Protocol Title:	A randomized, double-blind, parallel design, single dose, 2-arm study comparing the pharmacokinetic, safety and immunogenicity profiles of AVT03 and US-Xgeva® in healthy male subjects
NCT Number	NCT05876949
Protocol version and date	Version 1.0, 11 January 2023

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A randomized, double-blind, parallel design, single dose, 2-arm study comparing the pharmacokinetic, safety and immunogenicity profiles of AVT03 and US-Xgeva® in healthy male subjects
STUDY NUMBER:	AVT03-GL-P03
EUDRACT NUMBER:	2022-003659-32
SPONSOR:	Alvotech Swiss AG [redacted]
INITIAL PROTOCOL VERSION AND DATE:	Final V1.0, 11 Jan 2023

This clinical trial is to be conducted in compliance with the protocol, the Declaration of Helsinki, principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6(R2), and other applicable regulatory requirements.

CONFIDENTIAL

SPONSOR APPROVAL FORM

Protocol Title: A randomized, double-blind, parallel design, single dose, 2-arm study comparing the pharmacokinetic, safety and immunogenicity profiles of AVT03 and US-Xgeva® in healthy male subjects

Study No: AVT03-GL-P03

Original Protocol Version and Date: Final V1.0, 11 Jan 2023

This study protocol was subject to critical review and has been approved by the appropriate Alvotech Swiss AG protocol review team.

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]

[redacted] Date

Head of Clinical and Medical Affairs
Alvotech Swiss AG

[redacted]

[redacted] Date

Head of Clinical Development and
Patient Safety
Alvotech Swiss AG

[redacted]

[redacted] Date

Head of Biometrics
Alvotech Swiss AG

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

Protocol Title: A randomized, double-blind, parallel design, single dose, 2-arm study comparing the pharmacokinetic, safety and immunogenicity profiles of AVT03 and US-Xgeva® in healthy male subjects

Study No: AVT03-GL-P03

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 applicable national, state, and local regulations and will make a reasonable effort to complete the study within the time designated.

I will supervise and 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, single dose, 2-arm study comparing the pharmacokinetic, safety and immunogenicity profiles of AVT03 and US-Xgeva® in healthy male subjects
Study Number:	AVT03-GL-P03
Clinical Phase:	Pharmacokinetics (PK) study
Investigators/Study Centers:	This study is planned to be conducted in approximately 3 study centers, located in [redacted] If required, centers in other countries or affiliate sites attached to the main site may also be used. [redacted] a contract research organization, will oversee operational aspects of this study on behalf of Alvotech Swiss AG, the Sponsor of the study.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate pharmacokinetic (PK) biosimilarity of AVT03 and US-Xgeva in terms of C_{max} and AUC_{0-t}	The co-primary PK endpoints to be determined are: • C_{max}: maximum serum concentration • AUC_{0-t}: area under the serum concentration-time curve up to time t, where t is the last time point with a concentration above the lower limit of quantitation
Secondary	
• To further compare PK biosimilarity of AVT03 and US-Xgeva	The secondary PK parameters to be determined are: • $AUC_{0-\infty}$: comprised of AUC_{0-t} and AUC extrapolated from time t to time infinity, calculated as $AUC_{0-t} + C_t/K_{el}$ • t_{max}: time to attain maximal concentration • K_{el}: elimination rate constant • $t_{1/2}$: terminal elimination half-life • Volume of distribution (V_z/F) • Apparent clearance (CL/F)

• To assess and compare the safety and tolerability of AVT03 with US-Xgeva	The safety parameters to be assessed include: • Incidence, nature, and severity of adverse events (AE) including adverse drug reactions, clinical laboratory assessments (hematology, clinical biochemistry, coagulation, urinalysis and urine microscopy [if clinically indicated]), vital signs, electrocardiograms (ECG), physical examination findings, and injection site reactions • Calcium (Ca), parathyroid hormone (PTH) and vitamin D levels
• To assess and compare immunogenicity of AVT03 with US-Xgeva	• Presence and titer of anti-drug antibodies and presence of neutralizing antibodies against AVT03 and US-Xgeva

Study Design:

This multicenter, comparative clinical, randomized, double-blind, parallel group, 2-arm, single dose, active-comparator study is designed to demonstrate clinical similarity without evidence of meaningful differences between AVT03 and the reference product US-Xgeva in healthy male subjects 28 to 55 years old, inclusive.

Subjects will receive one dose of AVT03 or US-Xgeva (120 mg subcutaneous [SC] on Day 1).

Study Duration

Duration of the study is defined as the time from Screening to End-of-Study visit (EoS) (Day 196)/Early Termination (ET) visit, which will be up to approximately 32 weeks for each subject. This includes:

- Screening Visit (up to 28 days, or once all Screening requirements have been met).
- Day -1.
- Dosing (Day 1).
- Inpatient stay with testing (Day -1 to Day 3).
- Follow-up visits (Days 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 18, 22, 25, 29, 43, 57, 71, 85, 99, 112, 126, 141, and 162).
- EoS (Day 196)/ET Visit.

Planned Sample Size and Treatment Group(s):

A total of 206 subjects including approximately 24 (11.7%) Japanese subjects.

Target Population: Healthy male subjects, 28 to 55 years old, inclusive.

Eligibility Criteria: **Inclusion Criteria:**

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Male subjects who are 28 to 55 years old, inclusive, at the time of signing the ICF.

3. Have a body weight of 50.0 to 90.0 kg (inclusive) and body mass index of 17.0 to 32.0 kg/m^2 at Screening and Day −1.

4. For Japanese subjects only:

   Subjects in Japanese cohorts must be born in Japan, holding a Japanese passport.

   Not living outside Japan for more than 5 years (from the date of informed consent) and have all 4 grandparents Japanese, as confirmed by interview.

5. Medical history without evidence of a clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to subject safety.

6. Resting supine systolic blood pressure of ≤140 mm Hg and diastolic blood pressure of ≤90 mm Hg; and other vital signs showing no clinically relevant deviations according to the Investigator's judgment at Screening and Day −1.

7. 12-lead electrocardiogram (ECG) recording without signs of clinically relevant pathology or showing no clinically relevant deviations according to the Investigator's judgment at Screening and Day −1.

8. Have physical examination results without clinically significant abnormal findings according to the Investigator's judgment at Screening and Day −1.

9. Clinical safety laboratory results are within reference ranges or showing no clinically relevant deviations as judged by the

Investigator at Screening and Day – 1 (as per Schedule of Assessments table).

NOTE: Repeat evaluations of clinical laboratory tests will be permitted, at the discretion of the Investigator.

10. Tested negative for hepatitis B surface antigen, hepatitis B IgM core antibodies (confirmed with polymerase chain reaction if core test is reactive as per Investigator's discretion), anti-hepatitis C virus antibodies, and anti-human immunodeficiency virus 1/2 antibodies at Screening.

11. Have a negative urine drug screen and negative alcohol breath test at Screening and Day −1.

    NOTE: Repeat evaluation of the urine drug screen will be permitted, at the discretion of the Investigator.

12. Nonsmoker or occasional smoker, i.e., smokes ≤10 cigarettes or equivalent per week within 3 months of Screening, and ability and willingness to refrain from smoking during the inpatient stay at the study site.

13. Ability and willingness to abstain from alcohol from 48 hours prior to drug administration and during the inpatient stay in the study site until discharge from the inpatient stay period.

14. Non-sterilized male subjects with female partners of childbearing potential are eligible to participate if they agree to follow the contraceptive guidance from Screening (signing the ICF) until the EoS visit (28 weeks after investigational product [IP] administration) and refrain from donating sperm during this period.

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: osteoporosis, osteogenesis imperfecta, hyperparathyroidism,, non-controlled hyperthyroidism osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as glomerular filtration rate <45 mL/min), Paget's disease of the bone, malabsorption syndrome.

2. Have osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery) within 6 months prior to Day 1 or intend to undergo such procedures during the study period, poor oral hygiene, periodontal, and/or pre-existing dental disease.

3. Have bone fractures, presence of active healing fractures, or recent bone fracture within 6 months prior to Day −1.

4. Have a history of immunodeficiency.

5. Abnormal serum calcium: current hypocalcemia or hypercalcemia at Screening. Serum calcium levels must be within local laboratory reference ranges.

6. Known vitamin D deficiency (25[OH]D levels <20 ng/mL [37.5 nmol/L]) at Screening. Subjects can be supplemented and repeat tested at Day -1.

7. Known intolerance to calcium or vitamin D supplements.

8. Any current active infections, including localized infections, or any recent history (within 1 week prior to IP administration) of active infections, cough or fever, or a history of recurrent or chronic infections (includes coronavirus disease 19).

9. Known or suspected clinically relevant drug hypersensitivity to denosumab or any of its constituents, which in the opinion of the Investigator, contraindicates the subject's participation.

10. History or presence of malignancy (except for successfully treated basal or squamous cell carcinoma).

11. Recent history of major surgery within 3 months prior to Day −1 and/or plan to have an operation (including invasive dental procedures) during the study period.

12. Receipt of any investigational drug within 8 weeks or 5 half-lives of that drug (if known), whichever is longer, prior to IP administration in the current study.

13. Previous intake of denosumab (Prolia®/Xgeva or its biosimilars, including investigational denosumab).

14. Treatment with non-topical medications (including over-the-counter medications and herbal remedies such as St.

John's Wort extract) within 7 days or 5 half-lives of the drug (whichever is longer) prior to IP administration in the current study. This includes medications such as, but not limited to, supplemental vitamin D (>1000 IU/day), or anabolic steroids.

EXCEPTIONS:

- Prior use of low-dose inhaled corticosteroids or low-potency topical corticosteroids is allowed.
- Supplements for calcium, vitamin D (≤1000 IU/day), multivitamins, vitamin C, dietary supplements, and a limited amount of paracetamol/acetaminophen (up to 2 g in 24 hours, but no more than 1 g in 4 hours) or ibuprofen (<1.2 g per day) may be used throughout the study.

15. Have received vaccination with a live vaccine (except for influenza vaccine) during the past 4 weeks before Screening or have the intention to receive a live vaccine during the study period.

    NOTE: Receipt of inactivated vaccines (inactivated influenza vaccines and approved coronavirus disease 2019 vaccines) is not considered exclusionary if received at least 7 days prior to IP administration.

16. Donation of >500 mL of blood within 2 months prior to IP administration.

17. History (within the previous 3 years) or evidence of alcohol abuse (with an average intake exceeding 15 drinks/week: 1 drink = 360 mL of beer, 150 mL of wine, or 45 mL of 80 proof distilled spirits) or drug abuse (including soft drugs like cannabis products).

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

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

20. Any persons who are:

    a. An employee of the study site, Investigator, contract research organization (CRO) or Sponsor.

b. A first-degree relative of an employee of the study site, the Investigator, CRO, or the Sponsor.

Study Drugs:

IP: AVT03, 120 mg given as a SC injection.

Reference Product: US-Xgeva, 120 mg given as a SC injection.

Safety Outcome Measures:

- Incidence, nature, and severity of adverse events (AEs) including adverse drug reactions, clinical laboratory assessments (hematology, clinical biochemistry, coagulation, urinalysis and urine microscopy [if clinically indicated]), vital signs, ECG, physical examination findings, and injection site reactions.
- Calcium, parathyroid hormone, and Vitamin D levels.

Statistical Procedures:

Sample size calculations were performed using data from a previous study with Prolia (Study 20060286) (Food and Drug Administration Prolia Biologics License Application Assessment Report). Based on this study, the inter-subject coefficient of variation is as assumed to be 33.5% for maximum serum concentration (C_{max}) and 35.1% for area under the serum concentration-time curve up to time t, where t is the last time point with a concentration above the lower limit of quantitation (AUC_{0-t}). The assessment of PK similarity will be based on the 90% confidence intervals (CI) of the geometric mean ratio (GMR) between the 2 treatment groups to be contained within the prespecified margins of 80% to 125% for both co-primary endpoints C_{max} and AUC_{0-t}. Assuming a true GMR of 0.95 for each of the 2 co-primary endpoints C_{max} and AUC_{0-t}, 184 subjects will provide a study level power of 90.1% (i.e., power of 95.7% for C_{max} and 94.2% for AUC_{0-t}). Taking into consideration a non-evaluable rate of 20%, the total sample size will be 206 subjects (103 per treatment group). Of the 206 subjects, approximately 24 (11.7%) subjects of Japanese descent are planned to be enrolled.

