18 September 2025
EMA/CHMP/322239/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zvogra

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006552/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADCC	Antibody-dependent cellular toxicity
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
APAC	Affinity protein A chromatography
ATC	Anatomical therapeutic chemical
AUC0–inf	Total area under the curve after extrapolation from time t to infinity, where t is the last time point with a concentration above the LLOQ
AUC0–t	Area under the serum concentration–time curve up to time t, where t is the last time point with concentrations above the LLOQ
AUEC	Area under the effect versus time curve
AUEC0–6 months of %CFB sCTX-1	Area under the percent change from baseline in serum C-telopeptide of type 1 collagen up to 6 months
AUEC0–last	Area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point with concentrations above the LLOQ
AUEC0–t	Area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point
AQL	Acceptable quality limits
BET	Bacterial endotoxin test
BLA	Biologics license application
BLQ	Below the limit of quantification
BMI	Body mass index
b.w.	Body weight
BPR	Batch processing record
CCS	Container closure system
CDC	Complement-dependent cytotoxicity
CDR	Complementarity-determining regions

CE-SDS	Capillary electrophoresis–sodium dodecyl sulphate
CEX	Cation exchange
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum serum drug concentration
CMO	Contract manufacturing organisation
CO1	Cytochrome oxidase 1
CPP	Critical process parameter
CPV	Continued process verification
CQA	Critical quality attribute
CR	Characterisation range
CTX-1	C-telopeptide of type 1 collagen
CV%	Percent coefficient of variation
cGMP	Current good manufacturing practice
cIEF	Capillary isoelectric focusing
DFA	Double filtration assembly
DMSO	Dimethyl sulfoxide
DP	Drug product
DS	Drug substance
DSP	Downstream processing
EDTA	Ethylenediaminetetraacetic acid
EFF	Extended finger flange
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoS	End of study

EU	European Union
FDA	Food and Drug Administration
FSR	First subject randomised
FT	Flow-through
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GMR	Geometric mean ratio
HcDNA	Host cell deoxyribonucleic acid
HCP	Host cell proteins
HMW	High molecular weight
HMWS	High molecular weight species
ICH	International Council for Harmonisation
ICP-OES	Inductively coupled plasma optical emission spectroscopy
Imin	Minimum observed serum CTX-1 concentration
IPC	In-process controls
ISR	Injection site reaction
Kel	Elimination rate constant
LC-MS	Liquid chromatography–mass spectrometry
LS	Least squares
LSLV	Last subject, last visit
LLOQ	Lower limit of quantification
MAEX	Multimodal anion exchange
mAb	Monoclonal antibody
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of action

MSD ECL	Meso Scale Discovery electrochemiluminescence
MVM	Minute virus of mice
NA	Not applicable
nAb	Neutralising antibody
nCPP	Non-critical process parameter
NF	Nanofiltration
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLT	Not less than
NMT	Not more than
OD	Optical density
OOF	Out of fridge
OOS	Out of specification
OPG	Osteoprotegerin
PAR	Proven acceptable range
PCR	Polymerase chain reaction
PFS	Prefilled syringe
Ph. Eur.	European Pharmacopoeia
PI	Prescribing information
PK	Pharmacokinetic
PPQ	Process performance qualification
PPCB	Post-production cell bank
PR	Plunger rod
PT	Preferred term
PVDF	Polyvinylidene difluoride
qPCR	Quantitative polymerase chain reaction
q.s.	Quantum satis
RANKL	Receptor activator of nuclear factor kappa B ligand

RH	Relative humidity
RNS	Rigid needle shield
RP	Reference product
RP-HPLC	Reversed-phase high-performance liquid chromatography
rProA	Residual protein A
SB	Smart bag
SD	Standard deviation
SEC-HPLC	Size-exclusion high-performance liquid chromatography
SF	Shake flask
SmPC	Summary of product characteristics
SNS	Safe 'N' Sound
SOC	System organ class
s.c.	Subcutaneous
sCTX-1	Serum C-telopeptide of type 1 collagen
SUB	Single-use bioreactor
t½	Terminal half-life
TEAE	Treatment-emergent adverse event
TEM	Transmission electron microscope
TFF	Tangential flow filtration
tmax	Time to maximum serum concentration
Tmin	Time to Imin
TNF	Tumour necrosis factor
TRAF	TNF receptor-associated factor
TRAIL	TNF-related apoptosis-inducing ligand
UFDF	Ultrafiltration/diafiltration
UPLC	Ultra-high-performance liquid chromatography
UPLC-ELSD	Ultra-performance liquid chromatography–evaporative light scattering detector

US	United States
USP	United States Pharmacopeia
USP (alt.)	Upstream processing
VCD	Viable cell density
VI	Viral inactivated
vs	Versus
Vz/F	Apparent volume of distribution
WCB	Working cell bank
WFI	Water for injection
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WOMIC	Works order material issue confirmation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STADA Arzneimittel AG submitted on 16 September 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Zvogra, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

> Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
>
> Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Kefdensis simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; the Netherlands
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/11/703

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; the Netherlands
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/11/703

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.; Minervum 7061; 4817 ZK Breda; the Netherlands
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by: Union
- Marketing authorisation numbers: EU/1/11/703

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
16 December 2021	EMA/SA/0000061798	Linda Trauffler, Elina Rönnemaa
19 May 2022	EMA/SA/0000084481	Linda Trauffler, Juha Kolehmainen

The scientific advice pertained to the following quality and clinical aspects:

EMA/SA/0000061798:

- Comparative analytical similarity assessment including critical quality attributes and the corresponding analytical assays, number of batches used to demonstrate comparability between Prolia and Xgeva, the use of combined quality target product profile ranges from Prolia and Xgeva, number of batches to demonstrate similarity between AVT03 and Xgeva, overall approach to showing similarity between AVT03 pre-filled syringe and vial and Prolia and Xgeva; tests and corresponding limits included in the overall drug substance and drug product release testing program;.
- Design of a two-arm, single-dose pharmacokinetics similarity study (AVT03-GL-P01) in healthy male subjects including dose selection, study population, primary endpoint and secondary endpoints, safety and immunogenicity evaluation, sample size, and statistical assumptions; design of a two-arm, single-dose pharmacodynamics similarity study (AVT03-GL-P02) in healthy postmenopausal women including dose selection, study population, primary endpoint and secondary endpoints, safety and immunogenicity evaluation, sample size, and statistical assumptions; design of a two-arm, repeat-dose clinical efficacy and safety study (AVT03-GL-C01) in postmenopausal women with osteoporosis

including dose selection, study population, primary endpoint and secondary endpoints, safety and immunogenicity evaluation, sample size, and statistical assumptions; overall clinical development strategy; extrapolation analytical and clinical results to support all authorised indications, formulation and strengths of Prolia and Xgeva; the use of US-licensed comparator in clinical studies.

EMA/SA/0000084481:

- Design of a randomised, parallel design, single dose, 2-arm pharmacokinetics, pharmacodynamics, safety, and immunogenicity study of AVT03 and Prolia in healthy male subjects (AVT03-GL-P01) including PK sampling period, primary (PK) endpoint, secondary (PD) endpoint, sample size; design of a randomised, parallel design, repeat dose, 2-arm study comparing the clinical efficacy, safety, immunogenicity, and pharmacokinetics of AVT03 and Prolia in postmenopausal women with osteoporosis (AVT03-GL-C01) including primary and secondary endpoints, sample size, statistical assumptions.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christian Gartner Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	16 September 2024
The procedure started on	3 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 December 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 June 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	19 June 2025
The applicant submitted the responses to the CHMP List of Outstanding	19 August 2025

Issues on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zvogra on	18 September 2025

2. Scientific discussion

2.1. About the product

AVT03 (denosumab) is a fully human immunoglobulin G2 (IgG2)/kappa monoclonal antibody (mAb) directed against RANKL. Denosumab targets and binds with high affinity and specificity to human receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone, and cancer-induced bone destruction.

Zvogra (AVT03) contains the same amount and concentration of drug substance as the reference medicinal product, Xgeva, and is supplied in a vial of a 70 mg/mL or 120 mg/1.7 mL solution).

2.2. Type of application and aspects on development

During the development of Zvogra, the applicant sought scientific advice was obtained from the EMA Scientific Advice Working Party (SAWP) on two occasions.

Initial SA EMA/SA/0000061798

Quality

Advice was request on CMC aspects: with proposed critical quality attributes (CQAs) for similarity assessment, number of batches for demonstrating comparability between Xgeva and Prolia, and use of combined QTPP ranges from Prolia and Xgeva for analytical similarity assessment, proposed lists of tests and corresponding limits included in the overall DS and DP release testing program

Overall, the advice given concerning quality was appropriately followed. As pointed out in the EMA-SA and upon request the applicant appropriately tightened the limit for host cell proteins (HCP) in relation to the presented batch release results.

Clinical

- Agreement was sought on clinical development plan considering proposed clinical studies: AVT03-GL-P01 (PK similarity), AVT03-GL-P02 (PD similarity) and AVT03-GL-C01 (efficacy and safety similarity study) regarding the study design, proposed dose, study duration, study population with corresponding

stratification factors, in each of them, primary and secondary study endpoints with sampling timepoints, sample size and statistical assumptions. Main recommendations: increase lower age limit to 25 years (P01 study) and to assess primary efficacy endpoint at month 12. If, PD endpoint to be included in the P01 study, then to increase study duration to 36 weeks.

- Agreement was sought on the use non-EU reference comparator based on the availability of analytical comparability between EU and US reference products.
- Agreement was sought on extrapolation to all approved clinical indications for the reference products, based on totality of evidence and scientific justification

Follow up scientific advice EMA/SA/0000084481

Clinical only

Based on the response from CHMP on the clinical studies, specific agreements on components of PK similarity and clinical efficacy safety studies were sought:

- Agreement to perform 2 pivotal clinical studies (AVT03- GL-P01 and AVT03-GL-C01), that AVT03-GL-P01 study will include PK as primary endpoint and PD as secondary endpoint but with a larger follow time up to 36 weeks. And to include PD as a co-primary endpoint in the AVT03-GL-C01 study.
- Agreement on efficacy and safety study design, including sample size calculations and statistical assumptions based on updated primary efficacy endpoint at month 12 together with PD as co-primary endpoint.
- Agreement on proposed data package.

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP), also referred as AVT03-FP Vial, is presented as a solution for injection. Each vial of AVT03 contains 1.7 mL of solution (70 mg/mL) corresponding to 120 mg of denosumab in as active substance.

Other ingredients are: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, Poloxamer 188 and water for injections.

The product is available in one strength 120mg in a single-use, clear glass vial (type I glass) with a bromobutyl stopper and aluminium flip-off cap.

2.3.2. Active Substance

2.3.2.1. General information

The active substance (AS) denosumab (also referred to as AVT03) is a full-length human monoclonal antibody consisting of two identical heavy chains (448 amino acid residues with 4 intramolecular disulfides) of

the IgG2 subclass, and two identical light chains (215 amino acid residues with 2 intramolecular disulfides) of the kappa subclass.

The mode of action (MOA) of denosumab involves a blocking mechanism, where the antibody binds to RANKL and prevents the RANKL-RANK interaction on the cell surface of osteoclasts. This results in decreased osteoclast formation and bone resorption, as well as a significant increase in bone mass and density.

The relative molecular mass of the intact drug substance is approximately 145 kDA. The theoretically determined extinction coefficient has been experimentally confirmed (1.37 L x g^{-1} x cm^{-1}). The provided information on AVT03 AS is sufficient. Further details on the structure and biological characteristics of AVT03 are described in detail under 3.2.S.3.1 and 3.2.R.

2.3.2.1. Manufacture, characterisation and process controls

Manufacturers

All sites involved in manufacture, in-process-, release- and stability testing of the AS, as well as manufacture and storage of cell banks are in compliance with GMP requirements.

Description of manufacturing process and process controls

The AS denosumab is expressed in a CHO cell line. Manufacture of a single batch of AVT03-active substance (AVT03-AS) starts from a single vial of the working cell bank (WCB). After thawing, the cells are expanded by serial sub-cultivations. After reaching a specified total culture duration, the culture broth is harvested and clarified by a series of filtration.

AVT03-AS is purified by a combination of column chromatography steps. The number of chromatography cycles that may be performed per AS is specified. A sufficient number of dedicated, orthogonal virus clearance steps are integrated into the purification process.

AVT03 AS is stored until further processing to finished product manufacture. No reprocessing is foreseen in the manufacture of AVT03 AS. Batch and scale were clearly defined and traceability of AS batches is ensured by a unique alpha-numeric identifier.

Overall, the applicant provided a detailed description of the manufacturing process and controls that is regarded in-line with regulatory requirements.

Control of materials

The information provided about the origin and history of the CHO cell line is satisfactory.

Expression plasmids were established for transfection into CHO cells. The coding sequence was optimised for efficient expression in CHO cells. Molecular cloning of the plasmids is described in sufficient detail. The coding sequences of both heavy chain (HC) and light chain (LC) were sequenced and covered completely, revealing 100% homology to the reference nucleotide sequence. The generation and selection of the stable-transfected production cell line is described satisfactorily. The clonality of single cell clones was verified. Single cell clones were screened for expression level, cell-specific productivity and protein quality with regard to similarity to the reference product. A primary seed bank (PSB) was established and the process to the research working cell bank (WCB) was described.

In summary, the information on cell line development is satisfactory.

A two-tiered cell bank system with master cell bank (MCB) and working cell bank (WCB) has been established. Overall, the cell banking system is adequately described with sufficient details on manufacture and storage of the MCB and WCB.

Satisfactory protocols describing manufacture and qualification acceptance criteria of new WCBs and routine stability monitoring of master and working cell banks are available. The applicant confirms that all media used for the preparation of MCB, WCB and PPCB are free from components of animal origin. Documentation of the production of MCB and WCB has been attached to section 3.2.R.

The characterisation of the expression constructs and cell substrate including MCB, WCB, and PPCB is in line with ICH Q5A, Q5B and Q5D. State-of-the-art analytical methods were applied. Characterisation of the cell banks included tests for sterility, identity, purity in terms of potential microbial and viral contaminants (please refer to discussion under A.2 Adventitious agents safety evaluation), and genetic stability.

In summary, qualification and characterisation of the cell banks is satisfactory.

Raw materials and process materials used in the upstream and downstream process are listed together with their quality standard (in-house specification, compliant with Ph. Eur., USP, BP, JP, ChP), and their intended use. Specifications are attached for non-compendial materials indicating the supplier and representative certificate of analysis. Acceptable in-house specifications were implemented for the non-compendial raw materials. All raw materials with product contact, besides the cells themselves, used in the upstream and downstream manufacturing process are animal component-free. The excipients (AS is fully formulated) comply with Ph. Eur. requirements (L-histidine, sucrose, poloxamer 188, water for injection). Sufficient details on chromatographic resins, filters and single-use bags are provided as well.

Qualitative composition of media powders used for the manufacture of the active substance together with a confirmation that an agreement is in place with the supplier to notify the MAH in case of changes to the medium have been provided in the dossier.

Control of critical steps and intermediates

The in-process sampling and control program is presented in section S.2.4. IPCs and respective test methods, sampling point, criticality classification (CPP, nCPP, CQA), blocking/non-blocking, action limit and acceptance criteria are listed for the upstream and downstream process.

The only critical process intermediate is clearly stated and CQAs defined. A report summarising results of in-vitro adventitious virus testing showed no detection of in-vitro adventitious viruses in the AVT03 bulk harvest. Further information is presented in section A.2 "Adventitious agents safety evaluation". The applicant specified that failure of in-process control will result in deviation and/or OOS investigation and upon confirmation the batch will not be processed further, which is endorsed.

Hold times were defined at several process steps. Hold times were appropriately established at-scale during process performance qualification.

The IPC control strategy was applied during PPQ, and results were consistent. QTPP establishment and final CQA definition was presented in the section regional information. In conclusion, the presented in-process control testing strategy appears acceptable and consistent results were shown during PPQ.

Process validation

In accordance with the Guideline on process validation for manufacture of biotechnology-derived active substances the process validation activities for AVT03-AS manufacture include process

development/characterisation (in S.2.6), process performance qualification, and continued process verification along the lifecycle.

Performance of the intended commercial AVT03-AS manufacturing process was verified at the intended commercial manufacturing site Alvotech hf Reykjavik. Consecutive process performance qualification (PPQ) batches were manufactured at commercial scale.

In summary, the presented process verification data demonstrate that the intended commercial AS manufacturing process performs consistently and delivers AVT03-AS complying with the release specifications under commercial operating conditions.

Clearance of impurities was tested cumulatively for each PPQ batch across various stages of the downstream process. The results show at which purification step there is a significant decrease of the respective impurity. The data show that there is a consistent impurity clearance across the downstream process and support the proposed specification and control strategy. The results showed a consistent distribution of product related impurities across steps and PPQ batches.

Resin lifetime and potential carry-over have been investigated; a cycle number has been defined for the resins and microbial data shows effective cleaning of the resins. The applicant described the actions taken in case results do not comply with the defined acceptance criteria.

Suitable stability parameters (such as pH, conductivity, colour, clarity, endotoxin, bioburden, poloxamer 188 content) were applicable were tested. Acceptable verified hold times were established for the buffers.

A cumulative product hold time study for process intermediates was performed at commercial scale during PPQ confirming the established hold-times.

Upon request the applicant provided a summary of the AS shipping validation (applicable for vial presentation Zvogra); the presented data is considered satisfactory.

Leachable study results for in-process samples have been provided together with risk assessments.

Manufacturing process development

Over the course of development, a small-scale process, pilot process, and at-scale process AVT03-AS batches manufactured at the proposed commercial scale at Alvotech hf Reykjavik. It has been confirmed that no changes were introduced to commercial process.

Early development of the upstream manufacturing in R&D included clone selection, process development, clarification and depth filter development. The process parameters for the downstream manufacturing were also defined during small scale development.

Qualified scale-down models were implemented and these scale-down models were used for process characterisation studies. Overall, the scale-down models were appropriately qualified and appear suitable for process development studies.

The AS release specification changed minimally during development.

The manufacturing process for AVT03-AS is based on development studies and manufacturing experience. The process was characterised to understand the acceptable operating ranges and define criticality of process parameters. The criticality assessment i.e., the designation of parameters as critical process parameters (CPPs)/non-CPPs, as well as proven acceptable range (PAR) and characterisation range (CR) were summarised. The ranges and criticality designation of each parameter are based on the outcome of a process

risk assessment and the process characterisation (PC) studies. Process characterisation was performed in qualified scale down models.

For the upstream process characterisation, relevant steps were included in the process characterisation studies. No parameters were considered as potential CPPs (pCPPs) for the previous cell culture expansion process steps, which is reasonable. All downstream steps were included in the process characterisation study. The process characterisation studies included multivariate design of experiment (DoE) and univariate (OFAT) studies. In the presented summary, for every characterised parameter, the characterisation range, proven acceptable range and criticality was presented. While the conclusions of the process characterisation studies were included in the initial submission, the primary data from these studies has not been provided. Since these process characterisation studies underpin the AS control strategy a Major Objection (MO) was raised in this regard. In their response, the and applicant provided detailed reports on the process risk assessment and the process characterisation (PC) studies for the AVT03 AS manufacturing process as requested, and the MO was resolved. Overall, based on the presented risk assessments and process characterisation studies for the upstream and downstream manufacturing process, the parameter categorisation and proposed proven acceptable ranges are sufficiently justified.

The applicant notes that no major changes were implemented in the upstream or downstream process since establishment of the at-scale process. Reports including the changes applied during development and the analytical assessment were attached. The comparability reports for the upstream and downstream manufacturing process are detailed. None of the noted differences have an impact on process performance or product quality.

Comparability between material derived from pilot scale and at-scale AVT03 AS batches has been established as well. The composition of the AS and FP is the same and has only a difference in concentration. Therefore, the comparability of extended characterisation between pilot and at-scale is demonstrated with FP batches, which is acceptable. A report was attached with details of changes and the comparability assessment. The release data for pilot batches and at scale batches met specification limits and are comparable. Based on the presented data in the report and as indicated in the summary of extended characterisation between pilot scale and at-scale batches the material derived from pilot scale- and at-scale batches can be regarded comparable.

A pilot batch was used to establish the first in-house reference material that was also used for release testing of the clinical material. In head-to-head studies applying extended characterisation the reference material was shown to be comparable to Prolia/Xgeva batches. Stability data of the reference material has been presented as well, confirming long-term stability.

Overall, it is agreed that comparability between material derived from different batches during manufacturing processes development has been appropriately established.

Characterisation

Elucidation of structure and other characteristics
The characterisation studies were conducted as part of the comparative analytical similarity assessment alongside the reference products Prolia and Xgeva. The results included full information on physicochemical and functional characterisation and were presented, as requested, into section 3.2.S.3.1.

Impurities
Product related impurities such as size and charge variants are appropriately controlled, and consistent removal has been evaluated during process performance qualification. Overall, the characterised product

related impurities, were shown to be consistently at or below the level of the reference product; slight differences have been appropriately discussed with regard to potential effects on safety/immunogenicity (e.g. afucosylation, mannosylation, charge variants, high molecular weight species, disulfide isoform). The product related impurities are appropriately presented and discussed.
Toxicology data was evaluated to determine the acceptance criteria for residual level of process-related impurities in the FP. Satisfactory data of clearance test results was presented complying with the established acceptance criteria.

The overall control strategy for process- and product related impurities is considered adequate.

Furthermore, the applicant provided a risk assessment for the potential formation or introduction of nitrosamines in the manufacturing processes. The risk analysis demonstrates a low risk of the presence of nitrosamines in the AVT03-AS. This conclusion is supported based on the provided risk evaluation as no risk has been identified with regard to the risk factors related to nitrosamine formation as outlined in the Questions and answers on CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products.

Container Closure

The container closure system (CCS), is a pre-sterilised single use 6 L flexible freeze and thaw bag with sampling port and shell container and is adequately described. Specifications, technical drawings, and representative release certificates were provided. The pre-assembled CCS is delivered gamma-sterilised by the vendor. The bag layer in contact with the product conforms with EP 3.1.7 (polyethylene-vinyl-acetate) and complies with FDA 21 CFR177.1350. TSE-BSE status conforms with EMA/410/01 rev3 and Ph. Eur. 5.2.8. Endotoxin complies with Ph. Eur. 2.6.14 and bioburden complies with ISO11737 method by filtration.

Container closure integrity testing has been verified. Furthermore, the applicant ensures integrity by qualification testing on seals and connections as well as by bioburden testing during the stability study. Stability data so far does not indicate compatibility issues of the drug substance in the CCS. Extractable studies were performed. It is agreed that extractables detected are not expected to be leached under long-term conditions. A leachables study showed that there is no risk to the patient by potential leachables from the primary drug substance container closure.

2.3.2.2. Specification

The release and shelf life specification for AVT03-AS comprises tests for general attributes (colour, clarity, pH), identity, protein content, charge heterogeneity, purity and impurities, biological activity, and microbiological safety (bacterial endotoxins and bioburden).

Acceptance criteria for the release and shelf-life of the active substance (AS is final formulated) are justified based on compendial requirements, and batch release and stability data. To establish specific acceptance criteria for qualitative attributes, statistical evaluation has been performed. In some instances, acceptance limits are set very wide and batch release and stability data would allow tighter acceptance criteria. Thus, the applicant tightened the potency acceptance range as well as the size variant limits and updated respective dossier section, which is acknowledged. Charge variant limits were further justified based on characterisation and biosimilarity studies. The applicant committed that acceptance ranges/limits will be re-evaluated once enough at-scale batches are available, which is endorsed. To this respect a recommendation is proposed **(REC).**

Protein content assay was fully validated in-house and is based on Ph. Eur. 2.5.33 Method 1, which is acceptable. The applicant appropriately tightened the HCP acceptance criteria in order to align with current manufacturing capability. Upon request, identifiers for in-house analytical methods were included in the specification table and in the method validation summaries.

Analytical procedures and reference standards
The analytical procedures are sufficiently described. Standard methods such as appearance (clarity, colour), pH, endotoxin, and bioburden are conducted according to Ph. Eur. For non-compendial methods, an overview of the method, reagents and equipment, sample preparations, procedure, representative chromatograms and electropherograms (reference material and stressed samples), system suitability and assay acceptance criteria, data analysis and reporting were provided. The analytical methods appear adequate for their intended purpose, while the implemented system suitability tests and sample acceptance criteria appear suitable to provide adequate control over analytical method performance.

The applicant provided validation summaries as well as full validation reports for non-compendial methods. Compendial methods were verified, and verification reports were provide. The relevant parameters have been assessed in accordance with ICH Q2(R2). In conclusion, adequate information has been provided regarding methods validation.

So far two reference materials were implemented. Both reference materials were sufficiently qualified and are subjected to re-testing during storage. The panel of analytical tests applied for re-testing is deemed suitable. The acceptance criteria for retesting of the current primary reference material have been further tightened based on additional available batch data. No stability trends were observed so far for both reference materials.

The applicant currently implements a two-tiered reference material system using a primary- (PRS) and a secondary reference material (WRS/SRS), which is strongly endorsed. Until the two-tiered reference material system is implemented the current primary in-house reference material will be used for routine use, which is acceptable.

In summary, the reference materials have been appropriately established and the protocol for implementation of the two-tiered reference standard systems is deemed acceptable.

Batch analyses
Overall, data from representative AS batches manufactured at commercial scale were presented all of which have been subjected to analytical similarity assessment. All results comply with the specifications valid at the time of release. All results are consistent between batches indicating a robust manufacturing process.

2.3.2.3. Stability

Long-term real-time stability data was provided from batches representative of the commercial scale over and from batch over. In addition, of data was provided for the three PPQ batches. The full set of data for accelerated and stress stability testing for batches was provided. At long-term storage conditions all quality attributes were within their acceptance criteria and no apparent trend was observed. No apparent trends were shown at accelerated conditions either. Thus, the AS shelf-life is acceptable.

In addition, a summary of performed photostability, high temperature stress, pH stress and oxidising agents stress studies was also presented. Based on the results of those studies, the applicant it was conclude that that the AS and FP should be protected from light and the dossier has been updated accordingly.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product (FP), also referred to as AVT03-FP Vial, is a sterile, preservative-free solution for subcutaneous administration containing 120 mg of denosumab as active substance.

AVT03-FP Vial is a clear, colourless to slightly yellow, liquid solution and practically free of visible particles. The container closure system of AVT03-FP Vial consists of a single-use type I borosilicate glass vial, a rubber stopper and an aluminium flip-off crimp cap.

The finished product has been sufficiently described. The excipients used are of compendial quality. AVT03-FP Vial does not contain any excipients of animal or human origin or any novel excipients. AVT03-FP Vial does not contain any stability or manufacturing overages.

The FP and the AS have the same denosumab concentration (70 mg/mL) and formulation. The formulation of AVT03-FP Vial is different to that of the EU-approved reference medicinal product Xgeva. The excipients are listed, and their function described. All excipients are of compendial quality and are controlled in compliance with the tests and acceptance criteria of compendial monographs. There are no novel excipients or excipients of animal origin used in the manufacture of the FP. The primary packaging components comply with Ph. Eur.

The suitability of the formulation was evaluated in several studies. The formulation of AVT03 FP vial (Zvogra) was developed in parallel with the AVT03 FP PFS (Kefdensis) with some differences in the concentrations of active substance (70 mg/mL vs. 60 mg/mL) and excipients. The formulation was defined early in development and its quantitative and qualitative composition remained unchanged since its definition. The formulation development included screening and optimisation DOE, univariate, and stability studies to evaluate different buffer systems, stabiliser/tonicity modifier and surfactants, using the attributes of the reference product (Xgeva) formulation as reference. The differences of the final formulation from the reference product has been discussed. In addition, the applicant performed formulation robustness studies to assess the impact of formulation parameter variations on stability-indicating quality attributes and to define a Proven Acceptable Range (PAR) for all formulation parameters. In conclusion, the chosen formulation appears suitable and adequately justified.

Upon request, the applicant confirmed compliance of the applied product (excipients, manufacturing process, packaging) with guideline EMA/CHMP/QWP/805880/2012 Rev. 2 (Guideline on pharmaceutical development of medicines for paediatric use).

The applicant stated that the AVT03 FP manufacturing process was developed based on development and manufacturing experience. An overview of the process changes during development from the manufacturing of clinical and the manufacturing of the PPQ batches has been presented. All changes were considered to be minor modifications and therefore no further study to demonstrate comparability between the clinical batch and the PPQ batches was deemed necessary, which is acceptable. However, the justification for some process parameter ranges refers to initial development. Upon request, it was explained that process parameter ranges for each unit operation within the DP manufacturing process were established based on the respective development and characterisation studies, and the respective report was included in the dossier. As a result of the studies performed, PARs (proven acceptable ranges) and CRs (characterisation ranges) were defined for each unit operation. Process parameters including their proven acceptable range (PAR), characterisation range (CR) and criticality assignment (CPPs/non-CPPs) have been provided in tables. The characterisation risk assessment, where CPPs were identified, and the underlying study reports have been provided.

Stability studies of the formulated bulk AS/FP with different single-use bags that are used during AS and FP manufacturing were conducted. The study on in-process leachables from the single-use bags/system used in the FP manufacturing process identified three compounds above the analytical evaluation threshold (AET). These compounds were evaluated against the safety thresholds as per ICH Q3C (R9) and were within the exposure limits. Therefore, it can be concluded that there is no risk to the patient due to potential leachables from the single-use bags/systems used in the AVT03-FP-Vial manufacturing process.

Compatibility studies of AVT03 bulk product with the product contact materials were conducted and data presented.

Temperature excursion and cycling studies were conducted and detailed information about the study design, tested samples and product attributes, and the results were provided, supporting the use of FP proposed exposure.

