 weeks) Data Unblinding, only the unblinded team will become aware of the subject treatment allocation. Further details, including details of the assigned Sponsor and CRO blinded and unblinded teams, will be provided in the study's Blinded-Unblinded Plan.

- A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject in this study. If knowledge of the study drug is necessary for optimal emergency treatment, the blind may be broken by an Investigator through access of the Interactive Response Technology (IRT). Individual subject treatment assignments may be unblinded only in the case of an SAE or AE that requires knowledge of the study drug received by the subject in order to provide appropriate treatment or management of the SAE or AE or if required for regulatory reporting. Whenever possible, the Sponsor or its designee (ie, Sponsor Medical Lead or designee) will be consulted in the decision to unblind a subject; otherwise, the Sponsor or its designee will be notified as soon as possible in the event that unblinding of an individual subject's treatment assignment has occurred prior to study completion. Every effort is to be made to limit study site personnel unblinding to only those individuals providing direct care to that subject.

- Any intentional or unintentional breaking of the blind is to be reported immediately to the Sponsor.

6.3 Treatment Assignment

Once the subject has signed the ICF at Screening, site personnel will connect to the IRT system through an Internet browser to assign a subject identification number (ID). The subject ID will include the site number (4 digits), and 3-digit subject number, assigned sequentially starting with 001. This number will be utilized to identify the subject throughout the study period. Dropouts (subjects who discontinue study drug early and subjects who are randomized but did not receive at least 1 dose of study drug) will not be replaced. See Section 7.2.1 regarding rescreening. Rescreened subjects should be assigned a new subject ID. No individual is allowed to re-enter the study if previously randomized and/or dosed.

Eligible subjects will be assigned to study drug in accordance with the randomization schedule generated by an independent unblinded statistician using the interactive web response system.

On Day 1, approximately 476 subjects will be randomly assigned in a 1:1 ratio to receive 1 of the following treatments:

- **Group 1:** Subjects will be assigned to receive AVT03 60 mg s.c. on Day 1 and Day 180 (Month 6).

- **Group 2:** Subjects will be assigned to receive Prolia 60 mg s.c. on Day 1 and Day 180 (Month 6).

At Month 12, subjects in AVT03 treatment group will receive a third dose of AVT03 60 mg administered s.c. while subjects in Prolia treatment group will be re-randomized in a 1:1 ratio to receive either:

- **Group 2a:** Subjects will receive AVT03 60 mg administered s.c. on Day 365 (Month 12).

- **Group 2b:** Subjects will receive Prolia 60 mg administered s.c. on Day 365 (Month 12).

On Day 1, subject randomization will be stratified by number of years since menopause (≤5 years or >5 years) and prior biologic therapy for osteoporosis (Yes or No). The randomization list will be issued by [redacted] Biostatistical Operations.

6.4 Dose and Administration

The recommended dose of Prolia for subjects with postmenopausal osteoporosis is 60 mg administered as a single s.c injection once every 6 months.[15,16] In this study, AVT03 or Prolia will be administered per the approved dosing regimen for postmenopausal osteoporosis. Subjects will receive study drug on Day 1, Day 180 (Month 6), and Day 365 (Month 12).

The s.c. injection will be administered in the upper arm, the upper thigh, or the abdomen. Injection should never be given into areas where the skin is tender, bruised, red, or hard. The skin of the site of injection will be disinfected, gently pinched, and the injection needle will be inserted into the pinched skin at an angle of 45 degrees. Immediately after dosing, a cotton ball or gauze pad will be pressed over the injection site and held for 10 seconds. Subjects will be instructed not to rub the area after injection. Additional dosing instructions are provided in the pharmacy manual. The maximum delay allowed in drug administration is 4 weeks. The Month 12 visit should NOT be shifted if Month 6 study drug administrations is delayed by a month. In any case, all efforts should be made to ensure the subject is dosed within 4 weeks of the originally planned dosing points.

Study drug will be administered at the study center by study staff.

6.5 Dose Reduction and/or Discontinuation Rules

There will be no dose modifications in this study. Dose interruptions could occur for safety reasons (eg, AEs, urgent surgery, etc) at the discretion of the Investigator. If this occurs, subject should be dosed as soon as possible after Investigator's consultation with the Medical Monitor.

In the judgment of the Investigator, if the subject experiences intolerable AEs that appear to be related to the study drug, they should be permanently discontinued from study drug but will be encouraged to continue in the study (refer to Section 5.3).

6.6 Accountability

The study site will be supplied with a sufficient quantity of study drug to treat randomized subjects. Blinded study drug will be shipped under appropriate storage conditions to site personnel according to the regulations of the study country. Each delivery must be acknowledged by the addressee by confirming receipt of the study drug shipment in IRT. Study drug cannot be assigned to a subject until the site confirms receipt in the IRT.

A dispensing log will be kept by site personnel who will record the dates and quantity of the study drug administered to each subject. Used study drug syringes, after injections have been performed at sites, will be disposed of at sites per each Institution's standard operating procedure (SOP) or policy; empty carton kit boxes are to be stored until the CRA visit. All empty carton kit boxes and unused study drug kits are to be held at the site until the CRA has completed reconciliation. Once the site's CRA has reviewed and confirmed study drug accountability, empty carton kit boxes may be destroyed on site. The Sponsor may also request that the site return any unused syringes to the Sponsor or its designee once the site's CRA has reviewed and confirmed accountability.

At all times the syringes must remain in the masked package (as appropriate, see Section 6.2).

6.7 Treatment Compliance

Subjects will receive the study drug from a trained staff member. The date and time of each dose administered will be recorded in the source documents and in the eCRF.

6.8 Prior and Concomitant Medications and Conditions

Concomitant medications, both prescription and nonprescription (including over-the-counter medicine, vitamins, supplements, and herbal supplements), taken within 6 months before the Screening Visit and up to EoS visit will be recorded in the source documents and entered into the "Prior and Concomitant Medication" eCRF. Additionally, all medications received for osteoporosis, irrespective of when they were received, will be recorded. Doses of concomitant medications should remain stable, if possible, during the study. All concomitant medications taken throughout the course of the study, including any medications required to treat AEs or concomitant medical conditions and any changes in concomitant medications, will also be recorded in study files and entered into the "Prior and Concomitant Medication" eCRF.

Medical history findings (ie, significant medical conditions, diseases, or surgeries) that the subject has experienced within 6 months of Screening and started before signing of the ICF will be documented. Additional medical conditions present at the time informed consent is given will be regarded as concomitant medical conditions.

All recorded prior and concomitant medications will be coded according to the latest version of the World Health Organization Drug Dictionary (WHO Drug Global B3 2021 March 1 or later).

6.8.1 Allowed Medications

Throughout the study, the Investigator may prescribe any concomitant medication or treatment deemed necessary to provide supportive care except for those listed under Section 6.8.2.

6.8.2 Prohibited Medications

The following concomitant medications are prohibited during the study (and/or during the indicated time periods before the study) (see also Exclusion Criteria, Section 5.2):

1. Intravenous bisphosphonates, fluoride or strontium ranelate within 5 years prior to Screening
2. Oral bisphosphonates used >3 years cumulative use, and any dose within 12 months of Screening
3. PTH or PTH derivatives, eg, teriparatide, abaloparatide, and SERMs, eg, raloxifene within 1 year of Screening
4. Romozosumab within 30 days prior to Screening
5. Calcitonin within 6 months of Screening
6. Other bone metabolism drugs: administration of any of the following treatments within the last 3 months
    a. anabolic steroids or testosterone
    b. glucocorticoids (>5 mg/day prednisone or equivalent for >10 days)
    c. systemic hormone replacement therapy
    d. tibolone
    e. calcitriol
    f. anticonvulsants (except benzodiazepines and pregabalin)
    g. heparin
    h. systemic use of ketoconazole, androgens, ACTH, cinacalcet or any cathepsin K inhibitor (eg, odanacatib), aluminium, lithium, protease inhibitors, methotrexate, gonadotropin-releasing hormone agonists

7 STUDY CONDUCT

Unless otherwise indicated, all assessments will be performed by the Investigator or designated study personnel.

After signing the ICF, each subject will be screened to ensure eligibility for the study.

A pandemic public health emergency, like COVID- 19, may impact the conduct of this clinical trial. In the case of unforeseen circumstances, a decision for each individual subject to remain and/or start in the study has to be made. This should be done on a case-by-case basis by the Investigator on his/her best medical judgment. All applicable local laws and IEC regulations regarding study visits should be followed, including the use of personal protective equipment.