For the primary endpoints, the statistical analysis will be performed using an analysis of covariance model on the logarithmic scale (i.e., using natural log-transformed values of C_{max} and AUC_{0-t}) with treatment group as fixed effect and body weight at baseline as the continuous covariate. Point estimates (geometric means and GMRs) will be calculated by back transforming the least square (LS) means of the natural log-transformed values of C_{max} and AUC_{0-t} and the difference in the LS means. The PK similarity of AVT03 versus US-Xgeva will be determined if the 90% Cis for the GMRs of the primary endpoints (C_{max} and AUC_{0-t}) are entirely contained within the equivalence margin of 80% to 125%. Other exploratory analyses of

PK similarity by subgroups based on the randomization strata may be performed if appropriate.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-12}	area under the concentration-time curve from time of dosing up to 12 hours
AUC_{0-24}	area under the concentration-time curve from time of dosing up to 24 hours
$AUC_{0-\infty}$	area under the serum concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the serum concentration-time curve up to time t, where t is the last time point with a concentration above the lower limit of quantitation
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent total serum clearance after subcutaneous administration, where F is the fraction of drug absorbed
C_{max}	maximum serum concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EoS	end-of-study
ET	early termination

Abbreviation	Definition
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
H	hour(s)
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRT	interactive response technology
IP	investigational product
IU	international units
K_{el}	terminal elimination rate constant
LLOQ	lower limit of quantitation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
Min	minute(s)
OTC	over-the counter
ONJ	osteonecrosis of the jaw
PCR	polymerase chain reaction
PI	Principal Investigator
PK	pharmacokinetic
Po	by mouth, orally
PR	interval between the beginning of the P wave and the beginning of the next QRS complex
PT	preferred term

Abbreviation	Definition
PTH	parathyroid hormone
QRS	duration of ventricular depolarization and contraction interval
QT	interval between Q and T waves
QTcF	interval between Q and T waves corrected for heart rate using Fridericia's formula
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
RR	interval between 2 R waves on the electrocardiogram tracing
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SoA	schedule of assessments
SOC	system organ class
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergence adverse event
$t_{1/2}$	elimination half-life;
t_{max}	time to reach C_{max}
TNF	tumor necrosis factor
Tbil	total bilirubin
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution during the terminal phase after subcutaneous administration
WHO	World Health Organization
[redacted]	

1 INTRODUCTION AND RATIONALE

1.1 Background

The human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) is a member of the tumor necrosis factor (TNF) family of proteins and as such shares common structural characteristics of the family. Similar to TNF, RANKL exists in both membrane bound and soluble forms. These forms are biologically active in promoting osteoclast formation. A reduction of the circulating female sex hormones at menopause, leading to an increase in RANKL-RANK signaling is the leading cause of osteoporosis in postmenopausal women (Prolia Summary of Product Characteristics [SmPC]).

Denosumab (Anatomical Therapeutic Chemical Classification code: M05BX04), a fully human IgG2 kappa monoclonal antibody, binds with high affinity and specificity to the D-E loop of RANKL. The mechanism of action of denosumab involves a blocking mechanism, where the antibody binds to RANKL, prevents the RANKL-RANK interaction on the cell surface of osteoclasts thereby significantly decreasing bone resorption and cancer-induced bone destruction and increasing bone mineral density.

Due to its single mechanism of action, inhibition of RANKL activity, denosumab is a therapeutic target for treatment of several bone disorders associated with increased bone resorption. These include osteoporosis, skeletal-related events in patients with bone metastases from solid tumors, and treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (US Package Insert [Xgeva]; WHO 2017).

1.2 Study Rationale

Alvotech is developing AVT03 globally as a proposed biosimilar to the reference product, United States-approved Xgeva® (denosumab, Amgen Inc).

The study is designed as a randomized, double-blind, parallel design, single dose, 2-arm study in healthy male subjects. The study aims are to demonstrate pharmacokinetic (PK) similarity of the proposed biosimilar IP AVT03 and the reference product Xgeva, in addition to evaluating the safety and immunogenicity profiles of AVT03, when administered as a single 120 mg dose.

The study design follows the recommendation of the European Medicines Agency (EMA) (EMA 2010) and United States (US) Food and Drug Administration (FDA) guidance on biosimilars (FDA 2015). The study design is also based on previous published studies with denosumab in healthy subjects. A parallel group design has been selected considering the relatively long half-life of denosumab which is 30 days (US Prescribing Information [Xgeva]).

1.2.1 Study Population and Stratification

Healthy adult male subjects have been selected as the study population to reduce the variability in PK parameters, with the advantage of avoiding potential interference associated with concomitant medications or medical conditions. To date, no major safety concerns have been reported when denosumab is administered as a single subcutaneous (SC) injection in healthy

subjects (Section 1.5). Moreover, the assessments related to safety and immunogenicity will be representative of what may be observed in the target population (adults with advanced malignancies involving bone), as there are no differences in safety and immunogenicity profiles observed in these 2 populations. Although age is not an intrinsic factor and does not influence exposure to denosumab, an upper age boundary of 55 years has been implemented for safety reasons.

A population PK analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat SC administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject (US Prescribing Information [Xgeva]). Therefore, randomization will be stratified by body weight (measured at Day −1) to ensure balance between treatment groups. In addition, the statistical analysis of bioequivalence comparing treatment groups for each of the primary PK parameters will be adjusted for body weight through an analysis of covariance (ANCOVA) with weight at baseline as the covariate.

Furthermore, the Sponsor plans to include approximately 24 Japanese subjects (11.7% of the enrolled population) to demonstrate consistency of PK data between Japanese and non-Japanese subjects. Therefore, in addition to body weight, randomization will be stratified by ethnicity (Japanese and non-Japanese) to ensure balance between treatment groups.

1.2.2 Pharmacokinetic Assessments

In this study, after IP administration on Day 1, PK sampling will be performed up to Week 28 (Day 196) to capture the entire PK profile. Based on a reported mean half-life of denosumab 30 days (US Prescribing Information [Xgeva]), a duration of 28 weeks will cover >6.5 times the reported half-life of denosumab and is deemed sufficient to adequately characterize the PK profile. While there may be some subjects that have slightly longer half-life, this period will still capture at least 4 half-lives for subjects with a half-life of 49 days. Intensive PK sampling will be performed daily from Day 2 to Day 12 to cover t_{max}.

1.2.3 Safety and Immunogenicity Assessments

Safety and immunogenicity will be evaluated throughout the study. Safety assessments include incidence, nature, and severity of AEs including AEs of special interest (AESIs) and injection site reactions graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The double-blind data collected until Week 28 are considered adequate to support a comparative descriptive analysis of safety and immunogenicity between AVT03 and Xgeva.

Overall, immunogenicity of denosumab is very low and similar across all indications. In the few reported cases where anti-drug antibodies (ADA) were detected, signs of immunogenicity were highlighted within the first month of treatment.

1.3 Dose Rationale

In alignment with the EMA and FDA guidelines (EMA 2010; FDA 2015), the SC route of administration will be evaluated in this study, as the SC route represents the main approved route of administration for the Xgeva reference product. Furthermore, the SC route is expected to be the most sensitive in detecting differences in immunogenicity and can provide insight into potential PK differences during the absorption phase, in addition to the distribution and elimination phases (i.e., it covers both absorption and elimination phases).

The proposed dose for the study (120 mg/1.7 mL SC) is the most relevant dose level of AVT03 to be evaluated in this study for the following reasons:

- The 120 mg dose falls within the linearity range. The initial phase 1 studies of denosumab in healthy postmenopausal women, healthy men ≥ 50 years of age, and subjects with advanced cancer and bone metastasis (Studies 20010123, 20010124, 20030148, 20030164, and 20030180) explored a wide range of weight-based SC doses (0.01 to 3.0 mg/kg). An additional phase 1 study in Japanese subjects (Study 20040176) assessed single fixed doses of 60 and 180 mg and 3 fixed doses of 180 mg every 4 weeks (US Prescribing Information [Xgeva]).The results of these assessments consistently show that denosumab displays nonlinear clearance across a wide dose range. However, for doses 60 mg and above, approximately dose-proportional increases in exposure were identified. This feature is typical for the target-mediated drug disposition mechanism of the monoclonal antibody (US Prescribing Information [Xgeva]).

- The 120 mg dose represents 1 of the approved doses for denosumab (Xgeva) and has the largest safety database. A 120 mg dose (i.e., at the 1.0-mg/kg and the 3.0-mg/kg SC doses, which are in the proximity of the 120 mg dose) has been well tolerated in healthy subjects (male and female) and in healthy postmenopausal women. As a proposed biosimilar, the safety profile of AVT03 is expected to be similar to the safety profile of denosumab (Prolia and Xgeva). The overall safety profile of Prolia and Xgeva is similar across indications and populations with musculoskeletal pain and pain in the extremities being the most common adverse events. Most AE were mild, transient in nature, resolved without complication and did not necessitate discontinuation of study treatment (US Prescribing Information [Xgeva]; Prolia SmPC).

Based on the above considerations, a 120 mg/1.7 mL SC injection represents a sensitive dose to detect potential differences (if any) between Xgeva and AVT03.

1.4 Study Endpoint Rationale

The study design including selection of endpoints follows the recommendations of the EMA (EMA 2010) guidance for biosimilar products and the FDA guidance for industry, “Scientific Considerations in Demonstrating Biosimilarity with a Reference Product” (FDA 2015). The study was also designed following advice from regulatory agencies including the EMA, FDA, and Japanese Pharmaceutical and Medical Devices Agency.

Study design including endpoints is following

1.5 Risks and Benefits for Subjects

The safety profile of AVT03 is expected to be similar to that of Xgeva. The most common side effects with denosumab (seen in more than 1 subject in 10) are hypocalcemia, musculoskeletal pain and diarrhea (Xgeva SmPC). In patients with bone metastasis from solid tumors, the most common adverse reactions (per patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea. In patients with giant cell tumor of bone, the most common adverse reactions (per patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity (US Prescribing Information [Xgeva]).

No serious adverse drug reactions are expected for AVT03.

1.5.1 Coronavirus Disease 2019 Risks

Risks of acquiring infection with coronavirus disease 2019 (COVID-19) must be mitigated as much as possible during the ongoing pandemic. Safety of travelling to and attending the site visits must be evaluated, taking into account any local travel restrictions and regulations. Subjects are to be advised to use all possible measures to reduce the risk of infection, including social distancing, use of private transportation to the study site, frequent hand washing, and use of face masks as appropriate.

Due to the COVID-19 pandemic, health authorities, site Principal Investigators (Pis), or the Sponsor may consider that it is not appropriate for subjects to attend on site visits. The situation will be monitored on an ongoing basis, and the PI together with the Sponsor's Medical Monitor may decide to allow flexibility for on site or at home assessments.

Should home visits be performed, subjects and site staff will be advised to use all possible measures to reduce the risk of infection as per local regulations.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate pharmacokinetic (PK) biosimilarity of AVT03 and US-Xgeva in terms of C_{max} and AUC_{0-t}	The co-primary PK endpoints to be determined are: • C_{max}: maximum serum concentration • AUC_{0-t}: area under the serum concentration-time curve up to time t, where t is the last time point with a concentration above the lower limit of quantitation
Secondary	
• To further compare PK biosimilarity of AVT03 and US-Xgeva	The secondary PK parameters to be determined are: • $AUC_{0-\infty}$: comprised of AUC_{0-t} and AUC extrapolated from time t to time infinity, calculated as $AUC_{0-t} + C_t/K_{el}$ • t_{max}: time to attain maximal concentration • K_{el}: elimination rate constant • $t_{1/2}$: terminal elimination half-life • Volume of distribution (V_z/F) • Apparent clearance (CL/F)
• To assess and compare the safety and tolerability of AVT03 with US-Xgeva	The safety parameters to be assessed include: • Incidence, nature, and severity of adverse events (AE) including adverse drug reactions, clinical laboratory assessments (hematology, clinical biochemistry, coagulation, urinalysis and urine microscopy [if clinically indicated]), vital signs, electrocardiograms (ECG), physical examination findings, and injection site reactions • Calcium (Ca), PTH and vitamin D levels
• To assess and compare immunogenicity of AVT03 with US-Xgeva	• Presence and titer of anti-drug antibodies and presence of neutralizing antibodies against AVT03 and US-Xgeva

3 STUDY PLAN

3.1 Study Design

This multicenter, comparative clinical, randomized, double-blind, parallel group, 2-arm, single dose, active-comparator clinical study is designed to demonstrate clinical similarity without evidence of meaningful differences between AVT03 and the reference product US-Xgeva in healthy male subjects 28 to 55 years old, inclusive. Subjects will receive one dose of AVT03 or US-Xgeva (120 mg SC on Day 1).