The FP is packaged in 2 mL clear colourless borosilicate type I glass vial with a 13 mm bromobutyl rubber coated stopper and a 13 mm aluminium plastic combination cap (aluminium seal with plastic flip off cap). Standard packaging materials for a parenteral preparation have been used and compliance with pertinent EU regulations have been confirmed.

The components in direct contact with the product are the glass vial and the rubber stopper. Both components meet the Ph. Eur. compendial requirements. The compatibility of the chosen CCS with the AVT03 formulation is currently being investigated in the ongoing AVT03 FP vial stability studies. To data, no substantial glass delamination has been observed over the period of the proposed shelf-life of 24 months at 2–8°C. The CCS is therefore considered compatible with the AVT03 drug product formulation.

Satisfactory information about the sterilisation method of the vials, stoppers and caps was provided confirming and compliance with the appropriate ISO standards as appropriate. Results of extractables studies were presented. No nitrosamines or nitrosatable substances were detected in extracts from the rubber stopper. In addition, none of the target PNA/PAH were detected. However, one extractable compound (IPA) was detected for the vial and several extractable compounds were found in the extracts of the rubber stoppers. In addition, extractable elements were detected in the extracts of the vial and the stopper. The identified extractables were subjected to a desk-based preliminary toxicological risk assessment and are further monitored in the ongoing long-term leachable stability study. The toxicological implications of these results were adequately discussed and justified.

A leachables screening study with the AVT03 FP vial CCS was conducted. The screening was performed using various analytical methods and any compound identified above the AET, was evaluated against the safety thresholds as per ICH Q3C (R9) and was found within the exposure limits. In addition, no detectable levels of elemental impurities were found. Therefore, the risk of leachables and elemental impurities can be considered low. However, the presented results do not cover the proposed shelf-life of 24 months. Therefore, the applicant should commit to providing the results of the ongoing long-term leachable studies for the AVT03 FP vial CCS once they are available, in order to support the conclusion regarding leachables risk **(REC)**.

Overall, the suitability of the primary packaging (CCS) has been adequately evaluated by the applicant.

2.3.3.1. Manufacture of the product and process controls

Sites involved in the manufacturing, packaging and testing have also been clearly listed in the dossier. Valid GMP certificates and/or manufacturing authorisations have been provided for all FP manufacturing sites.

The FP manufacturing process comprises of AS thawing, pooling and mixing, followed by bioburden reduction filtration, sterile filtration as well as aseptic filling, stoppering, crimping, manual visual inspection, labelling and packaging. A narrative description of the manufacturing process accompanied by a flow diagram including the in-process controls has been provided.

The manufacturing process steps are sufficiently described. No reprocessing steps are defined.

As part of the overall control strategy, critical steps of the AVT03 DP manufacturing process have been identified. A list of in process controls (IPC) including acceptance criteria have been provided. The selection of critical process steps and the corresponding IPCs is considered adequate. The relevant process parameters were provided in tables including the proven acceptable range (PAR) and criticality classification (Non-CPP or CPP). No design space has been claimed. Upon request, the setpoints and/or manufacturing operation ranges (MOR) of the process parameters of the commercial process, as confirmed during process validation, were also included. Furthermore, it has been defined that a maximum of AS batches can be pooled to manufacture one FP batch, in accordance with the performed process validation.

Batch composition for the smallest and the biggest proposed batch sizes have been presented. The batch numbering system was explained in the dossier with sufficient details. The batch size range was covered by process validation.

Information on all possible holding time has been added to the manufacturing process description and are supported by relevant studies**.**

Depyrogenation and sterilisation processes of vials and sterilisation of stoppers have been described and have been validated in accordance with the Guideline of Sterilisation of the Medicinal Drug Products (EMA/CHMP/QWP/ 850374/2015). Critical equipment used during manufacturing has been clearly presented.

Process validation was based on process risk assessment and characterisation studies which led to the definition of critical process parameters and acceptable ranges. The formal process validation of the FP manufacturing process has been conducted with AVT03 FP vial (120 mg/1.7 mL) batches using different AS batches. Critical steps identified during product development have been addressed and the results were compared to predefined validation criteria. All in-process controls and release tests of the batches met the predefined acceptance criteria.

Hold times were challenged and validated during the PPQ runs and the hold limits for commercial production adjusted accordingly.

Aseptic filling was validated by media fill. The results of the media fill studies support the specified filling hold time. Sterile filtration of AVT03 FP was also satisfactorily validated.

Transport of AVT03 FP was validated by in-lab shipping simulation to assess the impact of non-temperature (physical) transportation hazards on product quality during simulated shipment. The real-world transport conditions do not impair FP quality.

Overall, the manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.3.3.2. Product specification

The finished product release and shelf life specifications, include tests for a specific identity method (peptide mapping), content in terms of total protein (OD280), purity/impurities by cIEF (charge variants: main, acidic

and basic variants), purity/impurities by CE-SDS non-reducing (IgG monomer and total fragments) and reducing (sum of heavy chain + light chain), impurities by SEC-HPLC (HMW species), potency (inhibition of RANKL induced RANK activation in Saos-2 reporter cells), microbial attributes (bacterial endotoxins, sterility) and general attributes (colour, clarity, particulate contamination, pH, osmolality, extractable volume, uniformity of dosage units). In addition, poloxamer 188 concentration and container closure integrity are included in the specifications.

The proposed release and stability test specifications for AVT03 FP vial comply with the requirements of the general monographs Ph. Eur. 2031 (Monoclonal Antibodies for Human Use), Ph. Eur. 0520 (Parenteral Preparations), ICH Guideline Q6B, and the EMA Guideline on development, production, characterisation and specification for monoclonal antibodies and related products (EMA/CHMP/BWP/532517/2008).

A number of AVT03 FP batches were used to establish release and shelf-life specifications. All batches were representative of the final manufacturing process. Acceptance criteria are further justified based on compendial requirements, and lot release and stability data. To set specific acceptance criteria for qualitative attributes, statistical evaluation, where applicable, has been performed on AS level and presented in the DS section of the dossier (mean value, standard deviation and mean ± xSD). Batch data from all FP batches considered for justification of the FP specifications have been included.

In some instances, acceptance limits are set very wide, and the batch release and stability data would allow for tighter acceptance criteria. However, given the limited number of available batches, the proposed FP specifications are considered acceptable. The acceptance criteria for potency and size variants were tightened (for DP in alignment with DS) based on actual batch data. The decision to keeping the acceptance criteria for charge variants was appropriately justified. However, it is recommended to re-evaluate the acceptance criteria once a sufficient number of batches have been manufactured **(REC)**. The acceptance criteria for clarity and colour are considered appropriate.

All other specification parameters and the corresponding limits are adequately justified.

Analytical methods and reference materials

The analytical methods for FP release and stability testing have been described. Several test methods are identical to those for the AS and were assessed including their validation in the AS section.

The non-compendial methods used for FP only have been described in sufficient detail and satisfactory validation or verification reports have been provided. The analytical methods are adequate for their intended purpose. Reference materials are described and assessed under the AS section.

Batch analysis

Batch analyses data have been presented for development, clinical, engineering and PPQ batches. All clinical, engineering and batches complied with the specifications valid at the time of release. The provided batch data confirmed batch-to-batch consistency and uniformity of the product, indicating that the AVT03 FP vial process is under control.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on PPQ batches using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

2.3.3.3. Stability of the product

The applicant proposed a shelf life of 24 months at 2–8°C.

Stability data from long term, accelerated and stress studies have been provided. The comparability of the batches used to assess stability of AVT03 FP has been demonstrated and a report is provided in section P.2. The containers used in the stability studies are the same as those proposed for routine storage.

In accordance with ICH guidelines Q5C and Q1A(R2), a minimum of three batches supporting the shelf-life claim are required, which have been provided.

The batches have been tested in accordance with the stability specifications. Under the intended long-term storage conditions of 2–8°C, all test results have so far been in line with the shelf-life specifications.

Under accelerated storage conditions all presented results at accelerated storage conditions remained within the shelf-life specifications, except for identity by peptide mapping, which did not comply for one at the 6-month time point.

Under stressed storage conditions various degree of degradation was observed, which is expected under stress conditions.

The applicant proposes an out of the fridge (OOF) shelf life of 30 days at 25±2°C within the 24 months shelf-life of AVT03 finished product vial. Stability data covering the proposed OOF shelf life have been presented and the results were within the acceptance criteria of the shelf-life specifications. An additional OOF study is ongoing.

The long-term stability results were within the acceptance criteria of the shelf-life specifications and support the proposed out of fridge period of 30 days at 25±2°C within the 24-month shelf-life of AVT03-FP vial as stated in SmPC 6.3.

No photostability study was presented for the AS or FP. However, photodegradation studies are presented in section 3.2.R. The photodegradation studies were performed in compliance with the recommendation in ICH guideline Q1B. However, additionally the applicant has provided new photostability studies results. Based on the available data from photostability, AVT03-FP vial packing is considered light resistant. Upon request, the applicant updated section 3.2.P.3.3 to include the measures implemented to avoid light exposure throughout the AVT03-FP vial manufacturing process. The following information on light protection is given in the SmPC: "Keep the vial in the outer carton in order to protect from light."

The applicant commits to conduct and complete the ongoing stability studies.

The proposed shelf life for AVT03-FP vial of 2 years and storage conditions "Store in a refrigerator (2°C – 8°C)", "Do not freeze", "Keep the pre-filled syringe in the outer carton in order to protect from light", as stated in the SmPC sections 6.3 and 6.4 are acceptable.

2.3.3.4. Biosimilarity

The applicant performed the comparative analytical similarity assessment in a stepwise manner, with initial analysis of reference product (RP) sourced from EU and US used as a guide for development of AVT03 and establishing the quality target product profile (QTPP). This is followed by head-to-head (H2H) comparative analytical similarity assessments. All this data is collected and assessed to form the cumulative comparative analytical similarity assessment. This included the confirmation of similarity between the two presentations (vial and PFS), as well as bridging between Prolia and Xgeva marketed in EU and US. Furthermore, a comparative forced degradation study and an additional comparative characterisation was performed.

The applicant used a two-step risk-based approach to assess the criticality of the quality attributes. First relevant CQAs are identified and assessed using an impact and uncertainty approach, with an impact assessment in four categories: biological activity, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity, and safety. In a second step the risk is then further evaluated based on additional product specific knowledge acquired from release testing and characterisation, as well as stability and forced degradation studies. The level of the attribute present in the product is also considered. This criticality risk ranking (CRR) allows for upgrading or downgrading of CQAs. A summary of the CQA assessment and its outcome was presented. Overall, the list of CQAs and their criticality risk ratings as well as their justification appear reasonable.

AVT03-FP vial batches were included in the analytical similarity assessment of AVT03 vial and EU-Xgeva and EU-Prolia. Overall, the number of lots is expected to reflect variability sufficiently and is deemed acceptable for evaluation of similarity.

At the time of testing a broad range of lot ages is covered for the proposed biosimilar and the reference product. The AVT03 stability results do not indicate a trend for selected quality attributes and the comparative degradation studies show similar degradation profiles of AVT03-FP and EU/US Prolia/Xgeva.

Batches of AVT03 were assessed using the same primary product container closure system as used in the finished product presentations.

The analytical methods used for the comparative analytical similarity studies are in-line with expectations to cover structural as well as biological quality attributes in sufficient detail. Concerning Fc-related functions additional characterisation studies sufficiently established data that was requested in EMA Scientific Advice (EMA/SA/0000061798).

For the evaluation of the analytical similarity data, the applicant used a quality range approach (mean RMP ± X SD). The multiplier "X" was assessed and justified for each analytical method. Overall, the applicant appropriately discussed the statistical approach as recommended in the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development.

Overall, the similarity testing strategy is deemed acceptable and in line with the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues.

Test Methods

The applicant applied a comprehensive set of orthogonal state-of-the-art analytical methods that cover primary structure, higher order structure, post-translational modifications, physicochemical attributes, process related impurities, potency and Fc related attributes. The validation or qualification status of all analytical methods was indicated, and short descriptions of characterisation assays provided. Except for validated methods that are also used for release testing the analytical methods used for characterisation purposes were confirmed to be fit for purpose.

Two cell-based assays have been applied to characterise the RANKL related mechanism of action (potency). The osteoclast differentiation assay, directly address the mechanism of action of denosumab, complemented by the validated cell-based reporter gene assay in Saos-2 cells.

Overall, the analytical methods used for the analytical comparability exercise are considered sufficient and are suitable for the intended use.

Bridging Study
A bridging study was performed in order to show similarity between the different presentations of EU and US Prolia and Xgeva i.e. PFS and vial respectively. Also, the similarity between EU and US Prolia and Xgeva was established. The bridging study report is based on data that were established across head-to-head analytical similarity studies.

Overall, it can be concluded that US-Prolia and US-Xgeva are comparable. Therefore, data from US-Prolia and US-Xgeva can be pooled for generation of the US-reference product quality range for comparative analytical similarity assessment. In addition, it can be concluded that EU-Prolia and EU-Xgeva are comparable and therefore data from EU-Prolia and EU-Xgeva can be pooled to establish the EU-reference product quality range for comparative analytical similarity assessment. Furthermore, the EU-reference product quality range can be regarded comparable to US-reference product quality ranges, which supports the extrapolation of clinical data generated with US-Prolia to EU-Prolia and EU-Xgeva. Comparability between AVT03-FP vial and PFS presentations has been demonstrated with data.

Comparative Forced Degradation Assessment
As part of the comparative analytical similarity assessment a head-to-head (H2H) comparative forced degradation study was conducted.

Under stress most quality attributes trended similar between AVT03 and EU/US Prolia/Xgeva batches.

Overall, forced degradation studies show a mostly similar behaviour of AVT03 batches (vial and PFS) compared to the reference products EU/US Prolia and Xgeva under different stress conditions.

Table 1: Results of comparative analytical similarity assessment

Summary of biosimilar assessment		
Molecular parameter / Attribute	**Methods**	**Key findings, conclusions**
Primary structure	Primary sequence determination (multiple methods including Edmans and various peptide mapping LC-MS & MS/MS)	Identical amino acid sequence for AVT03 and EU-Xgeva without discrimination of the isobaric amino acids leucine and isoleucine for AVT03.

		Intact, reduced, and de-N-glycosylated and reduced molecular mass (LC- MS)	Similar molecular mass and size were demonstrated at the intact and sub-unit level for AVT03-FP vial and EU-quality ranges.
		Peptide mapping (LC-MS)	Similar peptide map profiles and identical amino acid sequence observed in AVT03-FP vial and EU-quality ranges.
Higher order structure	Secondary structure	Far-UV CD	Similar secondary structure for AVT03-FP vial and EU-quality ranges.
		FT-IR	
		DSC	Similar DSC thermograms and Tm values for AVT03, EU-quality ranges, with a marginally lower melting temperature for AVT03.
	Tertiary structure including disulfide and trisulfide bonds	Near-UV CD	Similar tertiary structure observed for AVT03- FP vial and EU-Prolia and EU-Xgeva based on near-UV CD.
		Intrinsic fluorescence	Comparable intrinsic fluorescence ratios indicate a similar tertiary structure for AVT03-FP vial and EU-quality ranges.
		Non-reduced peptide mapping (LC-MS)	Similar disulfide and trisulfide bond connectivity was demonstrated for AVT03-FP vial and EU-quality ranges. Abundance of the trisulfide linkages in AVT03 are similar to the EU-quality ranges.
	Free thiols	Ellman’s reagent	Similar levels of free thiol were detected in AVT03-FP vial and EU-quality ranges.
	Afucosylation	Rapifluor	The levels of total afucosylation are marginally higher in AVT03 vial compared to EU-quality ranges, due to the lack of effector functions for denosumab, the marginal differences in afucosylation are not expected to impact the efficacy of AVT03
	Terminal galactose		The terminal galactosylation levels of AVT03 are similar to those of EU-quality ranges.
	High mannose		AVT03 shows slightly lower high mannose levels than EU-quality ranges, the marginally lower high mannose levels in AVT03 is not expected to translate to a meaningful difference in the PK profile, which is corroborated with similar FcRn binding of all samples analysed.
	Sialylation		The sialylation levels in AVT03 are similar to those of EU-quality ranges.
	Deamidation	Peptide mapping (LC-MS)	The deamidation levels at most of the sites are largely similar for AVT03-FP vial and EU- quality ranges.
	Met Oxidation Trp Oxidation		The Met oxidation and Trp oxidation in AVT03 vial and EU-quality ranges are comparable, with similar levels of oxidation detected in AVT03 at the most commonly oxidised M253 site.

	Succinimide		Similar succinimide formation was detected in AVT03, EU-Prolia and EU-Xgeva.
	Aspartate isomerisation		Similar levels of aspartic acid isomerisation detected in AVT03 vial, as compared to EU- quality ranges.
	N/C-terminal integrity		Similar HC and LC N-terminal pyroglutamate formation levels were detected in AVT03, EU- Prolia, and EU-Xgeva. C-terminal lysine levels are similar in AVT03 and EU-quality range. C-terminal proline amidation levels are higher in AVT03, compared to the EU-quality range.
	Cysteinylation		Cysteinylation of AVT03 was within the range observed in EU-Prolia and EU-Xgeva.
Functional activity	Potency	Inhibition of RANKL-induced RANK activation in Saos-2 reporter cells	The marginally lower potency observed in AVT03 is not expected to impact the efficacy of AVT03.
		Osteoclast differentiation	Similar potency observed between AVT03 vial and EU-quality ranges.
	RANKL binding	RANKL binding SPR kinetic	RANKL binding ability of AVT03-FP vial batches is similar to the EU-quality ranges.
	FcRn	FcRn binding SPR	FcRn binding ability of AVT03-FP vial is similar to the EU-quality ranges.
	FcγRIIa	FcγRIIa 131H binding by SPR	Overall, the FcγRIIa binding ability of AVT03-FP vial is similar to the EU-Prolia and EU-Xgeva batches.
Physicochemical analyses	Protein content	OD280	The protein content, in terms of protein concentration, in AVT03-FP vial is similar to EU-Xgeva.
	Charge variants	cIEF	The abundance of main variants in AVT03 is similar to EU-Prolia and EU-Xgeva, with acidic variants of most AVT03 batches sitting outside of the EU-quality range. The level of basic variants in AVT03 batches is higher than in EU-Prolia and EU-Xgeva, mainly due to the higher proline amidation present (see N-C terminal integrity section). The same result is confirmed for charge variants post CPB digestion, confirming that basic variants are not a result of C-terminal lysines.
		cIEF + CPB	
	Size variants	CE-SDS Non-Reduced	Similar fragmentation was detected in AVT03- FP vial and EU-quality ranges.
		CE-SDS Reduced	Overall, AVT03 is similar to EU-quality ranges.

		SEC-HPLC	The small differences observed in HMW contain are not expected to impact the efficacy of AVT03 either and the same is demonstrated through the potency and RANKL binding Additionally, the orthogonal SV-AUC method does not show similar high aggregation values for AVT03.
		SEC-MALS	Monomer and dimers with comparable molar mass observed in AVT03-FP vial and EU- quality ranges.
		SV-AUC	The abundance of dimer and higher order aggregates were similar in AVT03 vial and EU-quality ranges.
Particle analyses	Sub-visible particles	MFI	The AVT03 vial batches show similar size and distribution of sub-visible particles as EU- Xgeva min-max ranges. And qualitatively similar sub-visible particles in AVT03 and EU-Xgeva.
		DLS	
Disulfide Isoform Distribution		Disulfide isoform distribution RP-HPLC	It can be concluded that the differences observed between AVT03 and reference product with respect to the abundance of different disulfide isoforms are not expected to be clinically significant.

The amino acid sequence for AVT03 and EU/US-Xgeva is identical as determined by Edman sequencing and LC-MS sub-unit mass analysis and multienzyme peptide map LC-MS. Similar molecular masses were determined for intact-, reduced- and N-deglycosylated reduced mass analysis by LC-MS.

Far-UV circular dichroism and Fourier transformed-infrared spectroscopy (FT-IR) spectra are mostly similar and indicate similar secondary structure. The melting temperature as assessed by differential scanning calorimetry (DSC) is slightly lower for AVT03 batches than the quality ranges derived from the EU and US reference products. It is agreed that this most probably is due to differences in formulation or differences in relative abundance of different disulfide isoforms and is not expected to have an effect on safety and efficacy of AVT03.

Similar near-UV circular dichroism and intrinsic fluorescence spectra indicate similar tertiary structure. Disulfide bonds and trisulfide content as analysed by non-reduced peptide mapping (LC-MS) are similar to the EU and US quality range.

Denosumab contains 18 disulfide bridges and the disulfide isoforms in AVT03 were analysed. Compared to EU- and US-Prolia and Xgeva, AVT03 contains different levels of A and A/B isoforms and thus a lower level of B disulfide isoform. The applicant notes that IgG2 disulfide isoforms interconvert to the B isoform in vitro and in vivo and therefore differences in this quality attribute have little to no effect on safety or efficacy. Furthermore, epitope exposure of AVT03 is within the range of reference product batches (data not provided). In addition, a comparable immunogenicity profile was observed for AVT03 clinical studies. Enriched isoforms were also tested for binding affinity to RANKL as well as for potency in the Saos-RANKL cell-based assay. It was shown that disulfide isoform distribution seems to have a minimal effect on biological activity. Furthermore, the applicant referred to scientific literature, showing that different isoforms are not cleared differently from the bloodstream of patients, indicating that PK is unaffected in blood. In principle it can be agreed that the difference in disulfide isoforms in AVT03 are not expected to have an effect on safety and efficacy. This difference has been further discussed and justified with data to confirm high similarity

between biosimilar and reference product. Characterisation data for IgG2 isoforms in AVT03 and reference product has been provided (potency, PTMs, SEC profile).

Free thiols overall appear slightly higher for AVT03 batches and a few batches were slightly above the EU and US reference quality range. However, it is agreed that the free thiol levels are still low and are unlikely to impact efficacy and safety.

Total afucosylation AVT03 PFS batches and AVT03 vial batches are higher than the quality ranges derived from the EU reference product batches. Afucosylation without high mannose content in all the AVT03 batches are higher than the quality ranges derived from EU and US reference products. The mechanism of action of denosumab does not involve effector functions. In additional characterisation studies, the applicant showed that there is indeed a slight increase of binding to FcγRIIIa (158V) which can be expected based on the higher level of afucosylation. Thus, ADCC effector function was analysed using two different target cell lines (Saos-2, CHOmRANKL). AVT03 showed a similar lack of ADCC activity as Prolia and Xgeva. Therefore, the slight increased level of afucosylation is not expected to have an impact on efficacy and safety.

The galactosylation and sialylation levels of AVT03 are similar to the EU and US reference products. High mannose glycans in AVT03 are slightly lower than in the reference products and some AVT03 batches are outside the EU reference product quality range. As with afucosylsation, high mannose glycans can impact binding to FcγRIIIa and ADCC activity. As mentioned above, although there is slightly higher affinity to FcγRIIIa no increased ADCC activity was shown. Thus, the slightly lower high mannose glycan content can be accepted.

Oxidation levels of methionine and tryptophan were measurable and similar between AVT03 and EU/US reference products. Deamidation was detected and the levels were similar to the reference products or slightly lower for AVT03. Similar succinimide formation was detected in AVT03, EU-Prolia and EU-Xgeva.

Potency was evaluated using the inhibition of RANKL-induced RANK activation assay. The potency of all AVT03 vial batches is within the quality range derived from US reference product. All AVT03 PFS batches are within the quality range derived from EU reference product. The applicant has justified and that can be agreed that the slightly lower potency observed in one AVT03 vial batch is due to method variability and is not expected to impact the efficacy of AVT03.

The potency of AVT03, as determined by the osteoclast differentiation assay, is similar to EU-Prolia, EU-Xgeva, US-Prolia and US-Xgeva.

In addition, the binding affinity of AVT03 to RANKL as determined by surface plasmon resonance (SPR) is similar to EU-Prolia, EU-Xgeva, US-Prolia and US-Xgeva. Binding of AVT03 to FcRn as analysed by SPR is similar to EU-Prolia, EU-Xgeva, US-Prolia and US-Xgeva. Binding to FcγRIIa 131H is generally within the quality range derived from the US and the EU reference product batches. Since ADCP is not related to the MoA of AVT03, the slight differences in binding to FcγRIIa 131H are not expected to impact the efficacy of the product.

The protein concentrations of AVT03 PFS and vial are similar to EU- and US-Prolia and the protein concentration of AVT03 vial is similar to EU- and US-Xgeva.

Main variants in AVT03 are similar to EU-Prolia and EU-Xgeva, indicating similar pI. Certain differences were discussed. In addition, the applicant characterised isolated charge variant fractions. Importantly, RANKL binding is similar indicating similar potency for different charge variant. Overall, it is agreed that the differences observed in charge variants are not expected to impact the safety and efficacy of AVT03.

Non-reduced CE-SDS showed similar intact IgG monomer and product related impurities content. By reduced CE-SDS, lower deglycosylated heavy chain (DHC) and lower other fragments content, which is favourable.

High molecular weight species (HMW) as measured by SEC-HPLC were slightly higher for AVT03-FP vial than for EU-Prolia and EU-Xgeva. However, there are no differences in potency or RANKL binding and the generally low levels of HMWs detected in AVT03 batches are not expected to impact the immunogenicity of protein. Thus, it is agreed that the slightly higher HMW species are not expected to impact safety and immunogenicity of AVT03.

Polydispersity (PD) and Z-average were analysed by dynamic light scattering (DLS). All the values are of same order of magnitude and thus can be considered as similar.

Subvisible particles in AVT03, Prolia and Xgeva batches are also tested by micro-flow imaging (MFI). Subvisible particles in AVT03 PFS and AVT03 vial batches are similar to the EU- and US-Prolia and EU- and US-Xgeva batches, respectively, except AVT03 vial batch. This batch was used for clinical studies and any impact of the higher subvisible particle in safety or efficacy of this batch is reported and therefore in principle clinically justified.

Conclusion on biosimilarity

To conclude, the biosimilarity evaluation was performed based on an acceptable number of reference product batches for setting acceptance criteria for similarity evaluation. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. The presented analytical data demonstrate analytical similarity of the proposed biosimilar AVT03 and the reference products EU-Prolia, EU-Xgeva and US-Prolia, US-Xgeva. Minor analytical differences have been appropriately assessed by the applicant regarding their potential impact on clinical performance of the product. The observed differences are not expected to adversely impact safety or efficacy of AVT03.

2.3.3.5. Post approval change management protocol(s)

Not applicable.

2.3.3.6. Adventitious agents

Non-viral adventitious agents

All solid and liquid raw materials, solutions and buffers, and all excipients are tested for bacterial endotoxins (Ph. Eur. 2.6.14.). In addition, bioburden testing (Ph. Eur. 2.6.12) is performed on purified water and water for injection. No materials are used in the manufacture of AVT03 that are considered Transmissible Spongiform Encephalopathy (TSE) or Bovine Spongiform Encephalopathy (BSE) risk materials. Some product contact materials contain materials of animal origin but are in compliance with "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01)". Therefore, the BSE/TSE risk is considered negligible.

The MCB, the WCB and the PPCB were tested for sterility (Ph. Eur. 2.6.1) and mycoplasma (Ph. Eur. 2.6.7) in accordance with ICH guideline Q5D.

During the AVT03 manufacturing process, several measures are taken to control and monitor potential non-viral adventitious agent contamination. With respect to non-viral adventitious agents, the manufacturing process design and control strategy are considered adequate to ensure product safety.

Viral adventitious agents

In compliance with the ICH Q5A(R2) three complementary approaches are applied to control potential viral contamination of AVT03.

- The cell bank testing programme used to demonstrate the absence of adventitious viral agents complies with the ICH Q5A(R2) guideline.

- The unprocessed bulk harvest is routinely tested for the absence of adventitious viruses.

Robust and effective overall virus clearance by orthogonal manufacturing process steps has been demonstrated. Two dedicated virus clearance steps, as well as a chromatography step effectively reduce enveloped and non-enveloped viruses. The viral clearance study demonstrated an overall clearance which is considered acceptable for mAbs produced in CHO cells.

Brief descriptions of the virus testing methods and a summary of method validation and /or method qualification as appropriate have been provided.

Upon request, virus inactivation kinetics during low pH treatment have been provided.

In summary, the risk of potential contamination and transmission of bacterial, viral, or TSE agents appears to be adequately controlled and acceptably low.

2.3.3.7. GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Zvogra has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Xgeva.

Denosumab active substance is manufactured using a typical manufacturing process for monoclonal antibodies. The manufacturing process including process parameters and in-process controls was described in sufficient detail. A MO had been raised requesting the primary data from the process characterisation studies, which was resolved by the provision of the requested data. The provided process characterisation and process performance qualification (PPQ) data support the conclusion that the active substance manufacturing process reliably generates active substance (and subsequently finished product) meeting its predetermined specifications and quality attributes.

The overall control strategy was established in accordance with ICH Q11 and ensures that material of sufficiently high quality will enter the market. The proposed AVT03-AS release and stability specifications are acceptable. However, it is recommended to re-evaluate the acceptance criteria for potency, charge and size variants, once a sufficient number of batches have been manufactured. **(REC1)**

The manufacturing process of the finished product are sufficiently described. Process parameters, listed as CPP or non-CPP with MORs (manufacturing operating ranges) and proven acceptable ranges (PARs) are adequately justified. Appropriate controls with acceptance criteria have been defined for manufacturing steps, which are considered as critical.

Process validation and batch data indicate that the manufacturing process reliably generates FP meeting its predetermined specifications and quality attributes.