Attempts should be made to perform all assessments in accordance with the protocol where possible. Investigators should closely monitor and document all deviations to the study protocol and share with the Sponsor, or designated representative, in a timely manner.

In case it is not possible to perform all assessments due to an emergency, focus should be given to assessments necessary to ensure the safety of subjects and those of most scientific value to the study. Procedures to be considered in the event of a regional or national emergency declared by a governmental agency may include:

- If onsite visits are not possible, remote visits may be planned.
- If onsite visits are not possible, visit windows may be extended for efficacy or safety assessments that cannot be obtained remotely, following consultation with the Medical Monitor.
- If feasible, a phone call with the subject for assessments may be allowed.
- Use of local clinics/laboratories may be allowed for urinalysis, chemistry, coagulation, and hematology.

7.1 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (SoA) (Table 7.1).

Table 7.1: Schedule of Assessments

PERIOD			ACTIVE PERIOD												
			TREATMENT PERIOD										FOLLOW-UP PERIOD/EOS		
DAY[a]	SCREENING	PREDOSE DAY 1	DAY 1	DAY 2	DAY 12	DAY 30	DAY 60	DAY 90	DAY 180 (Month 6)	DAY 210	DAY 270	DAY 365 (Month 12) EoT[n]	Day 365 (Month 12 [+ 2] weeks)	Month 15	Month 18 EoS[b]
WINDOW(DAY)	DAY -28 TO -1	± 0 day	± 0 day	± 0 day	± 0 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	+ 2 day	± 5 day	± 5 day
Informed consent[c]	X														
Inclusion/exclusion criteria	X	X													
Demographics	X														
Medical history	X														
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[e]	X	X													
FSH (except surgically sterile or with spontaneous amenorrhea for ≥ 12 consecutive months)	X														
Hematology and coagulation[f]	X	X				X	X	X	X	X	X	X	X	X	X
Blood chemistry[f]	X	X				X	X	X	X	X	X	X	X	X	X
Urinalysis[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology (HBsAg, anti-HBc, HCV, and HIV tests)	X														
SARS-CoV-2 tests	X[g]														
Electrocardiogram	X	X							X			X			X
Randomization		X										X[h]			
Study drug administration[i]			X						X			X			
DXA scan of LS (L1 to L4), total hip and/or femoral neck for BMD	X								X			X			X
Lateral thoraco-lumbar spine x-ray	X											X			X

PERIOD			ACTIVE PERIOD												
			TREATMENT PERIOD										FOLLOW-UP PERIOD/EOS		
DAY[a]	SCREENING	PREDOSE DAY 1	DAY 1	DAY 2	DAY 12	DAY 30	DAY 60	DAY 90	DAY 180 (Month 6)	DAY 210	DAY 270	DAY 365 (Month 12) EoT[n]	Day 365 (Month 12 [+ 2] weeks)	Month 15	Month 18 EoS[b]
WINDOW(DAY)	DAY -28 TO -1	± 0 day	± 0 day	± 0 day	± 0 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	± 5 day	+ 2 day	± 5 day	± 5 day
Blood sampling for PK[j]		X	X[k]	X	X	X	X	X	X		X	X	X	X	X
Blood sampling for sCTX-1[j]		X	X[k]	X	X	X	X	X	X		X	X			X
Blood sampling for immunogenicity (ADA)[j]		X	X[k]	X	X	X	X	X	X		X	X	X	X	X
Prior and concomitant medications and conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site assessment[l]		X	X	X	X				X	X		X	X		
ISR diaries distribution			X						X			X			
Calcium and vitamin D supplements distribution[o]	X														
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety telephone call								X[m]							

a. Calculated using the first day of assigned treatment as Day 1 and unless otherwise specified in other footnotes for a specific activity.
b. Subjects who discontinue the study treatment prematurely for any reason will be encouraged to attend an early EoT visit. For these subjects, a safety follow-up visit should be performed at least 6 weeks after last dose of study drug. If the last study visit is at least 6 weeks after the last dose of study drug, this may be considered as early EoS and a separate safety follow-up visit is not required.
c. Should be obtained before any study-related procedures are performed.
d. Vital signs on Day 1 will be measured predose (within 60 min prior to dosing), and 1 h (±10 min), 4 h (±30 min) postdose. For details, refer Section 8.3.2.
e. Height and BMI will be measured at Screening only.
f. Laboratory assessments include hematology (CBC including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell and platelet count). Coagulation: prothrombin time, international normalized ratio, and partial thromboplastin time. Blood chemistry: HCO_3, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and BUN. Liver function tests: AST, ALT, LDH, alkaline phosphatase, total and direct bilirubin. Routine urinalysis: dipstick and microscopy including protein, specific gravity, glucose, and blood. Dipstick urinalysis is sufficient as long as the result is <2+ (urinalysis is also acceptable). If urine dipstick is ≥2+, 24-hour urine must demonstrate ≤1 g of protein in 24 hours. Other laboratory tests to be performed are described in Section 8.3.4.5.
g. Local or central polymerase chain reaction test will be done during Screening as per Investigator's discretion based upon subjects' signs and symptoms. Additional tests may be performed as per Investigator's discretion.
h. At Month 12, subjects in Prolia treatment group will be re-randomized.
i. Dose interruptions could occur for safety reasons (eg, AEs, urgent surgery, etc) at the discretion of the Investigator. If this occurs, subject should be dosed as soon as possible after Investigator's consultation with the Medical Monitor.

j. With the exception of Day 1, samples for all required timepoints (PREDOSE Day 1, D2, D12, D30, D60, D90, D180, D210, D270, D365, D365+2w, Month 15 and Month 18), will be collected following an overnight fast of at least 8 hours and should be drawn during morning hours between 07.30 and 10.00 AM. **On Day180 (Month 6), and Day 365 (Month 12) sampling should be performed PRIOR to dosing**.
k. **On Day 1** samples should be drawn during morning hours between 07.30 and 10.00 AM and **at least 6 ± 2 hours after dosing** and the subjects can have light meal after dosing.
l. Day 1, Day 180, and Day 365 (Month 12) injection site assessments will be performed predose (within 60 min prior to dosing) and at 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), and 2 h (±5 min) postdose. Further details are provided in Section 8.3.6.
m. Subjects will receive monthly phone calls between visits, from Day 90 to Month 18 to collect safety information (AE and concomitant medication review). Additionally, subjects will receive a phone call 7 (+ 2) days after administration of study drug on Day 180 and Day 365 to collect information on ISR. However, if the monthly phone call overlaps with the ISR call, then only 1 call is required.
n. Post trial treatment will be provided to the subject. The Investigator must ensure adequate osteoporosis treatment according to local guidelines is provided for all subjects who have been enrolled into the active period of the study.
o. Calcium and vitamin D supplements will be provided by the Sponsor. Dose adjustment can be done at the discretion of the Investigator. More details are provided in Section 9.1.5.2.

Abbreviations: ADA = anti- drug antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = hepatitis B core antibody; BMD = bone mineral density; BMI = body mass index; BUN = blood urea nitrogen; CBC = complete blood count; DXA = dual-energy x-ray absorptiometry; EoS = End of Study; EoT = End of Treatment; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCO_3 = bicarbonate; HIV = human immunodeficiency virus; ICF = informed consent form; ISR = injection site reaction; LDH = lactate dehydrogenase; LS = lumbar spine; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; sCTX-1 = serum C-terminal telopeptide of type 1 collagen;

7.2 Study Procedures by Time Point

7.2.1 Screening

The assessments during the Screening phase will determine the subjects' eligibility for the study and their ability to comply with protocol requirements by completing all screening assessments. Randomization cannot be done before Medical Monitor's approval, ie, eligibility review.

The Screening Visit is to occur within 28 calendar days prior to the start of study drug administration. After the subject has signed the ICF, screening assessments will be performed as indicated in the SoA (Table 7.1) and recorded in the subject's source documentation/medical record. Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Any subject designated as a screen failure may be rescreened once after consultation with the Medical Monitor or designated representative and will be required to recomplete the applicable screening activities. Rescreened subjects should be assigned a new subject ID (Section 6.3).

Data from subjects who fail screening will be recorded in source data. At a minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth, age, gender, race, ethnicity [if applicable])
- Version and date of informed consent
- Reason for screen failure
- Screening/Rescreening Visit date

For screen failures who experience an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- SAE page

All information related to the SAE not limited to but including concomitant medication, medical history, and any other information are needed for an SAE complementary page.