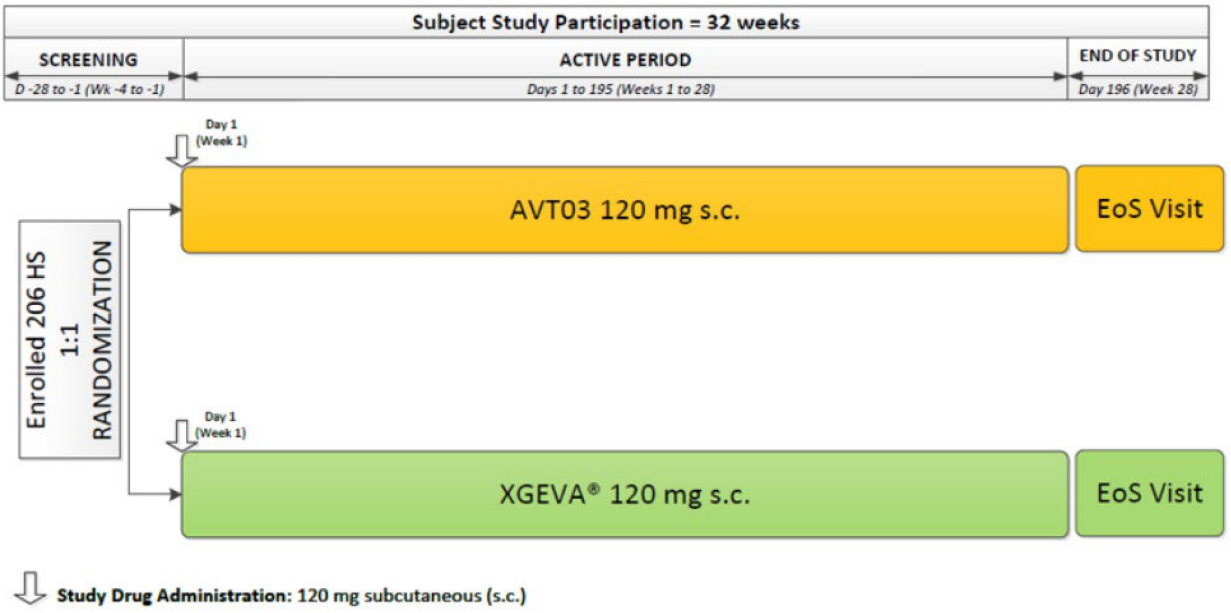
The study will enroll approximately 206 subjects including 24 (11.7%) Japanese subjects. The randomization will be stratified by ethnicity (Japanese/non-Japanese) and by weight.

An ICF form must be signed by the subject before any study-related procedures are performed.

The study duration per subject will be approximately 32 weeks. The study will consist of a 4 week Screening period, a 28 week treatment and assessment period, and an EoS visit on Day 196.

The study is summarized graphically in Figure 4.1.

Figure 4.1: Study Schematic



Abbreviations: D = day; EoS = end-of-study; HS = healthy male subjects; Wk = week

3.2 Study Stopping Criteria

3.2.1 Stopping Criteria for Individual Subjects

As only a single dose of IP will be administered, subjects cannot be withdrawn from treatment but can be withdrawn from the study.

3.2.2 Criteria for Stopping the Study

If either of the following scenarios occur, study enrollment and dosing will be paused:

- If ≥1 participant experiences a serious AE that is considered at least possibly related to the IP
- If ≥2 participants experience severe non-serious AEs that are considered at least possibly related to the IP, independent of within or not within the same system organ class (SOC).
- If the Sponsor or Investigator considers there to be an unfavorable benefit-risk ratio based on emerging safety data.

If the Sponsor becomes aware that the study has met stopping rules at a site, additional safety or toxicology information becomes available during the study, or any other situation that increases the risk to participants arises, they will immediately inform all sites.

If following consultation between the PI, Medical Monitor, and Sponsor it is considered appropriate to restart IP administration in the remaining subjects, a justification will be submitted to the Independent Ethics Committee (IEC) and/or regulatory authorities for restarting the study.

3.3 Study Duration

Duration of the study is defined as the time from Screening to EoS visit (Day 196)/ET visit, which will be up to approximately 32 weeks for each subject. This includes:

- Screening Visit (up to 28 days, or once all Screening requirements have been met).
- Dosing (Day 1).
- Inpatient stay with testing (Day 1 to Day 3).
- Follow-up visits (Days 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 18, 22, 25, 29, 43, 57, 71, 85, 99, 112, 126, 141, and 162).
- EoS (Day 196)/ET Visit.

4 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Subjects must meet all inclusion criteria and none of the exclusion criteria to be enrolled in the study. All entry criteria need to be confirmed by the PI at the randomization day and before any other procedure is done to ensure that eligibility is still fulfilled. No deviations will be permitted from the inclusion or exclusion criteria. The PI may call the Medical Monitor to discuss eligibility of any given subject.

Specific entry criteria are detailed in Section 4.1 and Section 4.2.

4.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2. Male subjects who are 28 to 55 years old, inclusive, at the time of signing the ICF.

3. Have a body weight of 50.0 to 90.0 kg (inclusive) and body mass index of 17.0 to 32.0 kg/m^2 (inclusive) at Screening and Day −1.

4. For Japanese subjects only:

   Subjects in Japanese cohorts must be born in Japan, holding a Japanese passport.

   Not living outside Japan for more than 5 years (from the date of informed consent) and have all 4 grandparents Japanese, as confirmed by interview.

5. Medical history without evidence of a clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to subject safety.

6. Resting supine systolic blood pressure of ≤140 mm Hg and diastolic blood pressure of ≤90 mm Hg; and other vital signs showing no clinically relevant deviations according to the Investigator's judgment at Screening and Day −1.

7. 12-lead ECG recording without signs of clinically relevant pathology or showing no clinically relevant deviations according to the Investigator's judgment at Screening and Day −1.

8. Have physical examination results without clinically significant abnormal findings according to the Investigator's judgment at Screening and Day −1.

9. Clinical safety laboratory results are within reference ranges or showing no clinically relevant deviations as judged by the Investigator at Screening and Day - 1 (as per Schedule of Assessments [SoA] Table 6.1).

   NOTE: Repeat evaluations of clinical laboratory tests will be permitted, at the discretion of the Investigator.

10. Tested negative for hepatitis B surface antigen, hepatitis B IgM core antibodies (confirmed with polymerase chain reaction if core test is reactive, as per Investigator's discretion), anti-hepatitis C virus antibodies, and anti-human immunodeficiency virus 1/2 antibodies at Screening.

11. Have a negative urine drug screen and negative alcohol breath test at Screening and Day-1

    NOTE: Repeat evaluation of the urine drug screen will be permitted, at the discretion of the Investigator.

12. Nonsmoker or occasional smoker, i.e., smokes ≤10 cigarettes or equivalent per week within 3 months of Screening, and ability and willingness to refrain from smoking during the inpatient stay at the study site.

13. Ability and willingness to abstain from alcohol from 48 hours prior to drug administration and during the inpatient stay in the study site until discharge from the inpatient stay period.

14. Non-sterilized male subjects with female partners of childbearing potential are eligible to participate if they agree to follow the contraceptive guidance from Screening (signing the ICF) until the EoS visit (28 weeks after IP administration) and refrain from donating sperm during this period.

4.2 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: osteoporosis, osteogenesis imperfecta, hyperparathyroidism,, non-controlled hyperthyroidism osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as glomerular filtration rate <45 mL/min), Paget's disease of the bone, malabsorption syndrome.

2. Have osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery) within 6 months prior to Day 1 or intend to undergo such procedures during the study period, poor oral hygiene, periodontal, and/or pre-existing dental disease.

3. Have bone fractures, presence of active healing fractures, or recent bone fracture within 6 months prior to Day −1.

4. Have a history of immunodeficiency.

5. Abnormal serum calcium: current hypocalcemia or hypercalcemia at Screening. Serum calcium levels must be within local laboratory reference ranges.

6. Known vitamin D deficiency (25[OH]D levels <20 ng/mL [37.5 nmol/L]) at Screening. Subjects can be supplemented and repeat tested at Day 1 Pre-dose.

7. Known intolerance to calcium or vitamin D supplements.

8. Any current active infections, including localized infections, or any recent history (within 1 week prior to IP administration) of active infections, cough or fever, or a history of recurrent or chronic infections (includes coronavirus disease 19).

9. Known or suspected clinically relevant drug hypersensitivity to denosumab or any of its constituents, which in the opinion of the Investigator, contraindicates the subject's participation.

10. History or presence of malignancy (except for successfully treated basal or squamous cell carcinoma).

11. Recent history of major surgery within 3 months prior to Day −1 and/or plan to have an operation (including invasive dental procedures) during the study period.

12. Receipt of any investigational drug within 8 weeks or 5 half-lives of that drug (if known), whichever is longer, prior to IP administration in the current study.

13. Previous intake of denosumab (Prolia®/Xgeva or its biosimilars, including investigational denosumab).

14. Treatment with non-topical medications (including over-the-counter medications and herbal remedies such as St. John's Wort extract) within 7 days or 5 half-lives of the drug (whichever is longer) prior to IP administration in the current study. This includes medications such as, but not limited to, supplemental vitamin D (>1000 IU/day), or anabolic steroids.

    EXCEPTIONS:

    - Prior use of low-dose inhaled corticosteroids or low-potency topical corticosteroids is allowed.

    - Supplements for calcium, vitamin D (≤1000 IU/day), multivitamins, vitamin C, dietary supplements, and a limited amount of paracetamol/acetaminophen (up to 2 g in 24 hours, but no more than 1 g in 4 hours) or ibuprofen (<1.2 g per day) may be used throughout the study.

15. Have received vaccination with a live vaccine (except for influenza vaccine) during the past 4 weeks before Screening or have the intention to receive a live vaccine during the study period.

NOTE: Receipt of inactivated vaccines (inactivated influenza vaccines and approved coronavirus disease 2019 vaccines) is not considered exclusionary if received at least 7 days prior to IP administration.

16. Donation of >500 mL of blood within 2 months prior to IP administration.

17. History (within the previous 3 years) or evidence of alcohol abuse (with an average intake exceeding 15 drinks/week: 1 drink = 360 mL of beer, 150 mL of wine, or 45 mL of 80 proof distilled spirits) or drug abuse (including soft drugs like cannabis products).

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

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

20. Any persons who are:

    a. An employee of the study site, Investigator, CRO or Sponsor.

    b. A first-degree relative of an employee of the study site, the Investigator, CRO, or the Sponsor. Discontinuation of IP and Subject Discontinuation/Withdrawal.

4.3 Discontinuation of Investigational Product

As only a single dose of IP will be administered, subjects cannot be discontinued from the IP but can be withdrawn from the study.

If a subject who does not meet the enrollment criteria is inadvertently enrolled, that subject must not be dosed and the Sponsor or Sponsor designee must be contacted.

4.4 Subject Discontinuation/Withdrawal from the Study

The study stopping criteria for individual subjects are described in Section 3.2.1.

A subject may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, positive COVID-19 test or suspected severe acute respiratory syndrome coronavirus 2 infection, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records.

Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. See the SoA (Table 6.1) for data to be collected at the time of the ET visit and for any further

evaluations that need to be completed. Subjects withdrawing due to an AE should be followed up according to the procedures for the EoS/ET visit.

Discontinuation of specific study sites or of the study as a whole are handled as part of Appendix 1.

4.4.1 Subject Replacement

Subjects who voluntarily withdraw from the study and subjects withdrawn due to ineligibility or protocol deviations prior to randomization and IP administration may be replaced following discussion with the Investigator and Sponsor. Subjects who withdraw after randomization and IP administration may be replaced following discussion with the Investigator and Sponsor. Subjects who are withdrawn due to an AE after dosing will not be replaced.

4.5 Screening and Screen Failures

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all subjects screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled or randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure), but at some point in the future meet all of the subject eligibility criteria, may be rescreened once (only if the Investigator considers the cause of the initial Screening failure to be of an acute and completely reversible nature). In the event of rescreening, all assessments performed at the initial Screening visit should be repeated during the rescreening visit. Each time a subject is screened/rescreened, they will be assigned a new Screening number. Reconsenting can be based on local regulatory processes.