The proposed FP specifications are tightly linked to the AS specifications and are generally in line with requirements of general monographs Ph. Eur. 2031 and 0520 and ICH Q6B and are acceptable considering the limited number of batches. However, it is recommended to re-evaluate the acceptance criteria for potency, charge and size variants, once a sufficient number of batches have been manufactured **(REC1).**

The container closure system has been adequately described and fully characterised. In principle, the risk of leachables and elemental impurities can be considered low. However, the results of the ongoing long-term leachable studies for AVT03 FP vial should be provided to further support the conclusion regarding leachables risk **(REC2)**.

Biosimilarity versus the reference product was sufficiently demonstrated. From the quality perspective, Zvogra is approvable as proposed biosimilar to Prolia. No quality aspects impacting on the Benefit-Risk balance have been identified.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to re-evaluating the AS and FP acceptance criteria for potency, charge and size variants, once a sufficient number of batches has been manufactured; and providing the results of the ongoing long-term leachable studies for the FP. These points are put forward and agreed as recommendations for future quality development.

Overall, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Biosimilarity has been demonstrated versus the reference product Xgeva. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should i) re-evaluate the specifications, i.e. for potency, charge and size variants, and potentially tighten the respective specification limits, once a sufficient number of batches is available and ii) introduce any resulting changes to release and stability specifications via a post-approval variation.
2. The applicant should commit to providing the results of the ongoing AVT03-FP vial long-term leachable study once they are available, in order to further support the conclusion regarding leachables risk. This is also important, to exclude any potential nonanal content (as a potential leachable from the dosing bag) in the AVT03-FP vial, when manufactured according to the

commercial manufacturing process (PPQ batches).

2.4. Non-clinical aspects

2.4.1. Introduction

Zvogra is under development as a biosimilar to Xgeva, which contains 120 mg denosumab monoclonal antibody as active ingredient presented as a solution for injection under the skin. The active substance (denosumab) is a human monoclonal antibody of the IgG2 subtype that inhibits the interaction of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) with RANK on the surface of osteoclasts. This inhibition prevents the development (genesis, maturation, activation and survival) of osteoclasts, the cells responsible for bone resorption that play a critical role in bone modelling and remodelling during growth. Pathological disturbance of this balance towards excessive bone resorption can be counteracted by means of RANKL-inhibition with denosumab.

Aspects of nonclinical development fall within the regulatory scope of *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010*), according to which nonclinical *in vivo* studies are deemed dispensable if no relevant factors (e.g., differences to the RMP in quality attributes or formulation) suggest otherwise. No such factors were identified for Zvogra.

Accordingly, no nonclinical in vivo studies were provided by the applicant under Module 4 of the eCTD.

2.4.2. Ecotoxicity/environmental risk assessment

The API of Zvogra is denosumab which is a IgG2 (RANK ligand inhibitor), and thus a protein without any non-protein conjugate. Denosumab is not expected to result in a significant risk to the environment. The applicant, therefore, regards the calculations of the potential environmental exposure, the conduct of environmental studies for an assessment of possible risks to the environment, and an evaluation of precautionary and safety measures regarding the environmental release from use in patients and disposal as not necessary. Proposals for labelling outlining safety measures for the purpose of reducing any risks to the environment is likewise regarded as not required.

2.4.3. Discussion on non-clinical aspects

It is supported that the applicant did not submit non-clinical in vivo studies as part of this application, in line with the *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), w*hich states that non-clinical *in vivo* studies are deemed dispensable if no relevant factors (e.g., differences to the RMP in quality attributes or formulation) suggest otherwise.

Environmental risk assessment

The use of medicinal product Zvogra is not expected to pose a risk to the environment as the active substance denosumab is a natural product (protein), therefore its use will not alter the concentration of distribution of the substance in the environment.

In conclusion, the marketing authorisation application for Zvogra is considered approvable based on non-clinical aspects.

2.4.4. Conclusion on the non-clinical aspects

The CHMP considers that the MAA for Zvogra is approvable from a non-clinical perspective.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
AVT03-GL-P01	Double blind, randomized, parallel-group, single dose	206 healthy male volunteers (n=99 in the AVT03 arm, 107 in the US-Prolia arm)	Single dose of 60 mg (s.c. injection)	Healthy volunteers
AVT03-GL-C01	Double-blind, randomized, parallel design, 2 arm, repeat dose	532 postmenopausal women with osteoporosis (n=266 in the AVT03 arm, 266 in the US-Prolia arm)	60mg (s.c. injection) on Day 1, Day180 (month 6), Day 365 (month 12) and month 18	Postmenopausal women

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The clinical pharmacology of AVT03 and the reference product has been investigated in two studies:

- Study AVT03-GL-P01: a double-blind, randomized, single centre, 2-arm, single-dose, parallel-group study in healthy male subjects to compare the pharmacokinetics, pharmacodynamics, safety and immunogenicity of AVT03 – proposed biosimilar to denosumab with US-Prolia.
- Study AVT03-GL-C01: a double-blind, randomized, multicentre, 2-arm, multiple-dose, parallel-group study with a transition/follow up period, to compare efficacy, safety, tolerability, and immunogenicity of the proposed biosimilar to denosumab AVT03 with US-Prolia (denosumab) in women with PMO. Bone biomarkers (PD) and PK were also assessed.

Bioanalytical methods

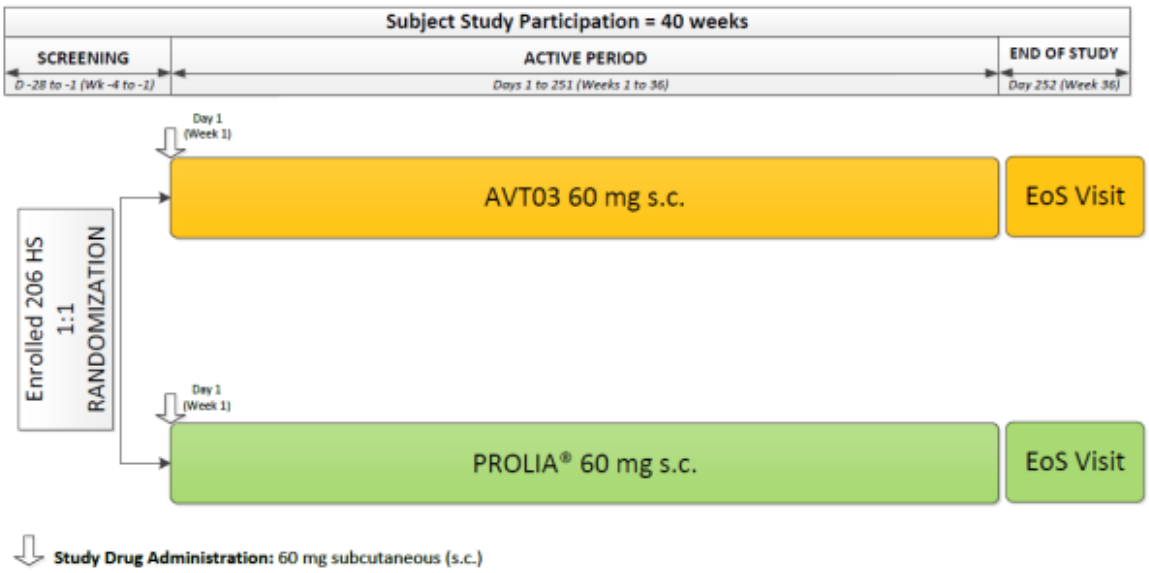
PK Assay

The applicant has adopted an electrochemiluminescence (ECL) sandwich immunoassay to quantitate AVT03 and Prolia/Xgeva (denosumab). The presented assay for determination of denosumab in human serum of healthy volunteers and patients with postmenopausal osteoporosis was well described and established. It is considered valid for its intended use.

Main study

Study AVT03-GL-P01 was a phase I, randomized, double-blind, single-dose, parallel-group design, 2-arm study comparing the PK, PD, safety, tolerability, and immunogenicity profiles of AVT03 and Prolia in healthy male participants. Subjects were randomly assigned to receive either 60 mg of AVT03 SC or 60mg of US-Prolia SC. The study consisted of a 4-week screening period, a 36-week treatment and assessment period and an end of study (EoS) visit on Day 252. The study duration per participant was approximately 40 weeks. A total of 209 participants were enrolled into the study and all enrolled participants were randomized to 1 of the 2 treatment groups: 101 to AVT03 and 108 to US-Prolia group.

Figure 1: Schematic of Study Design



Abbreviations: D = day; EoS = End of Study; s.c. = subcutaneous; Wk = week.
Notes: Screening was from Day −28 to −2. Eligible subjects were admitted to the study site on Day −1 following which their continued eligibility was assessed.

Study Participants

Key eligibility criteria

Healthy male or female subjects between 28 and 55 years of age with a Body mass index (BMI) of 17.0 to 32.0 kg/m² (inclusive) and a body weight of at least 50 kg were eligible for the study. The exclusion criteria were established to ensure the recruitment of a healthy population with no conditions that affect bone metabolism.

Treatments

Table 2: Investigational Product Details

	Test Product	**Reference Product**
IP Name	AVT03 (denosumab)	Prolia (denosumab)
Dosage formulation	60 mg/mL denosumab Formulated with: histidine buffer, sucrose, Poloxamer 188, and Water for Injection (USP)	60 mg/mL denosumab Formulated with: sorbitol, acetate buffer, polysorbate 20, and Water for Injection (USP)
Unit Dose Strength	The IP was supplied as a single-use prefilled syringe, which delivered 60 mg of AVT03 or Prolia; a single dose of 60 mg in 1 mL was administered.	
Packaging and Labelling	All clinical study material was packaged and labelled in compliance with GMP and local regulatory requirements.	
Storage Conditions	The Ips were to be stored refrigerated, at 2°C to 8°C.	
Manufacturer	Alvotech hf	Amgen Inc., US

Objectives

The **primary objective** of the study was to assess the bioequivalence of single s.c. doses of:

- AVT03 vs. US-Prolia in healthy subjects

The **secondary objectives** of the study were:

- To evaluate and compare the derived pharmacokinetics and pharmacodynamics of single s.c. doses of AVT03 and US-Prolia in healthy subjects.
- To evaluate the safety, tolerability, and immunogenicity of single s.c. doses of AVT03, US-Prolia healthy subjects.

Endpoints

Primary PK endpoints:

- Area under the serum concentration vs. time curve from time 0 to infinity (**AUC_{0-inf}**)
- Maximum observed serum concentration (**C_{max}**)

Secondary PK endpoints:

- AUC from time 0 to 24 (**AUC_{0-24}**)
- Time of reach the maximum observed serum concentration (**T_{max}**)
- Apparent total body clearance following extravascular administration (**CL/F**)
- Apparent terminal elimination half-life (**$t_{1/2}$**)
- Kel
- Vz/F

Sample size

The primary PK endpoints for this study were Cmax, and AUC0-inf. Sample size calculations were performed using SAS version 9.4 and were based on data from a previous study with Prolia (Study 20060286). Based on that study, the intersubject coefficient of variation (CV%) was assumed to be 33.5% for Cmax and 35.1% for AUC0-inf.

There were 2 treatment groups, AVT03 and US-Prolia. The assessment of PK similarity was to be based on the 90% confidence intervals (CI) of the geometric mean ratio (GMR) between the 2 treatment groups. To demonstrate PK similarity, the 90% CIs of the GMRs must be contained within the prespecified margins of 80% to 125% (when the ratio is expressed as a percentage) for the following primary endpoints:

- Cmax and AUC0-inf

Assuming a true geometric mean ratio of 95% for each of the primary endpoints Cmax, AUC0-last, and AUC0-inf, 164 subjects were required to provide a power of 95.7% for Cmax and 94.2% for AUC0-inf, this was planned to provide an overall study power of 90.1%. Taking into consideration a non-evaluable rate of up to 20%, the sample size was planned to be 206 subjects in total (103 per treatment group).

Randomisation and blinding

Randomisation

A computer-generated randomisation schedule was created by an unblinded statistician prior to study start and uploaded into the electronic data capture (EDC) system (Viedoc). Randomisation to AVT03 or Prolia was

performed in a 1:1 ratio. The randomisation was stratified by body weight (≤75 kg and >75 kg). After signing the ICF, each subject was assigned a Screening number according to the screening order. Following confirmation of eligibility on Day 1, subjects were allocated a unique randomisation number based on the predetermined strata-based randomisation schedule, and according to their chronological order of inclusion in the study.

Blinding

The study was a double-blind study and therefore, apart from prespecified unblinded individuals, the Investigator, site staff, Sponsor, Sponsor's delegates (if applicable) and all subjects were blinded to treatment. No individual subject information that could potentially unblind the Investigator or subject was reported until the end of the study. Appropriate IP blinding techniques were implemented during the study as per the sites' standard operating procedures. Appropriate steps were taken to ensure the blind was maintained – dosing was performed separate from other blinded study site staff. The Investigator remained blinded, unless knowledge of the subjects' treatment assignment was necessary for the clinical management or welfare of the subject. In case of an emergency, the Investigator had the sole responsibility for determining if unblinding of a subject's treatment assignment was warranted. If the Investigator decided that unblinding was warranted, the Investigator was to make every effort to contact the Medical Monitor and Sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment was unblinded, the Sponsor was to be notified within 24 hours after breaking the blind. The date and reason that the blind was broken was to be recorded in the source documentation and eCRF, as applicable. An unblinding form in the EDC (Viedoc) system allowed the Investigator to determine what treatment was administered to subject in the case of an emergency, if the pharmacist was not contactable. No unintentional or intentional unblinding occurred during the conduct of this study.

Statistical methods

Analysis populations

- Entered Population: All subjects who sign the ICF.
- Randomized Population: All subjects who were randomized into this study. Subjects were to be analysed according to their randomized treatment, regardless of which treatment the subject received.
- Safety Population: All randomized subjects who received any amount of the IP. Subjects were to be analysed according to the treatment they received, if this differed from that to which the subject was randomized.
- PK Population: All randomized subjects who received any amount of the IP and had at least 1 evaluable PK parameter. Subjects were to be analysed according to the treatment they received, if this differed from that to which the subject was randomized. Subjects with dosing deviations that could potentially affect the PK profile were to be excluded from the PK Population, at the discretion of the pharmacokineticist prior to analysis.
- PD Population: All randomized subjects who received any amount of the IP and had at least 1 evaluable PD variable collected postdose without important protocol deviations or events thought to significantly affect the PD. Subjects were to be analysed according to the treatment they received, if this differed from that to which the subject was randomized.

Serum denosumab concentrations were to be listed for all subjects in the Safety population. Summaries of serum denosumab concentrations, PK parameters and PK similarity assessment were to be undertaken with the PK population.

Serum Concentration data

Serum denosumab concentrations were to be listed for each subject and summarized with descriptive statistics (N, mean, standard deviation [SD], coefficient of variation as a percent [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by treatment and nominal PK sampling time point.

All serum denosumab concentrations that were below the limit of quantification (BLQ) were to be labelled as such in the concentration data listings. Serum concentrations of denosumab that were BLQ were to be designated a value of half of Lower Limit of Quantification (LLOQ) for the summary of concentration-time data except for pre-dose which was to be assigned zero.

The summaries of serum concentration data were also to include the subgroup presentations (see below "Examination of subgroups".

Individual and arithmetic mean (per treatment) concentration-time profiles were to be plotted with the concentration axis displayed on a linear scale (arithmetic mean ±SD) and on a logarithmic scale (arithmetic mean). Individual subject concentration-time plots were to be overlaid by treatment combination and nominal time post dose was to be used. For mean concentration-time plots, nominal (i.e. protocol specified) sampling time was to be used. For individual subject concentration-time plots, BLQ values were to be set to half of LLOQ. Figures were be produced for time-points up to Day 22 (504 hours) post-dose and for full time profile to facilitate better interpretation on concentration-time profiles. Concentration-time profiles were to also be presented for the subgroups presented in "Examination of subgroups" below.

Pharmacokinetic Parameters

Serum denosumab concentration-time data was to be used for the calculation of the following primary pharmacokinetic parameters:

C_{max}	Maximum observed serum concentration obtained directly from the concentration

	versus time data.
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from time zero extrapolated to infinity, calculated as $AUC_{0\text{–}last} + C_t/ K_{el}$), where C_t is the last quantifiable concentration.
$AUC_{0\text{–}last}$	Area under the serum concentration versus time curve, calculated using the linear trapezoidal rule from time 0 to the time of last quantifiable concentration above the lower limit of quantification [LLOQ], calculated by linear up/log down trapezoidal summation.
$AUC_{0\text{–}24}$	Area under the serum concentration versus time curve, calculated using the linear trapezoidal rule from time 0 to 24 hours post-dose, calculated by linear up/log down trapezoidal summation.
T_{max}	Time to maximum observed concentration, taken directly from the data. If the maximum serum concentration occurs at more than one time point, the first is chosen. A minimum of 3 non-zero data points will be used for estimation.
K_{el}	Terminal elimination rate constant obtained from the slope of the line, fitted by linear least squares regression through the terminal points of the logarithmic concentration-time profiles. A minimum of 3 non-zero data points will be used for estimation.
$t_{½}$	Apparent terminal half-life, calculated as $t_{½} = ln(2)/ K_{el}$. A minimum of 3 non-zero data points will be used for estimation.
Vz/F	Apparent volume of distribution during the terminal phase after subcutaneous (SC) administration, calculated as (CL/K_{el}).
CL/F	Apparent total serum clearance following SC administration, where F is the fraction of drug absorbed, calculated as (Dose / $AUC_{0\text{-}inf}$).

Additional pharmacokinetic parameters to de derived include:

R^2adj	Adjusted R-Square value obtained from the linear regression of terminal elimination phase.
$\%AUC_{extrap}$	The portion of $AUC_{0\text{-}inf}$ determined by extrapolation ($\%AUC_{extrap}$) will also be determined, as 100 x ($AUC_{0\text{-}inf}$ - $AUC_{0\text{–}last}$) / $AUC_{0\text{-}inf}$

All predose BLQ values were to be substituted by zeros. Thereafter BLQ values between evaluable concentrations and terminal BLQ were to be set to 0.5 x LLOQ. No additional imputation of missing PK concentrations with the exception that figures presented on the semi-logarithmic scale y-axis, serum concentration values that are BLQ were to be set to 0.5 x LLOQ. PK parameters were to be calculated using non-compartmental analysis methods with Phoenix WinNonLin Version 8.3 or higher (Certara, LP Princeton, New Jersey, USA) from the concentration-time data following these guidelines:

- Actual sampling times relative to dosing rather than nominal times were to be used in the calculation of all derived PK parameters, except for pre-dose data which were to be given the nominal time of 0.00 hr.
- The linear up and log down trapezoidal rule was to be used for AUC interpolation calculations.
- At least 3 observations for calculating the terminal slope Kel and R square adj ≥ 0.75 for estimating the terminal slope Kel.
- If any of these two criteria were not met, then Kel was to be deemed as not reportable. Consequently, those Kel dependent parameters were not reportable, for example CL/F, T1/2, Vz/F

and AUC0-inf. These parameters were to be excluded from the summary statistics and statistical analysis of PK similarity.

- If %AUCextrap was > 20% in more than 20% of the observations, then the study validity may need to be discussed. Furthermore, the AUC0-inf was to be flagged in the listing.
- Additionally, any changes from the WinNonlin best fit (such as extending the interval for determination of Kel or allowing Tmax to be included in the interval for determination of Kel) were to be noted as a comment in the data file of parameters.
- Flagged observations were to be captured in the Analysis data set using Analysis Flags (ANLXXFL), separately for each of the three criteria. Flagged values were to be included in the data listing maybe excluded in the derivation of summary statistics and statistical analysis of PK parameters.

Pharmacokinetic parameters of serum denosumab were to be summarized by treatment group using descriptive statistics (number of subjects, arithmetic mean, standard deviation, %CV, mean of log transformed values, standard deviation of log transformed values, median, minimum, maximum, geometric mean and geometric %CV).

Weight-adjusted PK parameters were to be derived by dividing the PK parameter by subject's body weight and include: Cmax/BW, AUC0-24/BW, AUC0-inf/BW, AUC0-t/BW, Kel/BW, CL/F/BW and Vz/F/BW. Weight adjusted PK parameters were to be summarized by treatment group and randomisation strata.

Statistical Analysis for PK similarity:

The primary PK parameters for the demonstration of PK similarity between the test product AVT03 and the reference product US-Prolia were Cmax and AUC0-inf. The statistical analysis was to be performed using an ANCOVA model on the logarithmic scale (i.e., using natural log transformed values of Cmax and AUC0- inf) with treatment group as fixed effect and body weight at baseline as the continuous covariate.

For each endpoint, the LS means (for Test and Reference), LS treatment difference (i.e. difference in the corresponding LS means), and 90% confidence interval (CI) for the treatment differences, on a log-scale (i.e. derived from the log transformed parameter values), were to be obtained. The LS treatment differences, and corresponding CIs were to be back transformed to the original scale, resulting in point estimates of the T/R ratios of geometric LS means and 90% CI for each comparison.

The PK similarity of AVT03 versus US-Prolia was to be determined if the 90% CIs for the GMRs of the primary endpoints (Cmax and AUC0-inf) were entirely contained within the equivalence margin of 80% to 125% (when the ratio was to be expressed as a percentage).

Examination of subgroups

The primary and secondary PK endpoints (including similarity) and selected safety and PD endpoints were to be presented for the following subgroups:

- Body Weight ≤ 75kg
- Body Weight > 75kg

Additionally, the following subgroup may also be used to present PK summaries (including similarity), PD summary and selected safety summaries:

- ADA Positive

- ADA Negative

If ADA positive:

- Neutralising Antibody (NAb) Positive
- Neutralising Antibody (NAb) Negative

Participant flow

A total of 209 male subjects were enrolled into the study and all enrolled subjects were randomized to 1 of the 2 treatment groups: 101 to AVT03 and 108 to Prolia. By country, 40 subjects were enrolled at 2 sites in New Zealand, 48 subjects were enrolled at 1 site in Australia and 121 subjects were enrolled at 1 site in South Africa.

Of the 209 randomized subjects, 192 (91.9%) subjects completed the study up to Day 252. Overall, 17 (8.1%) subjects prematurely discontinued the study (this included the 3 subjects that were not dosed). Of the remaining 14 subjects that discontinued the study: 8 subjects (3 subjects in the AVT03 group and 5 subjects in the Prolia group) discontinued due to other personal reasons pertaining to their availability to attend the site, 4 subjects in the Prolia group were lost to follow-up, and 2 subjects (1 subject each in the AVT03 and Prolia groups) withdrew their consent.

Table 3: Subject Disposition (Entered Population)

Status	Statistic	AVT03	Prolia	Overall
Entered	n			471
Failed Screening	n (%)			262 (55.6)
Eligibility Criteria not met	n (%)			241 (92.0)
Withdrawal by Subject	n (%)			14 (5.3)
Other Reason	n (%)			7 (2.7)
Enrolled	n (%)			209 (44.4)
Randomized	N	101	108	209
Did not receive IP	n (%)	2 (2.0)	1 (0.9)	3 (1.4)
Received IP as per planned IP assignment	n (%)	99 (98.0)	107 (99.1)	206 (98.6)
≤75 kg	n (%)	59 (59.6)	61 (57.0)	120 (58.3)
>75 kg	n (%)	40 (40.4)	46 (43.0)	86 (41.7)
Actual IP Received	n (%)	99 (98.0)	107 (99.1)	206 (98.6)
≤75 kg	n (%)	59 (59.6)	61 (57.0)	120 (58.3)
>75 kg	n (%)	40 (40.4)	46 (43.0)	86 (41.7)
Completed Study	n (%)	95 (94.1)	97 (89.8)	192 (91.9)
Study Discontinuation	n (%)	6 (5.9)	11 (10.2)	17 (8.1)
Primary Reason for Study Discontinuation				
Adverse event	n (%)	0	1 (9.1)	1 (5.9)
Lost to follow-up	n (%)	0	4 (36.4)	4 (23.5)
Other	n (%)	5 (83.3)	5 (45.5)	10 (58.8)
Withdrawal by subject	n (%)	1 (16.7)	1 (9.1)	2 (11.8)

Abbreviations: ICF = Informed Consent Form; IP = investigational product; n = number of subjects in each category; N = total number of subjects randomized. %: Percentages of subjects who failed screening and enrolled are based on the number of subjects entered; Percentages for the reasons for screening failure are based on the number of subjects who failed screening; Percentage of subjects under the strata for planned IP assignment are based on the number of dosed subjects grouped as per their planned IP assignment; Percentage of subjects under the strata for actual IP received are based on the number of dosed subjects grouped as per the actual IP received; Percentages for the primary reasons for study discontinuation are based on the number of subjects who discontinued from the study; All other percentages are based on the number of subjects randomized.

Entered Population is defined as subjects who signed the ICF.

Enrolled is defined as subjects who signed the ICF and had met all eligibility criteria.

Completed study is defined as randomized and completing the study up to Day 252 (±2 days) without the need for intervention per protocol. Study discontinuation is defined as subjects who discontinued from the study after being randomized but prior to Day 252 (end of study) assessment.

Overall, 17 (8.1%) subjects prematurely discontinued the study (this included the 3 subjects that were not dosed). Of the remaining 14 subjects that discontinued the study: 8 subjects (3 subjects in the AVT03 group and 5 subjects in the Prolia group) discontinued due to other personal reasons pertaining to their availability to attend the site, 4 subjects in the Prolia group were lost to follow-up, and 2 subjects (1 subject each in the AVT03 and Prolia groups) withdrew their consent.

Overall, the distribution of dosed subjects according to the predefined randomisation strata was well balanced between treatment groups. The majority of subjects (120 subjects [58.3%]) weighed ≤75 kg and remaining 86 subjects (41.7%) weighed >75 kg.

Conduct of Study

Changes in the planned conduct of the study:

The original protocol (Version 1.0) dated 09 November 2021 was amended 3 times. Amendment 1 (Version 2.0) was instituted before the first subject was enrolled.

Protocol deviations

Major protocol deviations were reported for 21 subjects (10% of randomized subjects). The percentage of subjects with major deviations was numerically lower in the AVT03 group (8.9%) compared with the Prolia group (11.1%). The most common major deviations were related to the visit schedule criteria (7 subjects [3.3%]), study procedures (5 subjects [2.4%]), informed consent and process (4 subjects [1.9%]), and concomitant medication (3 subjects [1.4%]). All other major protocol deviations were reported in no more than 1 subject overall. The major deviations reported were considered to have no meaningful influence on data integrity and/or subject safety and did not result in exclusion of the subjects from the final analyses. Minor protocol deviations were reported for 197 subjects (94.3%).

Baseline data

Table 4: Demographics and Other Baseline Characteristics (Safety Population)

Variable (Unit)/ Category	Statistic	AVT03 (N=99)	Prolia (N=107)	Overall (N=206)
Age (years)	n	99	107	206
	Mean	36.8	36.0	36.4
	SD	7.19	6.80	6.98
Race				
Asian	n (%)	3 (3.0)	3 (2.8)	6 (2.9)
Black or African American	n (%)	55 (55.6)	53 (49.5)	108 (52.4)
Caucasian / White	n (%)	33 (33.3)	39 (36.4)	72 (35.0)
American Indian or Alaska Native	n (%)	1 (1.0)	6 (5.6)	7 (3.4)
Native Hawaiian or other Pacific Islander	n (%)	0	2 (1.9)	2 (1.0)
Other	n (%)	7 (7.1)	5 (4.7)	12 (5.8)
Height (cm)	n	99	107	206
	Mean	172.06	172.36	172.22
	SD	7.367	6.593	6.960
Weight (kg)	n	99	107	206
	Mean	70.37	73.15	71.81
	SD	10.523	9.439	10.047
Weight Group [a]				
≤75 kg	n (%)	59 (59.6)	61 (57.0)	120 (58.3)
>75 kg	n (%)	40 (40.4)	46 (43.0)	86 (41.7)
BMI (kg/m²)	n	99	107	206
	Mean	23.74	24.61	24.19
	SD	3.041	2.873	2.980

Abbreviations: BMI = body mass index; SD = standard deviation; n = number of subjects in each category; N = total number of subjects in the relevant population; % = percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.
Age (years) is relative to the date the informed consent form was signed. One subject reported 2 races and is therefore counted twice in the race categories.
[a]Weight Group is derived from measured weight rather than the assigned stratum for each subject. There may be instances where the weight is different to the assigned strata.

In the Safety Population, the demographic and baseline characteristics were generally well balanced, with no notable differences in either of the treatment groups.

Medical History

In the Safety Population, 43.2% of subjects reported at least 1 pre-existing medical history event, and the percentage of subjects with medical history events were similar in both the treatment groups. The most frequently reported medical history events at Screening (>10% of subjects in any group) were COVID-19 (10.1% in the AVT03 group and 10.3% in the Prolia group) and seasonal allergy (10.1% in the AVT03 group and 6.5% in the Prolia group).

Prior medications and medical procedures

In the Safety Population, 19.9% of subjects received at least 1 prior medication and 20.4% of subjects underwent at least 1 prior medical procedure. None of the prior medications or prior procedures (by PT) were received by >10% of subjects in any group.