7.2.2 Active Period

The active period will include 14 in-clinic study visits (with study drug administered at study site at 3 of these 14 visits) from Day 1 through Month 18 in which safety, PD, PK, and efficacy assessments will be performed. Subjects will receive monthly phone calls between visits, from Day 90 to Month 18 to collect safety information. Subjects will receive a phone call 7 (+ 2) days after administration of study drug on Day 180 and Day 365 (Month 12) to collect information on ISR and will have a follow-up visit 2 weeks after the Month 12 administration to collect safety information as indicated in the SoA (Table 7.1), which will be recorded in the subject′s source

documentation/medical record. Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

7.2.3 End of Study

At this visit, safety, PK, and efficacy assessments will be performed, as indicated in the SoA (Table 7.1) and recorded in the subject′s source documentation/medical record. Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Note: Post trial treatment will be provided to the subjects. The Investigator must ensure adequate osteoporosis treatment according to local guidelines is provided for all subjects who have been enrolled into active period of the study.

7.2.4 Unscheduled Visits

Subjects may be asked to return to the study center for additional visits if considered necessary by the Investigator. Unscheduled visits will include hematology, chemistry, PK, ADA samples and may include any other procedures listed in the SoA (Table 7.1), with the exception of dosing.

7.3 Study Procedures for Early Termination

Please refer to Section 5.3 with regard to subject early withdrawal/discontinuation criteria.

8 DESCRIPTION OF ASSESSMENTS

All assessments will be performed throughout the study as noted in the SoA (Table 7.1).

8.1 Efficacy Assessments

All subjects will undergo DXA scans of LS (L1 to L4), total hip and/or femoral neck and lateral thoraco-lumbar spine x-rays as indicated in the SoA (Table 7.1). If left hip cannot be scanned (eg, due to left hip replacement, etc), right hip can be scanned instead. However, it is required to always scan the same hip. The DXA technician should always refer back to the baseline scans to be able to get the correct positioning.

Detailed instruction on scanning and x-ray procedure will be provided in a procedural manual. It is recommended that the same DXA machine should be used for a subject throughout the study. It is further recommended that the same technician performs the DXA scan for the subject throughout the study. Additionally, DXA scan images should be read centrally.

To minimize missing data in the statistical analysis of efficacy endpoints, efforts should be made to collect efficacy data for all subjects. Even for those subjects who discontinued study treatment but did not withdraw their consent, efforts should be made to collect efficacy data whenever possible.

8.2 Pharmacodynamic Assessments

A biomarker of bone resorption and formation (sCTX-1) will be collected in all subjects as indicated in the SoA (Table 7.1). Samples will be stored for up to 5 years and destroyed thereafter.

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

8.3 Safety Assessments

8.3.1 Physical Examinations

A physical examination consists of general, head, eyes, ears, nose, throat, respiratory, gastrointestinal, extremity, musculoskeletal, cardiovascular, central nervous system, lymph node, and skin evaluations and height and any other physical conditions of note.

Body weight without shoes will be recorded in kilograms. BMI will be calculated using the subject's body weight and height in cm at Screening.

A physical examination will be performed as indicated in the SoA (Table 7.1).

An AE is to be reported for all changes identified as clinically significant (or noteworthy) by the Investigator.

8.3.2 Vital Signs

Vital signs will include body temperature (C), respiratory rate, supine and sitting radial heart rate, and supine and sitting systolic and diastolic blood pressures. Sitting recordings are to be made after the subject has been sitting for at least 1 minute. Supine recordings will be made after the subject has been in the supine position for at least 3 minutes.

An AE is to be reported for all changes identified as clinically significant (or noteworthy) by the Investigator.

8.3.3 Electrocardiogram

A 12-lead ECG will be performed, as indicated in the SoA (Table 7.1), after the subject has been in the supine position for at least 10 minutes, will include all 12 standard leads, and will be recorded at a paper speed of 25 mm/second. Standard ECG parameters will be measured. Fridericia formula will be used to calculate QTc. A qualified physician (ie, Investigator) must evaluate all ECGs for the presence of abnormalities and clinical significance. A consulting cardiologist, per the Investigator's decision, may read any abnormalities of clinical concern to the qualified physician.

8.3.4 Clinical Laboratory Tests

Clinical laboratory tests are to be performed as indicated in the SoA (Table 7.1) and listed below. Tests can be repeated under certain circumstances as required by the Investigator after consultation with the Medical Monitor.

Laboratory samples will be analyzed by a central laboratory to ensure consistent interpretation of results. Details of procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

In the exceptional case that shipment to the central laboratory is impossible due to COVID-19 related restrictions or other unexpected problems with central laboratory, the safety samples may be analyzed by the local laboratory upon approval by the Medical Monitor and Sponsor. Local laboratory test results and normal ranges should be recorded in the eCRF in international units.

In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

8.3.4.1 Chemistry

Subjects will have the following tests: bicarbonate (HCO_3), calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and BUN, and liver function tests: AST, ALT, LDH, alkaline phosphatase, total and direct bilirubin.

8.3.4.2 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count (with differential), and platelet count will be assessed.

8.3.4.3 Coagulation

Prothrombin time, international normalized ratio, and partial thromboplastin time will be assessed.

8.3.4.4 Urinalysis

Dipstick and microscopy including protein, specific gravity, glucose, and blood will be assessed. Dipstick urinalysis is sufficient as long as the result is <2+ (urinalysis is also acceptable). If urine dipstick is ≥2+, 24-hour urine must demonstrate ≤1 g of protein in 24 hours.

8.3.4.5 Other Laboratory Tests

Human Immunodeficiency Virus and Hepatitis Screening

All subjects will be tested for HBsAg and anti-HBc, HCV antibodies, and HIV at Screening.

In accordance with local regulations, an additional consent will be obtained for HIV testing. Notification of state and federal/national authorities, as required by law, will be the responsibility of the Investigator.

Follicle-Stimulating Hormone Test

FSH testing will be performed at Screening. Subjects should have FSH >40 IU/L in order to be eligible for this study if not surgically sterile or with spontaneous amenorrhea for ≥12 consecutive months.

Thyroid Stimulating Hormone and Parathyroid Hormone

TSH and PTH testing will be performed at Screening. Subjects should have TSH between ≥0.5 and <5.0 mIU/L in order to be eligible for this study.

25-Hydroxy Vitamin D Test

25-hydroxy vitamin D testing will be performed at Screening. Subjects should have 25-hydroxy vitamin D level ≥20 ng/mL (50 nmol/L) after supplementation at Screening in order to be eligible for this study. At the discretion of the Investigator and based on standard of care, additional 25-hydroxy vitamin D testing can be performed during the study if vitamin D deficiency is suspected or if calcium levels are low.

Severe Acute Respiratory Syndrome Coronavirus 2 Tests

Local or central polymerase chain reaction test will be done during Screening as per Investigator's discretion based upon subject's signs and symptoms. Additional tests may be performed as per Investigator's discretion.

8.3.5 Adverse Events

All AEs occurring after signing the ICF up to the EoS Visit will be recorded.

See Section 9 for additional information.

8.3.6 Injection Site Reactions

The Investigator will assess study drug injection sites as per the SoA (Table 7.1). Subjects will need to be present on site during 2 hours after the injection. Any findings (eg, pain/tenderness, erythema/redness, swelling/induration, pruritus/itching, hematoma/ecchymosis/bruising) will be recorded by the Investigator in the source documents (progress notes) and assessed if they meet the AE criteria.

Subjects will be issued with a paper ISR diary at each of the 3 visits when study drug is administered (ie, Day 1, Day 180, and Day 365). This paper diary is to be used as a "memory aid" so that, if necessary, subjects can record information relating to ISRs. Subjects will also be provided with a ruler on the Day 1 visit to measure the size of ISRs. Subjects will be trained on collecting ISR symptoms on the Day 1 visit and will be re-trained on Day 180 and Day 365 visits. Procedures related to ISR diary are outlined below:

1. Subjects will be issued with a paper ISR diary on Day 1 for them to fill in at home. Subjects will attend study visits 1 day and 11 days (Day 2 and Day 12) post first study drug administration and should bring the paper ISR diary with them to these visits. Study staff should record the data contained within them.

2. The second study drug administration occurs on Day 180. At this visit subjects will be issued with a paper ISR diary to be filled in at home. Subjects will receive a follow-up safety call 7 (+2) days later, and data from the paper ISR diary should be collected over the phone. The subject should be instructed to continue to fill in the paper ISR diary and to bring it with them to their next study visit.