4.6 Lost to Follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, at least 3 contact attempts including and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.

4.7 Lifestyle Considerations

4.7.1 Meals and Dietary Restrictions

- Subjects will receive a standard diet while residing at the study site; no additional food or beverages may be consumed while in the study site with the exception of water.

- On the day of dosing (Day 1), subjects will fast for at least 8 hours prior to IP administration and for 1 hour after IP administration. Water will be allowed as desired.

- On days of clinical laboratory tests (including at Screening) subjects should not take calcium and/or vitamin D supplements within 8 hours before blood sampling.

4.7.2 Caffeine, Alcohol, and Tobacco

- Subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before admission to the study site on Day −1, for the duration of the inpatient stay period of the study, and for 48 hours prior to outpatient appointments. Decaffeinated products are allowed.

- Subjects will abstain from alcohol for 48 hours before admission to the study site on Day −1, during the inpatient stay at the study site until discharge, and for 48 hours prior to outpatient appointments. At all other times during the study until completion of the study, subjects are discouraged to consume alcohol, but may consume no more than 2 drinks per day or 15 drinks per week. One drink is equivalent to 12 g alcohol = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of 80-proof distilled spirits.

- Subjects will be permitted to smoke ≤10 cigarettes or equivalent per week until the EoS visit, but use of tobacco- or nicotine-containing products will not be allowed during the inpatient stay at the study site.

4.7.3 Activity

- Subjects should refrain from strenuous exercise within 48 hours prior to admission to the study site on Day −1 up to Day 7. Subjects may participate in light recreational activities during this period (e.g., watching television, reading). After Day 7, normal physical activity can be resumed.

- Subjects will be advised not to donate blood or undergo plasma donation for at least 3 months after IP administration.

- Oral Hygiene and Invasive Dental Procedures

All subjects should be encouraged to maintain good oral hygiene during the study. If subjects have any oral symptoms, such as dental mobility, prolonged pain involving the jaw or gingival swelling or non-healing ulcers, it should be reported immediately to the Investigator. These subjects may be referred to a registered dentist or other qualified oral specialist for follow-up assessments, as clinically indicated.

Subjects should avoid invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) 6 months prior to randomization on Day 1 until EoS.

5 STUDY TREATMENT AND MANAGEMENT

5.1 Description

Information about the IP is provided in Table 5.1.

Table 5.1: Details of Investigational Products

	AVT03	US-Xgeva® (denosumab)
Manufacturer	[redacted]	Amgen Inc.
Doses	120 mg	120 mg
Route	Subcutaneous	Subcutaneous
Dosage Form	Single Use Vial	Single Use Vial
Strengths	120 mg/1.7 mL or 70 mg/mL	120 mg/1.7 mL or 70 mg/mL

5.1.1 Formulation and Preparation

AVT03 and Xgeva will be supplied as single use vials, containing a single dose of 120 mg of AVT03 or US-Xgeva in 1.7 mL (or 70 mg/mL) for SC injection..

Xgeva is a clear, colorless to slightly yellow solution. It may contain trace amounts of clear to white particles.

Complete instructions for proper IP handling will be provided in the Pharmacy Manual.

5.1.2 Labeling

IPs will be packaged and labeled in accordance with Good Manufacturing Practice and applicable country-specific requirements.

5.1.3 Non-Investigational Products

Subjects will receive adequate supplementation of calcium and vitamin D to correct hypocalcemia and low vitamin D levels (particularly those with Screening 25(OH)D levels <20 ng/mL [50 nmol/L]) starting at Screening and during the study period.

The need for supplementation and dose and will be managed individually for each subject at the Investigator's discretion, based on the subject's calcium, parathyroid hormone (PTH), and vitamin D levels and general health condition prior to IP administration and during the study. If hypocalcemia or hypercalcemia occurs, the Investigator can adjust the calcium and/or vitamin D dosage if needed. Also, the dose regimen for these non-IPs may be modified per the Investigator's discretion when intolerance to calcium and/or vitamin D is reported. The use and dose of calcium and vitamin D supplements, including any change in dosing should be recorded in the subject's source documents and eCRF.

On the day of blood sampling for clinical laboratory analysis, subjects must not take calcium and vitamin D supplements within 8 hours before sampling.

Hypocalcemia will be reported as an AE and AESI if it is determined as clinically significant by the Investigator in accordance with Section 8.1.2 and Section 8.1.7.

5.1.4 Handling/Storage/Accountability of Investigational Products

1. On receipt of the IP, the Investigator or designee must confirm appropriate temperature conditions (refrigerated, 2°C to 8°C) have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

2. Only subjects enrolled in the study may receive the IP and only authorized study site staff may supply or administer the IP. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions (refrigerated, 2°C to 8°C). Access to the storage area will be limited to the Investigator and authorized study site staff. The Sponsor reserves the right to inspect the IP storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator File.

3. The pharmacist and site team are responsible for IP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The amount of IP received from the Sponsor, the amount supplied and/or administered to subjects, if applicable, will be documented.

4. The pharmacist and site team must maintain an adequate record of the receipt and distribution of all IP using drug accountability records. These records must be available for inspection at any time.

5. The study monitor will review the IP accountability logs and check all IP returns (both unused and used) prior to authorizing the destruction of used IP by the study site. Used IP will be destroyed by the site according to their procedures and unused IP will be returned to the Sponsor. Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual.

5.2 Randomization and Blinding

5.2.1 Randomization

A computer-generated randomization schedule will be created by an unblinded statistician prior to study start and uploaded into the electronic data capture (EDC) system [redacted]

Randomization to AVT03 or Xgeva will be performed in a 1:1 ratio on Day 1. The randomization will be stratified by body weight measured at Day −1 and Japanese ethnicity as follows: body weight ≤75 kg and >75 kg, and Japanese versus non-Japanese.

After signing the ICF, each subject will be assigned a unique number through an interactive response technology (IRT) system, which will be used to identify the subject throughout the

study period and on all study-related documentation. The subject unique number generated by IRT system will be captured and integrated into the EDC system. Following confirmation of eligibility on Day 1, subjects will be randomized through an IRT system that will generate the randomization number and allocate a study drug number based on the randomization scheme. Both numbers will be integrated into the EDC system.

5.2.2 Blinding

This is a double-blind study and therefore, the Investigator, site staff (with the exception of unblinded staff trained to inject the product), Sponsor, Sponsor's delegates (if applicable) and subjects will all be blinded to treatment. No individual subject information that can potentially unblind the Investigator or subject will be reported until the end of the study. Appropriate IP blinding techniques will be implemented during the study as per the site's procedures; refer to the Pharmacy Manual for further details.

The Investigator will remain blinded unless knowledge of the subjects' treatment assignment is necessary for the clinical management or welfare of the subject. The reason for unblinding will be clearly documented.

In case of an emergency, the PI has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the PI decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor and Sponsor Medical Lead prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. The eCRF completion guidelines will describe the procedure for subject-level unblinding of the study. An unblinding form will be designed in the EDC system to allow the Investigator to determine what treatment was administered to subject in the case of an emergency. A notification of the unblinding event to the IEC and/or regulatory authorities may be required, as per local requirements.

5.3 Dose and Administration

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

On the day of dosing (Day 1), subjects will fast for at least 8 hours prior to IP administration and for 1 hour after IP administration. Water will be allowed as desired.

Before SC injection, the solution will be inspected visually by trained, unblinded staff for particulate matter or discoloration. Administration of the IP will be performed in the study site by unblinded staff trained to inject this product. The IP will be administered as a single dose on Day 1 with the subjects in bed in a supine position. The subject should be blindfolded to maintain blinding. The SC injection will be administered by unblinded staff in the abdomen (preferred site) or thigh (secondary site).

Injections should never be given into areas where the skin is tender, bruised, red, or hard.

Further details will be provided in the Pharmacy Manual.

5.4 Treatment Compliance

The IP administration will be performed in the study site under supervision by appropriately trained, unblinded staff. The details of IP administration, including pre-dose and post-dose weight of the vial, will be recorded in both the source documents and eCRF.

Further details will be provided in the Pharmacy Manual.

5.5 Measures to Ensure Subject Safety at the Study Site

The study site staff is responsible for the ongoing safety and wellbeing of the subjects while they are at the study site. There is a paging system to alert the clinical staff to any area in the study site where a subject may need medical attention. In the case of an emergency, cardiac resuscitation trolleys are found in the main ward areas of the study site. These trolleys contain drugs, equipment for airway insertion, circulation lines, defibrillation etc., together with oxygen cylinders with delivery apparatus and portable suction machines. There will be a physician on site for at least 3 hours post-dose or per site procedures, whichever is longer. In addition, if necessary, the site staff can contact further on-call physicians or public emergencies services in the event of a serious medical event. Equipment and emergency drugs are available to treat common medical emergencies that might occur in this study.

5.6 Warnings and Precautions

Considering that AVT03 is being developed as a biosimilar to Xgeva, the warnings and precautions for Xgeva are also expected to be applicable to AVT03 (US Package Insert [Xgeva]).

5.7 Prior and Concomitant Medications

Any medication or vaccine (including over the counter [OTC] or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment (within 30 days before Screening) or receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose, dose form, route, and frequency.
- For vaccines: include brand name and manufacturer (plus lot number, if available).

If the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.7.1 Prohibited Medications

Subjects must abstain from taking prescription drugs or nonprescription drugs (including OTC medications and herbal remedies such as St. John's Wort extract) within 7 days or 5 half-lives of the medication (whichever is longer) starting prior to IP administration until completion of the EoS visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

In particular, the following medications are not allowed:

- Any medications associated with bone metabolism which may interfere with the study are not recommended during the study period. This includes medications such as but not limited to: supplemental vitamin D (>1000 IU/day), calcitonin, calcitriol, fluoride, strontium, glucocorticoids (apart from low-dose inhaled or low-potency topical steroids, as specified in Section 5.7.2), bisphosphonates or anabolic steroids.

- No live vaccines are allowed (apart from inactivated vaccines as specified in Section 5.7.2) from 4 weeks before Screening until completion of the EoS visit or at least 28 weeks after IP administration.

Use of prohibited medications during the study will be captured as protocol deviations and discussed with the Sponsor.

5.7.2 Allowed Medications

With the exception of calcium and vitamin D supplementation >1000 IU/day (Section 5.1.3), the following medications are allowed at any time during the study:

- Paracetamol/acetaminophen, at doses of up to 2 g in 24 hours, but no more than 1 g in 4 hours.

- Ibuprofen at doses <1.2 g in 24 hours.

- Use of multivitamins, vitamin C, or dietary supplements at daily recommended doses.

- Low-dose inhaled corticosteroids or low-potency topical corticosteroids.

- Inactivated vaccines (e.g., inactivated influenza vaccines or approved COVID-19 vaccines) are allowed after an interval of at least 7 days following IP administration.

Other concomitant medication, including herbal medication, are permitted on a case-by-case basis if the Investigator and Medical Monitor agree that the use is not contradicted.

5.8 Dose Modification

Dose adjustments and modifications are not planned or allowed in this study.

5.9 Treatment After the End of the Study

Not applicable, as this is a study in healthy subjects.

5.9.1 Acceptable Contraceptive Methods

The methods of contraception in Table 5.2, if used properly and used for the duration of the study, are generally considered reliable (these methods of contraception also apply to female partners of male subjects). Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods, and tubal ligation/occlusion are not acceptable forms of contraception for this study.

The Investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study. This will be documented at Screening in the subject's source documentation/medical record and confirmed pre-dose.

5.9.1.1 Egg and Sperm Donation

Information related to this class of medications is emerging but, based on available data it is advised to avoid egg and sperm donation (this recommendation includes egg and sperm donation by a subject or subject's partner) until the EoS (28 weeks after IP administration) (ACOG 2019).

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to 1 of the following from Screening (signing the ICF) until the EoS (28 weeks after IP administration):
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study.
    - Agree to use a male condom and have their partner use a contraceptive method with a failure rate of <1% per year as described in Table 5.2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male subjects must refrain from donating sperm for the duration of the study (28 weeks after IP administration).
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration from Screening (signing the ICF) until EoS (28 weeks after IP administration).

Table 5.2: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a]
Failure rate of <1% per year when used consistently and correctly.