Concomitant Medications and Medical procedures

In the Safety Population, 85.0% of subjects received at least 1 concomitant medication; the percentage of subjects was comparable in both the treatment groups. The most frequently received concomitant medications (>10% of subjects in any group) were ergocalciferol (vitamin D2 supplements), paracetamol, calcium gluconate, and ibuprofen sodium; the values were comparable in both the treatment groups. During the study, the subjects were allowed to receive calcium and vitamin D supplements for cases of hypocalcaemia and low vitamin D levels. Three subjects had major protocol deviations in the concomitant medications category, since the subjects received medications that were prohibited in the study: • Subject 301-028 (AVT03 group) received a live vaccine for Monkeypox which was considered a major protocol deviation because only inactivated vaccines were allowed in the study. • Subject 501-203 (AVT03 group) received vitamin D supplements at a weekly dose of 50000 IU, to treat severe vitamin D deficiency. The administered dose was much higher than the allowed dose (Concomitant medical procedures were infrequent, reported by 11 subjects (5.3%) overall; there were no notable differences in the percentages of these subjects between both the treatment groups: 4 subjects (4.0%) in the AVT03 group and 7 subjects (6.5%) in the Prolia group. Concomitant procedures (by PT) were reported by not more than 3 subjects in any group.

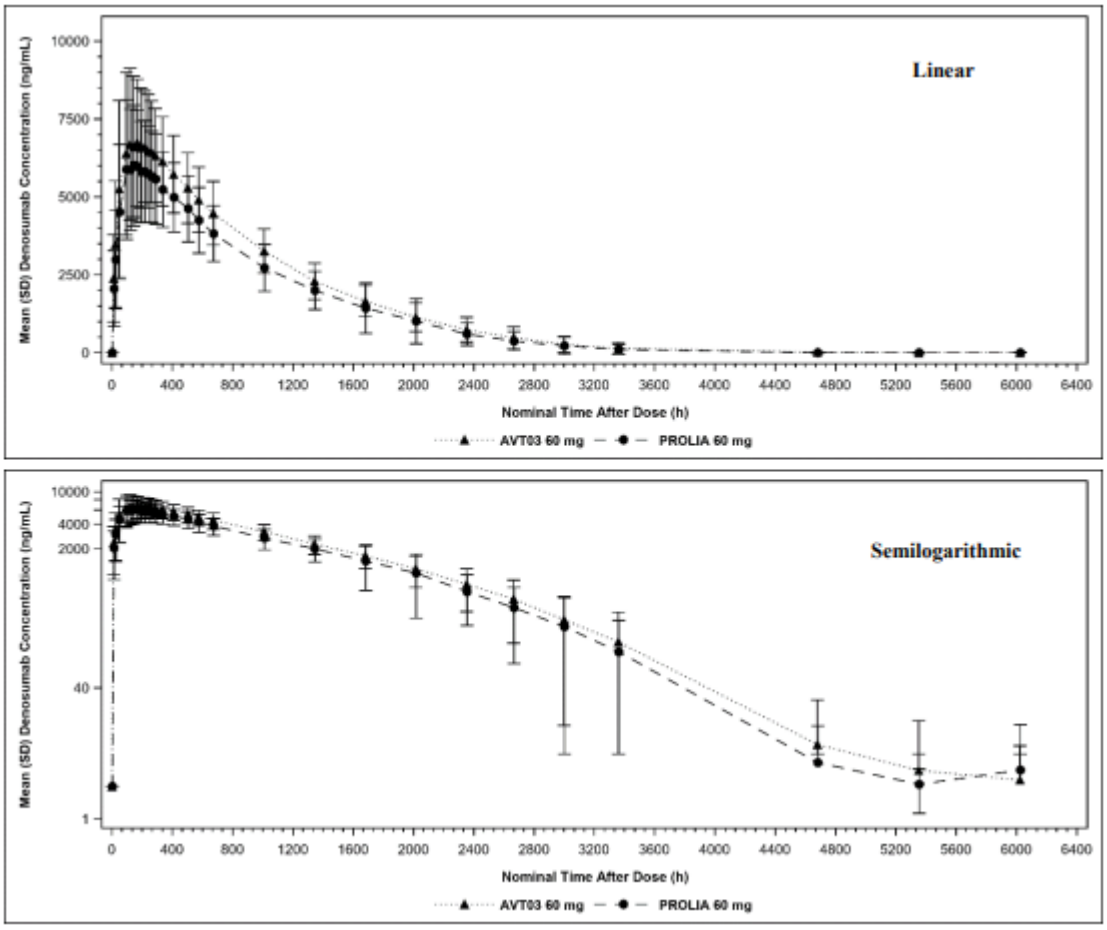
Numbers analysed

Of the 209 randomized subjects, excluding 3 subjects who were not dosed, a total of 206 subjects (98.6%) received the IP, and were therefore included in the Safety and PD Populations. One subject in the Prolia group was excluded from the PK Population before formal study unblinding, as the subject had a PK profile that was suggestive of inadvertent vascular compromise during the SC administration procedure. Therefore, a total of 205 subjects (98.1%) were included in the PK Population.

Outcomes

Serum Denosumab Concentrations

Figure 2: Mean (±Standard Deviation) Serum Denosumab Concentrations Over Time by Treatment on Linear and Semilogarithmic Scales (Pharmacokinetic Population)



Abbreviation: SD = standard deviation.

PK Parameters

Table 5: Summary of Serum Denosumab Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

	Median (Range)	Geometric Mean (Geometric CV%)						
Treatment	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-inf} (h·ng/mL)	AUC_{0-last} (h·ng/mL)	K_{el} (1/Day)	$t_{1/2}$ (h)	V_z/F (L)	CL/F (L/Day)
AVT03 (N = 99)	167.92 (48–602.42)	7382.1 (29%)	7637731.8 (22%)	7559695.8 (25%)	0.0401 (19.408%)	414.023 (19.33%)	4.683 (29.99%)	0.188 (22.43%)
Prolia (N = 106)	167.96 (47.90–1677.70)	6513.4 (31%)	6578675.2 (26%)	6465342.9 (28%)	0.0393 (22.371%)	424.119 (22.42%)	5.565 (34.85%)	0.219 (26.51%)

Abbreviations: AUC_{0-last} = area under the concentration-curve from time zero to time t, here t is the last time point with concentrations above the LLOQ, calculated by linear up/log down trapezoidal summation; AUC_{0-inf} = area under the concentration-curve from time zero extrapolated to infinite time; BLQ = below the limit of quantification; CL/F = apparent clearance; C_{max} = maximum serum concentration; CV% = coefficient of variation; Geometric CV% = calculated as gCV% = SQRT(es2-1)*100; where s is the standard deviation of the log-transformed values; K_{el} = terminal elimination rate constant; LLOQ = lower limit of quantification; N = total number of subjects in the relevant population; PK: pharmacokinetic. $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time of maximum serum concentration; Vz/F = apparent volume of distribution. Serum concentrations that are BLQ prior to T_{max} were designated a value of zero for PK parameter analysis. Serum concentrations that are BLQ after T_{max} were designated as missing and not considered in the estimation of PK parameters.
PK parameters were determined using WinNonlin v8.3 or higher.

Statistical analysis of pharmacokinetic similarity

Table 6: Pharmacokinetic Similarity Assessment of Primary Serum Denosumab Pharmacokinetic Parameters by Treatment (Pharmacokinetic Population)

		Test		Reference		Ratio of Geometric LS Means (%)	90% Confidence Interval for Ratio of LS Means	
Comparison (Test/Reference)	Parameter (Units)	n	Geometric LS Mean	n	Geometric LS Mean	Test/ Reference	Lower 5% CL (%)	Upper 5% CL (%)
AVT03 60 mg / Prolia 60 mg	C_{max} (ng/mL)	99	7192.87	106	6673.32	107.79	**102.231**	**113.642**
	$AUC_{0\text{-}inf}$ (h·ng/mL)	98	7528147.75	103	6669757.41	112.87	**107.169**	**118.874**
	$AUC_{0\text{-}last}$ (h·ng/mL)	99	7457574.92	106	6547992.79	113.89	**107.719**	**120.416**

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration-curve from time zero extrapolated to infinite time; $AUC_{0\text{-}last}$: area under the serum concentration-curve from time zero to time t, where t is the last time point with concentrations above the LLOQ, calculated by linear up/log down trapezoidal summation; EMA = European Medicines Agency; CL = confidence limit; C_{max}: maximum serum concentration; LLOQ = lower limit of quantification; LS = least-squares; n: number of subjects used in calculation; PMDA = Pharmaceutical and Medical Devices Agency; PK = pharmacokinetic; US FDA = US Food and Drug Administration.
Treatment comparison by analysis of covariance of log-transformed parameters with model: log(parameter) = treatment + body weight at baseline as the covariate.
90% confidence interval for ratio of LS mean is constructed from the one-sided lower 5% CL and one-sided upper 5% CL.
Bioequivalence is determined if, for each pairwise comparison, the 90% confidence intervals for the ratios of geometric LS means are entirely contained with the equivalence margin 80.00% to 125.00%.
It is noted that the parameters of C_{max} and $AUC_{0\text{-}last}$ are presented for US FDA and Japanese PMDA, and C_{max} and $AUC_{0\text{-}inf}$ are presented for EMA.
Values in **bold** text indicate that the PK similarity criteria were met.

Individual denosumab serum concentration-time profiles

Individual denosumab serum concentrations vs time profiles were provided for all subjects. In some profiles, a sudden drop in concentration is recorded, as can be seen in the following examples points have been identified as outliers. However, no root cause could be determined. In order to understand the impact of the identified implausible datapoints on the biosimilarity assessment two sensitivity analyses have been performed.

•Scenario 1: replace incorrect datapoint with the correct bioanalytical value and exclude all other data points.
•Scenario 2: replace incorrect datapoint with the correct bioanalytical value, replace the concentrations for the potential switched samples, and exclude all other data points.

Table 7: AVT03/Prolia PK Similarity (replacing one datapoint with correct bioanalytical value and excluding all other identified data points)

Comparison (Test/Reference)	Parameter (Units)	Test n	Test Geometric LS Mean	Reference n	Reference Geometric LS Mean	Ratio of Geometric LS Means (%) Test/ Reference	90% Confidence Interval for Ratio of LS Means Lower 5% CL (%)	Upper 5% CL (%)
AVT03 60 mg / PROLIA 60 mg	Cmax (ng/mL)	99	7121.40	106	6630.70	107.40	101.842	113.263
	AUC0-inf (h*ng/mL)	98	7528215.59	103	6655603.41	113.11	107.490	119.026
	AUC0-last (h*ng/mL)	99	7457619.98	106	6534357.61	114.13	108.027	120.576

For scenario 1 the analysis of Cmax, AUC0-inf, and AUC0-last were comparable between the treatments and allow the conclusion for PK similarity with the 90% upper and lower confidence intervals between 85.00% and 125.00%. These results are in line with those reported in the CSR.

Table 8: Sensitivity analysis 2: AVT03/Prolia PK Similarity (replacing one datapoint with correct bioanalytical value, swapping potentially switched samples and excluding all other identified data points _

Comparison (Test/Reference)	Parameter (Units)	Test n	Test Geometric LS Mean	Reference n	Reference Geometric LS Mean	Ratio of Geometric LS Means (%) Test/ Reference	90% Confidence Interval for Ratio of LS Means Lower 5% CL (%)	Upper 5% CL (%)
AVT03 60 mg / PROLIA 60 mg	Cmax (ng/mL)	99	7121.40	106	6630.70	107.40	101.842	113.263
	AUC0-inf (h*ng/mL)	98	7528192.08	103	6656706.49	113.09	107.469	119.009
	AUC0-last (h*ng/mL)	99	7457596.33	106	6535410.53	114.11	108.007	120.559

To further support the PK similarity, another sensitivity analysis (scenario 2) was performed whereby an additional step was performed where the concentrations of the potentially mixed samples were replaced (*Table 8*). This also resulted in PK similarity.

Table 9: Summary Comparison of Sensitivity Analysis

	CSR	Scenario 1	Scenario 2
C_{max} (ng/mL)	107.79 (102.231, 113.642)	107.40 (101.842, 113.263)	107.40 (101.842, 113.263)
$AUC_{0\text{-}inf}$ (h·ng/mL)	112.87 (107.169, 118.874)	113.11 (107.490, 119.026)	113.09 (107.469, 119.009)
$AUC_{0\text{-}last}$ (h·ng/mL)	113.89 (107.719, 120.416)	114.13 (108.027, 120.576)	114.11 (108.027, 120.576)

In both statistical sensitivity analyses, the way of handling of these unexpected PK data had minimal impact on the comparison of AVT03 vs Prolia and allows for a conclusion on PK similarity. Despite the lack of a root cause for the PK phenomenon, an impact of the implausible datapoints to the overall PK similarity is not expected.

Pharmacokinetics in the target population – Study AVT03-GL-C01

The study was a randomized, double-blind, parallel design, repeat dose, 2-arm, multicentre study comparing the efficacy, safety, immunogenicity and PK profile of AVT03 and US-Prolia in postmenopausal women with osteoporosis.

Pharmacokinetic analyses

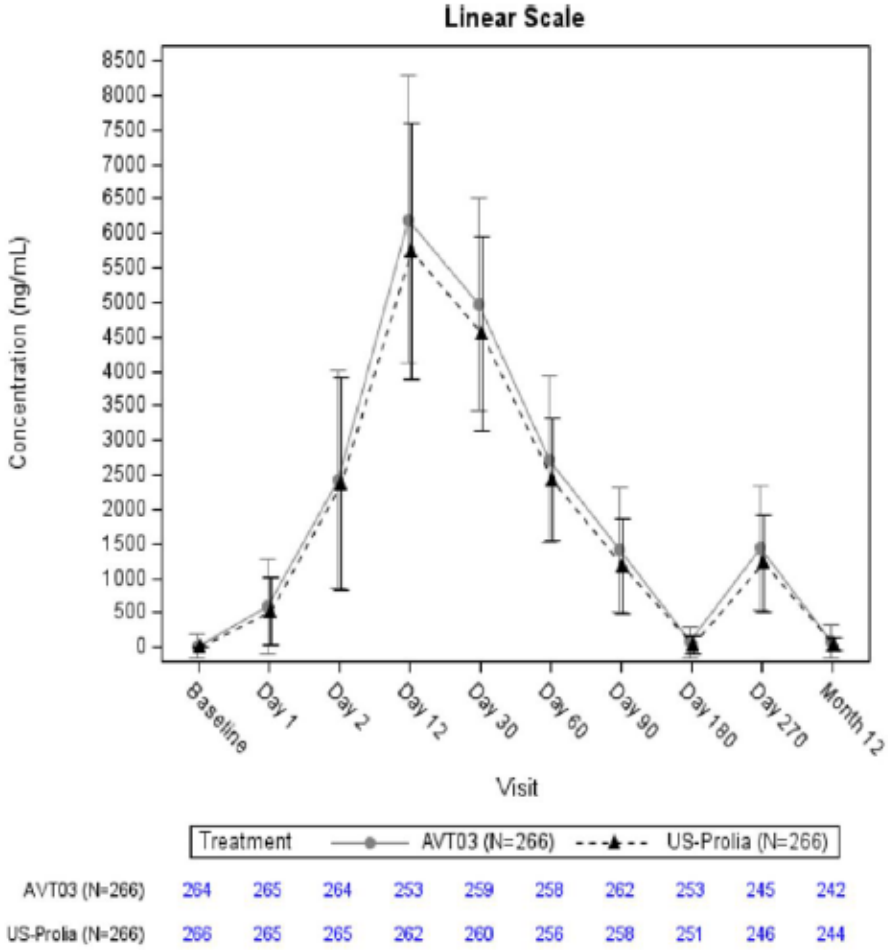
Descriptive statistics for serum trough concentrations of AVT03 and US-Prolia were to be tabulated over time by visit and study period based on the Safety Analysis Set. Descriptive statistics were to be also calculated by the ADA and NAb status. Mean (±SD) of Serum Trough Concentration vs Time was to be plotted on linear and semi-logarithmic scales.

A listing for subjects with serum trough concentrations was also to be presented.

Pharmacokinetic results

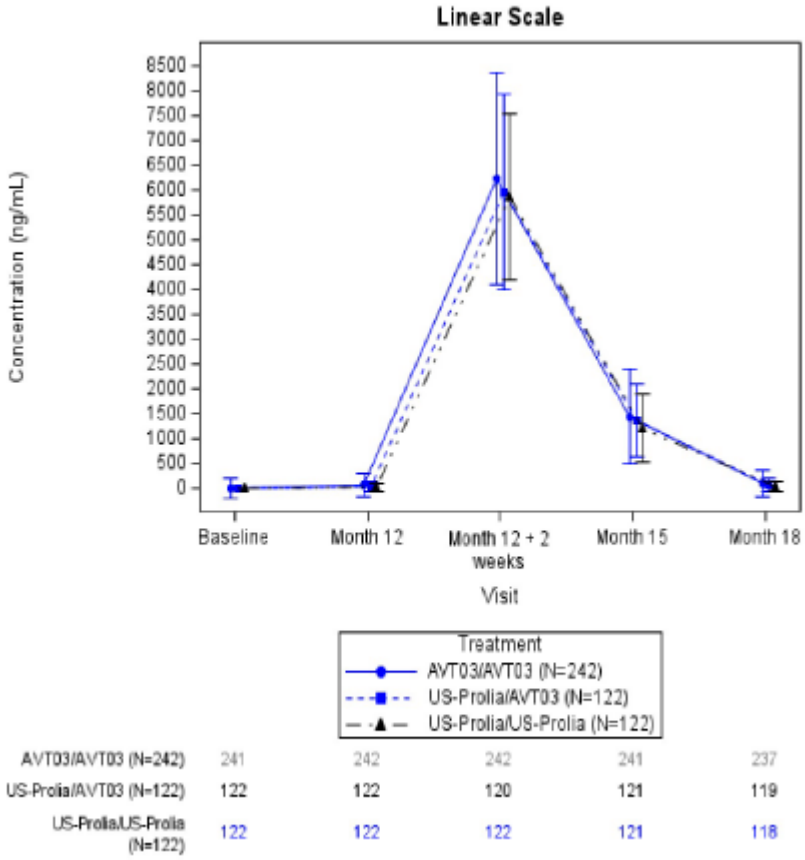
Overall, in both treatment groups, the mean serum concentration increased from Baseline, peaking around Day 12, and then decreasing steadily to Day 180 (Month 6). The mean concentration profiles for AVT03 and Prolia were similar in magnitude and trend at all timepoints assessed. By Day 180, prior to second study drug administration, the geometric mean (GEO CV%) trough concentration was 10.52 ng/mL (599.356%) in the AVT03 group and 7.46 ng/mL (401.2%) in the Prolia group. The geometric mean (GEO CV%) trough concentrations at Month 12 prior to the third dose, were 10.23 ng/mL (642.3%) in the AVT03 group and 7.091 ng/mL (392.9%) in the Prolia group. At Month 12 + 2 weeks, the geometric mean (GEO CV%) serum concentration increased to 5625.96 ng/mL (73.9%) in the AVT03/AVT03 group, 5189.22 ng/mL (113.5%) in the Prolia/AVT03 group, and to 5603.87 ng/mL (33.6%) in the Prolia/Prolia group. Switching from Prolia to AVT03 had no effect on serum concentrations. From Month 12 to Month 18/EoS, after the third dose administration, switching from Prolia to AVT03 had no effect on serum concentrations. From Month 12 to Month 18, the serum concentrations of AVT03 and Prolia decreased to levels similar to those observed at Month 12 before study drug administration The PK profile was comparable for all treatment groups (AVT03/AVT03, US-Prolia/AVT03, and US-Prolia/US-Prolia).

Figure 3: Mean (±SD) of Serum PK Concentration vs Time - Safety Analysis Set – From Baseline to Month 12



Abbreviations: PK = pharmacokinetic(s); SD = standard deviation.

Figure 4: Mean (±SD) of Serum PK Concentration vs Time - Safety Analysis Set – From Month 12 to End of Study



2.5.2.2. Pharmacodynamics

Mechanism of action

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, a transmembrane protein that plays a significant role in osteoclast mediated bone resorption. By binding to RANKL, denosumab prevents activation of RANKL's receptor, RANK. Denosumab thus inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and cancer-induced bone destruction.

sCTX, or serum C-terminal telopeptide of Type 1 collagen, is a biochemical marker of bone resorption. The measurement of sCTX levels in the blood is used to assess the rate of bone turnover, particularly bone resorption.

Analytical methods

PD Assay

A partial validation of the ECLIA test kit (Elecsys β-CrossLaps kit; Roche Diagnostics)was performed. The assay is a method to quantify CTX-I in human serum. In principle, the presented PD method appears suitable for the intended purpose.

Primary and secondary pharmacology

The pharmacodynamic of AVT03 and the respective reference product have been investigated in 2 clinical studies, a phase I PK study (AVT03-GL-P01) and a phase 3 efficacy and safety study AVT03-GL-C01. For a detailed assessment of the design of the study AVT03-GL-P01 please refer to section 2.5.2. For a detailed assessment of the design of the study AVT03-GL-C01 please refer to section 2.5.5.

Study AVT03-GL-P01

Table 10: Serum Pharmacodynamic Parameter for CTX-1

Pharmacodynamic Parameters	Definition
$AUEC_{0-t}$	Area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point
$AUEC_{0-last}$	Area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point with concentrations above the LLOQ
I_{max}	Maximum observed percentage of serum CTX-1 inhibition
I_{min}	Minimum observed serum CTX-1 concentration
T_{min}	Time to I_{min} (for serum CTX-1)

Abbreviations: CTX-1 = C-terminal telopeptide of type 1 collagen; LLOQ = lower limit of quantitation.

Pharmacodynamic data analysis

Pharmacodynamic concentrations for serum C-terminal 1 collagen (CTX-1) were to be listed for all subjects in the Safety population. Summaries of serum CTX-1 PD parameters were to be undertaken with the PD population.

The absolute values and percent changes from baseline for serum CTX-1 were to be listed and summarized using descriptive statistics by treatment group and nominal sampling time point. Serum CTX-1 concentrations were to be listed for each subject and summarized with descriptive statistics (N, mean, standard deviation [SD], coefficient of variation as a percent [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by treatment and nominal PD sampling time point. All serum CTX-1 concentrations that were below the limit of quantification (BLQ) were to be labelled as such in the concentration data listings. Serum concentrations of CTX-1 that were BLQ were to be designated a value of half of Lower Limit of Quantification (LLOQ) for the summary of concentration-time data except for predose which was to be assigned zero.

Individual and arithmetic mean (per treatment) concentration-time profiles were to be plotted with the concentration axis displayed on a linear scale (arithmetic mean ±SD) and on a logarithmic scale (arithmetic mean). Individual subject concentration-time plots were to be overlaid by treatment and nominal time post

dose to be used. For mean concentration-time plots, nominal (i.e. protocol specified) sampling time was to be used. For individual subject concentration-time plots, BLQ values were to be set to half of LLOQ.

Pharmacodynamic parameters were to be derived using similar noncompartmental methods used for PK parameters. Actual elapsed time from dosing was to be used for the final PD parameter calculations. The percentage of serum CTX-1 inhibition from baseline to t, where t is the last time point, was to be used to generate AUEC.

Pharmacodynamic parameters of CTX-1 were to be listed and summarized by treatment group using descriptive statistics (number of subjects, arithmetic mean, standard deviation, %CV, mean of log transformed values, standard deviation of log transformed values, median, minimum, maximum, geometric mean and geometric %CV); the AUEC0-t was also to be presented graphically.

Study AVTO3-GL-C01

PD variables

- Area Under the percent change from baseline in serum C-telopeptide of type 1 collagen up to 6 months (AUC0-6months of %Cfb sCTX-1) (co-primary efficacy endpoint)
- Percent change from baseline in sCTX-q at 3, 6, 9, 12 and 18 months

Pharmacodynamic data analysis

Calculation of Area Under the Effect Curve

Area under the effect curve (AUEC) calculation for serum C-telopeptide of type 1 collagen up to 6 months (AUEC0-6months of %Cfb sCTX-1) was to be based on the assumption that the baseline assessment takes place at time zero. Computations were to also use actual assessment times rather than the nominal assessment times. If the actual time was not recorded the nominal time was to be used. AUEC0-6 months was to be calculated using the trapezoidal rule and was to be divided by the actual time in months of the assessment at 6 months for ease of interpretation. The Inhibition values (-1 * PCHG) were to be used in the calculation of AUEC instead of percent change from baseline. If a subject had no pre-dose value or if the percent Change from Baseline at 6 months for the sCTX-1 was not available, the AUEC was not to be calculated. In the case where a subject had two values recorded at exactly the same time, the two scores were to be averaged.

Primary Pharmacodynamic Analysis

The analysis for the primary PD endpoint was to be produced using the PD Analysis Set which was defined as all randomized subjects who received at least 1 dose of randomized study treatment and have at least 1 evaluable PD endpoint collected without any protocol deviation that thought to significantly affect the PD.

The log transformed PD data (AUEC0-6months of %Cfb sCTX-1) were to be analysed using an analysis of covariance (ANCOVA) model including the treatment as factor and the baseline sCTX-1 as continuous covariate. The negative AUEC0-6months of %Cfb sCTX-1 were not to be included to the analysis as a log transformation is not possible on such values. The geometric mean ratio was to be obtained by back-transforming the mean difference to the original scale. The 2-sided 95% CI for the geometric mean ratio between treatment groups will be calculated.

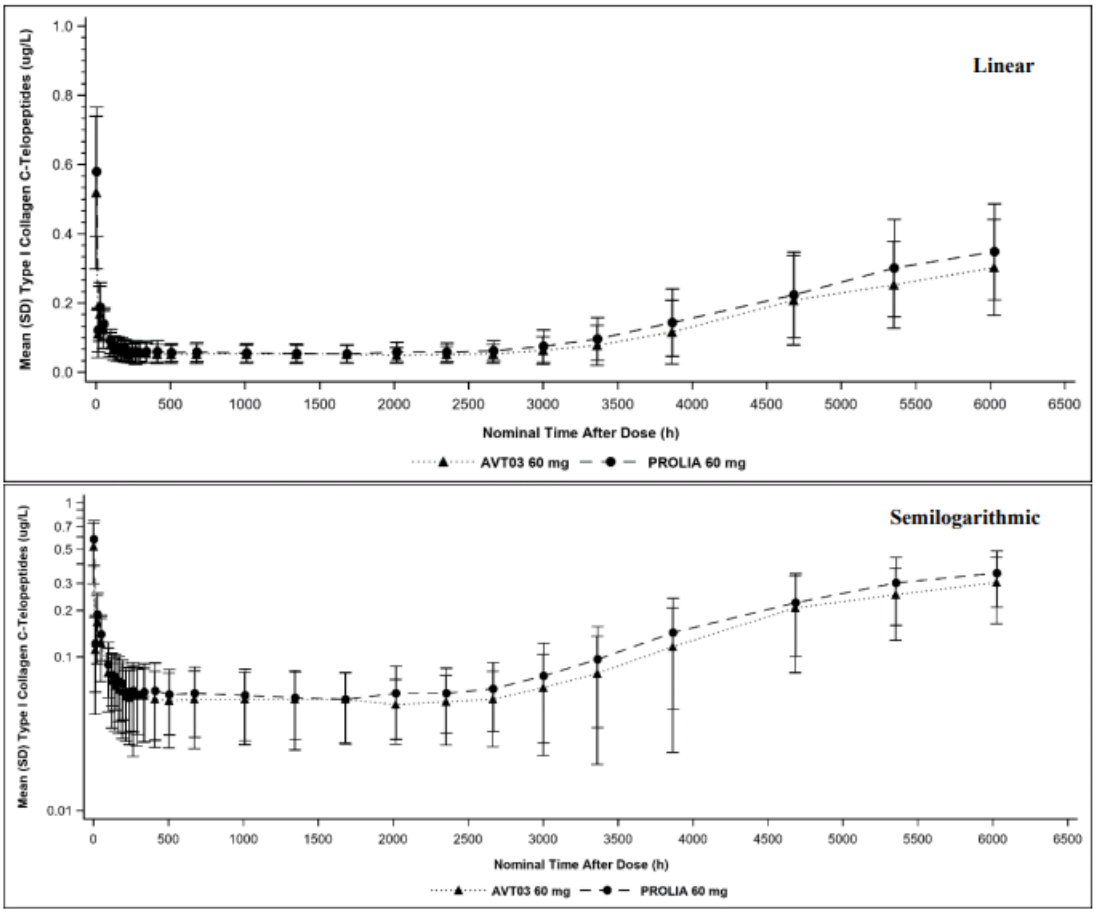
The descriptive statistics of CTX-1 level between treatment groups over all time points were to be provided and to be presented graphically including individual and mean (per treatment) concentration-time profiles.

Results

Study AVT03-GL-P01

In the PD Population, following a single SC dose of 60 mg/mL, the mean serum CTX-1 concentration-time profile for AVT03 and Prolia were comparable, both showing initially normal serum levels of CTX-1 at baseline (predose levels), followed by a rapid decrease in the serum CTX-1 levels immediately after IP administration. The inhibition in levels of CTX-1 continued until Day 141 (3360 h) approximately, followed by a slow increase in CTX-1 serum concentrations until Day 252 (EOS, 6024 h). However, the CTX-1 levels in the serum did not reach the predose levels at EOS. The mean serum CTX-1 concentration had decreased by >75% on Day 1 within 12 hours postdose (77.68% in the AVT03 group and 78.10% in the Prolia group). At Day 252 (EOS), the CTX-1 levels were still below the baseline concentration in both the groups (37.46% in the AVT03 group and 35.61% in the Prolia group).

Figure 5: Mean (±Standard Deviation) CTX-1 Concentrations Over Time by Treatment (Linear and Semilogarithmic Scales) (Pharmacodynamic Population)



Abbreviations: BLQ = below limit of quantification; CTX-1 = C-terminal telopeptide of type 1 collagen; LLOQ = lower limit of quantification; SD = standard deviation.
Serum concentrations below BLQ are set to 0.5*LLOQ.