3. The third and final study drug administration occurs on Day 365. At this visit subjects will be issued with a paper ISR diary to be filled in at home. Subjects will receive a follow-up safety call 7 (+2) days later, and the data from the paper ISR diary should be collected over the phone. The subject should be instructed to continue to fill in the paper ISR diary and to bring it with them to their next study visit.

Subjects will return this diary at the EoS visit.

Only ISRs which are at least Grade 1 should be recorded as AEs (Refer to Appendix 14.3 for the injection site reaction grading scheme). Not all ISRs classified as AEs should be recorded as AESIs.

8.4 Immunogenicity Assessments

The formation of ADAs will be assessed in serum samples collected as indicated in the SoA (Table 7.1).

Subjects who test positive for anti-denosumab antibody will be characterized for titer and neutralizing capacity.

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

8.5 Pharmacokinetic Assessments

Serum samples for PK assessments will be collected as indicated in the SoA (Table 7.1).

Details of the procedures to be followed for sample collection, storage, and shipment will be documented in a separate Laboratory Manual.

9 ADVERSE EVENT REPORTING

9.1 Definitions and Criteria

9.1.1 Adverse Events

Per International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2A,[18] an AE is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the actions taken to treat the medical condition. They should be recorded as treatment(s) of the AEs.

Medical History versus Adverse Event

In the following differentiation between medical history and AEs, the term "condition" may include abnormal physical examination findings, symptoms, diseases, laboratory findings, ECG findings, or other abnormal findings.

- Conditions that started up to 6 months, and up to 5 years for medically significant conditions, eg, carcinoma before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (eg, seasonal allergy without acute complaints).

- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (eg, allergic pollinosis).

- Conditions or laboratory abnormalities diagnosed as part of screening assessments are recorded as medical history (eg, newly detected hypertension, diabetes mellitus, elevated liver enzymes).

- Conditions that started or deteriorated after the administration of study drug will be documented as AEs (see also Section 10.4.6.2). This includes intercurrent illnesses.

9.1.2 Serious Adverse Events

An SAE or a serious adverse drug reaction is any untoward event that at any dose meets any of the following criteria:

- Results in death

- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor]).

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; eg, an overnight hospitalization for a diagnostic procedure, or therapeutic procedure for an AE, must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

9.1.3 Unexpected Adverse Drug Reactions

An unexpected ADR is a reaction for which the nature or severity is not consistent with the applicable product information (see US Package Insert[15] and EU summary of product characteristics for Prolia[16]). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator′s Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis, and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 9.2.

9.1.4 Clinical Laboratory Changes

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded on the AE pages of the eCRF:

- Is judged by the Investigator as clinically significant and/or including, but limited to:

a. Requires therapeutic intervention or diagnostic tests

b. Leads to discontinuation of study drug

c. Has accompanying or inducing symptoms or signs

d. Meets at least the Common Terminology Criteria for Adverse Events v5 Grade 3 criteria.[18]

9.1.5 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to study drug, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such AESIs may require further investigation to characterize and understand them. The AESIs for this study encompass all relevant warnings and precautions from the Prolia label[15,16] and AESIs include:

- Hypersensitivity
- Hypocalcemia (based on corrected calcium)
- ONJ
- Osteonecrosis of the external auditory canal
- Atypical subtrochanteric and diaphyseal femoral fractures
- Multiple vertebral fractures (MVF) following discontinuation of study treatment
- Musculoskeletal Pain
- Diverticulitis
- Lichenoid Drug Eruptions
- Cellulitis

See Section 9.2.3 for reporting requirements.

9.1.5.1 Hypersensitivity

If an anaphylactic or other clinically significant allergic reaction occurs, appropriate therapy should be initiated, and further use of the study drug should be discontinued.

9.1.5.2 Hypocalcemia

Hypocalcemia may be exacerbated by the use of study drug. Known pre-existing hypocalcemia (Grade 1 hypocalcemia as per Common Terminology Criteria for Adverse Events v5[19]: corrected

serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; ionized calcium <LLN - 1.0 mmol/L) must be corrected prior to initiating therapy with study drug. Clinical monitoring of calcium levels is recommended before each dose and, in subjects predisposed to hypocalcemia within 2 weeks after the initial dose. If any subject presents with suspected symptoms of hypocalcemia during treatment, calcium levels should be measured. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcemia.

All subjects should receive adequate supplements of calcium and vitamin D throughout the study. Calcium and vitamin D supplements will be provided by the Sponsor. Investigators will be instructed to ensure that all subjects receive at least 1000 mg/day of calcium supplement and 800 IU/day of vitamin D supplement, however the doses can be adjusted at the discretion of the Investigator.

9.1.5.3 Osteonecrosis of the Jaw

Good oral hygiene practices include daily brushing, flossing, and use of antibacterial oral rinses, and attending recommended dental check-ups, denture fittings, and routine cleanings, to decrease rates of periodontal disease and oral infection should be maintained during treatment with study drug. Subjects who are suspected of having or who develop ONJ while on study drug should receive care by a dentist or an oral surgeon. In these subjects, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of study drug should be considered based on individual benefit-risk assessment.

9.1.5.4 Osteonecrosis of the External Auditory Canal

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in subjects receiving denosumab who present with ear symptoms including chronic ear infections.

9.1.5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

During the treatment with study drug, subjects should be advised to report new or unusual thigh, hip, or groin pain. Any subject who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Subject presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of study drug should be considered, pending a benefit-risk assessment, on an individual basis.

9.1.5.6 Multiple Vertebral Fractures Following Discontinuation of Study Treatment

Following discontinuation of study treatment, fracture risk increases, including the risk of MVF. Treatment with study drug results in significant suppression of bone turnover and cessation of study drug results in increased bone turnover above pretreatment values 9 months after the last dose of study drug. Subjects will be followed for at least 6 months after the last dose of the study drug in order to capture this AE.

If study treatment is discontinued, subjects should be transitioned to an alternative antiresorptive therapy.

9.1.5.7 Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in subjects taking Prolia. The time to onset of symptoms varied from one day to several months after starting Prolia. Consider discontinuing use of study drug if severe symptoms develop.

9.1.5.8 Diverticulitis

In a single phase 3 placebo-controlled clinical trial in subjects with prostate cancer receiving androgen deprivation therapy an imbalance in diverticulitis AEs was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for non-metastatic breast cancer.

9.1.5.9 Lichenoid Drug Eruptions

Lichenoid drug eruptions (eg, lichen planus-like reactions) have been reported in subjects in the post-marketing setting.

9.1.5.10 Cellulitis

Subjects receiving denosumab may develop skin infections, predominantly cellulitis, leading to hospitalization. Subjects should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

9.1.6 Assessment of Severity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the subject's normal level of functioning.
Moderate:	The AE produces some impairment of functioning, but is not hazardous to the subject's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself may be of relatively minor medical significance (such as severe headache). Severity is not the same as "seriousness," which is based on subject/event outcome at the time of the event.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience should be noted. If the severity category changes over several days, those changes should be recorded as separate AEs (with distinct onset dates).

9.1.7 Assessment of Relationship

Each AE will be assessed as to its relationship to the study drug, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the study drug will be assumed sufficient for at least plausible association.

Not related:	No causal relationship exists between the study drug and the AE, but an obvious alternative cause exists, eg, the subject's underlying medical condition or concomitant therapy.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the study drug.

When assessing the relationship to the study drug, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping the suspect study drug, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation (eg, a concomitant drug or disease)

9.1.8 Action Taken Regarding Study Drug(s)

The action taken regarding the study drug as a result of an AE should be selected from one of the categories listed below and recorded on the eCRF:

- Dose Not Changed: No change in study drug dose was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to the start of treatment.
- Unknown.

9.1.9 Other Action Taken for Event

Other action(s) taken as a result of the AE should be selected from 1 of the categories listed below and recorded on the eCRF:

- None (ie, no treatment was required)

- Therapy(ies) required (ie, prescription and/or OTC medication was required to treat the AE)
- Hospitalization or prolongation of hospitalization required (ie, hospitalization was required or prolonged because of the AE, whether medication was required)
- Other

9.1.10 Adverse Event Outcome

The outcome of the AE should be selected from one of the categories listed below and recorded on the eCRF:

- Recovered/Resolved (ie, the subject fully recovered from the AE with no residual effect observed)
- Recovering/Resolving (ie, the AE improved but has not fully resolved)
- Not Recovered/Not Resolved (ie, the AE is still present and observable)
- Recovered/Resolved with Sequelae (ie, the residual effects of the AE are still present and observable, including sequelae/residual effects)
- Fatal (ie, "fatal" should be used when death is a direct outcome of the AE)
- Unknown

9.2 Reporting Procedures and Requirements

9.2.1 Adverse Events

Each time the subject is seen or contacted by the Investigator or the study staff, be it at the study clinic, hospital, or over the telephone, the Investigator will determine whether any AE has occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject, or by questioning the subject at each contact. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. If AEs occur, the first concern will be the safety of the study subjects. All AEs will be followed until resolved or stable and the outcome documented in the subject's source documentation/medical record, and on the eCRF.