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation Oral. Intravaginal. Transdermal.
Progestogen-only hormonal contraception associated with inhibition of ovulation Oral. Injectable.
Highly Effective Methods That Are User-Independent [a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation Intrauterine device. Intrauterine hormone-releasing system. Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

Abbreviations: IP = investigational product.
Footnotes:
[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
Note: Condoms alone are not highly effective methods of contraception. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

6 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.

6.1 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the SoA (Table 6.1).

Table 6.1: Schedule of Assessments

Screening to Day 57

DAY[a]	Screening	-1	1 (Pre-Dose)	1	2	3	4	5	6	7	8	9	10	11	12	13	15	18	22	25	29	43	57
WINDOWS (DAYS)	**-28 to -2**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**
Inpatient stay		X	X	X	X	X																	
Discharge from inpatient stay							X																
Ambulant visit							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent[b]	X																						
Inclusion/exclusion criteria	X	X	X																				
Demographics	X																						
Medical history	X	X																					
Surgical history	X	X																					
Physical examination[c]	X	X	X																		X		X
Dentist or other qualified specialist assessment[d]	IF CLINICALLY INDICATED																						
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and BMI	X	X																					
Height	X																						
Hematology[f]	X	X					X								X					X			X
Blood chemistry[f] (including Ca, PTH and Vitamin D)	X	X[o]					X								X					X			X
Coagulation	X	X					X								X					X			X
Urinalysis[f]	X	X					X								X					X			X

DAY[a]	**Screening**	**-1**	**1 (Pre-Dose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**15**	**18**	**22**	**25**	**29**	**43**	**57**
WINDOWS (DAYS)	**-28 to -2**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 0**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**
Drug and alcohol screen	X	X																					
Serology (HBsAg, anti-HBc[g], HCV and HIV tests)	X																						
Electrocardiogram[h]	X	X					X													X			
Randomization			X																				
IP administration[i]				X																			
Ca and vitamin D supplementation[j]	As needed; doses managed individually																						
Blood sampling for PK[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity (ADA, NAb)			X								X						X				X		X
Concomitant medications	X	X	X	X	X	X	X	X	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					X								
Adverse events[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
COVID-19 testing[n]	X																						

Day 71 to Day 196 (EoS)

DAY[a]	**71**	**85**	**99**	**112**	**126**	**141**	**162**	**196 (EoS)**
WINDOWS (DAYS)	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Inpatient stay								
Discharge from inpatient stay								
Ambulant visit	X	X	X	X	X	X	X	X
Informed consent[b]								
Inclusion/exclusion criteria								
Demographics								
Medical history								
Surgical history								
Physical examination[c]		X		X	X	X	X	X
Dentist or other qualified specialist assessment[d]	IF CLINICALLY INDICATED							
Vital signs[e]	X	X	X	X	X	X	X	X
Weight and BMI								
Height								
Hematology[f]				X		X		X
Blood chemistry[f] (including Ca, PTH and Vitamin D)				X		X		X
Coagulation				X		X		X
Urinalysis[f]				X		X		X
Drug and alcohol screen								
Serology (HBsAg, anti-HBc[g], HCV and HIV tests)								
Electrocardiogram[h]								X

DAY[a]	71	85	99	112	126	141	162	196 (EoS)
WINDOWS (DAYS)	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2
Randomization								
IP administration[i]								
Ca and vitamin D supplementation[j]								
Blood sampling for PK[k]	X	X	X	X	X	X	X	X
Blood sampling for immunogenicity (ADA, NAb)	X			X		X		X
Concomitant medications	X	X	X	X	X	X	X	X
Injection site assessment[l]								
Adverse events[m]	X	X	X	X	X	X	X	X
COVID-19 testing[n]								

General: At visits when multiple post-dose procedures are required, the timing of PK blood sample collections will take priority over all other scheduled activities. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling in accordance with the time tolerance windows. When ECGs are to be taken at the same time as vital signs and blood sampling, the following order of procedures should be followed to the extent possible: perform vital signs first, followed by ECGs; perform PK sampling at the scheduled time point; and then perform all other sampling.

a. Calculated using the first day of assigned treatment as Day 1 and unless otherwise specified, in other footnotes, for a specific activity.
b. Must have been obtained before any study-related procedures are performed.
c. At Screening, the full physical examination will also include a visual examination of the oral cavity, including teeth, mucosa, and gums to establish baseline oral health conditions. Brief symptom-directed physical examination will be performed on Day 1 prior to IP administration, and at any time throughout the study, as clinically indicated.
d. If clinically indicated during the Screening assessment or during the course of the study, subjects with oral symptoms may be referred to a registered dentist or other qualified specialist for follow-up assessments.
e. Vital signs on Day 1 will be measured pre-dose (within 60 min prior to dosing), and 1 h (±10 min), 4 h (±30 min), 8 h (±30 min), and 12 h (±30 min) post-dose.
f. On days of clinical safety laboratory tests, subjects should not take calcium and vitamin D within 8 hours before blood sampling. See Appendix 2 for a complete list of laboratory assessments.
g. Reactive anti-HBc test is to be confirmed by a quantitative HBV DNA PCR test at the Investigator's discretion.
h. Fridericia formula will be used to calculate QTcF
i. Subjects will fast for at least 8 hours prior to IP administration and for 1 hour after IP administration. Water will be allowed as desired. The IP will be administered as a single dose with the subjects in bed in a supine position. The subject should be blindfolded to maintain blinding. Before SC injection,

the solution will be inspected visually by trained, unblinded staff for particulate matter or discoloration. Administration of the IP will be performed in the study site by unblinded staff trained to inject this product. The SC injection will be administered in the abdomen (preferred site) or thigh (secondary site). See Section 5.3 for further details.

j. Subjects will receive adequate supplementation of calcium and vitamin D to correct hypocalcemia and low vitamin D levels (particularly those with Screening 25(OH)D levels <20 ng/mL [50 nmol/L]) starting at Screening and during the study period except within 8 hours before blood sample collection. The need for supplementation and the dose will be managed individually for each subject at the Investigator's discretion, based on the subject's calcium, PTH, and vitamin D levels and general health condition prior to IP administration and during the study.
k. Blood samples for PK and immunogenicity assessments will be collected as per the time points specified in Table 6.2.
l. Day 1 injection site assessments will be performed pre-dose (within 60 min prior to dosing) and at 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), 2 h (±5 min), and 8 h (±15 min) post-dose.
m. SAEs will be recorded from the time the subject signs the ICF. Any AEs that occur after obtaining informed consent but before IP administration will be recorded as medical history. Reporting of TEAEs will begin from the time of IP administration.
n. Full PCR test during Screening, and further testing will be performed at the Investigator's discretion following local health requirements and regulations, or if clinically indicated.
o. If the PTH screening values are within the reference range and subjects are on adequate calcium and vitamin D supplementation, they can be dosed on Day 1 even if PTH levels at Day -1 are not available.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; HBV = hepatitis B virus; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; Ca = calcium; CBC = complete blood count; COVID-19 = coronavirus disease 2019; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EoS = End-of-Study; ET = Early Termination; h = hour(s); HbsAg = hepatitis B surface antigen; HCO_3 = bicarbonate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; LDH = lactate dehydrogenase; min = minute(s); NAb = neutralizing antibodies; PCR = polymerase chain reaction; PK = pharmacokinetic; PTH = parathyroid hormone; SC = subcutaneous; TEAE = treatment-emergent adverse event; +/- 1 day = 24 hours.

Table 6.2: Sampling Time Points for Pharmacokinetic and Immunogenicity Assessments

Study Day	Time Point Relative to Dosing	Dosing Allowed Window	Blood Sampling	
			PK	Immunogenicity (ADA and NAb)
Day 1	Pre-dose	Within 1 h prior to dosing	X	X
	8 h post-dose	±15 min	X	
	12 h post-dose	±30 min	X	
Day 2	24 h post-dose	±1 h	X	
Day 3	48 h post-dose	±2 h	X	
Day 4	72 h post-dose	±2 h	X	
Day 5	96 h post-dose	±2 h	X	
Day 6	120 h post-dose	±2 h	X	
Day 7	144 h post-dose	±2 h	X	
Day 8	168 h post-dose	±2 h	X	X
Day 9	192 h post-dose	±4 h	X	
Day 10	216 h post-dose	±4 h	X	
Day 11	240 h post-dose	±4 h	X	
Day 12	264 h post-dose	±4 h	X	
Day 13	288 h post-dose	±4 h	X	
Day 15	336 h post-dose	±4 h	X	X
Day 18	408 h post-dose	±4 h	X	
Day 22	504 h post-dose	±24 h	X	
Day 25	576 h post-dose	±24 h	X	
Day 29	672 h post-dose	±48 h	X	X
Day 43	1008 h post-dose	±48 h	X	
Day 57	1344 h post-dose	±48 h	X	X
Day 71	1680 h post-dose	±48 h	X	X
Day 85	2016 h post-dose	±48 h	X	
Day 99	2352 h post-dose	±48 h	X	
Day 112	2664 h post-dose	±48 h	X	X
Day 126	3000 h post-dose	±48 h	X	
Day 141	3360 h post-dose	±48 h	X	X
Day 162	3864 h post-dose	±48 h	X	
Day 196/EoS	4680 h post-dose	±48 h	X	X

Abbreviations: ADA = anti-drug antibodies; EoS = end-of-study; h = hours; Nab = neutralizing antibodies; PK = pharmacokinetic.

7 DESCRIPTION OF ASSESSMENTS

Study procedures and their timing are summarized in the SoA (Table 6.1). Additional tests and investigations may be performed at any time during the study at the discretion of the local Investigators or required by local laboratory standard operating procedures.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately on occurrence or awareness to determine if the subject should continue or discontinue the study.

The maximum amount of blood collected from each subject, including any extra assessments that may be required, will not exceed 450 mL in any 30-day period. Blood samples will be collected either by direct venipuncture (any suitable vein) or via an indwelling cannula inserted in a vein (depending on the timepoint). The actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF.

Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in the Laboratory Manual.

The processing, shipping, and analysis of samples for protocol-required laboratory tests will be carried out as per the study site's procedures. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

At visits when multiple post-dose procedures are required, the timing of PK blood sample collections will take priority over all other scheduled activities. All other procedures should be performed as close as possible to the scheduled time point but may be obtained before or after PK sampling in accordance with the time tolerance windows. When ECGs are to be taken at the same time as vital signs and blood sampling, the following order of procedures should be followed to the extent possible: perform vital signs first, followed by ECGs; perform PK sampling at the scheduled time point; and then perform all other sampling.

7.1 Demographics and Other Baseline Characteristics

At Screening, the following demographic data will be collected and reported in the eCRF: age at enrollment and year of birth (full date of birth will be documented in source documents), sex, race, and ethnicity. Furthermore, history of substance use, including tobacco use, alcohol intake, and recreational drug use will be documented in the source documents.

7.2 Medical, Surgical, and Medication History

A complete medical history will include evaluation for any past or present medical conditions, history of all known allergies, and surgical history.

A review of prior medications/therapies will be completed as specified in Section 5.7. Prior medications are those used within 30 days of Screening until Day 1 prior to IP administration.

7.3 Pharmacokinetics

7.3.1 Collection of Samples

Venous blood samples for PK (approximately 4 mL per sample) will be collected in all subjects for measurement of serum concentrations of denosumab at time points specified in Table 6.2.

Blood samples will be taken either by direct venipuncture (any suitable vein) or an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF. Instructions for the collection and handling of biological samples, including details for sample collection, labeling, storage, and shipping will be provided in a Laboratory Manual.

7.3.2 Determination of Denosumab Concentrations

Samples for the determination of denosumab concentrations in serum will be analyzed using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

7.3.3 Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.3.4 or higher (Certara, LP Princeton, New Jersey, USA) and/or Statistical Analysis Software (SAS®) Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final serum PK parameter calculations.

The PK parameters in Table 7.1 will be determined for serum denosumab, when possible. Additional serum PK parameters may be calculated if deemed appropriate. Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Table 7.1: Serum Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum serum concentration, obtained directly from the observed concentration versus time data
$AUC_{0-\infty}$	Area under the serum concentration-time curve extrapolated to infinity, calculated as $AUC_{0-\infty} = AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable concentration
AUC_{0-t}	Area under the serum concentration-time curve up to time t, where t is the last time point with a concentration above the lower limit of quantitation
t_{max}	Time to $C_{max,}$ obtained directly from the data
K_{el}	Terminal elimination rate constant; a minimum of 3 non-zero data points will be used for estimation
$t_{1/2}$	Elimination half-life; a minimum of 3 non-zero data points will be used for estimation

V_z/F	Apparent volume of distribution during the terminal phase after SC administration
CL/F	Apparent total serum clearance after SC administration, where F is the fraction of drug absorbed

Abbreviations: LLOQ = lower limit of quantitation; SC = subcutaneous.