The mean serum CTX-1 parameters in the AVT03 group were comparable with those in the Prolia group (Table 11-3). The geometric mean area under the effect-time curve (AUEC) values in the AVT03 group (AUEC0-t: 447909.13 h·%; AUEC0-last: 427782.68 h·%) were comparable to those in the Prolia group

(AUEC0-t: 448112.18 h·%; AUEC0-last: 421988.99 h·%). The PD profiles in terms of AUEC0-t for percentage change from baseline in serum CTX-1 until EOS, were comparable following IP administration in both the groups. The geometric mean values of maximum observed percentage of serum CTX-1 inhibition, Imax (91.37% in AVT03 group and 92.28% in Prolia group) and minimum observed serum CTX-1 concentration, Imin (0.036 µg/mL in AVT03 group and 0.038 µg/mL in Prolia group) were also comparable in both the groups. The median time to Imin (Tmin) was 193.98 hours in the AVT03 group and 216.10 in the Prolia group, with values ranging from 12 to 3863.95 hours and 12 to 3337.30 hours, respectively.

Table 11: Summary of Serum CTX-1 Pharmacodynamic Parameters by Treatment (Pharmacodynamic Population)

	Median (Range)	Geometric Mean (Geometric CV%)			
Treatment	T_{min} (h)	$AUEC_{0-t}$ (h·%)	$AUEC_{0-last}$ (h·%)	I_{max} (%)	I_{min} (µg/mL)
AVT03 (N = 99)	193.98 (12–3863.95)	447909.1359 (13.086%)	427782.6871 (29.923%)	91.374 (5.24%)	0.036 (36.16%)
Prolia (N = 107)	216.10 (12–3337.30)	448112.1881 (13.308%)	421988.9997 (27.811%)	92.283 (4.22%)	0.038 (39.96%)

Abbreviations: $AUEC_{0-t}$ = area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point; $AUEC_{0-last}$ = area under the effect curve for percentage change from baseline in serum CTX-1 from time zero to time t, where t is the last time point with concentrations above the LLOQ; BLQ = below limit of quantification; CTX-1 = C-terminal telopeptide of type 1 collagen; geometric CV% = calculated as gCV% = SQRT(es2-1)*100, where s is the standard deviation of the log-transformed values; I_{max} = maximum observed percentage of serum CTX-1 inhibition; I_{min} = minimum observed serum CTX-1 concentration; N = total number of subjects in the relevant population; PD = pharmacodynamic; T_{min} = time to I_{min} (for serum CTX-1).
Serum concentrations that are BLQ prior to I_{max} were designated a value of zero for PD parameter analysis.
Serum concentrations that are BLQ after I_{max} will be designated as missing and not considered in the estimation of PD parameters.
PD parameters determined using WinNonlin v8.3 or higher.

Study AVT03-GL-C01

The analysis for the primary PD endpoint was produced using the PD Analysis Set. The geometric mean for AUEC0-6months for percent change from Baseline in sCTX-1 was 2361.29 for the AVT03 group and 2327.63 for the Prolia group, with the GMR (SE) for AVT03 vs Prolia of 1.00 (1.016). The study results demonstrated PD similarity between the treatment groups, as 95% CI of GMR (0.97, 1.03) lies entirely within the pre-specified margins of 0.80, 1.25.

Table 12: Area Under the Effect Curve for Percent Change from Baseline in sCTX-1 up to Month 6 – ANCOVA PD Analysis Set (Excluding Data Impacted by ICEs)

	AVT03 (N=266)	Prolia (N=266)
n	243	248
m	240	246
Geometric mean	2361.29	2327.63
Least squares mean (SE) (%)	2345.55 (1.011)	2342.87 (1.011)
GMR (SE) (AVT03 vs Prolia)	1.00 (1.016)	
95% CI	0.97, 1.03	
Prespecified margin	0.8, 1.25	

$AUEC_{0\text{-}6\ months}$ was not calculated for subjects without an evaluable baseline and/or Month 6 sCTX-1 measurement, but they were not considered to have an ICE.

Two-sided 95% CI for the geometric mean ratio between AVT03 and Prolia groups were obtained from an ANCOVA model including $AUEC_{0\text{-}6\ months}$ as response variable, randomized treatment as categorical covariate and baseline sCTX-1 value as continuous covariate. Clinical similarity of AVT03 and Prolia was established for the EMA if the 95% CI is contained within the equivalence margin of (-0.80, 1.25).

Unit is Day × %.

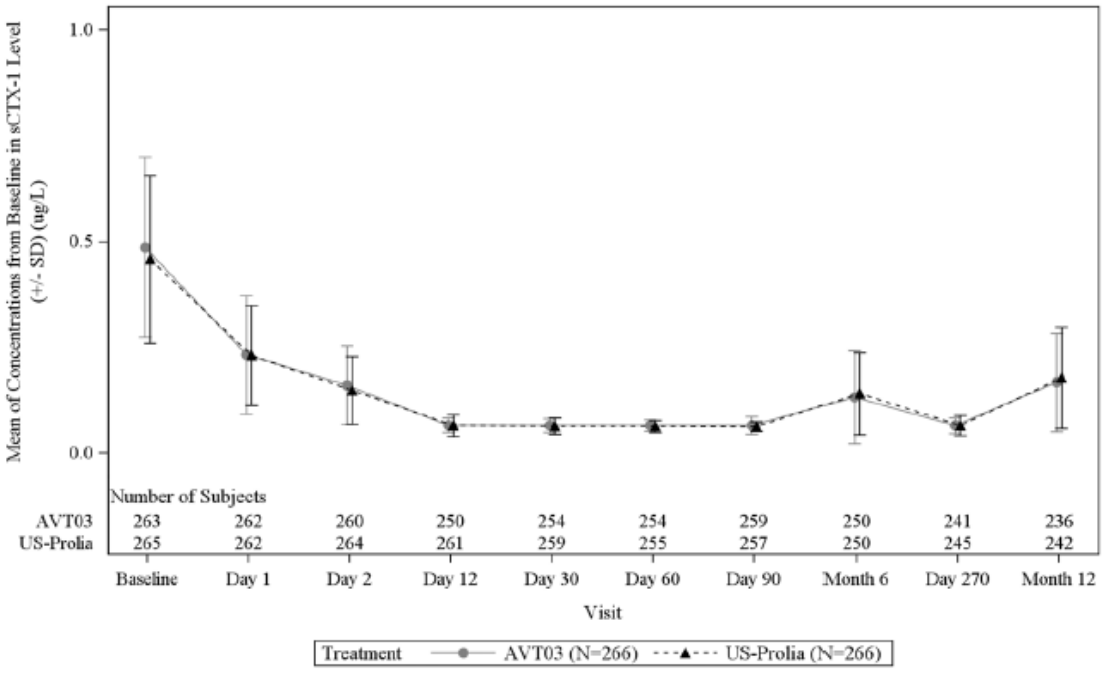
Abbreviations: ANCOVA = analysis of covariance; EMA = European Medicines Agency; GMR = geometric mean ratio; CI = confidence interval; n = number of subjects in the PD Analysis Set without ICEs per group; m = number of subjects with an evaluable AUEC per group; ICE = intercurrent event; PD = pharmacodynamic(s); sCTX-1 = serum C-terminal cross-linked telopeptide of type I collagen; SE = standard error.

Table 13: Sensitivity Analysis: Area Under the Effect Curve for Percent Change from Baseline in sCTX-1 up to Month 6 – ANCOVA PD Analysis Set (All Observed Data)

	AVT03 (N=266)	Prolia (N=266)
n	266	266
m	249	250
Geometric mean	2366.23	2328.73
Least squares mean (SE) (%)	2348.71 (1.011)	2346.03 (1.011)
GMR (SE) (AVT03 vs Prolia)	1.00 (1.016)	
95% CI	0.97, 1.03	
Prespecified margin	0.8, 1.25	

AUEC was not calculated for subjects without an evaluable Baseline and/or Month 6 CTX-1 measurement, but they were not considered to have an ICE.
Two-sided 95% CIs for the GMR between AVT03 and Prolia groups were obtained from an ANCOVA model including $AUEC_{0\text{-}6\ months}$ as response variable, randomized treatment as categorical covariate, and baseline sCTX-1 value as continuous covariate.
Unit is Day × %.
Abbreviations: ANCOVA = analysis of covariance; $AUEC_{0\text{-}6\ months}$ = area under the effect curve from 0 to 6 months; GMR = geometric mean ratio; CI = confidence interval; ICE = intercurrent event; n = number of subjects in the PD Analysis Set; m = number of subjects with an evaluable AUEC per group; PD = pharmacodynamic(s); sCTX-1 = serum C-terminal cross-linked telopeptide of type I collagen; SE = standard error.

Figure 6: Mean (±SD) of Concentrations in sCTX1-Level by Visit – PD Analysis Set – From Baseline to Month 12



Abbreviations: PD = pharmacodynamic(s); sCTX-1 = serum C terminal cross-linked telopeptide of type I collagen; SD = standard deviation.

PD similarity of AUEC0-6months for percent change from Baseline of sCTX-1 was demonstrated as the 95% CIs of GMR between the two treatment arms (0.97, 1.03) was entirely within the pre-specified margin (0.80, 1.25). Results of a sensitivity analysis were similar to the primary analysis. Time since menopause (≤ 5 or > 5 years), prior biologic therapy for osteoporosis, the presence of ADAs, and the presence of nAbs did not have a clinical meaningful effect on these results.

Percent Change from Baseline in the sCTX-1 Levels to Months 3, 6, 9, 12 and 18

Overall, the decrease from Baseline in the sCTX-1 levels over time showed a similar trend in the AVT03 and Prolia treatment groups. The geometric means (GEO CV%) of change in the ATV03 and Prolia groups were 82.147% (20.9) and 82.759% (13.1) at Month 3; 67.058% (44.0) and 65.108% (37.1) at Month 6; 81.843% (22.7) and 81.322% (20.7) at Month 9; and 60.023% (52.8) and 54.450% (61.3) at Month 12. No marked differences among the treatment groups in the decrease from Baseline in the sCTX-1 levels to Month 18 were observed.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetics of AVT03 and respective reference products was thoroughly investigated in a Phase 1 PK/PD study in healthy subjects (AVT03-GL-P01). Supportive PK data were generated in a Phase 3 efficacy and safety study in patients with postmenopausal osteoporosis (PMO) (AVT03-GL-C01).

AVT03-GL-P01 (PK in healthy subjects)

Study design/methods

Study AVT03-GL-P01 was a phase I, randomised, double-blind, single-dose, parallel study to compare the PK, PD, safety, and immunogenicity profile of AVT03 and US-Prolia in healthy male volunteers.

Eligibility criteria pertaining to gender (men only), age (exclusion of subjects <25 to 55 years of age to ensure bone maturity), body mass index (17.0.0-32.0 kg/m^2) are appropriate to decrease PK variability in these parameters. Inclusion and Exclusion criteria are acceptable. The applicant implemented the CHMP advice to increase the lower age limit to 25 years. This is acknowledged. Subjects who met all inclusion and none of the exclusion criteria were randomly assigned to 1 of the 2 study arms (1:1) to receive either AVT03 or US-Prolia. The randomisation was stratified by body weight measured at Day −1 as follows: body weight ≤75 kg and >75 kg. The processes of randomisation and blinding were adequately described and are considered acceptable.

Denosumab was administered as a single 60 mg s.c. dose. Denosumab displays non-linear PK due to target-mediated drug elimination at lower doses (>20 mg and <60 mg). However, for doses of ≥60 mg, approximately dose proportional increases in exposure are seen (linear non-target-mediated drug disposition). Dose selection for the Phase 1 study is acceptable.

Due to the long half-life of denosumab (mean half-life 28 days), a parallel design is appropriate. The duration of the study was approximately 40 weeks, which covers 5 half-lives and captures the entire PK and PD profile.

The timepoints for blood samples for PK analysis are acceptable to characterize the PK and PD profile of denosumab.

All included subjects were to receive adequate calcium and vitamin D supplements during the study as required (based on 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 hypocalcaemia or hypercalcemia occurred, the Investigator could adjust the calcium and/or vitamin D dosage if needed. Also, the dose regimen for these non-IPs could be modified per the Investigator's discretion when intolerance to calcium and/or vitamin D was reported.

In study AVT03-GL-P01, the primary objective was to assess the PK equivalence of a single s.c. dose of AVT03 vs. US-Prolia. The secondary objectives were to evaluate and compare PK, PD, safety, tolerability, and immunogenicity. The objectives are endorsed. The co-primary PK endpoints were Cmax and AUC0-inf. These endpoints are in line with the EMA "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* (EMA/CHMP/BMWP/403543/2010)", which states that in case of s.c. administration, AUC0-inf and Cmax should be evaluated as co-primary PK parameters. Therefore, these endpoints are appropriate. Other secondary PK endpoints included are also acceptable.

Statistical methods:

PK Population included all randomized subjects who received any amount of the IP and had at least 1 evaluable PK parameter. The general specifications for handling and presenting the concentration-time data are standard and acceptable. The definition of the PK population which requires having sufficient subject data for evaluating at least one PK parameter is considered appropriate.

The use of an ANCOVA model for the log-transformed co primary endpoints is considered suitable to establish PK equivalence. Determination of PK equivalence based on 90% CIs for the GMRs of the primary endpoints to be within the equivalence margin of 80.00% and 125.00% is also in line with the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

All subjects in the PK population were included in PK Cmax analysis. Four subjects (1 in the AVT group, 3 in the Prolia groups respectively) were excluded from the analysis of AUC0-inf endpoint. The applicant clarified that the exclusion of four subjects from the PK analysis of AUC0-inf was due to having an R square adjusted value below 0.75 (one of the criteria introduced in Section 15.2 of SAP, according to which subjects were excluded from the PK similarity analysis of AUC0-inf). The revised equivalence test for AUC0-inf, including the four subjects, resulted in a slightly larger CI within the equivalence margin.

The sample size calculations could be followed from computational perspective.

The descriptive analyses of the primary as well as secondary PK endpoints are considered acceptable.

Results

A total of 206 subjects were enrolled in study AVT03-GL-P01 (99 and 107 subjects in the AVT03, US-Prolia, respectively). Of the 209 randomized subjects, 192 (91.9%) subjects completed the study up to Day 252. The number of subjects completing the study was high and well balanced between treatment arms (95 (94.1%) and 97 (89.8%) subjects in the AVT03 and US-Prolia, respectively).

In total, protocol deviations have been reported for 21 (10%) subjects [AVT03; US-Prolia group: 8.9%; 11.1%]. According to the applicant, no protocol deviation has been considered significant. No deviation led to discontinuation from the study. No significant implications on PK/PD results are expected.

The baseline characteristics were overall balanced across treatment arms. Overall, the majority of subjects were Black or African American (52.4%) and 35% were Caucasian/White. The percentage of Black or African

American subjects was higher in the AVT03 (55.6%) group as compared with the Prolia (49.5%) group. The overall mean age of the subjects was 36.4 years (age range, 28 to 55 years). The overall mean weight of the subjects was 71.81 kg (mean weights of 70.37 kg in the AVT03 group and 73.15 kg in the Prolia group), with 58.3% of subjects weighing ≤75 kg. The overall mean BMI value was 24.19 kg/m2 (mean BMI values of 23.74 kg/m2 in the AVT03 group, and 24.61 kg/m2 in the Prolia group). The mean weight and BMI of subjects were similar in both the treatment groups. In the PK Population, the demographic and baseline characteristics indicated that there were no issues that would unduly influence the PK similarity assessments. The results were also well balanced between the treatment groups and were consistent with those of the Safety Population. No relevant imbalances between study arms were noted regarding medical/surgical history or prior and concomitant medication.

Of the 209 randomized subjects, excluding 3 subjects who were not dosed, a total of 206 subjects (98.6%) received the IP, and were therefore included in the Safety and PD Populations. One subject in the Prolia group was excluded from the PK Population. Therefore, a total of 205 subjects (98.1%) were included in the PK Population.

Overall, denosumab serum concentration vs. time profiles were comparable between the treatment arms for all treated subjects in total. The mean serum denosumab PK parameters in the AVT03 group were comparable with those in the Prolia group. The geometric mean Cmax value in the AVT03 group (7382.1 ng/mL) was comparable to that in the Prolia group (6513.4 ng/mL). The geometric mean AUC values in the AVT03 group (AUC0-inf: 7637731.8 h·ng/mL; AUC0-last: 7559695.8 h·ng/mL) were also comparable to those in the Prolia group (AUC0-inf: 6578675.2 h·ng/mL; AUC0-last: 6465342.9 h·ng/mL). The geometric CV% was <30% for the Cmax and AUC parameters in the AVT03 group and for AUC parameters in the Prolia group; while the geometric CV% was 31% for Cmax in the Prolia group. The median Tmax was around 168 hours in both the treatment groups, with values ranging from 48 to 602.42 hours in the AVT03 group and from 47.90 to 1677.70 hours in the Prolia group. There was no significant difference in the time to attain maximum serum concentrations of denosumab (Tmax) between the treatment groups.

Systemic elimination parameters of denosumab showed comparable profile in both the treatment groups. The geometric mean terminal half-life (t1/2) in the AVT03 group (414.02 hours) was comparable with that in the Prolia group (424.12 hours). The geometric mean apparent volume of distribution (Vz/F) and geometric mean apparent clearance (CL/F) values were also comparable in the AVT03 and Prolia groups. The geometric CV% values for t1/2, Vz/F, and CL/F ranged from 19.33% to 34.85% and were comparable between groups. The 90% CIs of the GMRs for the primary PK endpoints, Cmax, AUC0-inf, and AUC0-last were entirely contained within the prespecified margins of 80.00% and 125.00% for the comparison of AVT03 versus Prolia, thus supporting PK similarity between the test product AVT03 and the reference product Prolia.

In some of the PK profiles, a sudden drop in concentration at a single evaluation time point followed by recovery to previous concentration levels at the subsequent evaluation time point was observed.

All individual concentration PK curves were provided by the applicant. Furthermore, the applicant performed a systematic and thorough root cause analysis regarding the validity of the PK concentration read outs. 19 individual PK samples have been identified as outliers. However, no root cause could be determined. Since this phenomenon has been also observed in other denosumab biosimilar applications, the CHMP consulted the MWP on the topic. In contrast to other cases, in the current application although there were a few cases in which the issue occurred in the elimination phase (see corresponding plots above), while for the majority of other cases, the issue was observed in the absorption phase (at lower time points) and therefore it might not be classified as occurring “at random time points”. In addition, including a comparable (between arms) number of “extreme values” in bioequivalence analysis is not considered conservative, assuming that such

cases occurred due to ICEs (i.e., the consideration of Treatment policy strategy in the estimand framework). This might contribute to the arms looking more similar than they are. Excluding them from the analysis, on the other hand, violates the intention to treat principle, is subject to bias, and does not reassure the robustness of conclusion. Assuming that those cases occurred due to the effects of ICEs, consideration of hypothetical strategies by means of MI analysis might be a more conservative option.

In order to understand the impact of the identified implausible datapoints two sensitivity analyses have been performed.

• Scenario 1 : replace incorrect datapoint with the correct bioanalytical value and exclude all other data points.

• Scenario 2 : replace incorrect datapoint with the correct bioanalytical value, replace the concentrations for the potential switched samples, and exclude all other data points.

For both statistical analyses, the way of handling the unexpected PK profiles had minimal impact on the comparison of AVT03 vs Prolia. Despite the lack of a root cause for the PK phenomenon, a relevant impact of the implausible datapoints on the overall PK similarity does not exist. Therefore, the sensitivity analyses further support a conclusion on PK equivalence between AVT03 and Prolia.

Equivalence criteria were also met for the secondary comparisons AVT03/US-Prolia for all PK parameters before and also upon the sensitivity analysis.

AVT03-GL-C01 (PK in the target population)

Study design/methods

This was a Randomised, Double-Blind, Parallel, Multicentre, Study to Compare the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of AVT03 Versus US-Prolia in Postmenopausal Women with Osteoporosis. The study consisted of two periods: a Main Treatment Period (Day 1 to Month 12), during which patients received 2 doses of denosumab 60 mg s.c. at a 6-month interval (Day 1 and Month 6); and a Safety Follow-up Period (Month 12 to Month 18/End of Study), during which patients received an additional dose of 60 mg s.c. (at Month 12).

The PK endpoint Serum trough concentration of AVT03 and Prolia was assessed.

The selected endpoint is acceptable; the PK during the Main period is of main interest. Blood samples for PK analysis were collected pre- and at least 6 hours postdose at Day 1, Day 2, Day 12, Day 30, Day 60, Day 90, Day 180, Day 270, Day 365, day 365 [(2 weeks), month15. The sampling time points are adequate for characterizing the PK endpoint.

Descriptive PK on serum trough concentrations of AVT03 and Prolia was planned to be assessed over time with similar calculation to be done by the ADA and NAb status. Point estimates and 90% CIs for serum trough PK concentrations were provided as requested during the scientific advice procedure (EMA/SA/0000084481).

Results

Following the first dose, denosumab concentrations were highest at Day 12 and declined slowly through Month 6 for both treatments. The concentration-time curves of two products were overall comparable. The two concentration curves then decreased in parallel to Day 180 (Month 6). The mean serum trough concentrations prior to Month 6 and Month 12 dosing were comparable between the treatment groups supporting biosimilarity. By Day 180, prior to second study drug administration, the geometric mean (GEO CV%) trough concentration was 10.52 ng/mL (599.4%) in the AVT03 group and 7.46 ng/mL (401.2%) in the

Prolia group). The geometric mean (GEO CV%) trough concentrations at Month 12 prior to the third dose, were 10.23 ng/mL (642.3%) in the AVT03 group and 7.09 ng/mL (392.9%) in the Prolia group. Numerically, there was a higher trough concentration in the AVT03 group compared to the Prolia group at month 12. Of note the Ctrough values exhibited a high between-subject variability, which was also different between treatment. However, as the pivotal phase 1 study met demonstrated biosimilarity in PK, this descriptive observation is not of concern. Furthermore, at Month 12 + 2 weeks, the geometric mean (GEO CV%) serum concentrations were similar between groups with a CV% (5625.96 ng/mL (73.9%) in the AVT03/AVT03 group 5189.22 ng/mL (113.5%) in the Prolia/AVT03 group, and to 5603.87 ng/mL (33.6%) in the Prolia/Prolia group). From Month 12 to Month 18, the serum concentrations of AVT03 and Prolia decreased to levels similar to those observed at Month 12 before study drug administration. Switching from Prolia to AVT03 had no effect on serum concentrations. The mean concentration profiles for AVT03 and Prolia were similar in magnitude and trend at all timepoints assessed. Again, the results support biosimilarity in PK between AVT03 and US-Prolia.

Overall, the PK data from the phase 3 study in the target population support equivalence of AVT03 to EU-Prolia.

Pharmacodynamics

Pharmacodynamics of AVT03 and respective reference products was investigated in two clinical studies, a Phase 1 PK/PD study in healthy subjects (AVT03-GL-P01) and a Phase 3 efficacy and safety study in patients with postmenopausal osteoporosis (PMO) (AVT03-GL-C01). The investigation of PD in both studies included serum C-terminal telopeptide of Type 1 collagen (sCTX), a biochemical marker of bone turnover, particularly bone resorption. This is considered a dynamic marker with high sensitivity that correlates with bone turnover rate and bone remodelling.

No other PD markers were used. The additional investigation of P1NP (procollagen Type I N-terminal propeptide) would have been beneficial and could strengthen the biosimilarity claim, however it is not considered indispensable, therefore its omission can be accepted.

AVT03-GL-P01 (PD in healthy volunteers)

Study design/methods

The blood samples for PD analysis were collected after overnight fasting (at least 8 hours) in the morning before drug administration. The frequency and duration of sampling was adequate from the PD perspective.

PD parameters were evaluated using $AUEC_{0\text{-}t}$, $AUEC_{0\text{-}last}$, t_{min}, I_{max} and I_{min}.

The selected PD endpoints are appropriate for PD evaluation as a secondary objective in study AVT03-GL-P01.

According to the definition of PD population set, subjects with important protocol deviations or events thought to significantly affect the PD were planned to be excluded, which is not accurate enough as it leaves open which data are necessary for calculating the endpoint or what is considered a major protocol deviation. However, as all dosed subjects were included in PD analyses, no concern is raised about the PD population set.

For both of AUEC0-last and AUEC0-t, the mean rebound areas (respectively defined as the areas under the effect curve below baseline from time zero to last time point or t) were negligible and comparable between treatment groups. For AUEC0-last, the mean rebound areas were only approximately 0.03% of the areas above baseline, in both treatment groups. Similarly, for AUEC0-t the mean rebound areas were approximately 0.03%

and 0.04% of the areas above baseline in AVT03 and Prolia respectively. Therefore, the handling of the rebound areas is of minor relevance as it has approximately no impact.

The PD analyses were planned descriptively, to be summarized by treatment arms and/or to be presented graphically. The considerations of PD analyses were discussed and agreed during the scientific advice procedure (EMA/SA/0000084481).

Results

In the PD Population, following a single s.c. dose of 60 mg/mL, the mean serum CTX-1 concentration-time profile for AVT03 and Prolia were comparable, both showing initially normal serum levels of CTX-1 at baseline (predose levels), followed by a rapid decrease in the serum CTX-1 levels immediately after IP administration. The inhibition in levels of CTX-1 continued until Day 141 (3360 h) approximately, followed by a slow increase in CTX-1 serum concentrations until Day 252 (EOS, 6024 h). However, the CTX-1 levels in the serum did not reach the predose levels at EOS. The mean serum CTX-1 concentration had decreased by >75% on Day 1 within 12 hours postdose (77.68% in the AVT03 group and 78.10% in the Prolia group). At Day 252 (EOS), the CTX-1 levels were still below the baseline concentration in both the groups (37.46% in the AVT03 group and 35.61% in the Prolia group).

The mean serum CTX-1 parameters in the AVT03 group were comparable with those in the Prolia group. The geometric mean area under the effect-time curve (AUEC) values in the AVT03 group (AUEC0-t: 447909.13 h·%; AUEC0-last: 427782.68 h·%) were comparable to those in the Prolia group (AUEC0-t: 448112.18 h·%; AUEC0-last: 421988.99 h·%). The PD profiles in terms of AUEC0-t for percentage change from baseline in serum CTX-1 until EOS, were comparable following IP administration in both the groups. The geometric mean values of maximum observed percentage of serum CTX-1 inhibition, Imax (91.37% in AVT03 group and 92.28% in Prolia group) and minimum observed serum CTX-1 concentration, Imin (0.036 µg/mL in AVT03 group and 0.038 µg/mL in Prolia group) were also comparable in both the groups. The median time to Imin (Tmin) was 193.98 hours in the AVT03 group and 216.10 in the Prolia group, with values ranging from 12 to 3863.95 hours and 12 to 3337.30 hours, respectively.

Additionally, sCTX has been investigated in the Phase 3 study in a more relevant patient model and with more stringent assessment criteria, and PD data from the Phase 1 PK study are considered supportive for the biosimilarity conclusion.

AVT03-GL-C01

Study design/methods

Blood samples collection for PD analysis was acceptable.

Percent change from baseline in sCTX-1 at 3, 6, 9, 12 and 18 months and Area Under the percent change from baseline in serum C-telopeptide of type 1 collagen up to 6 months (AUC0-6months of %Cfb sCTX-1 = co-primary efficacy endpoint) have been evaluated as PD endpoints.

The applicant presented descriptive statistics for AUEC up to EOS. However, for AUEC0-6months, a comparison of the summary statistics for the potential rebound area (i.e., the area under the effect curve below baseline from time 0 to 6 months) and the area under the effect curve above baseline between treatment groups was requested, similar to what is presented in the related concern in study AVT03-GL-P01 (see above). It is unclear whether such cases occurred and, if so, whether the mean rebound areas were negligible and comparable between treatment groups. However, in light of the results, which are well within the equivalence margin, and also considering the tipping point sensitivity analyses - which included

(negative) penalties added to the imputed AUEC values (see below)- the corresponding effect on the overall conclusion is considered negligible. Therefore, the issue is not further pursued.

Wording of the last ICE defined in the estimand for the coprimary PD endpoint as "additional protocol deviations that impact the assessment of primary PD endpoint", is unspecific and does not allow further assessment of adequacy of corresponding data exclusion. The applicant provided a list of subjects with specific reasons considered as "additional protocol deviations" that led to exclusion of subjects from PD analysis. As all but one case (with a negative AUEC value) were included in the analysis requested during the procedure, implementing a multiple imputation model, adequacy of the corresponding data exclusion is of no concern.

The primary PD analysis was based on an ANCOVA model including log transformed AUEC0-6 months as the response variable, treatment as categorical covariate, and baseline sCTX-1 value as a continuous covariate. Log-transformed PD data (AUEC0-6months of %Cfb sCTX-1) were analysed.

For the primary PD analysis 23 subjects in the AVT03 and 19 subjects in the US-Prolia groups with ICEs and additionally 7 subjects (5 in the AVT03 and 2 in the US-Prolia) due to evaluability issues of AUEC were excluded before performing the analysis. Upon request, a multiple imputation model under the MAR assumption was implemented to impute (missing) inhibition values due to the ICE strategy or initially missing values. It is unclear why MI was not implemented for subjects with missing baseline CTX-1 levels. However, as it affects 4 subjects with missing baseline CTX-1 levels and the results are well within the margin, the corresponding effect is considered negligible to change the conclusion. The results are similar to those of the primary PD analysis, with minor differences.

Tipping point sensitivity analyses were conducted using the same penalty levels applied to both arms. It would have been more informative to conduct the analyses also for the interaction of penalty levels. In addition, tipping point analyses are typically conducted until a condition is no longer fulfilled (e.g., a lower/upper 95% confidence bound falls outside the equivalence margin or a computational issue arises - for example AUIC becomes negative). However, as for the considered penalties, the 95% CI is still far from the equivalence limits, the impact of the mentioned limitations is unlikely to change the conclusion.