Any AE that occurs after signing the ICF up to the EoS Visit will be recorded in the subject's source documentation/medical record and on the AE page of the eCRF. In case of early EoS, if the Investigator detects an AE in a subject up to 6 weeks after the last dose of the study drug and

considers the event possibly related or related to prior study drug, the Investigator should report it to the Sponsor or designated representative.

For each reported AE, the following are to be reported:

- Description of the AE:

  a. Whenever possible, an AE or SAE will be reported using a diagnostic term, (eg, "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever").

  b. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available.

  c. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AEs or SAEs.

- Start and end date of the AE
- Whether the AE is an SAE, AESI, or unexpected ADR
- Severity (Section 9.1.6)
- Relationship to the study drug (Section 9.1.7)
- Action taken regarding the study drug (Section 9.1.8)
- Other action taken for the AE (Section 9.1.9)
- Outcome (Section 9.1.10)

Illnesses that are present at the time informed consent is given are to be regarded as concomitant illnesses and recorded in the medical history. Investigators should document all significant illnesses that the subject has experienced within 6 months of Screening as a prior illness and all previous significant ones which are important for interpretation of subject overall medical condition. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs.

All clinical laboratory results, vital signs, and ECG results or findings should be evaluated by the Investigator to determine their clinical significance. Isolated abnormal clinical laboratory test results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

9.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 9.1.2). If the AE is considered serious, the Investigator should report this event to the Pharmacovigilance CRO as outlined below and to the IEC/regulatory authorities according to its SOPs.

Any SAE that occurs after signing the ICF up to the EoS Visit will be recorded in the subject's source documentation/medical record and on the AE page of the eCRF. In case of early EoS, if the Investigator detects an SAE in a study subject up to 6 weeks after the last dose of the study drug, and considers the SAE related or possibly related to this study's study drug administration, the Investigator should report it to the Pharmacovigilance CRO.

All information about SAEs will be collected and reported via the SAE Form within electronic data capture (EDC) and sent by email message or facsimile (contact information will be contained in the investigator site file). If the EDC system is not available or if the site experiences a temporary disruption of the EDC system, the site staff will complete the back-up paper SAE Form and sent it by email message or facsimile. If notification is made via email or fax, site staff must enter the SAE information into the EDC system as soon as the system becomes available. The Investigator should send the initial report within 24 hours of becoming aware of the SAE regardless of relationship to study drug.

At minimum, the initial report of the SAE should include the following information:

- AE description
- Study code/protocol number
- Subject number and year of birth
- Study drug
- Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization, and for reported deaths the Investigator should supply Pharmacovigilance CRO and the IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

The original paper SAE Form submitted should be kept at the study site with the subject's source documentation/medical record or in the site's study files. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs that are ongoing should be followed until resolved or stabilized.

Any suspected unexpected serious adverse reaction must be reported according to applicable regulatory requirements.

9.2.3 Adverse Events of Special Interest

Adverse events of special interest, encompassing all relevant warnings and precautions from the Prolia label, will be defined for safety analysis. Further details will be given in the Safety Management Plan and the statistical analysis plan (SAP). AESIs are listed in Section 9.1.5.

While these are noted to be of special interest, these AEs will be reported and assessed in the same manner as standard AEs.

10 STATISTICS

10.1 General Procedures

The statistical analysis will be undertaken by [redacted] in collaboration with Alvotech.

A detailed SAP will be finalized and signed before database lock and unblinding. Additional details will be provided in the SAP. Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report (CSR).

All data summaries and statistical analyses will be performed using Safety Analysis Set (SAS) version 9.4 or higher.[0]

10.2 Sample Size

Approximately 476 subjects will be randomized to demonstrate the clinical similarity of AVT03 and Prolia in terms of the percent change from Baseline in LS BMD at 12 months. Assuming a 0.05% true difference between treatment groups, 18% non-evaluable subjects, a common standard deviation (SD) of 4.06%, using an equivalence margin of (-1.45%, 1.45%), 476 subjects will provide power of 93.7% and 87.8% at a significance level of 5% (corresponding to 90% confidence interval (CI) as required by FDA) and 2.5% (corresponding to 95% CI as required by EMA), respectively.

From a clinical practice point of view, a percent change of less than 2 to 3% in LS BMD is considered as not a clinically meaningful change.[21] Therefore, an equivalence margin of (-1.45%, 1.45%) is considered as a clinically relevant threshold to detect potential difference between the proposed biosimilar and reference product in terms of mean percent change from Baseline in BMD at Month 12.

The equivalence margin and the common SD are derived based on the data from the historical clinical trials with denosumab 60 mg and placebo; details are provided in the table below.

Table 10.1: Historical Data for Percent Change from Baseline in Lumbar Spine Bone Mineral Density at 12 Months and Meta-Analysis Results

Publications	Sample size (Denosumab 60 mg vs. Placebo)	Mean difference between group	Pooled SD
Cummings et al. 2009[22]	220 vs. 221	5.47%	3.55%
Bone et al. 2008[23]	164 vs. 165	4.98%	4.06%*
McClung et al. 2006[24]	46 vs. 46	5.54%	3.49%
Meta-analysis (mean difference and 95% CI)		5.32% (4.83%, 5.82%)	
Equivalence margin based on 70% retention		[-1.45%, 1.45%]	

*To be conservative, the largest SD of 4.06% among historical trials is used for the sample size calculation in Study AVT03-GL-C01.
Abbreviations: CI = confidence interval; SD = standard deviation.

In addition, for the submission to EMA, the $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 will be analyzed as the primary PD endpoint. The coefficient of variation (CV%) of $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 is estimated from simulation using a published denosumab PD model[25,26] which was developed based on Prolia data. Assuming a true geometric mean ratio (GMR) of 0.95, using the standard equivalence margin of (0.80, 1.25), 476 randomized subjects (considering 18% of non-evaluable rate) will provide a power of 99.9% for the PD similarity analysis of $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1.

10.3 Analysis Populations

10.3.1 Enrolled Set

The Enrolled Set includes all subjects who have given informed consent to participate in the study.

10.3.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects who received at least 1 dose of randomized study treatment. Subjects will be analyzed according to the study treatment arm they were randomized to.

10.3.3 Pharmacodynamic Analysis Set

The PD Analysis Set is defined as all randomized subjects who received at least 1 dose of randomized study treatment and have at least 1 evaluable PD endpoint collected without any protocol deviation that thought to significantly affect the PD. Subjects will be analyzed according to the actual study treatment received.

10.3.4 Safety Analysis Set

The SAS includes all randomized subjects who received at least 1 dose of study treatment. Subjects will be analyzed according to the actual study treatment received.

10.4 Statistical Methods

10.4.1 Protocol Deviations

Any deviations from the protocol should be collected and documented as described in Protocol Deviation Handling Plan. All protocol deviations will be reviewed and classified as minor or major on a case-by-case basis by the Sponsor or its representative. The protocol deviations leading to exclusion of subjects from the primary endpoint analysis will be determined prior to database freeze.

Protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment should be described in the study report. These might include, but are not limited to, the following:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who developed withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong treatment or incorrect dose.
- Those who received an excluded concomitant treatment.

All protocol deviations including those related to COVID-19 will be captured and presented in tables and listings.

10.4.2 Subject Disposition

Details for the reasons and number of the screening failures will be tabulated.

Subject disposition at EoT and EoS including reasons for premature discontinuation of treatment and study will be presented separately.

10.4.3 Demographic and Baseline Characteristics

Treatment arms will be compared with respect to subject demographics and baseline subject and disease characteristics and will be summarized using descriptive statistics, but no formal statistical analysis tests will be performed. The following demographics and baseline characteristics will be summarized: age (in years, at time of signing informed consent), gender, race, and ethnicity.