7.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 6.1).

7.4.1 Body Weight and Height

Body weight (in kg) (wearing light clothes, no shoes) and height (in cm, only at Screening) will be measured to allow the calculation of body max index (BMI) (rounded to 1 decimal place, calculation to be conducted by trained site staff) to be recorded in both the source documents and the eCRF.

7.4.2 Vital Signs

Vital signs measurements (body temperature, pulse rate, and BP) will be measured at time points outlined in the SoA (Table 6.1).

Blood pressure and pulse measurements should be preceded by at least 3 minutes of rest for the subject in the supine position in a quiet setting without distractions (e.g., television, cell phones) and will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Wherever possible, vital signs measurements must be taken using the same body position at subsequent visits and consistent methods between subjects.

All vital signs measurements will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The Investigator (or a qualified delegate at the investigational site) will also evaluate the overall results using 1 of the following categories: normal, abnormal not clinically significant, or abnormal clinically significant and record their evaluation in the eCRF.

7.4.3 Electrocardiograms

Single 12-lead ECGs will be obtained at time points outlined in the SoA (Table 6.1) after the subject has rested comfortably in the supine position in a quiet setting without distractions (e.g., television, cell phones) for at least 3 minutes using an ECG machine that automatically calculates the heart rate and measures PR interval, interval between 2 R waves on the electrocardiogram tracing (RR), duration of ventricular depolarization and contraction interval (QRS), QT interval. The QTcF interval will be derived using Fridericia's correction formula, $QTcF = QT / (RR \times 0.33)$. Wherever possible, ECG measurements must be taken using the same body position at subsequent visits and consistent methods between subjects. The ECGs may be repeated at the discretion of the Investigator to confirm errant readings.

All ECG data will be documented at each visit, and the details will be recorded in both the source documents and the eCRF. The Investigator (or a qualified delegate at the investigational site) will interpret the ECG using 1 of the following categories: normal, abnormal not clinically significant, or abnormal clinically significant and record their evaluation in the eCRF.

7.4.4 Physical Examinations

Full physical examinations will be performed by a study-delegated registered physician at time points outlined in the SoA (Table 6.1). A full physical examination will include, at a minimum, assessments of the general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory, system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. At Screening, the full physical examination will also include a visual examination of the oral cavity, including teeth, mucosa, and gums to establish baseline oral health conditions.

A brief symptom-directed physical examination, including areas with previously noted abnormalities and/or that are associated with any new complaints from the subject, will be performed on Day 1 prior to IP administration and at any time throughout the study, as clinically indicated.

Any findings made during the physical examination must be noted regardless of if they are part of the subject's medical history. The Investigator (or a qualified delegate at the investigational site) will evaluate the findings using 1 of the following categories: normal, abnormal not clinically significant, or abnormal clinically significant and record their evaluation in the eCRF. If clinically indicated, subjects with oral symptoms may be referred to a registered dentist or other qualified specialist for follow-up assessments.

7.4.5 Clinical Laboratory Assessments

Safety clinical laboratory samples will be analyzed at the study sites' local laboratory. See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency (Table 6.1).

Venous blood samples will be collected for the following clinical laboratory evaluations:

- Hematology.
- Clinical chemistry (including calcium, PTH, and 25[OH]-vitamin D levels).
- Coagulation.
- Viral serology (including HBsAg, anti-HBc, HCV and HIV tests).
    - A reactive anti-HBc test can be confirmed by a quantitative HBV DNA polymerase chain reaction (PCR) test at the Investigator's discretion.

Additionally, the following clinical laboratory assessments will be performed:

- *Urine collection:* urine will be collected for urinalysis (and urine microscopy, if required) and urine drugs of abuse screen.

- *Alcohol breath test:* a commercially available breathalyzer test will be used to determine the concentration of alcohol in the subject's breath.

The laboratory reports must be filed with the source documents. The Investigator or delegate must review the laboratory report, document this review, and for protocol-specified laboratory parameters, evaluate all out-of-range (abnormal) laboratory values for clinical significance using 1 of the following categories: normal, abnormal not clinically significant, or abnormal significant; the evaluation will be recorded in the eCRF. Refer to Section 8.1.1.3 for details on reporting of laboratory abnormalities as AEs.

All laboratory tests with values considered to be abnormal and clinically significant during the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

7.4.6 Local Injection Site Reaction Assessments

Injection site evaluations will be made by clinical staff following SC administration of AVT03 and Xgeva at specific time points outlined in the SoA (Table 6.1). The injection sites will be monitored for pain, tenderness, erythema, and swelling. If an injection site reaction is observed, a physician will characterize and document the reaction as an AE or AESI (see Section 8.1.7) using the FDA Toxicity Grading Scale presented in Table 7.2 (e.g., a moderate intensity injection site reaction may be recorded as a mild AE if considered appropriate according to the Investigator's judgment). Only injection site reactions that are at least Grade 1 should be recorded as AEs. Review of the injection site reaction will continue until the AE is resolved.

Table 7.2: Injection Site Reaction Grading Scheme

Injection Site Reaction	Absent (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 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 (A&E) or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Hospital visit (A&E) or hospitalization
Erythema/ redness	0 to ≤2.4 cm [a]	2.5 to 5.0 cm [a]	5.1 to 10.0 cm [a]	>10.0 cm [a]	Necrosis or exfoliative dermatitis
Induration/ swelling	0 to ≤2.4 cm [a]	2.5 to 5.0 cm [a] and does not interfere with activity	5.1 to 10.0 cm [a] or interferes with activity	>10.0 cm [a] or prevents daily activity	Necrosis

Abbreviations: A&E = accident and emergency department.
a. Measurements refer to the reaction at the greatest single diameter.

7.4.7 Adverse Events

All AEs/SAEs will be recorded from the time of signing the ICF until the end of the subject's participation in the study. Lab findings considered to be clinically significant and detected during Screening will be recorded as medical history.

See Section 8 for additional information.

7.5 Immunogenicity Assessments

Venous blood samples (approximately 8 mL per sample) will be collected from all subjects at the time points specified in the SoA (Table 6.1) for the measurement of ADA and neutralizing antibodies (NAb) to denosumab in serum at a central bioanalytical laboratory.

Blood samples will be collected either by direct venipuncture (any suitable vein) or via an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, including the reason for any samples not collected, will be recorded in the eCRF.

For the immunogenicity assessments, serum samples will be screened for antibodies binding to denosumab in AVT03 and Xgeva, and the titer of confirmed positive samples will be reported. Antibodies will be further characterized and/or evaluated for their ability to neutralize the activity of the IPs. All samples collected for detection of antibodies to denosumab will also be evaluated for denosumab serum concentrations to enable interpretation of the antibody data.

The immunogenicity assessments will be performed using a validated immunoassay method. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

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

8 ADVERSE EVENTS

AEs will be reported by the subject, and the Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IP or study procedures, or that caused the subject to discontinue the study (see Section 5.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in the sections below.

8.1.1 Definitions

8.1.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject, temporally associated with the use of an IP, whether or not considered related to the IP. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the IP.

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements, physical examinations, or injection site reaction assessments), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after IP administration.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

AEs which commence or worsen in severity on or after the time of IP administration or those that pre-existed and worsened in severity after IP administration will be considered as treatment-emergent AEs (TEAEs) and will be analyzed for the purpose of safety analyses.

Events that do NOT meet the definition of an AE include:

- Medical or surgical procedures (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant exacerbation or worsening.

8.1.1.2 Serious Adverse Events

If an event is not an AE per definitions above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that:

- Results in death.

- Is life-threatening: 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, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving a stay of at least 24 hours) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

    - Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect: Intrauterine development of an organ or structure that is abnormal in form, structure, or position.

- Is a medically important event or reaction: Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent 1 of the other outcomes listed above. These events should usually be considered serious. Examples of such events include:
    - Laboratory abnormalities that meet the CTCAE version 5.0 Grade 4 criteria.
    - Invasive or malignant cancers, 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.

8.1.1.3 Recording of AEs Based on Other Safety Assessments

For protocol-specified laboratory parameters, any laboratory abnormality that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF if not captured as part of an overarching diagnosis (e.g., hemoglobin of 8 g/dL captured as part of anemia):

- Requires therapeutic intervention or additional diagnostic tests.
- Has accompanying clinical symptoms or signs.
- Is judged by the Investigator as clinically significant.

Additionally, any abnormalities in protocol-specified laboratory parameters that meet CTCAE version 5.0 Grade ≥3 criteria are considered to be clinically significant and will be recorded as AEs.

Any injection site reaction or clinically significant deterioration in vital signs, ECGs, and physical examinations as compared with baseline should also be recorded as AEs.

8.1.2 Recording of AEs

All AEs occurring after the subject signs the ICF and up to 30 calendar days after the last study visit will be recorded, with the exception of lab findings considered significant that occur after obtaining informed consent but before IP administration, which will be recorded as medical history. All SAEs will be recorded from the time of Screening (signing the ICF).

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the eCRF, including the following details (each event must be recorded separately):

- A description of the event.

- Onset and resolution dates and times.
- Seriousness.
- Severity (as defined in Section 8.1.2.1).
- Relationship to the IP (as defined in Section 8.1.2.2).
- Action taken (none, treatment given, withdrawn from study, nondrug therapy, other).
- Outcome (Fatal, Not recovered/Not resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving, or Unknown).

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

It is **not** acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the AE/SAE eCRF page. However, there may be instances when copies of medical records for certain cases are requested by the Medical Monitor and/or Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Medical Monitor and/or Sponsor.

Investigators are not obligated to actively seek new AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE up to 30 calendar days after the last study visit, including a death, and they consider the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

8.1.2.1 Assessment of Severity

Based on their clinical judgment, the Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild:** An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** An AE that prevents normal everyday activities; treatment or other intervention usually needed.

Note: the term "severe" does not necessarily equate to "serious". Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be recorded. If an AE changes in frequency or intensity over a number of days, a new entry of the event must be made in the eCRF (with distinct onset dates).

8.1.2.2 Assessment of Causality

The Investigator is obligated to assess the relationship between the IP and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The Investigator will also consult the Investigator's Brochure (IB) for AVT03 and/or Product Information for Xgeva, in their assessment.

The causal relationship of the AE to the IP or study procedures should be assessed by the Investigator (or medically qualified delegate) using the World Health Organization (WHO)-Uppsala Monitoring Centre classification (WHO) (Table 8.1).

Table 8.1: Causal Relationship of Adverse Events to the Investigational Product

Category	Description
Highly probable/Certain	Adverse event or laboratory test abnormality, with plausible time relationship to IP intake
	Cannot be explained by disease or other drugs
	Response to withdrawal plausible (pharmacologically, pathologically)
	Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
	Rechallenge satisfactory, if necessary
Probable	Adverse event or laboratory test abnormality, with reasonable time relationship to IP intake
	Unlikely to be attributed to disease or other drugs
	Response to withdrawal clinically reasonable
	Rechallenge not required
Possible	Adverse event or laboratory test abnormality, with reasonable time relationship to IP intake
	Could also be explained by disease or other drugs
	Information on drug withdrawal may be lacking or unclear
Unlikely	Adverse event or laboratory test abnormality, with a time to IP intake that makes a relationship improbable (but not impossible)
	Disease or other drugs provide plausible explanations

Abbreviations: IP = investigational product.

8.1.3 Reporting of SAEs

All SAEs, whether related or unrelated, will be recorded on a paper SAE Form and submitted to the Sponsor and/or designee within 24 hours of site awareness. The Investigator will submit any clinically or medically significant updated SAE information to the Sponsor and/or designee within 24 hours of it being available. The procedures for completing and transmitting SAE reports and contact information for SAE reporting can be found in the SAE Form.

Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the study monitor.

8.1.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs and AESIs (as defined in Section 8.1.7) documented at a previous visit/contact that are designated as ongoing will be followed up until resolution, stabilization, the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 4.6). This activity will continue up to EoS/Day 196 (28 weeks after IP administration). The Investigator will ensure that follow-up includes any supplemental investigations as medically indicated or requested by the Medical Monitor and/or Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. For AEs or SAEs that are reported close to or on Day 196 that are considered related to the IP, follow-up of these ongoing events will continue only up to the time of database lock.