As there were only 2 subjects with the use of prohibited concomitant medications, and at maximal 12 subjects had additional protocol deviations, and as treatment discontinuation mainly led to missing Month 6 dose, an additional analysis based on the treatment policy strategy is anticipated not to result in a different conclusion in light of the results being well within the acceptance ranges. Moreover, such an analysis was partly considered in the provided sensitivity analysis.

Results

The analysis for the primary PD endpoint for the EMA submission was produced using the PD Analysis Set. The geometric mean for AUEC0-6months for percent change from Baseline in sCTX-1 was 2361.29 for the AVT03 group and 2327.63 for the Prolia group, with the GMR (SE) for AVT03 vs Prolia of 1.00 (1.016).

PD similarity of AUEC0-6months for percent change from Baseline of sCTX-1 was demonstrated as the 95% CIs of GMR between the two treatment arms (0.97, 1.03) was entirely within the pre-specified margin (0.80, 1.25). Results of a sensitivity analysis were similar to the primary analysis. Time since menopause (≤ 5 or > 5 years), prior biologic therapy for osteoporosis, the presence of ADAs, and the presence of nAbs did not have a clinical meaningful effect on these results. Analysis of percent change in the sCTX-1 levels up to Month 12 showed a similar trend in the AVT03 and Prolia treatment groups, thus supporting the PD similarity

of the test and reference product. No marked differences among the treatment groups in the decrease from Baseline sCTX-1 levels to Month 18 were observed.

2.5.4. Conclusions on clinical pharmacology

In the pivotal Phase I study, the 90% CIs for the GLSM of the ratio test/reference for the primary PK parameters (AUC0-inf, AUC0-last, and Cmax) were fully contained within the predefined bioequivalence limits of [80.00% to 125.00%]. Additional sensitivity analyses support a conclusion on PK equivalence between AVT03 and Prolia.

The PK profiles from the osteoporosis patients were similar between the AVT03 and Prolia group and support PK similarity of the test and reference product.

The PD results of study AVT03GL-C01 support the PD similarity of the denosumab biosimilar candidate AVT03 and the reference product Prolia. The AUEC(month6) for serum CTX concentration was a co-primary endpoint and was met. Secondary PD endpoints of this study also support the PD similarity of the test and reference product.

Taking into account the common mechanism of action across all indications and the known comparable PK profile of Prolia and Xgeva, the CHMP considers that the results of the studies using Prolia as comparator demonstrate comparable PK and PD between AVT03 and Prolia.

2.5.5. Clinical efficacy

The clinical development programme of AVT03 includes 2 clinical studies: a Phase 1 bioequivalence study conducted in healthy volunteers and a Phase 3 confirmatory efficacy study in postmenopausal women with osteoporosis to assess the therapeutic equivalence of AVT03.

2.5.5.1. Dose response study(ies)

No dose response studies were performed and are not deemed necessary in the biosimilarity setting.

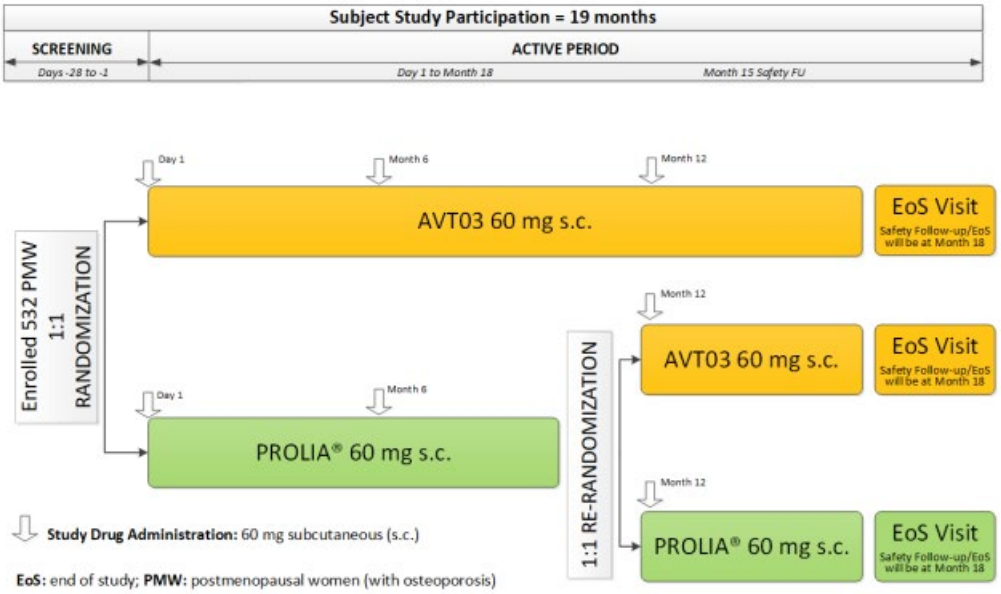
2.5.5.2. Main study(ies)

Study AVT03-GL-C01

Study AVT03-GL-C01 is a randomised, multicentre, double-blind, active-controlled, parallel group, Phase 3 study to compare the efficacy, PK, PD, immunogenicity and overall safety of AVT03 and US-Prolia in postmenopausal women with osteoporosis. The study comprised 4-week screening period, 12 months treatment period upon rerandomisation of the US-Prolia group and a safety follow up until the end of the study visit at Month 18, including a third dose of the study treatment at Month 12.

During the Main Treatment Period, therapeutic equivalence between AVT03 and US-Prolia was evaluated based on lumbar spine bone mineral density (BMD) measured at Month 12, after administration of two doses of study drug (primary objective). The Safety Follow-up Period intends to focus on the safety of AVT03 and EU-Prolia.

Figure 7: Schematic of Study Design



Methods

- **Study Participants**

Main Inclusion Criteria

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

2. Aged: ≥ 50 years.

3. Female subjects who were postmenopausal according to 1 of the following criteria:

a. Spontaneous amenorrhea for ≥ 12 consecutive months

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

except surgically sterile

c. Had bilateral oophorectomy ≥ 6 weeks prior to Screening

4. Body Mass Index (BMI): 18.5.0-32.0 kg/m2

5. A baseline DXA scan with a T score ≤ -2.5 and ≥ -4.0 at the LS (L1 to L4) and/or total hip and/or femoral neck. A subject must have had a T score within the stated range of ≤ -2.5 and ≥ -4.0 in at least 1 of the 3 areas: - Lumbar spine (L1 to L4) - Total hip - Femoral neck. On the contrary, subjects were excluded from the trial if the T score was less than -4.0 in at least 1 of the 3 areas (i.e., at the LS [L1 to L4], or total hip, or femoral neck). Note: The left hip should be scanned for the calculation of total hip T score. If the left hip could not be scanned (e.g., due to left hip replacement), the right hip could be scanned instead. The same hip should be used for all DXA scans.

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

7. Willing to receive calcium plus vitamin D supplements.

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

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

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

11. Subject smoked < 10 cigarettes per day within 3 months of Screening. Note: It was strongly recommended that subjects did not smoke during their participation in the study. 12. Recommended to abstain from alcohol from 48 hours prior to drug administration, and 24 hours prior to study visits.

Main Exclusion Criteria

1. Evidence of clinically relevant pathology, especially prior diagnosis of bone disease, or any uncontrolled condition that would affect bone metabolism such as, but not limited to: osteogenesis imperfecta, hyperparathyroidism, non-controlled hyperthyroidism (thyroid stimulating hormone (TSH) < 0.5 mIU/L), non-controlled hypothyroidism (TSH ≥ 5.0 mIU/L), osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as creatinine clearance < 50 mL/min as calculated by Cockcroft-Gault formula), Paget's disease of the bone, recent bone fracture (within 6 months), and malabsorption syndrome. For potential causes of secondary osteoporosis, please see Appendix 14.2. of the protocol (Appendix 16.1.1).

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

3. History of hip fracture.

4. Presence of active healing fractures.

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

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

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

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

d. Romozosumab within 30 days prior to Screening

e. Calcitonin within 6 months of Screening

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

i. anabolic steroids or testosterone

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

iii. systemic hormone replacement therapy

iv. tibolone

v. calcitriol

vi. anticonvulsants (except benzodiazepines and pregabalin)

vii. heparin

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

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

7. Evidence of hypo/hypercalcemia at Screening defined as < 8.6 or > 10.5 mg/dL. Note: If hypocalcaemia could be excluded based on calcium, corrected calcium, albumin, PTH, vitamin D3 values but ionized calcium was pending, the subject may have been randomized, as per investigator assessment and confirmation that exclusion criterion #7 had not been met. This was to be recorded on source documents.

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

9. Known intolerance to calcium or vitamin D supplement.

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

11. Presence of known current infection with hepatitis B or presence of positive serology –i.e., hepatitis B surface antigen (HBsAg) and/or anti-HBc, hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) at Screening discretion whether to extend diagnostics to exclude current infection of hepatitis B. A local hepatitis B virus (HBV) quantitative DNA by polymerase chain reaction (PCR) test may have been performed within the screening window visit.

12. Haematology and chemistry laboratory results outside the reference ranges, which were clinically significant, and, in the opinion of the investigator or designee, could have caused this study to be detrimental to the subject.

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

14. Hypersensitivity to denosumab or its constituents.

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

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

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

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

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

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

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

- **Treatments**

The patients received 60 mg of either AVT03 or US-licensed Prolia on Day 1, day 180 and day 365 (month 12) for the safety follow up phase, as per the first randomisation. The study drug was administered as a single SC injection in the upper arm, upper thigh, or abdomen.

AVT03 and US-Prolia were both supplied as pre-filled syringes containing 1 mL of liquid with 60 mg of denosumab (60 mg/mL), as summarized in the following table.

Table 14: Study Interventions Administered

Name	AVT03 (IMP)	Prolia (reference product)
Formulation	Solution for injection	Solution for injection
Strength	60 mg/1 mL	60 mg/1 mL
Dose (unit)	60 mg	60 mg
Route of administration	Subcutaneous	Subcutaneous
Manufacturer	Alvotech hf	Amgen Inc., US
Storage Conditions	Stored refrigerated, at 2°C to 8°C	

Abbreviations: IMP = investigational medicinal product

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

- **Concomitant and rescue therapies**

Prohibited Medications:

1. Intravenous bisphosphonates, fluoride or strontium ranelate within 5 years prior to Screening

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

3. PTH or PTH derivatives, e.g., teriparatide and SERMs, e.g., raloxifene within 1 year of Screening

4. Calcitonin within 6 months of Screening

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

a. anabolic steroids or testosterone

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

c. systemic hormone replacement therapy

d. tibolone

e. calcitriol

f. anticonvulsants (except benzodiazepines)

g. heparin

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

- **Objectives**

Primary objectives:

- To demonstrate clinical similarity of AVT03 and Prolia in terms of percent change from Baseline in BMD at 12 months.
- To demonstrate clinical similarity of AVT03 and Prolia in terms of AUEC0-6months of %Cfb sCTX-1.

Secondary objective

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

- **Outcomes/endpoints**

Primary Efficacy Endpoint

- Percent change from Baseline in LS BMD at 12 months.
- AUEC0-6months of %Cfb sCTX-1.

Secondary Endpoints

Efficacy

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

Safety

- Incidence, nature, and severity of AEs, including ADRs.
- Frequency and severity of ISRs.
- Frequency and severity of findings in routine safety parameters, including clinical laboratory assessments (haematology, clinical biochemistry, coagulation, urinalysis, and urine microscopy), vital signs, ECG, and physical examination.

Pharmacokinetics

- Serum trough concentration of AVT03 and Prolia.

Pharmacodynamics

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

- AUEC0-6months of %Cfb sCTX 1.

Estimands for the primary objectives

Table 15: Estimands for Primary Objective

Population	**Patients with postmenopausal osteoporosis, who were randomized and received at least 1 dose of study treatment (based on FAS).**
Treatment condition<s>	Assignment to AVT03 or US-Prolia.
Endpoint (variable)	Percent change from Baseline in LS BMD at 12 months.
Population-level summary	Difference in mean percent change from baseline in LS BMD at 12 months between AVT03 and US-Prolia groups.
Intercurrent events and strategy to handle them	
Discontinuation from study treatment prior to 6 months.	-
Taking prohibited concomitant medications prior to 12 months that impact the primary endpoint.	-
Receiving incorrect study treatment instead of the randomized treatment.	-
Additional protocol deviations that impact the assessment of primary efficacy endpoint	-

Table 16: Estimands for Primary PD Objective

Population	**Patients with postmenopausal osteoporosis, who were randomized and received at least 1 dose of study treatment and had at least 1 evaluable PD endpoint collected without any protocol deviation that was thought to significantly affect the PD (based on the PD set).**
Treatment condition<s>	Assignment to AVT03 or US-Prolia.
Endpoint (variable)	Area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months (AUEC0-6months of %Cfb sCTX-1).
Population-level summary	Ratio of geometric mean for AUEC0-6months of %Cfb sCTX-1 between AVT03 and US-Prolia groups.

Population	Patients with postmenopausal osteoporosis, who were randomized and received at least 1 dose of study treatment and had at least 1 evaluable PD endpoint collected without any protocol deviation that was thought to significantly affect the PD (based on the PD set).
Intercurrent events and strategy to handle them	
Discontinuation from study treatment prior to 6 months.	-
Taking prohibited concomitant medications prior to 6 months that impact the primary endpoint.	-
Additional protocol deviations that impact the assessment of primary PD endpoint	-

Estimands for the secondary efficacy and PD objectives

Not defined.

- **Sample size**

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

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

The equivalence margin and the common SD were derived based on the data from the historical clinical trials with denosumab 60 mg and placebo.

Table 17: Historical Data for Percentage Change from Baseline in Lumbar Spine Bone Mineral Density at 12 Months and Meta-Analysis Results

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

In addition, the AUEC0-6months of %Cfb sCTX-1 was to be analysed as the primary PD endpoint. The coefficient of variation (CV%) of AUEC0-6months of %Cfb sCTX-1 was estimated from simulation using a published denosumab PD model (25,26) which was developed based on Prolia data. Assuming a true geometric mean ratio (GMR) of 0.95, using the standard equivalence margin of (0.80, 1.25), 476 randomized subjects (considering 18% of non-evaluable rate) were to provide a power of 99.9% for the PD similarity analysis of AUEC0-6months of %Cfb sCTX-1.

- **Randomisation and Blinding (masking)**

This is a double-blind study. Blinding of the study included study intervention, investigator, and subject masking.

Once the subject had signed the ICF at Screening, site personnel contacted the Interactive Response Technology (IRT) system through an Internet browser to assign a subject identification number (ID). The subject ID included the site number (4 digits) and 3-digit subject number, assigned sequentially starting with 001. This number was used to identify the subject throughout the study period. Dropouts (subjects who discontinued study drug early and subjects who were randomized but did not receive at least 1 dose of study drug) were not replaced. Procedure for rescreening is detailed in the protocol. On Day 1, after successfully completing screening activities, eligible subjects were randomized into Groups 1 and 2, in a 1:1 ratio (AVT03: Prolia). Subjects were stratified by number of years since menopause (≤ 5 years or > 5 years) and prior biologic therapy (for osteoporosis Yes or No). Group 1: Subjects received AVT03 60 mg administered s.c. on Days 1 and 180 (Month 6). Group 2: Subjects received Prolia 60 mg administered s.c. on Days 1 and 180 (Month 6). At Month 12, subjects in the Group 1 (AVT03) received a third dose of AVT03 60 mg administered s.c., while subjects in the Group 2 (Prolia) were rerandomized in a 1:1 ratio to receive, either: Group 2a: Subjects received AVT03 60 mg administered s.c. on Day 365 (Month 12). Group 2b: Subjects received Prolia 60 mg administered s.c. on Day 365 (Month 12).

- **Statistical methods**

<u>Planned analyses</u>

The Statistical Analysis Plan (SAP) and Table, Figure, Listing (TFL) Shells (and any amendments) were to be approved prior to breaking the blind for the Month 12 (+ 2 weeks) analysis. If post database lock, additional statistical analyses or changes to the statistical analysis were required, then those were to be documented in a Post Database Lock SAP Addendum.

Analysis sets

The **Enrolled Set** included all subjects who were given informed consent to participate in the study.

The **Randomized Set** included all subjects who were allocated a randomisation number.

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

The **Pharmacodynamic** (**PD) Analysis Set** was defined as all randomized subjects who received at least 1 dose of randomized study treatment and had at least 1 evaluable PD endpoint collected without any protocol deviation that is thought to significantly affect the PD. Subjects were to be analysed according to the actual study treatment received.

The **Safety Analysis Set** included all randomized subjects who received at least 1 dose of study treatment. Subjects were to be analysed according to the actual study treatment received.

Primary analysis

The analysis for the primary endpoint was to be performed using FAS excluding subjects following the ICEs or additional protocol deviation that impact assessment of the primary endpoint. All missing data, including data not actually collected and data excluded due to the impact of ICEs or protocol deviations were to be handled by the mixed model for repeated measures (MMRM) under the missing at random (MAR) assumption.

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

The least square mean estimates were to be provided for each treatment group at each visit with their standard errors (SE). The difference of least square means between the treatment groups and associated SE, 2 sided 95% CI (as required by EMA) were to be provided for 12 months.

Sensitivity Analysis for Primary Endpoint (percent change from Baseline in LS BMD at 12 months)

For the primary endpoint percent change from Baseline in LS BMD at 12 months, the following sensitivity analysis were to be performed:

<u>Sensitivity analysis (1):</u>

The percent change from Baseline in LS BMD was to be repeated based on the FAS excluding subject's data following the ICE's or additional protocol deviation that impact the assessment of the primary endpoint. All missing data, including data not actually collected and data excluded due to the impact of ICEs or protocol deviations were to be handled by Multiple Imputation (MI) under the missing not at random (MNAR) assumption. The MI was to be conducted separately under the non-inferior and non-superior assumptions. The penalty equal to the lower limit of the equivalence margin (-1.45%) was to be included for the imputed values for the AVT03 treatment group for non-inferior assumption. The penalty equal to the upper limit of the equivalence margin (1.45%) was to be included for the imputed values for the AVT03 treatment group for non-superior assumption. The reference group was not penalized. Details of MI and SAS codes are provided below.

Sensitivity analysis (2):

The percent change from Baseline in LS BMD was to be repeated based on the FAS without exclusion of any subjects data due to the ICEs or additional protocol deviation that might impact the assessment of the primary endpoint. The missing data (i.e., data not actually collected), if any, were to be handled by the mixed model for repeated measures (MMRM) under the missing at random (MAR) assumption.

Sensitivity analysis (3):

The percent change from Baseline in LS BMD was to be repeated based on the FAS without exclusion of any subject's data due to the ICEs or additional protocol deviation that impact the assessment of the primary endpoint. The missing data (i.e., data not actually collected), if any, were to be handled by Multiple Imputation (MI) under the missing not at random (MNAR) assumption. The same MI method as for sensitivity analysis (1) was to be used.

Multiple imputation methods:

Multiple imputation inference involved three distinct phases:

Step 1. The missing data were filled in m times to generate m complete datasets (m = 50). The SAS Proc MI were to be used for the MI using MNAR statement together with fully conditional specification (FCS) which could handle both monotone and non-monotone missing patterns. Details are as follows: The FCS specifies univariate models that impute variables sequentially. FCS involves two phases referred to as the filled-in phase and the imputation phase. In the filled-in phase, the missing values are initially filled in by randomly drawing from the conditional distribution of the observed outcome given the preceding variables. In the imputation phase, the missing values are drawn from the posterior distribution of the observed outcome given the remaining variables in the VAR statement. The imputation phase is an iterative process, and the imputed values are used after a number of iterations to achieve stationary distribution. The variables are imputed sequentially in the order specified in the VAR statement. The observations used to derive posterior distribution contain the observed response variable, and the covariates can be observed or filled in (filled-in phase) or imputed (imputation phase). In addition, when used with MNAR statements, the intermittent missing values will be imputed under the assumption of MNAR together with the monotone missing values.

The MI was to be conducted separately under the non-inferior and non-superior assumptions. The penalty equal to the lower limit of the equivalence margin (-1.45%) was to be included for the imputed values for the AVT03 treatment group for non-inferior assumption. The penalty equal to the upper limit of the equivalence margin (1.45%) was to be included for the imputed values for the AVT03 treatment group for non-superior assumption. The reference group was not penalised.

Step 2. The m complete datasets were analysed by using standard procedures. The same statistical method as for the primary endpoint analysis was to be used in this step.

Step 3. The results from the m complete data sets were to be combined for the inference. With m imputations, m different sets of the point and variance estimates for the parameters of interest were to be computed. The final result was to be constructed by combining the m sets of results using Robin's rule (Rubin 1987). The PROC MIANALYZE was to be utilized for the least squares (LS) mean for each treatment, and the LS mean difference between treatment groups as estimated from the MMRM model.

The LS means and SEs for each treatment group, and treatment difference with associated CIs were to be presented at Month 12. The lower bound of 95% CI was to be presented for the non-inferior assumption

(where a penalty equal to the lower limit of the equivalence margin (-1.45%) was included for the imputed values for the AVT03 treatment group), and the upper bound of 95% CI was to be presented for the non-superior assumption (where a penalty equal to the upper limit of the equivalence margin (1.45%) was included for the imputed values for the AVT03 treatment group).

Primary pharmacodynamic analysis for EMA submission

The analysis for the primary PD endpoint of the area under the percentage change from baseline in serum C-telopeptide of type 1 collagen up to 6 months (AUEC0-6months of %Cfb sCTX-1) for the EMA submission was to be produced using the PD Analysis Set.

The log transformed PD data (AUEC0-6months of %Cfb sCTX-1) were to be analysed using an analysis of covariance (ANCOVA) model including the treatment as factor and the baseline sCTX-1 as continuous covariate. The negative AUEC0-6months of %Cfb sCTX-1 were not included to the analysis as the log transformation is not doable. The geometric mean ratio was to be obtained by back-transforming the mean difference to the original scale. The 2-sided 95% CI for the geometric mean ratio between treatment groups was to be calculated.

Sensitivity analysis for the primary endpoint for EMA submission

The primary PD endpoint analysis for the EMA submission was to be repeated based on the PD Analysis Set without exclusion of any subjects data due to the ICEs or additional protocol deviation that impact the assessment of the endpoint specified for the main estimator.

Analysis of secondary endpoints

The secondary efficacy endpoints were:

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

For the percent change from Baseline in LS BMD and hip and femoral neck BMD the MMRM model described for the primary endpoint was to be used for the data up to Month 12. The MMRM model included treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD (LS, hip or femoral neck) and number of years since menopause as continuous covariates. An unstructured covariance structure was to be used to model the within-subject error and an adjustment to the degrees of freedom was to be made using the Kenward-Roger's approximation.

The least square mean estimates were be provided for each treatment group at each visit with their standard errors (SE). The difference of least square means between the treatment groups and associated SE, 2 sided 95% CI were to be provided for visits at 6, and 12 months.

The Month 18 assessments were to be analysed using an analysis of covariance (ANCOVA) model including treatment, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. The 2-sided 95% CI for the least square mean difference between treatment groups was to be calculated.

For the incidence of new morphometric vertebral fractures at 12 and 18 months the number and percentage of subjects were to be calculated by visit.

The analysis results of secondary efficacy endpoints were to be interpreted descriptively.

Planned subgroup analyses

The subgroup analyses of the primary efficacy and PD endpoint were to be performed by key baseline characteristics and ADA/NAb status based on the FAS. Within each subgroup, the primary endpoint was to be analysed using the same method as for the primary endpoint using FAS with actual data without imputations. The results of the subgroup analysis were to be interpreted descriptively. Subgroups of interest for the primary efficacy endpoint included:

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

For the analysis from baseline to Month 12 and from Month 12 to end of study the ADA status and NAb status were to be defined separately. The following definitions were to be used:

- From Baseline to Month 12

ADA status: Positive if any positive ADA before Month 12 dose; ADA Negative, otherwise.

NAb status: Positive if any positive NAb before Month 12 dose; NAb Negative, otherwise.

- From Month 12 to Month 12 + 2 Weeks

ADA status: Positive if any positive ADA from Month 12 to Month 12 + 2 Weeks; ADA Negative, otherwise.

NAb status: Positive if any positive NAb from Month 12 to Month 12 + 2 Weeks; NAb Negative, otherwise.

- From Month 12 to End of Study

ADA status: Positive if any positive ADA from Month 12 to End of Study; ADA Negative, otherwise.

NAb status: Positive if any positive NAb from Month 12 to End of Study; Nab Negative, otherwise.

- For the PD endpoint the following definitions were to be used:

ADA status: Positive if any positive ADA before or at Month 6; ADA Negative, otherwise.

NAb status: Positive if any positive Nab before or at Month 6; NAb Negative, otherwise.

Forest plots were to be produced to show the difference of least square means between the treatment groups at 12 months and associated 2 sided 95% CI were to be provided.

Results

- **Participant flow**

First Subject, First Visit: 23 Aug 2022

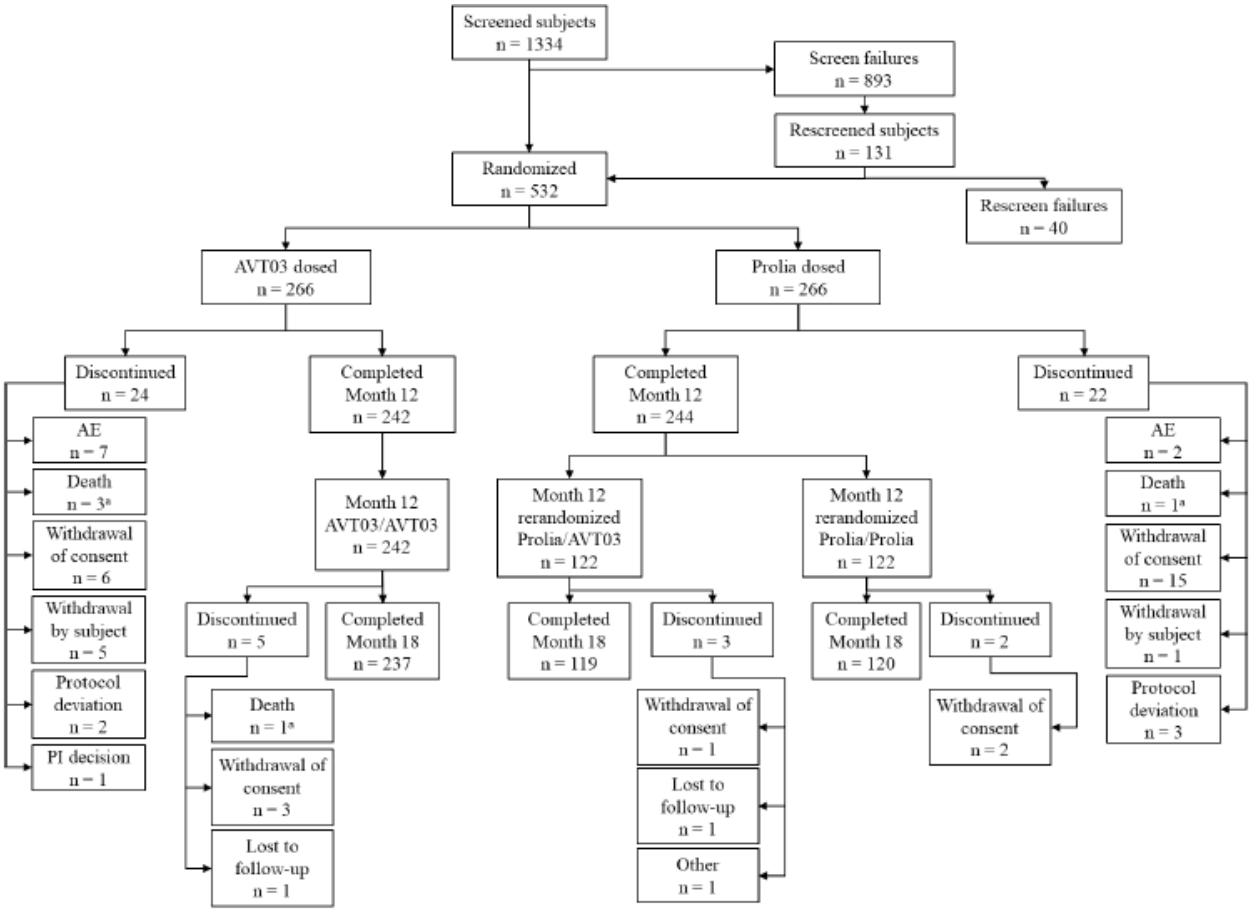
Last Subject, Last Visit (with respect to data included in this report): 28 Oct 2024

The applicant provided a primary clinical study report (CSR1) that includes data through Month 12 + 2 Weeks database freeze. The applicant also provided the final CSR (CSR2) including data collected through Month 18.

Overall, 1334 subjects were initially screened in the study; 893 subjects (66.9%) were screen failures. One hundred and thirty-one subjects were rescreened, and of these 40 subjects (3.0%) were screen failures. The key reasons for screen failures included failure to meet eligibility criteria (84.9%) and withdrawal of consent (12.6%).