10.4.4 Analysis of Efficacy

10.4.4.1 Primary Efficacy Endpoint(s)

The following estimand attributes are defined with regards to the primary efficacy endpoint analysis:

Endpoint: Percent change from Baseline in LS BMD at12 months.

Treatment: Randomized treatment groups, AVT03 and Prolia.

Population:

The primary endpoint analysis will be based on the FAS which includes all randomized subjects who received at least 1 dose of randomized study treatment. Subjects will be analyzed according to the study treatment arm they were randomized to. In order to provide the most sensitive analysis set to detect potential differences between AVT03 and Prolia, the following intercurrent

events (ICEs) that can lead to attenuation of treatment differences are defined.[27] Subjects with any of the following ICEs will be excluded from the analysis of primary endpoint:

- Discontinuation from study treatment prior to 12 months.
- Took prohibited concomitant medications prior to 12 months that impact the primary endpoint.
- Received incorrect study treatment instead of the randomized treatment.
- Additional protocol deviations that impact the assessment of primary endpoint, which will be determined in a blinded data review meeting prior to database lock.

As a sensitivity analysis, the primary endpoint analysis will be repeated based on the FAS without exclusion of any subjects due to the ICEs specified for the main estimator.

Population Level Summary:

The following statistical hypotheses will be tested to demonstrate the clinical similarity of AVT03 and Prolia in terms of percent change from Baseline in LS BMD at 12 months.

The null hypothesis,

$$H_0\colon\ \mu_{AVT03} - \mu_{\text{Prolia}} \leq -1.45\%\ \ or\ \mu_{AVT03} - \mu_{\text{Prolia}} \geq -1.45\%,$$

the alternative hypothesis

$$H_A\colon |\ \mu_{AVT03} - \mu_{\text{Prolia}}\ | < 1.45\%$$

where μ_{AVT03} and μ_{Prolia} are the mean percent change from Baseline in LS BMD at 12 months in AVT06 and Prolia group respectively.

The percent change from Baseline in LS BMD at 6 and 12 months will be analyzed using a mixed model for repeated measures (MMRM) including treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. An unstructured covariance structure will be used to model the within-subject error and an adjustment to the degrees of freedom will be made using the Kenward-Roger's approximation.

The least square mean estimates will be provided for each treatment group at each visit with their standard errors (SE). The difference of least square means between the treatment groups and associated SE, 2- sided 95% CI (as required by EMA) and 2-sided 90% CI (as required by FDA) will be provided for 12 months. At 12 months, if the 95%/90% CIs are completely contained within the pre-specified equivalence margin of [-1.45%, 1.45%], a clinical similarity will be demonstrated respectively.

For the primary analysis and sensitivity analysis of the primary endpoint, the missing values of percent change from Baseline in LS BMD at 12 months may be handled using multiple imputation as needed, details of which will be provided in the SAP.

In addition, for the submission to EMA, the area under the percentage change from baseline in serum C-telopeptide of type 1 collagen up to 6 months ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1) will be analyzed as primary PD endpoint. The following statistical hypotheses will be tested to demonstrate the PD similarity of AVT03 and Prolia in terms of $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1.

The null hypothesis,

$$H0: GM_{AVT03}/GM_{Prolia} \leq 80\% \text{ or } GM_{AVT03}/GM_{Prolia} \geq 125\%$$

The alternative hypothesis is:

$$H1: 80\% < GM_{AVT03}/GM_{Prolia} < 125\%$$

where GM_{AVT03} and GM_{Prolia} denote the geometric means of $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 in the AVT03 and Prolia groups, respectively.

The analysis of the PD endpoint will be based on the PD Analysis Set. The similar ICE strategy as for the primary endpoint (percent change from Baseline in LS BMD at 12 months) will be implemented for the analysis of PD endpoint $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1, ie, the subjects with the ICEs that can lead to attenuation of treatment differences will be excluded from the analysis of $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1. The log transformed PD data ($AUEC_{0\text{-}6months}$ of %Cfb sCTX-1) will then be analyzed using an analysis of covariance (ANCOVA) model including the treatment as factor and the baseline sCTX-1 as continuous covariate. The 95% CI for the GMR between treatment groups will be calculated. The PD similarity will be demonstrated if the 95% CIs of GMR lie entirely within the pre-specified margin of (0.80, 1.25).

Subgroup Analysis

The subgroup analyzes of the primary efficacy endpoint will be performed by key baseline characteristics based on the FAS. Within each subgroup, the primary endpoint will be analyzed using the same method as for the primary endpoint. The results of subgroup analysis will be interpreted descriptively. Subgroups of interest for the primary efficacy endpoint include:

- Number of years since menopause (≤5 years, >5 years)
- Prior biologic therapy for osteoporosis (Yes/No)

Other subgroup analysis will be defined in the SAP as needed.

10.4.4.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints for this study are the percent change from Baseline in the LS BMD at 6 and 18 months, percent change from Baseline in hip and femoral neck BMD at 6, 12, and 18 months, and incidence of new morphometric vertebral fractures at 12 and 18 months.

The same analysis methods used for the primary will also be used for the secondary continuous efficacy endpoints. The number and percentage of subjects who had new morphometric vertebral fractures will be provided by visit.

The analysis results of secondary efficacy endpoints will be interpreted descriptively.

10.4.4.3 Handling of Dropouts and Missing Observations

The multiple imputation method (to handle the missing primary endpoint data) may be undertaken and detailed in the SAP prior to unblinding the study.

10.4.4.4 Multiplicity

The secondary efficacy endpoint analysis results will be interpreted descriptively only. No alpha adjustments are planned for this study.

As mentioned in Section 10.4.4.1, for the submission to EMA, the $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 will be analyzed as primary PD endpoint. For EMA, the primary efficacy endpoint (ie, Percent change from Baseline in LS BMD at 12 months) and primary PD endpoint will share the familywise type 1 error rate of 5%, no alpha adjustment is needed for the additional PD primary endpoint analysis.[28]

10.4.5 Pharmacodynamics

For the submission to EMA, the $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 will be analyzed as primary PD endpoint (see details in Section 10.4.4.1).

For the submission to other agencies, the $AUEC_{0\text{-}6months}$ of %Cfb sCTX-1 will be analyzed as secondary PD endpoint, and the analysis result will be interpreted descriptively.

The descriptive statistics of CTX-1 level between treatment groups over all time points will be provided and will be presented graphically including individual and mean (per treatment) concentration-time profiles.

Details will be provided in the SAP.

10.4.6 Analysis of Safety

Safety analyzes will be presented by the treatment received for all subjects in the SAS. Safety summaries will be presented by treatment and overall.

10.4.6.1 Extent of Exposure

For the study drug (AVT03 or Prolia), study drug exposure will be summarized.

10.4.6.2 Adverse Events

All AEs occurring after signing the ICF up to the EoS Visit or 6 weeks after the last scheduled study visit will be recorded. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher.

A treatment-emergence adverse event (TEAE) is defined as any AE that has an onset on or after the dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug.

The incidence of TEAEs (number and percent of subjects reporting the AE at least once during the study), SAEs, AEs related to study drug, SAEs related to treatment, and AEs leading to study discontinuation will be summarized by treatment.

The incidence of TEAEs and treatment-related AEs will also be summarized by maximum severity by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of subjects reporting a particular event.

In counting the number of events reported, a continuous event, ie, reported more than once and which did not cease, will be counted only once; non-continuous AEs reported several times by the same subject will be counted as multiple events.

AESIs will be listed and may be summarized separately.

10.4.6.3 Electrocardiogram

Shift tables for change in 12-lead ECG parameters from Baseline to each post-baseline visit will be presented by treatment and visit.

10.4.6.4 Vital Signs and Body Weight

Vital sign data and body weight (observed and change from Baseline) will be listed and summarized using descriptive statistics by treatment and visit.

10.4.6.5 Physical Examination

Abnormal physical examination data will be summarized by treatment and visit. Clinically significant findings will be listed.

10.4.6.6 Clinical Laboratory Tests

Each hematology, coagulation, urinalysis, and serum chemistry parameter (observed and change from Baseline) will be summarized using descriptive statistics by treatment and visit. In addition, each measurement will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables for change in laboratory parameters from Baseline to each post-baseline visit will be presented.

Presence of HBsAg, HCV antibodies and HIV at Screening will be summarized by treatment. SARS-CoV-2 antigens will be summarized by treatment and visit.