8.1.5 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of the IP are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IP. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, national clinical trial pharmacovigilance database (if applicable), IEC, and Investigators.

If an SAE is considered a suspected unexpected serious adverse reaction (SUSAR), it will be reported to the appropriate regulatory authorities by the Sponsor/Investigator (or designee) within the predefined expedited timelines and according to country-specific regulatory requirements.

Investigator safety reports (alert letters) must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB. If required, individual or expedited reports of SAEs or SUSARs will be submitted by the Sponsor/Investigator or designee to IEC, if appropriate according to local requirements.

8.1.6 Pregnancy

There is no information about the effects that AVT03 could have on the development of the fetus in humans. It is important that male subjects agree to use adequate contraception and their female partners do not become pregnant during the study.

Subjects will be instructed that known or suspected pregnancy occurring during the study in female partners of the subjects should be confirmed and reported to the Investigator. Details of all pregnancies in female partners of the subjects (after obtaining the necessary signed informed consent from the pregnant female partner directly) will be collected via a Pregnancy Report Form from the time of IP administration until at least 28 weeks after IP administration. Reporting of pregnancies applies only to female partners of male subjects who received the IP.

The Investigator will record pregnancy information on a Pregnancy Report Form and submit it to the Sponsor and/or designee within 24 hours of learning of the pregnancy. The procedures for completing and transmitting pregnancy reports and contact information for pregnancy reporting can be found in the Pregnancy Report Form.

The pregnant female partner of the subject will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up period for a pregnancy will be deemed to have ended when the health status of the child has been determined on its birth. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, hospitalizations for complications during pregnancy or elective termination of a pregnancy will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria of an SAE (e.g., spontaneous abortions, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) (Sections 8.1.3 and 8.1.5), these events should be reported as such.

8.1.7 Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to denosumab, for which ongoing monitoring 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 Xgeva Product Information and include:

- Hypocalcemia, as considered clinically significant by the Investigator, and decline in phosphorus or magnesium levels.
- Bone conditions: ONJ, osteonecrosis of the external auditory canal, atypical femoral fractures, and fracture healing complications.
- Musculoskeletal pain (all severities).
- Diverticulitis.
- Serious infections, including skin infection such as cellulitis.
- Serious dermatological reactions.

- Hypersensitivity reactions, including anaphylaxis (details in Section 8.1.7.1) and lichenoid drug eruptions.

- Local injection site reactions: pain, tenderness, erythema/redness, and induration/swelling (all Grades, further details in Section 7.4.6). In addition, pruritus/itching, hematoma/ecchymosis/bruising will be considered as injection site reactions.

AESIs will be reported and assessed in the same manner as standard AEs (unless seriousness criteria are met). Investigators are encouraged to report AESIs within 24 hours.

8.1.7.1 Anaphylaxis

Anaphylaxis (Sampson et al., 2006). may be defined when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing, swollen lips-tongue-uvula), with at least 1 of the following:

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).

    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula).

    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).

    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).

    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that subject (minutes to several hours): systolic BP <90 mmHg or >30% decrease from the subjects' baseline.

8.2 Treatment of Overdose

For this study, any dose of AVT03 or Xgeva greater than the protocol-specified single dose of 120 mg/mL SC will be considered an overdose. However, considering the controls in place for subjects in this study and given that the IP will be administered by trained site staff, it can be assumed that the risk of overdose with AVT03 is very low and that treatment of overdose should consist of general supportive measures.

9 STATISTICS

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

9.1 Statistical Hypotheses

- The null hypothesis is:
  - H_0: $GM_{AVT03}/GM_{Xgeva} \leq 80\%$ or $GM_{AVT03}/GM_{Xgeva} \geq 125\%$.
- The alternative hypothesis is:
  - H_1: $80\% < GM_{AVT03}/GM_{Xgeva} < 125\%$.

Where GM_{AVT03} and GM_{Xgeva} denote the geometric means of the PK parameters (e.g., C_{max}, area under the serum concentration-time curve [AUC] up to time t [AUC_{0-t}], where t is the last time point with a concentration above the lower limit of quantitation, and AUC after extrapolation from time t to infinity [$AUC_{0-\infty}$]) in the AVT03 and Xgeva groups, respectively.

9.2 Sample Size Determination

Sample size calculations were performed using data from a previous study with Prolia (Study 20060286) (FDA Prolia Biologics License Application Assessment Report). Based on this study, the inter-subject coefficient of variation is as assumed to be 33.5% for C_{max} and 35.1% for AUC_{0-t}. The assessment of PK similarity will be based on the 90% CI of the geometric mean ratio (GMR) between the 2 treatment groups to be contained within the prespecified margins of 80% to 125% for both co-primary endpoints C_{max} and AUC_{0-t}. Assuming a true GMR of 0.95 for each of the 2 co-primary endpoints C_{max} and AUC_{0-t}, 184 subjects will provide a study level power of 90.1% (i.e., power of 95.7% for C_{max} and 94.2% for AUC_{0-t}). Taking into consideration a non-evaluable rate of 20%, the total sample size will be 206 subjects (103 per treatment group). Of the 206 subjects, approximately 24 (11.7%) subjects of Japanese descent are planned to be enrolled.

9.3 Analysis Populations

For purposes of analysis, the analysis populations in Table 9.1 are defined.

Table 9.1: Analysis Populations

Analysis Population	Description
Enrolled Set	All subjects who sign the ICF.
Randomized Set	All subjects who are randomized into this study. Subjects will be analyzed according to their randomized treatment, regardless of which treatment the subject receives.
Safety Analysis Set	All randomized subjects who receive any amount of the IP. Subjects will be analyzed according to the treatment they receive, if this differs from that to which the subject is randomized.
PK Analysis Set	All randomized subjects who receive any amount of the IP and have at least 1 evaluable PK parameter. Subjects will be analyzed according to the treatment they receive, if this differs from that to which the subject is randomized. Subjects with dosing deviations that could potentially affect the PK profile will be excluded from the PK Population, at the discretion of the pharmacokinetics prior to analysis.

Abbreviations: ICF = informed consent form; IP = investigational product; PK = pharmacokinetic.

9.4 Statistical Analyses

The following sections describe the statistical analysis as it is foreseen when the study is being planned. A detailed Statistical Analysis Plan (SAP) will be developed and finalized before database lock and unblinding and will describe the subject analysis populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. The SAP will also provide the format of listings, tables, and figures to be provided for completion of the Clinical Study Report (CSR). Any deviations from the SAP will be presented in the final CSR. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All statistical analyses, summaries, and listings will be performed using SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

In general, data will be presented by treatment group. Data for all study subjects combined will also be presented when appropriate. Individual subject data will be presented in listings.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (N), number of non-missing counts (n), mean, standard deviation, median, minimum, and maximum. The coefficient of variation % (CV), geometric mean, and geometric CV% will be presented for PK parameters, where applicable.

- Categorical variables: frequency counts and percentages.

Baseline values are defined as the last available, valid, non-missing assessment (scheduled or unscheduled) prior to dosing. Only data from protocol-scheduled visits/time points will be included in the summary tables and figures. All data, including those from all unscheduled visits/time points, will be included in the listings.

9.4.1 Subject Disposition and Protocol Deviations

All subjects who provide informed consent (i.e., the Enrolled Set) will be accounted for in this study. Subject enrollment and disposition will be summarized by treatment group and for all subjects and will include: the number of subjects entered, screen failed, enrolled, randomized (overall and by randomization strata), and dosed with the IP; the total number of subjects who complete the study; and the number of subjects who discontinue from the study, along with the reason for discontinuation.

The number and percentage (%) of subjects included in each analysis set will also be presented.

Subjects who have protocol deviations by severity classification and deviation type by treatment group and for all subjects based on the Randomized Set will be listed and summarized using frequency counts and percentages. If applicable, the protocol deviation listing will flag subjects whose study participation is impacted by the global pandemic COVID-19.

9.4.2 Demographics, Other Baseline Characteristics, and Medical History

All demographic and baseline data recorded prior to dosing will be summarized using descriptive statistics or frequency counts and percentages, as appropriate, by treatment group and for all subjects in the Randomized Set and the PK Analysis Set. Individual subject demographics and baseline characteristics will also be presented in listings.

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and the data will be listed and summarized using frequency counts and percentages by system organ class (SOC) and preferred term (PT) by treatment group and for all subjects in the Safety Analysis Set.

9.4.3 Prior and Concomitant Medications/Therapies

Prior and concomitant medications will be coded using the latest version of the WHO Drug Global Dictionary. Prior medications are those medications that are stopped prior to IP administration. Concomitant medications are medications that are taken at least once after IP administration. Medications stopping on the same day as IP administration will be considered as concomitant medications.

Prior and concomitant medications will be listed and summarized separately using frequency counts and percentages by Anatomical Therapeutic Chemical system (Level 2) and drug PT by treatment group and for all subjects in the Safety Analysis Set.

9.4.4 Pharmacokinetic Analyses

Serum denosumab concentrations will be listed for all subjects in the Safety Analysis Set. Summaries of serum denosumab concentrations, PK parameters, and PK similarity assessment will be based on the PK Analysis Set.

Serum denosumab concentrations will be listed and summarized using descriptive statistics by treatment group and nominal PK sampling time point. All concentrations that are below the limit

of quantification will be labeled as such in the concentration data listings. Individual and arithmetic mean (per treatment) concentration-time profiles will also be presented graphically.

Pharmacokinetic parameters of serum denosumab will be listed and summarized by treatment group using descriptive statistics. In addition, PK parameters will be summarized by treatment and randomization strata.

9.4.4.1 Statistical Analysis for PK Similarity:

For the primary endpoints, the statistical analysis will be performed using an analysis of covariance model on the logarithmic scale (i.e., using natural log-transformed values of C_{max} and AUC_{0-t}) with treatment group as fixed effect and body weight at baseline as the continuous covariate.

Point estimates (geometric means and GMRs) will be calculated by back transforming the LS means of the natural log-transformed values of C_{max} and AUC_{0-t} and the difference in the LS means. The PK similarity of AVT03 versus Xgeva will be determined if the 90% CIs for the GMRs of the primary endpoints (C_{max} and AUC_{0-t}) are entirely contained within the equivalence margin of 80% to 125%. Other exploratory analyses of PK similarity by subgroups based on the randomization strata may be performed if appropriate.

9.4.5 Safety Analyses

9.4.5.1 Adverse Events

All safety analyses will be performed on the Safety Analysis Set. AEs will be coded using the latest version of MedDRA.

All AEs occurring after the subject signs the ICF and up to 30 calendar days after the last study visit will be presented.

An overview summary of the frequency and percentage of subjects with TEAEs overall and by TEAE category will be presented by treatment group and for all subjects. -TEAEs will also be grouped by SOC and PT and summarized by treatment group and for all subjects.

For the summaries of TEAEs, subjects who experience the same TEAE (in terms of the MedDRA SOC and PT) more than once will be only counted once for that event in the number of subjects, but all occurrences of the same event will be counted in the number of events.

Separate summaries are provided for TEAEs by maximum severity (mild, moderate, or severe) and related TEAEs. Any TEAEs with a missing or unknown severity will be considered as severe in the summary tables. Related TEAEs are considered as those reported as having a relationship to IP of possible, probable, or highly probable.

AESIs, TEAEs of clinically significant laboratory abnormalities, TEAEs of Grade ≥3 laboratory abnormalities, TEAEs leading to discontinuation from the study, SAEs, and TEAEs leading to death will be summarized and listed separately.

9.4.5.2 Local Injection Site Reactions

Local injection site reactions will be listed and summarized using frequency counts and percentages by treatment group and for all subjects: by most severe reaction (pain, tenderness, erythema/redness, induration/swelling, and other reactions) and by each reaction for each scheduled time point, and intensity grade (including Grade ≥1). The worst postbaseline injection site reaction intensity grade observed at any time (scheduled or unscheduled) during the study will also be presented.

9.4.5.3 Clinical Laboratory Evaluations

Observed values and change from baseline for clinical laboratory data will be listed and summarized using descriptive statistics at each protocol-specified time point by treatment group. Separate listings will be produced for all subjects with at least 1 out-of-range or abnormal clinical laboratory result.

In addition, each reading will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Shifts in from baseline to each postbaseline protocol-scheduled time point will be summarized by treatment group, using frequency tabulations.

9.4.5.4 Vital Signs, Electrocardiograms, and Physical Examinations

All vital signs and ECG data and the Investigator's evaluation of abnormal physical examination findings will be presented in data listings.