There were 532 subjects who were randomized in the study, of whom 266 subjects received AVT03, and 266 subjects received Prolia. Overall, 486 subjects (91.4%) completed treatment up to Month 12 and 46 subjects (8.6%) discontinued treatment (24 [9.0%] in the AVT03 group and 22 [8.3%] in the Prolia group). A total of 46 subjects (8.8%) terminated the study early (24 [9.0%] in the AVT03 group and 22 [8.3%] in the Prolia group). One subject in the Prolia group discontinued treatment but continued in the study for safety follow-up. Primary reasons for early study treatment discontinuation were withdrawal of (21 subjects; 6 subjects in the AVT03 group and 15 subjects in the Prolia group) and AEs (7 subjects in the AVT03 group and 2 subjects in the Prolia group). Overall, 486 subjects received the Month 12 treatment administration. Of these, 242 subjects who completed 12 months on AVT03 continued receiving AVT03. The 244 subjects who up to Month 12 were receiving Prolia, were rerandomized to either continue on Prolia (Prolia/Prolia group; n=122) or start receiving AVT03 as of the Month 12 treatment administration (Prolia/AVT03 group; n=122). All 486 subjects completed Month 12 + 2 weeks. 10 subjects discontinued study from Month 12 to Month 18. The most common reason for discontinuations was withdrawal of consent (6 subjects; 3 subjects in the AVT03/AVT03 group, 2 subjects in the Prolia/Prolia group, and 1 subject in the Prolia/AVT03group). Two subjects (1 subject in AVT03/AVT03 group and 1 subject in Prolia/AVT03 group) were lost to follow up, 1 subject in the AVT03/AVT03 group died (not related to study drug), and 1 subject in the Prolia/AVT03 group discontinued due to other reason.

Figure 8: Disposition of Study Subjects



[a] None of the deaths were related to study drug.
Abbreviations: AE = adverse event; PI = principal investigator.

Table 18: Subject Disposition up to Month – Full Analysis Set

	AVT03 (N=266) n (%)	Prolia (N=266) n (%)	Overall (N=532) n (%)
From Baseline to Month 12[a]			
Randomized	266	266	532
Dosed	266	266	532
Completed Month 12	242 (91.0)	244 (91.7)	486 (91.4)
Discontinued from study drug before Month 6	14 (5.3)	15 (5.6)	29 (5.5)
Discontinued from study drug before Month 12	24 (9.0)	22 (8.3)	46 (8.6)
Discontinued from study before Month 12	24 (9.0)	22 (8.3)	46 (8.6)
Primary reason for early study drug discontinuation[b]			
Adverse event	7 (29.2)	2 (9.1)	9 (19.6)
Death	3 (12.5)	1 (4.5)	4 (8.7)
Withdrawal of consent	6 (25.0)	15 (68.2)	21 (45.7)
Withdrawal by subject	5 (20.8)	1 (4.5)	6 (13.0)
Protocol deviation	2 (8.3)	3 (13.6)	5 (10.9)
Lost to follow-up	0	0	0
Investigator decision	1 (4.2)	0	1 (2.2)
Other	0	0	0
Primary reason for early termination from study[c]			
Adverse event	7 (29.2)	2 (9.1)	9 (19.6)
Death	3 (12.5)	1 (4.5)	4 (8.7)
Withdrawal of consent	6 (25.0)	15 (68.2)	21 (45.7)
Withdrawal by subject	5 (20.8)	1 (4.5)	6 (13.0)
Protocol deviation	2 (8.3)	3 (13.6)	5 (10.9)
Lost to follow-up	0	0	0
Investigator decision	1 (4.2)	0	1 (2.2)
Other	0	0	0

From Month 12 to Month 18[d]					
		Prolia			
	AVT03/AVT03 (N=242) n (%)	Prolia/AVT03 (N=122) n (%)	Prolia/Prolia (N=122) n (%)	All Prolia (N=244) n (%)	Overall (N=486) n (%)
Completed study	237 (97.9)	119 (97.5)	120 (98.4)	239 (98.0)	476 (97.9)
Discontinued from study between Month 12 and EoS	5 (2.1)	3 (2.5)	2 (1.6)	5 (2.0)	10 (2.1)
Primary reason for early termination from study[f]					
Adverse event	0	0	0	0	0
Death	1 (20.0)	0	0	0	1 (10.0)
Withdrawal of consent	3 (60.0)	1 (33.3)	2 (100.0)	3 (60.0)	6 (60.0)
Withdrawal by subject	0	0	0	0	0
Protocol deviation	0	0	0	0	0
Lost to follow-up	1 (20.0)	1 (33.3)	0	1 (20.0)	2 (20.0)
Investigator decision	0	0	0	0	0
Other	0	1 (33.3)	0	1 (20.0)	1 (10.0)

- **Protocol deviations**

Protocol deviations

Up to Month 12, 457 subjects (85.9%) had at least 1 protocol deviation, of whom 63 subjects (11.8%) had major and 453 subjects (85.2%) had minor protocol deviations. The most common major protocol deviations were related to subject visits (27 subjects; 5.1%), study procedures - other (14 subjects; 2.6%) and study procedures related to randomisation (13 subjects; 2.4% each). The most common minor protocol deviations were related to subject visits (329 subjects; 61.8%), study procedures related to lab issues (257 subjects; 48.3%) and study procedures - out of window (123 subjects; 23.1%). From Month 12 to Month 18, 364 subjects (74.9%) had at least 1 protocol deviation, of whom 25 subjects (5.1%) had major protocol deviations and 361 subjects (74.3%) had minor protocol deviations. All major protocol deviations were related to study procedures - other (21 subjects; 4.3%) or subject visits (5 subjects; 1.0%). The most common minor protocol deviations were related to subject visits (246 subjects; 50.6%)

Table 19: Protocol Deviations – Full Analysis Set From Baseline to Month 12

Deviation Classification Deviation Category	AVT03 (N=266) n (%)	Prolia (N=266) n (%)	Overall (N=532) n (%)
Subjects Reporting Protocol Deviations	**227 (85.3)**	**230 (86.5)**	**457 (85.9)**
Major	**34 (12.8)**	**29 (10.9)**	**63 (11.8)**
Exclusion Criteria-Did Not Satisfy Entry Criteria	4 (1.5)	2 (0.8)	6 (1.1)
Informed Consent	1 (0.4)	1 (0.4)	2 (0.4)
Safety	1 (0.4)	3 (1.1)	4 (0.8)
Study Procedures (Other)	6 (2.3)	8 (3.0)	14 (2.6)
Study Procedures - Lab Issues	4 (1.5)	4 (1.5)	8 (1.5)
Study Procedures - Randomization	9 (3.4)	4 (1.5)	13 (2.4)
Subject Visits	16 (6.0)	11 (4.1)	27 (5.1)
Minor	**226 (85.0)**	**227 (85.3)**	**453 (85.2)**
Informed Consent	7 (2.6)	8 (3.0)	15 (2.8)
Study Procedures (Other)	49 (18.4)	50 (18.8)	99 (18.6)
Study Procedures - Dosing	7 (2.6)	4 (1.5)	11 (2.1)
Study Procedures - Lab Issues	136 (51.1)	121 (45.5)	257 (48.3)
Study Procedures - Out of Window	62 (23.3)	61 (22.9)	123 (23.1)
Study Procedures - Randomization	0	2 (0.8)	2 (0.4)
Subject Visits	162 (60.9)	167 (62.8)	329 (61.8)

Percentages were based on the number of subjects in the Full Analysis Set by treatment group/sequence.
Subjects were counted only once in each row; however, a single subject may have had more than one major or minor deviation reported across different categories.
All protocol deviation categories were independent, and one protocol deviation is reported only under one protocol deviation category.

Table 20: Protocol Deviations – Full Analysis Set – From Month 12 to Month 18

Deviation Classification Deviation Category	AVT03 (N=242) n (%)	US-Prolia			Overall (N=486) n (%)
		US-Prolia/ AVT03 (N=122) n (%)	US-Prolia/ US-Prolia (N=122) n (%)	All US-Prolia (N=244) n (%)	
Subjects Reporting Protocol Deviations	179 (74.0)	89 (73.0)	96 (78.7)	185 (75.8)	364 (74.9)
Major	8 (3.3)	7 (5.7)	10 (8.2)	17 (7.0)	25 (5.1)
Study Procedures (Other)	7 (2.9)	5 (4.1)	9 (7.4)	14 (5.7)	21 (4.3)
Subject Visits	1 (0.4)	2 (1.6)	2 (1.6)	4 (1.6)	5 (1.0)
Minor	178 (73.6)	89 (73.0)	94 (77.0)	183 (75.0)	361 (74.3)
Study Procedures (Other)	20 (8.3)	13 (10.7)	10 (8.2)	23 (9.4)	43 (8.8)
Study Procedures - Lab Issues	76 (31.4)	34 (27.9)	37 (30.3)	71 (29.1)	147 (30.2)
Study Procedures - Out Of Window	55 (22.7)	27 (22.1)	36 (29.5)	63 (25.8)	118 (24.3)
Subject Visits	123 (50.8)	59 (48.4)	64 (52.5)	123 (50.4)	246 (50.6)

- **Conduct of the study**

Changes in the planned conduct of the study

The original study protocol, version 1.0 dated 15 February 2022 was amended 3 times. Study enrolment was initiated as per protocol version 1.0 at all sites. Local protocol was developed for the sites in the Czech Republic (starting with protocol version 3.1).

Changes that impacted study conduct are described below. The protocol, amendments, and the administrative change document are provided in the protocol.

Following are the main changes made from protocol version 1.0 to protocol version 2.0 (dated 03 March 2022):

• Study "Active Treatment" period was clarified to include Month 18 and safety follow-ups after the last treatment administration.

• Pharmacodynamic endpoints of bone specific alkaline phosphatase, urine N-terminal telopeptide of type 1 collagen/creatinine, serum procollagen 1 intact N-terminal propeptide, and osteocalcin were removed.

• Text clarifying investigator responsibility for provision of adequate osteoporosis treatment after the trial was added.

• Clarified that subjects were to receive paper diaries at all injection visits and be provided with a ruler only on the Day 1 visit. Following are the main changes made from protocol version 2.0 to protocol version 3.0 (dated

03 August 2022):

• Serbia, Ukraine, and the option for potentially other countries were removed to reflect the updated study countries.

• Dual-energy x-ray absorptiometry (DXA) scan procedure was clarified to specify that left hip should be preferentially scanned and that the same hip should be scanned at every visit.

• Exclusion criterion #22 was added to clarify that subjects with compromised immune system or on immunosuppressant treatment will not be enrolled. Additional previous treatments (abaloparatide, romozosumab, and pregabalin) were defined in exclusion criterion #5.

• Synopsis was amended to correspond to the Schedule of Assessments.

• The confidence interval (CI) for the geometric mean ratio (GMR) between treatment groups was changed from 90% to 95% per the comments from European Medicines Agency (EMA).

• Text was amended to state that the posttrial treatment will be provided to the subjects.

• Clarified that the Medical Monitor must check the eligibility of every subject prior to randomisation.

• Specified that maximum delay allowed in drug administration was 4 weeks and that Month 12 visit should not be shifted if Month 6 study drug administrations is delayed by a month.

• Additional assessments at Day 60 were added.

• Clarified that haematology, chemistry, PK, and anti-drug antibody (ADA) samples will be collected at all unscheduled visits.

• Further criteria were added around eligibility with respect to menopausal status.

• Clarified that additional vitamin D tests will be available during the study if deficiency is suspected. Importance of calcium and vitamin D supplementation and its dosing during the study was detailed.

• Procedures related to injection site reactions diary supply, usage, and review were detailed.

• Statistical analysis strategy for the pharmacodynamic (PD) endpoint was updated to correspond to that of the primary endpoint (i.e., the subjects with the ICEs that can lead to attenuation of treatment differences will be excluded from the analysis of the area under the percent change from Baseline in serum C-telopeptide of type 1 collagen up to 6 months (AUEC0-6months of %Cfb sCTX-1), per comments from EMA.

Following are the main changes made from protocol version 3.0 to protocol version 4.0 (dated 10 March 2023):

• Inclusion criterion #5 was amended to describe the DXA scan procedure in more detail.

• A note was added to exclusion criterion #7 to clarify the procedure for assessment and exclusion of subjects with hypocalcaemia.

• A note was added to exclusion criterion #11 to clarify that subjects with positive hepatitis B core antibodies (anti-HBc) at Screening should evaluated to exclude active infection and that it is at the investigator’s discretion to pursue further diagnosis.

• Changes were made to the Schedule of Assessments to align with the rationale with respect to timing of samples for bioanalytics at Month 6 and Month 12 should be collected prior to dosing.

• Body surface area measurement was removed as it was not being done. Following are the main changes made from protocol version 3.0 to the Czech Republic-specific protocol version 3.1 (dated: 14 October 2022):

• Exclusion criterion #11 was amended to add that hepatitis B core antigen test can be performed to conclude subject status.

• The requirement that the investigator consult with the Medical Monitor if treatment was to be restarted after a dose interruption for safety reasons was changed from required to recommended.

• The requirement that the investigator consult with the Medical Monitor if clinical laboratory testing was to be repeated was changed from required to recommended.

• Body surface area measurement was removed as it was not being done.

• Changed the definition of hypocalcaemia from Grade 1 hypocalcaemia as per Common Terminology Criteria for Adverse Events (CTCAE) v5 to at least Grade 1.

Following are the main changes made from the Czech Republic-specific protocol version 3.1 to the Czech Republic-specific protocol version 4.1 (dated 10 March 2023):

• Inclusion criterion # 5 was amended to describe the DXA scan procedure in more detail.

• A note was added to exclusion criterion #7 to clarify the procedure for assessment and exclusion of subjects with hypocalcaemia.

• A note was added to exclusion criterion #11 to clarify that subjects with positive anti-HBc at Screening should evaluated to exclude active infection and that it is at the investigator's discretion to pursue further diagnosis.

• Changes were made to the Schedule of Assessments to align with the rationale with respect to timing of samples for bioanalytics at Month 6 and Month 12 should be collected prior to dosing.

- **Baseline data**

Demographic Data

Majority of the subjects were White (93.0%), not Hispanic or Latino (99.1%). Most subjects met the postmenopausal criterion of spontaneous amenorrhea (91.5%), while 5.3% and 3.2% had bilateral oophorectomy and met the biochemical criteria of menopause, respectively. Only 0.8% of subjects received prior biologic therapy for osteoporosis. Majority of the women were more than 5 years postmenopausal (92.5%). Most subjects were non-smokers (78.9%). The demographics and baseline characteristics were well balanced across both treatment groups. There were no notable differences between the treatment groups in age and weight. The treatment groups were similar in the time since menopause and prior biologic therapy for osteoporosis. There was a wide range of time from osteoporosis diagnosis to informed consent, resulting in a large difference between the mean and median times. However, both the mean and median times were similar between the groups.

Table 21: Demographics and Baseline Disease Characteristics – Safety Analysis Set – From Baseline to Month 12

	AVT03 (N=266)	Prolia (N=266)	Overall (N=532)
Age at informed consent, years			
n	266	266	532
Mean (SD)	65.2 (6.94)	64.5 (7.04)	64.9 (7.00)
Median	65.0	65.0	65.0

	AVT03 (N=266)	Prolia (N=266)	Overall (N=532)
Min, max	50, 85	50, 81	50, 85
Postmenopausal criteria, n (%)			
Spontaneous amenorrhea	243 (91.4)	244 (91.7)	487 (91.5)
Biochemical criteria of menopause	9 (3.4)	8 (3.0)	17 (3.2)
Bilateral oophorectomy	14 (5.3)	14 (5.3)	28 (5.3)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	13 (4.9)	11 (4.1)	24 (4.5)
Native Hawaiian or other Pacific Islander	0	0	0
White	246 (92.5)	249 (93.6)	495 (93.0)
Other	5 (1.9)	6 (2.3)	11 (2.1)
Multiple race	2 (0.8)	0	2 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	5 (1.9)	0	5 (0.9)
Not Hispanic or Latino	261 (98.1)	266 (100)	527 (99.1)
Height at Screening, cm			
N	266	266	532
Mean (SD)	159.27 (6.293)	159.94 (6.066)	159.61 (6.184)
Median	160.00	160.00	160.00
Min, max	140.0, 174.0	141.0, 178.0	140.0, 178.0
Weight at Screening, kg			
N	266	266	532
Mean (SD)	63.71 (9.552)	64.49 (10.040)	64.10 (9.797)
Median	62.35	63.30	63.00
Min, max	44.2, 87.0	43.5, 91.0	43.5, 91.0
BMI at Screening, kg/m^2			
N	266	266	532
Mean (SD)	25.12 (3.547)	25.20 (3.605)	25.16 (3.573)
Median	24.50	25.00	24.80

	AVT03 (N=266)	Prolia (N=266)	Overall (N=532)
Min, max	18.6, 32.0	18.6, 32.0	18.6, 32.0
Country, n (%)			
Bulgaria	14 (5.3)	11 (4.1)	25 (4.7)
Czech Republic	28 (10.5)	33 (12.4)	61 (11.5)
Georgia	33 (12.4)	37 (13.9)	70 (13.2)
Poland	144 (54.1)	144 (54.1)	288 (54.1)
South Africa	47 (17.7)	41 (15.4)	88 (16.5)
Prior biologic therapy for osteoporosis, n (%)			
Yes	2 (0.8)	2 (0.8)	4 (0.8)
No	264 (99.2)	264 (99.2)	528 (99.2)
Number of years since menopause, n (%)			
≤ 5 years	20 (7.5)	20 (7.5)	40 (7.5)
> 5 years	246 (92.5)	246 (92.5)	492 (92.5)
Smoking status, n (%)			
Non-smoker	209 (78.6)	211 (79.3)	420 (78.9)
Ex-smoker	33 (12.4)	25 (9.4)	58 (10.9)
Current smoker	24 (9.0)	30 (11.3)	54 (10.2)
Time from diagnosis of osteoporosis to informed consent, months			
n	266	266	532
Mean (SD)	23.4 (41.75)	26.8 (49.77)	25.1 (45.92)
Median	3.0	4.0	3.0
Min, Max	-2, 279	-4, 394	-4, 394

Percentages were based on the number of subjects in the Safety Analysis Set by treatment group.
Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation.

Table 22: Demographics and Baseline Disease Characteristics – Safety Analysis Set – From Month 12 to End of Study

	AVT03 (N=242)	Prolia			Overall (N=486)
		Prolia/AVT03 (N=122)	Prolia/Prolia (N=122)	All Prolia (N=244)	
Age at informed consent, years					
n	242	122	122	244	486
Mean (SD)	64.8 (6.66)	64.5 (7.17)	64.5 (6.87)	64.5 (7.01)	64.7 (6.83)
Median	65.0	66.0	65.0	66.0	65.0
Min, max	50, 85	51, 81	50, 80	50, 81	50, 85
Postmenopausal criteria, n (%)					
Spontaneous amenorrhea	222 (91.7)	112 (91.8)	113 (92.6)	225 (92.2)	447 (92.0)
Biochemical criteria of menopause	7 (2.9)	6 (4.9)	1 (0.8)	7 (2.9)	14 (2.9)
Bilateral oophorectomy	13 (5.4)	4 (3.3)	8 (6.6)	12 (4.9)	25 (5.1)
Race, n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Black or African American	8 (3.3)	3 (2.5)	7 (5.7)	10 (4.1)	18 (3.7)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
White	227 (93.8)	119 (97.5)	110 (90.2)	229 (93.9)	456 (93.8)
Other	5 (2.1)	0	5 (4.1)	5 (2.0)	10 (2.1)
Multiple Race	2 (0.8)	0	0	0	2 (0.4)
Ethnicity, n (%)					
Hispanic or Latino	5 (2.1)	0	0	0	5 (1.0)
Not Hispanic or Latino	237 (97.9)	122 (100)	122 (100)	244 (100)	481 (99.0)

	AVT03 (N=242)	Prolia			Overall (N=486)
		Prolia/AVT03 (N=122)	Prolia/Prolia (N=122)	All Prolia (N=244)	
Height at Screening, cm					
n	242	122	122	244	486
Mean (SD)	159.51 (6.246)	160.51 (5.918)	159.41 (6.292)	159.96 (6.120)	159.74 (6.181)
Median	160.00	160.00	160.00	160.00	160.00
Min, max	140.0, 174.0	146.1, 178.0	141.0, 176.0	141.0, 178.0	140.0, 178.0
Weight at Screening, kg					
n	242	122	122	244	486
Mean (SD)	63.71 (9.513)	64.89 (9.839)	64.89 (9.994)	64.89 (9.896)	64.30 (9.715)
Median	62.35	65.15	63.45	64.25	63.00
Min, max	47.0, 87.0	43.5, 86.0	46.0, 91.0	43.5, 91.0	43.5, 91.0
BMI at Screening, kg/m²					
n	242	122	122	244	486
Mean (SD)	25.05 (3.534)	25.17 (3.490)	25.53 (3.614)	25.35 (3.550)	25.20 (3.542)
Median	24.45	25.00	25.20	25.10	24.90
Min, max	18.6, 32.0	18.6, 32.0	18.7, 32.0	18.6, 32.0	18.6, 32.0
Country					
Bulgaria	14 (5.8)	9 (7.4)	2 (1.6)	11 (4.5)	25 (5.1)
Czech Republic	28 (11.6)	22 (18.0)	11 (9.0)	33 (13.5)	61 (12.6)
Georgia	32 (13.2)	14 (11.5)	20 (16.4)	34 (13.9)	66 (13.6)
Poland	130 (53.7)	60 (49.2)	69 (56.6)	129 (52.9)	259 (53.3)
South Africa	38 (15.7)	17 (13.9)	20 (16.4)	37 (15.2)	75 (15.4)
Prior biologic therapy for osteoporosis, n (%)					
Yes	2 (0.8)	1 (0.8)	0	1 (0.4)	3 (0.6)
No	240 (99.2)	121 (99.2)	122 (100)	243 (99.6)	483 (99.4)
Number of years since menopause, n (%)					
≤ 5 years	19 (7.9)	9 (7.4)	9 (7.4)	18 (7.4)	37 (7.6)
> 5 years	223 (92.1)	113 (92.6)	113 (92.6)	226 (92.6)	449 (92.4)
Smoking status, n (%)					
Non-smoker	191 (78.9)	98 (80.3)	97 (79.5)	195 (79.9)	386 (79.4)
Ex-smoker	28 (11.6)	14 (11.5)	9 (7.4)	23 (9.4)	51 (10.5)
Current smoker	23 (9.5)	10 (8.2)	16 (13.1)	26 (10.7)	49 (10.1)

	AVT03 (N=242)	Prolia			Overall (N=486)
		Prolia/AVT03 (N=122)	Prolia/Prolia (N=122)	All Prolia (N=244)	
Time from diagnosis of osteoporosis to informed consent, months					
n	242	122	122	244	486
Mean (SD)	23.3 (41.83)	26.6 (46.23)	30.3 (55.85)	28.4 (51.19)	25.9 (46.79)
Median	3.0	5.0	4.5	5.0	4.0
Min, max	-2, 279	0, 337	-4, 394	-4, 394	-4, 394

Percentages were based on the number of subjects in the Safet Analysis Set by treatment group.
Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation.

Medical History

A total of 285 subjects (53.6%) reported a prior medical/surgical history through Month 12. The most common prior medical/surgical history by SOC were Injury, Poisoning and Procedural Complications (22.6%; which included a large number of fractures), Infections and Infestations (14.1%), Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps) (13.0%), Reproductive System and Breast Disorders (10.5%), Gastrointestinal Disorders (6.6%), and Hepatobiliary Disorders (5.1%). All 532 subjects (100%) reported an ongoing medical/surgical history through Month 12. The most common ongoing medical/surgical history by SOC were Social Circumstances (100%; which included menopause), Injury, Poisoning and Procedural Complications (74.1%; which included fractures), Vascular Disorders (46.2%), Musculoskeletal and Connective Tissue Disorders (44.5%), and Metabolism and Nutrition Disorders (42.9%). All 486 subjects (100%) who received their third dose of the study drug reported an ongoing medical/surgical history. The most common prior and ongoing medical/surgical history were generally comparable between the treatment groups.

A total of 256 subjects (52.7%) reported prior medical/surgical history through Month 12 to End of Study (i.e., Month 18) (Table 14.1.3.5b). All 486 subjects (100%) who received their third dose of the study drug reported an ongoing medical/surgical history. The most common ongoing medical/surgical history by SOC were Social Circumstances (100%; which included menopause), Injury, Poisoning and Procedural Complications (73.9%; which included fractures), Vascular Disorders (46.7%), Musculoskeletal and Connective Tissue Disorders (44.9%), and Metabolism and Nutrition Disorders (42.2%). The most common prior and ongoing medical/surgical history were generally comparable among the treatment groups.

Prior and Concomitant Therapy

Overall, 517 subjects (97.2%) reported using a medication prior to the start of their participation in the study up to Month 12. The prior medications reported by the therapeutic main group in at least 10% of subjects included: vitamin D and analogues (67.9%), calcium (33.8%), calcium combinations with vitamin D and/or other drugs (33.8%), hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (i.e., statins) (26.1%), selective beta-blocking agents (17.9%), thyroid hormones (15.6%), proton pump inhibitors (11.1%), plain angiotensin-converting enzyme (ACE) inhibitors (11.1%), and COVID-19 vaccines (10.0%). In the AVT03 group, 263 subjects (98.9%) received at least 1 concomitant therapy during the study up to Month 12 and in the Prolia group 264 subjects (99.2%) received concomitant therapy. The most common therapies in the AVT03 and Prolia group, respectively, were: vitamin D and analogues (69.5% and 74.4%), calcium combinations with vitamin D and/or other drugs (56.0% and 54.9%), calcium (37.2% and 39.8%), HMG-CoA reductase inhibitors (31.2% and 25.6%), selective beta-blocking agents (20.7% and 18.4%), thyroid hormones (18.4% and 13.9%), proton pump inhibitors (13.9% and 11.7%), plain ACE inhibitors (14.7% and

12.8%), and dihydropyridine derivatives (11.3% and 11.3%) . There were no notable changes in concomitant medication in the 2 weeks after rerandomisation compared with the first 12 months of treatment. Calcium supplements continued to be the most common concomitant medication.

There were no notable changes in concomitant medication after rerandomisation and up to Month 18 compared with the first 12 months of treatment. Calcium supplements continued to be the most common concomitant medication.

- **Outcomes and estimation**

Primary efficacy analysis

The co-primary efficacy endpoints of the study were the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 and percent change from baseline in the AUEC of s-CTX at Month 6. The results and assessment of the co-primary endpoint percent change from baseline in the AUEC of s-CTX are included in the results section.

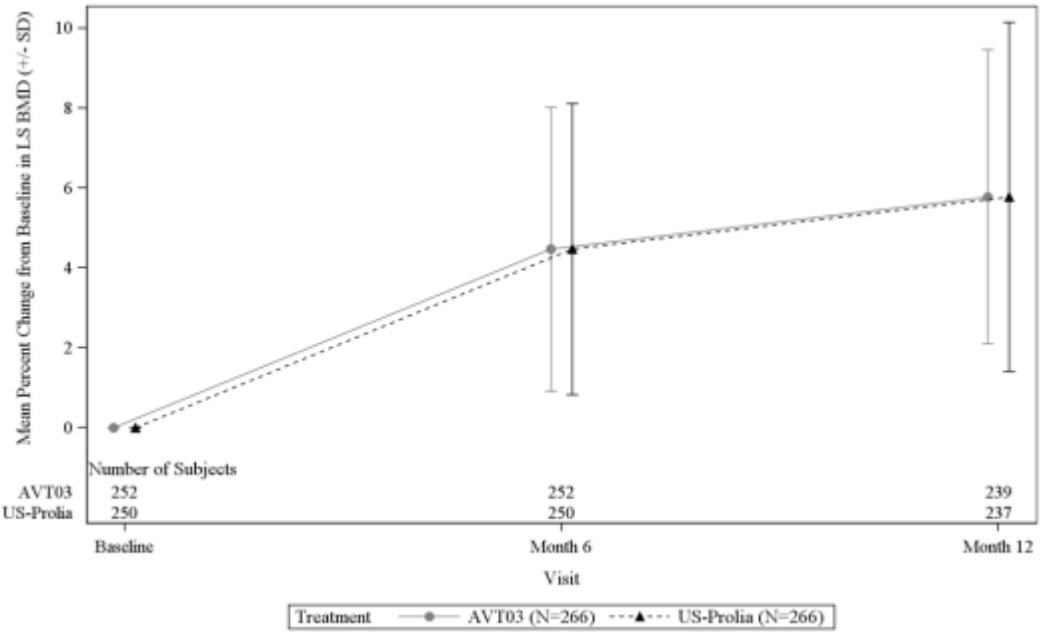
The least squares mean (SE) for percent change from Baseline in LS BMD to Month 12 were 5.30% (0.870) in the AVT03 group and 5.18% (0.872) in the Prolia group, with the least square mean (SE) difference of 0.12 (0.356). The 90% and 95% CIs for the comparison between the treatment groups were -0.47, 0.71 and -0.58, 0.82, respectively. Therefore, the study results demonstrated clinical similarity for treatment group comparisons as the 90% and 95% CI, per FDA and EMA criteria, respectively, for the difference of the least square means between test and reference groups at Month 12 were contained within the predefined range (-1.45%, 1.45%).

Table 23: MMRM of Percent Change From Baseline in LS BMD to Month 12 – Full Analysis Set (Excluding Data Impacted by ICEs)

Statistic	AVT03 (N=266)	Prolia (N=266)
n	252	250
m	239	237
Least squares mean (SE) (%)	5.30 (0.870)	5.18 (0.872)
Least squares mean difference (SE) (AVT03 vs Prolia)	0.12 (0.356)	
90% CI	-0.47, 0.71	
95% CI	-0.58, 0.82	

Two-sided 90% and 95% CIs for the difference in least squares means between AVT03 and Prolia groups were obtained from an MMR model including percent change from Baseline for LS BMD as response variable, treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. An unstructured covariance structure was used to model the within-subject correlation and an adjustment to the degrees of freedom was made using the Kenward-Roger's approximation.
The primary endpoint analysis was based on FAS excluding the data that were impacted by the ICEs. The data that were excluded due to ICEs were treated as missing. All missing data (including the data that were excluded due to ICEs and the actual missing data, e.g., BMD not measured etc.) were not imputed but were handled by the MMRM under the MAR assumption.
Clinical similarity of AVT03 and US-Prolia will be established if the 95% and 90% CIs (for the EMA and the FDA, respectively) are contained within the equivalence margin of [-1.45%, 1.45%].