10.4.6.7 Concomitant Medications

Concomitant medications include all medications and therapies during the study except for planned study drugs. Concomitant medications will be coded according to the latest version of the WHO Drug Dictionary (WHO Drug Global B3 2021 March 1 or later) and will be summarized by treatment with number and percentage of subjects receiving each category of medication.

10.4.7 Immunogenicity

Presence of ADAs and neutralizing antibodies will be compared between treatments.

The number and percentage of subjects developing ADAs will be tabulated for each treatment-by-visit and the nAbs and the titers will be summarized for ADA positive subject.

10.4.8 Pharmacokinetics

Serum concentrations of AVT03 and Prolia will be summarized by treatment and visit using descriptive statistics. The steady-state serum trough concentrations of AVT03 and Prolia will be compared.

10.4.9 Interim Analysis

No interim analysis is planned for this study.

11 STUDY MANAGEMENT AND RESPONSIBILITIES

11.1 Ethics

11.1.1 Good Clinical Practice

The study will be performed in accordance with this protocol, local national laws (as applicable), ICH guideline for Good Clinical Practice,[29] and the most recent guidelines of the Declaration of Helsinki.[30]

11.1.2 Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC. Approval is required for the study protocol, Investigator's Brochure, protocol amendments, ICFs, subject information sheets, and advertising materials. No study drug will be shipped to a site until written IEC authorization has been received by the Sponsor or its representative.

11.1.3 Informed Consent

For each study subject, a written ICF will be obtained before any protocol-related activities are performed. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The consenting/re-consenting process will be explained in detail and documented in source documents. The Investigator or a designated representative will provide the Sponsor or its representative with a copy of the IEC-approved ICF before the start of the study.

11.1.4 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IEC personnel, the Sponsor and its authorized representatives are allowed full access to the records.

11.2 Auditing and Monitoring

To ensure accurate, complete, and reliable data [redacted] will provide instructional material to the study sites and the Sponsor at a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. A Monitoring Plan will be developed and approved by the Sponsor and [redacted] using a risk-based monitoring approach with the primary focus on critical data and processes that if inaccurate, not performed, or

performed incorrectly, would threaten the protection of human subjects or the integrity of the study results. Monitoring may include remote monitoring, personal visits, and/or telephone communication to assure that the investigation is conducted according to the protocol, SOPs, Good Clinical Practice guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. As defined in the Monitoring Plan, eCRFs may be reviewed remotely or onsite for completeness, clarity, and consistency with source documents available for each subject. At the conclusion of the study, [redacted] will conduct a quality review of the database.

The study may be audited by the Sponsor, [redacted] and/or regulatory agencies at any time. Investigators will be given a notice before an audit occurs.

Medical advisors and CRAs or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

11.3 Data and Safety Monitoring Board

No data safety monitoring board or committee will be used in this study.

11.4 Data Handling, Documentation, and Record Keeping

11.4.1 Source Documentation

Note that a variety of original documents, data, and records for a given subject (eg, hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study) will be considered as source documents in this study. eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

11.4.2 Direct Access to Source Data and Documents

The Investigator/institution will provide direct access to source data and documents for trial-related monitoring, audits, IEC review, and regulatory inspection.

11.4.3 Record Retention

The Investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority but should not be less than 2 years after the first marketing approval. In addition, the retention period must meet the requirements of the most stringent authority. The Investigator should take measures to prevent accidental or premature destruction of these documents. The responsible Investigator will notify the Sponsor prior to destruction of study records (eg, site master file) after end of required retention period or/and if the Investigator intends to move (relocate) or retires.

11.4.4 Study Documentation

By signing a copy of the country-specific regulatory form(s), the Investigator or designated representative acknowledges that he/she has received a copy of the Investigator's Brochure on AVT03 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in the country-specific regulatory form(s). No changes in this protocol can be made without the Sponsor's written approval.

11.4.5 Data Management Considerations

The data collection tool for this study will be a validated EDC system called [redacted] Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet-based EDC software system [redacted], which the CRO has licensed from [redacted] and the CRO have validated [redacted] for use in clinical studies and the CRO will validate the system configuration for this specific protocol. [redacted] allows for the application of software logic to set up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. The CRO extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Alvotech trained staff will perform User Acceptance Testing in conjunction with the CRO to ensure the application of this logic to confirm data are complete and reflect the clinical data requirements of the study. The site personnel resolve data queries resulting from the application of the software logic. The data are stored at a secure host facility maintained by [redacted] who own their own set of backup and disaster recovery plans and can be transferred to the URL owner whenever required.

All access to th[redacted]system is through a password-protected security system that is part of the[redacted] software. All internal Alvotech and external investigator site personnel seeking access must go through a thorough [redacted] training process before they are granted access to [redacted] for use in Alvotech's clinical study. Training records are maintained.

Alvotech as the Sponsor will ensure that the Investigator has control of and continuous access to eCRF data.

A service desk is staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner and supports all personnel with access to the [redacted] system.

The [redacted] ystem contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time, it was made. This information is available both at the investigator's site and at Alvotech based on specific user data access permission. Data entries made in the [redacted] EDC screens are supported by source documents maintained for all subjects enrolled in this study.

11.5 Indemnification

The Sponsor's indemnification of the Investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

11.6 Amendments

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IEC is notified within 5 calendar days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IEC and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study subject, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

11.7 Study Termination

The Sponsor reserves the right to terminate the study at any time. Both the Sponsor and the Investigator or designated representative reserve the right to terminate the study at the Investigator′s site at any time. Should this be necessary, the Sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination , and the Investigator or designated representative will inform the IEC of the same within the required time frame. In terminating the study, the Sponsor and the Investigator or designated representative will assure that adequate consideration is given to the protection of the subjects' interests. Alvotech will not provide Prolia after termination of the study or upon discontinuation of the study for the subject.

In addition, the trial may be terminated by the IEC or further to any regulatory inspection findings. In case of suspension, the study may resume once the raised concerns are addressed, and satisfy the Sponsor, IEC, and/or the regulatory authorities.

11.8 Clinical Study Report

A primary CSR will be prepared including data available at the Month 12 + 2 weeks database freeze for all subjects and Month 18 data for 10% of the subjects and a final CSR including data collected up to Month 18 for all subjects.

Both CSRs will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final CSR will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report for retention.

12 PUBLICATION POLICY

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors are to meet conditions 1, 2, and 3.

- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.

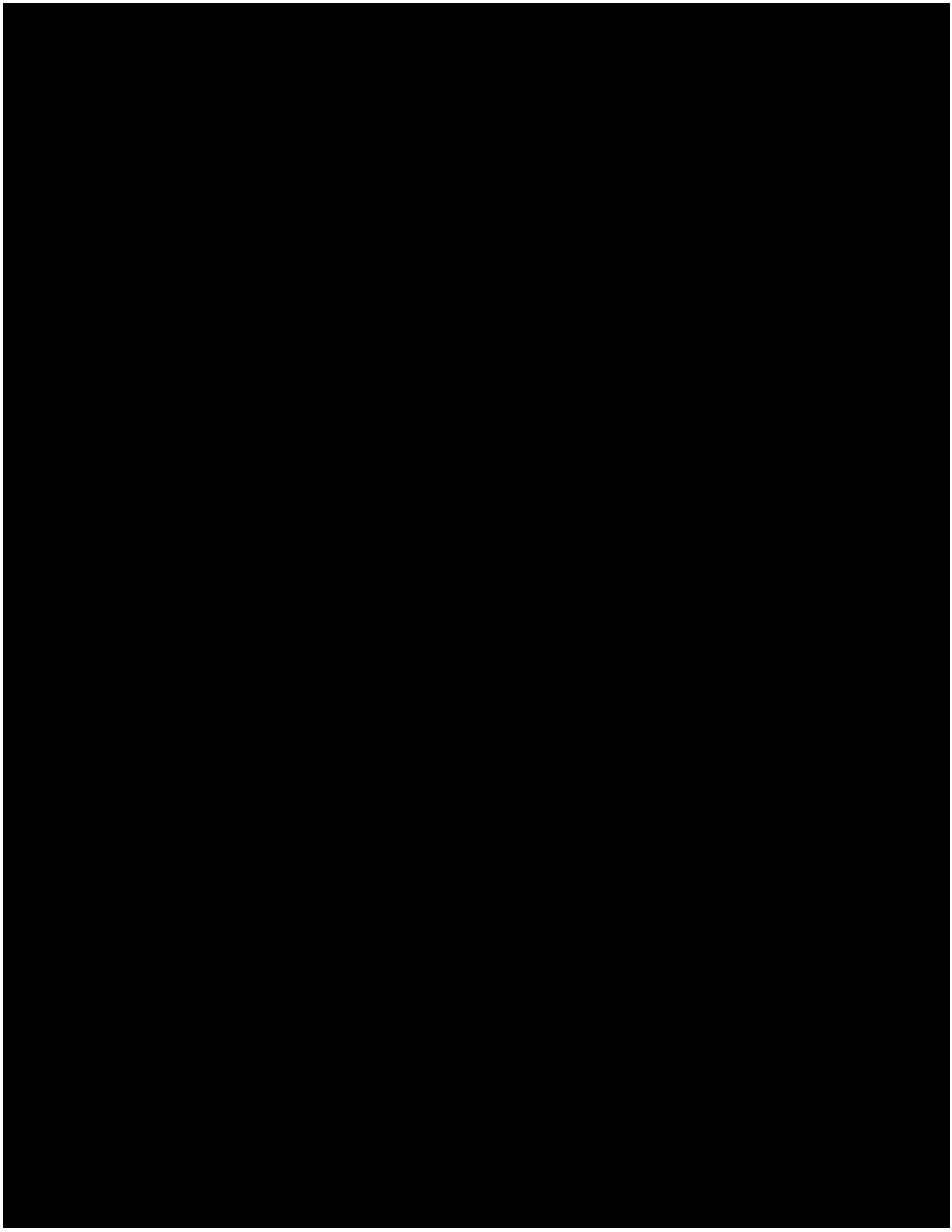
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