In addition, observed values and change from baseline for vital signs and ECG data will be summarized at each protocol-specified time point, by treatment group. Shifts in the Investigator's evaluation of the results (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each postbaseline protocol-scheduled time point will also be summarized by treatment group using frequency tabulations.

9.4.6 Immunogenicity Analyses

Individual immunogenicity sample collection and ADA results (including NAb results, if available) will be listed for all subjects. Detection of ADA and NAb (i.e., positive or negative) will be summarized with frequency counts by treatment group and scheduled time point for the Safety Analysis Set. The ADA titer values will also be summarized if >20% of subjects within a single treatment group have positive ADA results.

9.4.7 Handling of Missing Data

For subjects who are withdrawn from the study prior to their completion for any reason, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal. There will be no imputation for missing data, unless otherwise stated.

9.5 Interim Analyses

No interim analyses are planned for this study.

10 STUDY MANAGEMENT AND RESPONSIBILITIES

10.1 Regulatory, Ethical, and Study Oversight Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP Guidelines.
    - All other applicable laws and regulations.
- The protocol, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IEC by the Investigator and reviewed and approved by the IEC before the study is initiated.
- Any amendments to the protocol will require IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The PI or designee will be responsible for the following, with the support of a CRO, [redacted] where necessary:
    - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
    - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
    - Providing oversight of the conduct of the study at the study site and adherence to requirements of ICH guidelines, the IEC, and all other applicable local regulations.
- After reading the protocol, each PI will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the PI has not signed the protocol.

10.2 Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement

procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.3 Finance and Insurance

Financing of this study is outlined in a separate agreement.

Subjects may be compensated for the time that they spend participating in the study using a formula determined by the study site.

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files. The subject should not take part in any other clinical study while they are enrolled in this study. The subject should report any health injury that could have occurred as a result of the clinical study to the Investigator without delay.

10.4 Informed Consent Process

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to ICH GCP guidelines. The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the subject has given written informed consent to participate in the study.

The Investigator or their representative will explain the nature of the study to the subject and answer all questions regarding the study. Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH GCP guidelines, the IEC, and study site.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF. A copy of the ICF(s) must be provided to the subject or the subject's partner in the case of a pregnancy. Representative written information for the subject (subject information sheet) and sample ICF(s), designated as the master version, is provided in the Trial Master File.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, new ICF(s) will be approved by the IEC (and regulatory authorities, if required). Subjects, or the subject's partner in the case of a pregnancy, must be reconsented to the new version of the ICF(s).

For subjects who are rescreened, reconsenting can be based on local regulatory processes.

10.5 Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. The subject must be informed that their pseudoanonymized personal study-related data will be used by the Sponsor in

accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.6 Administrative Structure

The Sponsor will enlist the support of a CRO, [redacted] to coordinate the study. The Sponsor will supervise all outsourced activities. The administrative structure for the study will be covered in a separate document.

10.7 Dissemination of Clinical Study Data

After completion of the study, a CSR will be written by the CRO in consultation with the Sponsor and Investigator(s) following the guidance in ICH E3. The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the regulatory authority and the IEC a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.8 Data Quality Assurance

- All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). Data collection must be completed for each subject who signs an ICF.

- The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The CRO is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Details of study monitoring, including actions required due to the COVID-19 pandemic, will be included in a separate Study Monitoring Plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.9 Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study site. Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Definition of what constitutes source data can be found in the eCRF completion guidelines.

10.10 Management of Protocol Amendments and Protocol Deviations

10.10.1 Protocol Amendments

No changes (amendments) to the protocol may be implemented without prior approval from the Sponsor and the appropriate IEC, except where necessary to eliminate an immediate hazard to subjects, or when the change involves only logistical or administrative aspects of the study. If a protocol amendment requires changes to the ICF, the revised ICF must be approved by the IEC.

10.10.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes that were approved by the Sponsor and the IEC and agreed to by the Investigator. Protocol deviations will be classified by severity ratings of critical, major, or minor, as determined by clinical staff:

- A minor protocol deviation is any change, divergence, or departure from the study design or procedures of the study protocol, and which does not have a major impact on the subject's rights, safety or wellbeing, or the completeness, accuracy, and reliability of the study data.

- A major protocol deviation is a deviation that has an impact on subject safety, can substantially alter risks to subjects, have an effect on the integrity of the study data, or affect the subject's willingness to participate in the study.

- A critical protocol deviation is defined as any conditions, practice or process that adversely affects the rights, safety, or wellbeing of the subjects and/or the quality and integrity of data.

Major deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to a regulatory agency's regulations or ICH GCP guidelines and may lead to the subject being withdrawn from the study or being excluded from statistical analyses.

The Investigator or designee will document and explain in the subject's source documentation any deviation from the approved protocol. Protocol deviations will also be documented by the study monitor throughout the course of monitoring visits, and the Investigator will be notified of any deviations in writing by the monitor. The IEC will be notified of all major protocol deviations, if appropriate, in a timely manner.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. The Investigator may only implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the IEC (and regulatory authorities if applicable) for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock and/or relevant data transfer.

10.11 Study Termination and Study Site Closure

The Sponsor designee reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site close-out visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator or designee will promptly inform the IEC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant study termination or suspension or early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- The Investigator (or delegate) and the Sponsor consider that the number and/or severity of AEs justify discontinuation of the study.

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further IP development.
- The Sponsor makes a unilateral request to do so.

The Investigator understands that the Sponsor shall notify the regulatory authorities concerned about a serious breach of the version of this protocol applicable at the time of the breach or of the GCP, without undue delay but not later than 7 days of becoming aware of such a breach (the 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical study; or as defined by the applicable regulatory authority).

10.12 Publication Policy

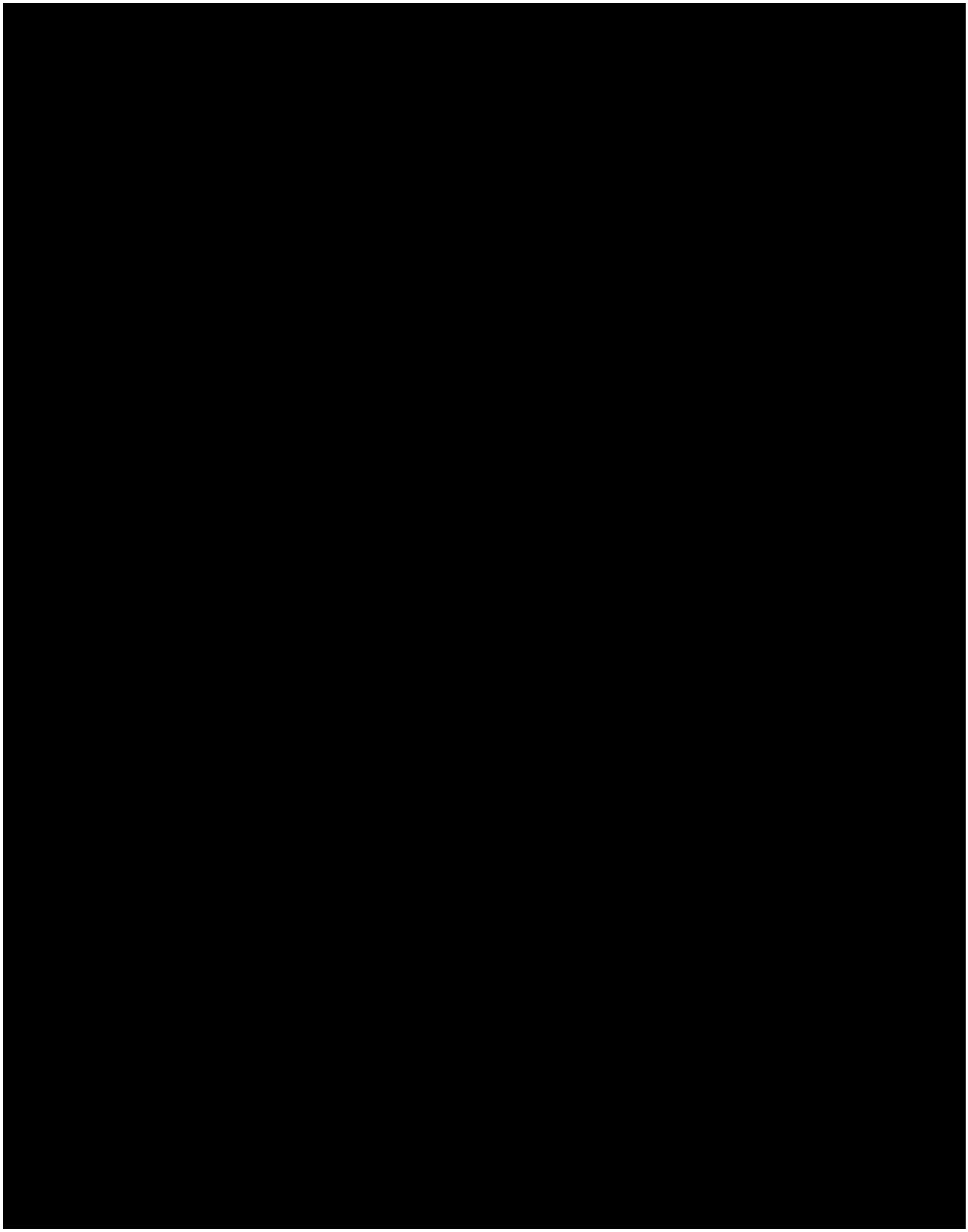
The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements (ICMJE 2003).

11 REFERENCES



12 APPENDICES

Appendix 1

Names of Study Personnel

The names of study personnel are provided in separate documentation to the site.

Role	Name and Contact Information
Sponsor:	[redacted]
Sponsor Medical Point of Contact	[redacted]
Medical Monitor:	[redacted]
CRO:	[redacted]
Central Laboratory:	[redacted]

Abbreviations: CRO = contract research organization

Appendix 2

Clinical Safety Laboratory Tests

The tests detailed in Table 12.1 will be performed by the local laboratory as per the time points specified in the SoA (Table 6.1).

Protocol-specific laboratory-related requirements for inclusion or exclusion of subjects are detailed in Section 4 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations or the local laboratory procedures.

On days of clinical laboratory tests (including at Screening), subjects should not take calcium and/or vitamin D supplements within 8 hours before blood sampling.

Investigators must document their review of each laboratory safety report. Laboratory/analyte results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

Table 12.1: Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Red blood cell (erythrocyte) count	White blood cell (leukocyte) count with differential:
	Hemoglobin	Neutrophils
	Hematocrit	Lymphocytes
	Platelet count	Monocytes
	Red blood cell indices:	Eosinophils
	Mean corpuscular volume	Basophils
	Mean corpuscular hemoglobin	
	Mean cell hemoglobin concentration	
Clinical Chemistry [a]	Bicarbonate	Creatine kinase
	Calcium	AST
	Phosphorus	ALT
	Magnesium	ALP
	Sodium	GGT
	Potassium	Lactate dehydrogenase
	Chloride	Total and direct bilirubin
	Albumin	Triglycerides
	Glucose (fasting)	Total cholesterol
	Serum creatinine (and eGFR)	Vitamin D (25[OH]D)

Laboratory Assessments	Parameters	
	Total protein	PTH
	Urea	
Coagulation	INR	Activated partial thromboplastin time
	Prothrombin time	
Urinalysis	Leukocytes	Red blood cells (Blood)
	Protein (result must be "not detected" or if urine dipstick result is ≥2+, 24 hour urine must demonstrate ≤1 g of protein in 24 hours)	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Viral serology	HIV 1 and 2 antibodies	Anti-HBc[b]
(Screening only)	HBsAg	HCV antibody
Drugs of abuse	Amphetamines	Benzodiazepines
(Screening and Day –1 only)	Methamphetamines	Methadone metabolites
	Tetrahydrocannabinol	Barbiturates
	Cocaine metabolites	Methylenedioxymethamphetamine
	Opioids and opiates	Phencyclidine
Alcohol testing *(Screening and Day –1 only)*	Alcohol breath test using a commercial breathalyzer	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; anti-HBc = hepatitis B core antibody; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PTH = parathyroid hormone; SAE = serious adverse event; ULN = upper limit of normal.

NOTE:

a. All events of ALT ³3 × ULN and bilirubin ³2 × ULN (>35% direct bilirubin) or ALT ³3 × ULN and INR >1.5, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.
b. A reactive anti-HBc test can be confirmed by a quantitative HBV DNA PCR test at the Investigator's discretion.