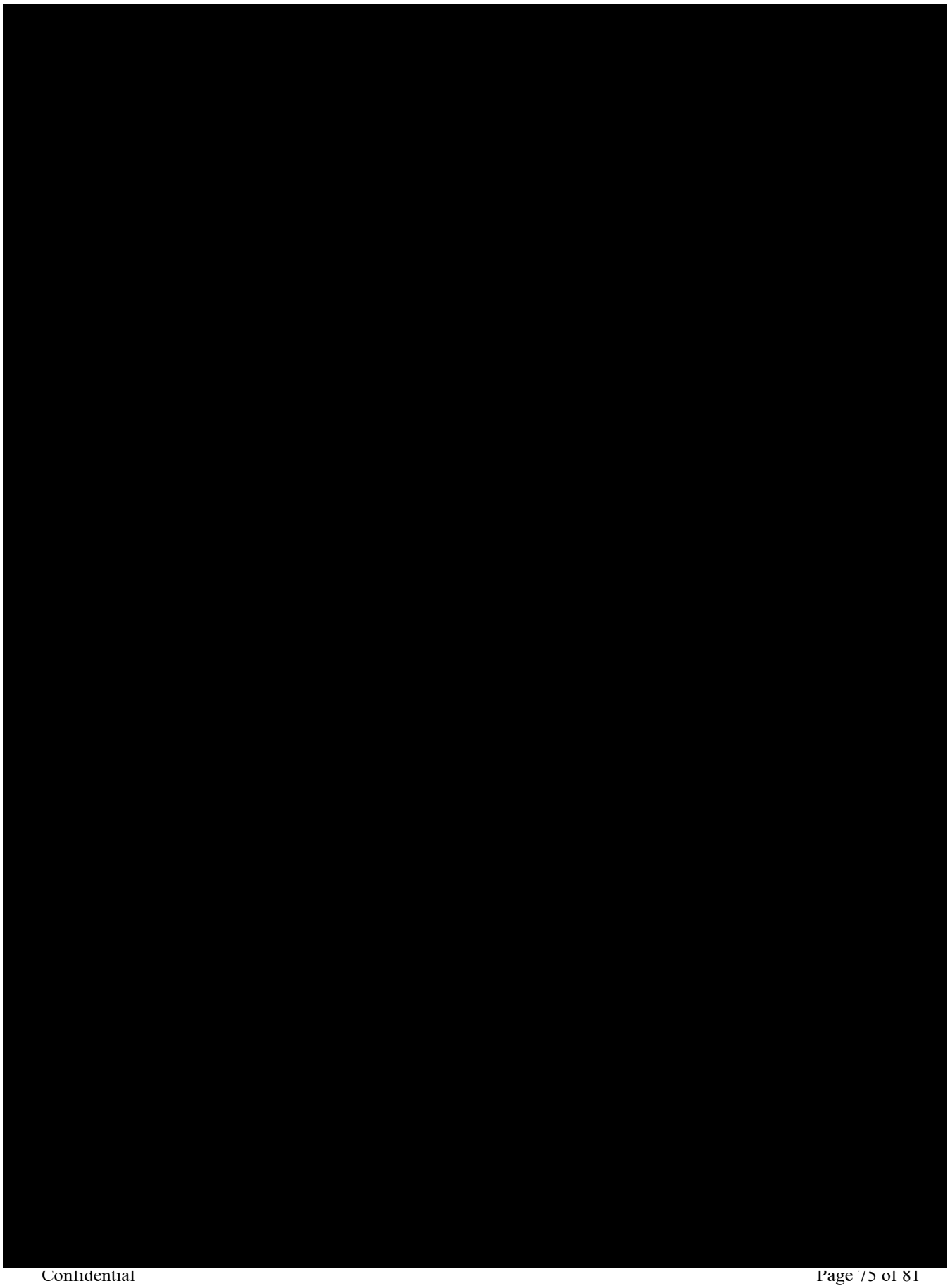
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.

- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Alvotech for review. The Clinical Trial Agreement among the institution, Investigator, and Alvotech will detail the procedures for, and timing of, Alvotech's review of publications.

13 REFERENCES





14 APPENDICES

14.1 Contact Information

Role	Name and Contact Information
Sponsor Medical and Development Lead	[redacted]
Sponsor Project Management	[redacted]
Medical Monitor	[redacted]
CRO Project Management	[redacted]
EDC System Provider	[redacted]
Central Laboratory	[redacted]
Investigational Product Distribution	[redacted]

Role	Name and Contact Information
Central Imaging	[redacted]
Interactive Response Technology	[redacted]

Abbreviations: CRO = contract research organization; EDC = electronic data capture

The names of other study personnel are provided in a separate vendor management plan to the site.

14.2 Causes of Secondary Osteoporosis

Note: This appendix is a guideline for the Investigators. Controlled conditions that are not specifically mentioned in the exclusion criteria 1 are to be evaluated and subjects can be included as per Investigator's criteria and/or after discussion with the medical monitor on a case-by-case basis (eg, well controlled diabetes type 1 or 2; history of anorexia nervosa, etc.). Medical conditions or prohibited medications specified in the inclusion and exclusion criteria are exclusionary.

- Anorexia nervosa
- Gastrointestinal malabsorption (eg, celiac disease, postoperative states)
- Vitamin D and/or calcium deficiency
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's syndrome
- Hypogonadism (hypogonadotropic or hypergonadotropic)
- Hypercalciuria
- Rheumatoid arthritis and other inflammatory conditions

- Alcoholism
- Smoking
- Renal disease
- Liver disease
- Homocystinuria
- Hereditary hemochromatosis
- HIV infection and/or medications
- Diabetes (types 1 and 2)
- Bone marrow processes
- Systemic mastocytosis
- Gaucher disease
- Thalassemia major

Medications

- Glucocorticoids
- Immunosuppressants (cyclosporine)
- Antiseizure medications (particularly phenobarbital and phenytoin)
- Gonadotropin-releasing hormone agonists (when used to suppress ovulation)
- Heparin
- Chemotherapy leading to amenorrhea
- Thiazolidinediones
- Depot medroxyprogesterone acetate

Possible contributors

- Excess thyroid hormone
- Depression and/or SSRI use

- Proton pump inhibitors

14.3 Injection Site Reaction Grading Scheme

Injection Site Reaction Grading Scheme					
Intensity Grading					
Reaction	**Absent (0) or not clinically significant**	**Mild (1)**	**Moderate (2)**	**Severe (3)**	**Potentially Life-threatening (4)**
Pain	Absent	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Hospital visit or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit or hospitalization
Erythema/redness	Not clinically significant, <2.5 cm	2.5 to 5.0 cm	5.1 to 10.0 cm	>10.0 cm	Necrosis or exfoliative dermatitis
Induration/swelling	Not clinically significant, <2.5 cm	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis
Pruritus/Itching	Absent	Mild	Moderate	Severe	Hospital visit or hospitalization
Hematoma/Ecchymosis/Bruising	Not clinically significant, <2.5 cm	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	>10.0 cm or prevents daily activity	Necrosis