Figure 9: Mean (±SD) of Percent Change from Baseline in LS BMD to Month 12, by Visit – Full Analysis Set (Excluding data impacted by ICEs)



Abbreviations: BMD = bone marrow density; ICE = intercurrent event; LS = lumbar spine; SD = standard deviation.

Secondary efficacy endpoints

Percent Change From Baseline in the LS BMD at Month 6 and 18

The mean (SD) percent change in LS BMD from Baseline to Month 6 was 3.96% (0.863) in the AVT03 group and 3.88% (0.863) in the Prolia group. The mean percent change in LS BMD from Baseline to Month 18 was 5.86% (1.260) in the AVT03/AVT03 group, 6.16% (1.290) in the Prolia/AVT03 group, and 5.58% (1.310) in the Prolia/Prolia group. These results were in line with the percent change in LS BMD at Month 12, showing that the changes in LS BMD from Baseline to Month 6 and Baseline to Month 18 were comparable among the treatment arms.

Table 24: Percent Change from Baseline in LS BMD to Month 6 – MMRM Full Analysis Set

Time point Statistic	AVT03 (N=266)	Prolia (N=266)
n	266	266
m	253	252
LS mean (SE)	3.96 (0.863)	3.88 (0.863)
LS mean difference (SE) (AVT03 vs Prolia)	0.08 (0.314)	
90% CI	-0.44, 0.59	
95% CI	-0.54, 0.69	

Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the subject received the first dose of study drug (Day 1).
Two-sided 90% and 95% CI for the difference in least squares means between AVT03 and Prolia groups were obtained from an MMRM model including percent change from Baseline for LS BMD as response variable, treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. An unstructured covariance structure was used to model the within-subject correlation and an adjustment to the degrees of freedom was made using the Kenward-Roger's approximation.
Abbreviations: BMD = bone marrow density; LS = lumbar spine; N = number of subjects assigned to each group in FAS; n = number of evaluable subjects per group; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.

Table 25: Percent Change from Baseline in LS BMD from Month 12 to End of Study – Full Analysis Set

	AVT03/AVT03 [1] (N=242)		US-Prolia/AVT03 [2] (N=122)		US-Prolia/US-Prolia [3] (N=122)	
Time Point Statistic	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline
Baseline						
n	242		122		122	
Mean (SD)	0.81936 (0.094477)		0.81066 (0.088727)		0.81735 (0.095082)	
Median	0.82425		0.82052		0.82370	
Min, Max	0.6277, 1.3091		0.6152, 1.1188		0.6043, 1.1558	
Month 12						
n	239	239	121	121	118	118
Mean (SD)	0.86621 (0.099672)	5.78666 (3.675960)	0.85806 (0.088198)	6.01677 (4.191729)	0.86157 (0.102607)	5.50084 (4.535858)
Median	0.87042	5.51710	0.86736	5.88540	0.85408	5.26805
Min, Max	0.6529, 1.3348	-5.4718, 16.4748	0.6577, 1.1266	-2.1876, 19.8759	0.6118, 1.2356	-4.0004, 17.6439
LS Mean (SE)		5.64 (1.148)		5.74 (1.175)		5.35 (1.195)
Comparison		[1] vs [3]		[1] vs [2]		[2] vs [3]
LS Mean Difference (SE)		0.29 (0.442)		-0.10 (0.439)		0.39 (0.510)
95% Confidence Interval		-0.58, 1.16		-0.96, 0.76		-0.61, 1.39
90% Confidence Interval		-0.44, 1.02		-0.82, 0.62		-0.45, 1.23

Percent Change From Baseline in Hip and Femoral Neck BMD at Months 6, 12 and 18

The mean (SD) percent change in the hip BMD from Baseline to Month 6 was comparable between the AVT03 group and the Prolia group, with a least squares mean difference (SE) of -0.45 (0.253) (95% CI -0.95, 0.05). Similarly, the mean (SD) percent change from Baseline to Month 12 was also comparable between the groups (-0.08 [0.247], 95% CI -0.56, 0.41). The mean percent change in hip BMD from Month 12 to Month 18 was comparable among the treatment groups, with a least squares mean difference (SE) of -0.21 (0.314) (95% CI -0.83, 0.41) between the AVT03/AVT03 and Prolia/AVT03 groups, 0.29 (0.313) (95% CI -0.33, 0.90) between the AVT03/AVT03 and Prolia/Prolia groups, and 0.50 (0.362) (95% CI -0.21, 1.21) between the Prolia/AVT03 and Prolia/Prolia groups.

Table 26: Percent Change From Baseline in Hip BMD to Months 6 and 12 – Full Analysis Set

Time point Statistic	AVT03 (N=266)		Prolia (N=266)	
	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline
Baseline				
n	266		266	
Mean (SD)	0.764 (0.0940)		0.758 (0.1014)	
Median	0.756		0.750	
Min, Max	0.5440, 1.0063		0.5416, 1.0602	
Month 6				
n	253	253	252	252
Mean (SD)	0.785 (0.0980)	2.470 (2.6586)	0.781 (0.0993)	2.959 (3.0742)
Median	0.778	2.607	0.779	2.780
Min, Max	0.5235, 1.0488	-6.6470, 15.3106	0.5469, 1.0434	-3.9971, 27.5309
Least squares mean (SE) (%)		2.44 (0.671)		2.89 (0.670)
Least squares mean difference (SE) (AVT03 vs Prolia)	-0.45 (0.253)			
95% CI	-0.95, 0.05			
Month 12				
n	240	240	239	239
Mean (SD)	0.793 (0.0992)	3.510 (2.3392)	0.785 (0.1011)	3.617 (3.1550)
Median	0.788	3.422	0.783	3.486
Min, Max	0.5485, 1.0655	-2.2252, 11.3005	0.5526, 1.0498	-3.3438, 22.1091
Least squares mean (SE) (%)		3.47 (0.670)		3.55 (0.671)
Least squares mean difference (SE) (AVT03 vs Prolia)	-0.08 (0.247)			
95% CI	-0.56, 0.41			

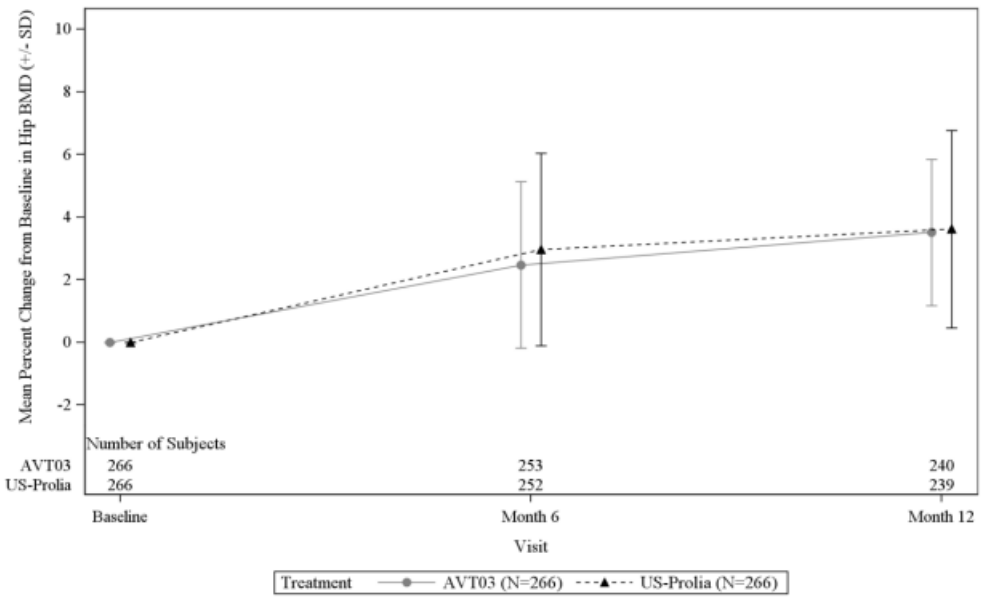
Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the subject received the first dose of study drug (Day 1). BMD is reported with unit g/cm^2.

Two-sided 95% CI for the difference in least squares means between AVT03 and Prolia groups were obtained from an MMRM model including percent change from Baseline for BMD as response variable, treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. An unstructured covariance structure was used to model the within-subject correlation and an adjustment to the degrees of freedom was made using the Kenward-Roger's approximation.

Missing observations were not imputed.

Abbreviations: BMD = bone marrow density; CI = confidence interval; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.

Figure 10: Mean (±SD) of Percent Change from Baseline in Hip BMD by Visit – Full Analysis Set – From Baseline to Month 12

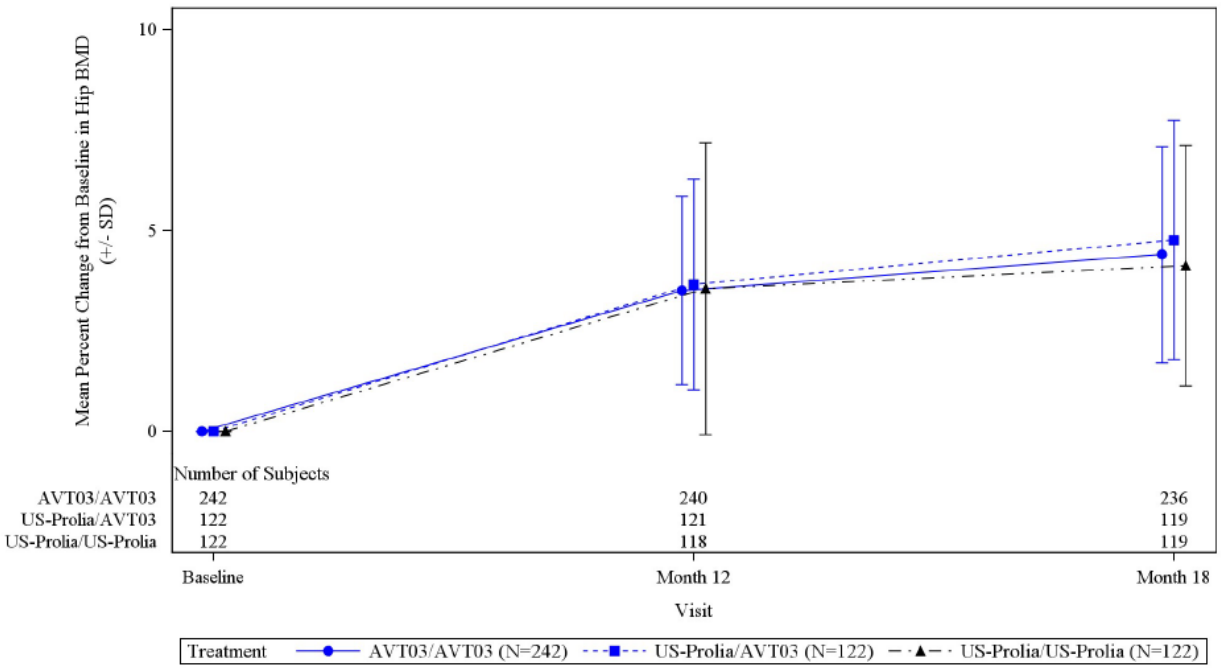


Abbreviations: BMD = bone marrow density; LS = lumbar spine; SD = standard deviation.

Table 27: Percent Change from Baseline in Hip BMD from Month 12 to End of Study – Full Analysis Set

	AVT03/AVT03 [1] (N=242)		US-Prolia/AVT03 [2] (N=122)		US-Prolia/US-Prolia [3] (N=122)	
Time Point Statistic	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline
Baseline						
n	242		122		122	
Mean (SD)	0.76670 (0.094737)		0.74815 (0.095111)		0.76827 (0.106387)	
Median	0.76333		0.73852		0.77487	
Min, Max	0.5440, 1.0063		0.5523, 0.9885		0.5416, 1.0283	
Month 12						
n	240	240	121	121	118	118
Mean (SD)	0.79327 (0.099227)	3.51032 (2.339156)	0.77510 (0.096282)	3.67281 (2.625627)	0.79474 (0.105223)	3.56041 (3.629158)
Median	0.78800	3.42190	0.76592	3.80090	0.79834	3.05890
Min, Max	0.5485, 1.0655	-2.2252, 11.3005	0.5582, 1.0184	-3.3438, 12.8491	0.5526, 1.0498	-2.7172, 22.1091
LS Mean (SE)		3.90 (0.804)		3.96 (0.822)		3.97 (0.837)
Comparison		[1] vs [3]		[1] vs [2]		[2] vs [3]
LS Mean Difference (SE)		-0.07 (0.309)		-0.06 (0.308)		0.00 (0.357)
95% Confidence Interval		-0.68, 0.54		-0.67, 0.54		-0.71, 0.70
90% Confidence Interval		-0.58, 0.44		-0.57, 0.44		-0.59, 0.58

Figure 11: Mean (±SD) of Percent Change from Baseline in Hip BMD by Visit – Full Analysis Set – From Month 12 to End of Study



Change in Femoral Neck BMD

The mean (SD) percent change in the femoral neck BMD from Baseline to Month 6 was comparable between the AVT03 group and the Prolia group, with least squares mean difference (SE) of -0.30 (0.337) (95% CI -0.96, 0.36). Similarly, the mean (SD) percent change from Baseline to Month 12 was also comparable between the groups (-0.33 [0.316], 95% CI -0.95, 0.30). The mean percent change in the femoral neck BMD from Month 12 to EoS was comparable among the treatment groups, with a least squares mean difference (SE) of 0.58 (0.430) (95% CI 0.27, 1.42) between the AVT03/AVT03 and Prolia/AVT03 groups, 0.43 (0.430) (95% CI -0.41, 1.28) between the AVT03/AVT03 and Prolia/Prolia groups, and -0.15 (0.496) (95% CI -1.12, 0.83) between the Prolia/AVT03 and Prolia/Prolia groups.

Table 28: Percent Change in Femoral Neck BMD From Baseline to Months 6 and 12 – Full Analysis Set

Time point Statistic	AVT03 (N=266)		Prolia (N=266)	
	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline
Baseline				
n	266		266	
Mean (SD)	0.686 (0.0978)		0.692 (0.1000)	
Median	0.684		0.692	
Min, Max	0.4511, 0.9643		0.4837, 1.0061	
Month 6				
n	253	253	252	252
Mean (SD)	0.702 (0.0978)	1.831 (3.8117)	0.706 (0.1020)	2.120 (3.8244)
Median	0.691	1.812	0.701	2.032
Min, Max	0.4819, 1.0024	-10.1372, 15.2020	0.4130, 1.0290	-18.6545, 23.0748
Least squares mean (SE) (%)		1.63 (0.864)		1.93 (0.864)
Least squares mean difference (SE) (AVT03 vs Prolia)	-0.30 (0.337)			
95% CI	-0.96, 0.36			
Month 12				
n	240	240	239	239
Mean (SD)	0.708 (0.0950)	2.581 (3.7291)	0.710 (0.1004)	2.945 (3.3912)
Median	0.700	2.254	0.708	2.624
Min, Max	0.5105, 0.9504	-12.7094, 18.1011	0.4834, 1.0299	-6.8980, 15.1469
Least squares mean (SE) (%)		2.40 (0.860)		2.73 (0.863)
Least squares mean difference (SE) (AVT03 vs Prolia)	-0.33 (0.316)			
95% CI	-0.95, 0.30			

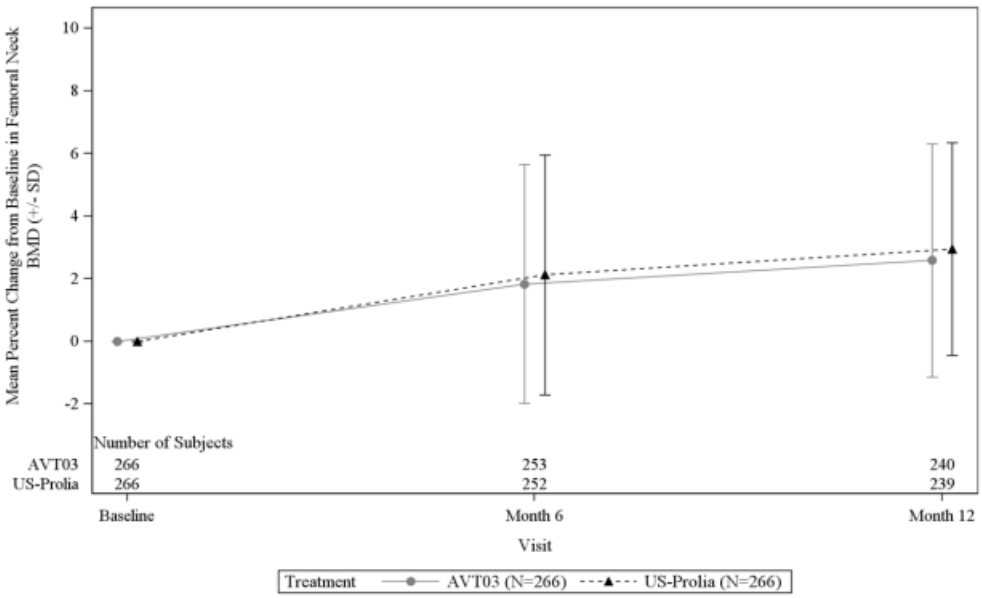
Baseline was defined as the last non-missing value (either scheduled, unscheduled, or repeat) before the subject received the first dose of study drug (Day 1). BMD was reported with unit g/cm^2.

Two-sided 95% CI for the difference in least squares means between AVT03 and Prolia groups were obtained from an MMRM model including percent change from Baseline for BMD as response variable, treatment, visit, treatment-by-visit interaction, and prior biologic therapy for osteoporosis (Yes/No) as categorical variables, and the baseline BMD and number of years since menopause as continuous covariates. An unstructured covariance structure was used to model the within-subject correlation and an adjustment to the degrees of freedom was made using the Kenward-Roger's approximation.

Missing observations were not imputed.

Abbreviations: BMD = bone marrow density; CI = confidence interval; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.

Figure 12: Mean (±SD) of Percent Change from Baseline in Femoral Neck BMD by Visit – Full Analysis Set – From Baseline to Month 12

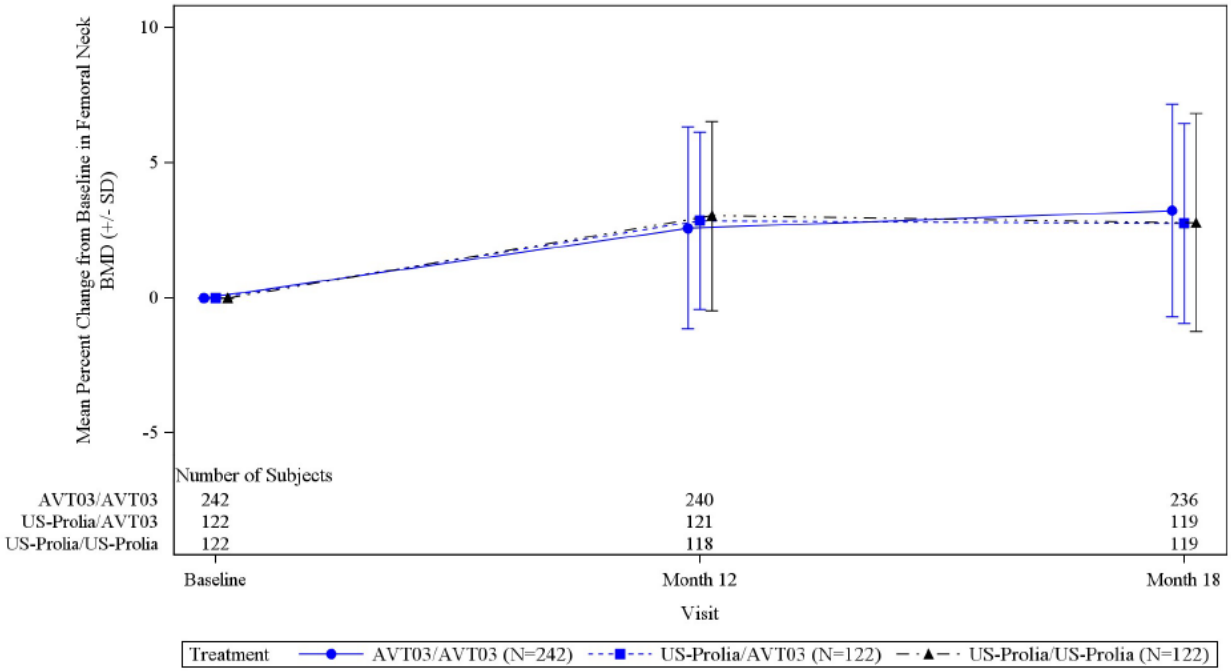


Abbreviations: BMD = bone marrow density; SD = standard deviation.

Table 29: Percent Change in Femoral Neck BMD from Month 12 to End of Study – Full Analysis Set

	AVT03/AVT03 [1] (N=242)		US-Prolia/AVT03 [2] (N=122)		US-Prolia/US-Prolia [3] (N=122)	
Time Point Statistic	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline	Actual Value	Percent Change from Baseline
Baseline						
n	242		122		122	
Mean (SD)	0.69143 (0.095447)		0.68622 (0.097519)		0.69657 (0.105324)	
Median	0.68784		0.68811		0.69547	
Min, Max	0.4511, 0.9583		0.4948, 0.9276		0.4837, 1.0061	
Month 12						
n	240	240	121	121	118	118
Mean (SD)	0.70829 (0.095013)	2.58147 (3.729140)	0.70533 (0.099242)	2.86033 (3.285649)	0.71553 (0.101664)	3.03087 (3.508058)
Median	0.70010	2.25410	0.70563	2.55380	0.71176	2.77955
Min, Max	0.5105, 0.9504	-12.7094, 18.1011	0.4834, 0.9357	-6.8980, 15.1349	0.4958, 1.0299	-5.4095, 15.1469
LS Mean (SE)		2.10 (1.008)		2.33 (1.032)		2.58 (1.049)
Comparison		[1] vs [3]		[1] vs [2]		[2] vs [3]
LS Mean Difference (SE)		-0.48 (0.388)		-0.23 (0.385)		-0.25 (0.447)
95% Confidence Interval		-1.24, 0.28		-0.99, 0.53		-1.13, 0.63
90% Confidence Interval		-1.12, 0.16		-0.87, 0.40		-0.99, 0.49

Figure 13: Mean (±SD) of Percent Change from Baseline in Femoral Neck BMD by Visit – Full Analysis Set – From Month 12 to End of Study



Incidence of New Morphometric Vertebral Fractures at Month 12

In the AVT03 group 8 subjects (3.3%) experienced a new vertebral fracture and in the Prolia group 6 subjects (2.5%) experienced a new vertebral fracture. The number of subjects with new fractures is comparable between the 2 treatment groups. In the AVT03/AVT03 group, from Month 12 to Month 18, 4 subjects (1.7%) experienced a new vertebral fracture, in the Prolia/AVT03 group, 1 subject (0.9%) experienced a new vertebral fracture, and in the Prolia/Prolia group, 1 subject (0.9%) experienced a new vertebral fracture. The number of subjects with new fractures is comparable among AVT03 and Prolia treatment groups.

Table 30: Percentage of Subjects with New Morphometric Vertebral Fractures Over Time (From Baseline to Month 12) – Full Analysis Set

Treatment Parameter	Number of subjects with assessment (m)	Number of subjects (n)	Percentage of subjects (n of m)
AVT03 N=266			
Yes	241	8	3.3
No	241	233	96.7
Prolia N=266			
Yes	242	6	2.5
No	242	236	97.5

Number of subjects in treatment group with assessment was used as the denominator for percentage calculations.

Table 31: Percentage of Subjects with New Morphometric Vertebral Fractures Over Time (From Month 12 to End of Study) – Full Analysis Set

Visit Treatment Parameter	Subjects with Assessment [m]	Subjects [n]	% [n of m]
Month 12			
AVT03/AVT03 N=241			
Yes	241	8	3.3
No	241	233	96.7
US-Prolia/AVT03 N=121			
Yes	121	2	1.7
No	121	119	98.3
US-Prolia/US-Prolia N=121			
Yes	121	4	3.3
No	121	117	96.7

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 32: Summary of Efficacy for Trial AVT03-GL-C01

Title: A Randomised, Double-Blind, Parallel, Multicentre, Multinational Study to Compare the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of AVT03 (Proposed Denosumab Biosimilar) Versus Prolia® (US-sourced) in Postmenopausal Women with Osteoporosis			
Study identifier	Study code: AVT03-GLC01 EudraCT: 2021-005071-40		
Design	Randomised, double-blind, parallel, multi-centre, fixed-dose response		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase*:		12 months not applicable 6 months
Hypothesis	Equivalence		
Treatments groups	AVT03-AVT03		AVT03 60 mg/mL, one 60 mg dose on Day 1 and at Month 6, 266 subjects randomized
	Prolia-Prolia		Prolia 60 mg/mL, one 60 mg dose on Day 1 and at Month 6, 266 subjects randomized
	Prolia–AVT03		AVT03 60 mg/mL, one 60 mg dose at Month 12; 122 subjects from Prolia arm re-randomized
	Prolia-Prolia		Prolia 60 mg/mL, one 60 mg dose at Month 12; 122 subjects from Prolia arm re-randomized
Endpoints and definitions	Primary endpoint	%CfB in lumbar spine BMD-m12	Percentage of change from baseline in lumbar spine bone mineral density (BMD) after 12 months

	Co-Primary endpoint	AUEC of CTX up to month 6	Area under the effect curve (AUEC) of serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) up to month 6 (ng*h/L).
	Secondary endpoints	%CfB in lumbar spine BMD-m6	Percentage of change from baseline in lumbar spine BMD after 6 months
		%CfB in lumbar spine BMD-m18	Percentage of change from baseline in lumbar spine BMD after 18 months
		%CfB in hip BMD-m6	Percentage of change from baseline in hip BMD after 6 months
		%CfB in femur neck BMD-m6	Percentage of change from baseline in femur neck BMD after 6 months
		%CfB in hip BMD-m12	Percentage of change from baseline in hip BMD after 52 weeks
		%CfB in femur neck BMD-m12	Percentage of change from baseline in femur neck BMD after 52 weeks
		%CfB in hip BMD-m18	Percentage of change from baseline in hip BMD after 18 months
		%CfB in femur neck BMD-m18	Percentage of change from baseline in femur neck BMD after 18 months
Database lock	18-Nov-2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Primary Endpoint Analysis: MMRM of %CfB in LS BMD to Month 12- Excluding the data that are impacted by ICEs (Full Analysis Set)**		

Descriptive statistics and estimate variability	**Treatment group**	**AVT03**	**Prolia**
	Number of subjects	252	250
	%CfB in lumbar spine BMD-m12 LS mean	5.30	5.18
	Variability statistic	NA	NA
	%CfB in lumbar spine BMD-m6 LS mean	3.96 (N=266)	3.88 (N=266)
	%CfB in lumbar spine BMD-m18 LS mean	7.32 (N=236)	7.07 (N=119)
	Variability statistic	NA	NA
	%CfB in hip BMD-m6 LS means	2.47 (N=253)	2.95 (N=252)
	Variability statistic	NA	NA

	%CfB in femur neck BMD-m6 LS means	1.83 (N=253)	2.12 (N=252)
	Variability statistic	NA	NA
	%CfB in hip BMD-m12 LS means	3.51 (N=240)	3.61 (N=239)
	Variability statistic	NA	NA
	%CfB in hip BMD-m18 LS means	4.40 (N=236)	4.13 (N=119)
	Variability statistic	NA	NA
	%CfB in femur neck BMD-m12 LS means	2.58 (N=240)	2.94 (N=239)
	Variability statistic	NA	NA
	%CfB in femur neck BMD-m18 LS means	3.22 (N=236)	2.78 (N=119)
	Variability statistic	NA	NA
Effect estimate per comparison	Primary endpoint: %CfB in lumbar spine BMD-m12	Comparison groups	AVT03 - Prolia
		LS mean difference	0.41
		95% CI	-0.84, 1.12
		P-value	NA
	Co-primary endpoint: AUEC of s-CTX1	Comparison groups	AVT03 - Prolia
		LS mean difference	1.00
		95% CI	0.97, 1.03
		P-value	NA
	Secondary endpoint: %CfB in lumbar spine BMD-m6	Comparison groups	AVT03 - Prolia
		LS mean difference	0.08
		95% CI	-0.54, 0.69
		P-value	NA
	Secondary endpoint: %CfB in lumbar spine BMD-m18	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.29
		95% CI	-0.66, 1.24

		P-value	NA
	Secondary endpoint: %CfB in hip BMD-m6	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.45
		95% CI	-0.95, 0.05
		P-value	NA
	Secondary endpoint: %CfB in femur neck BMD-m6	Comparison groups	AVT03 - Prolia
		LS mean difference	0.30
		95% CI	-0.96, 0.36
		P-value	NA
	Secondary endpoint: %CfB in hip BMD-m12	Comparison groups	AVT03 - Prolia
		LS mean difference	0.08
		95% CI	-0.56, 0.41
		P-value	Not applicable
	Secondary endpoint: %CfB in hip BMD-m18	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.07
		95% CI	-0.68, 0,54
		P-value	Not applicable
	Secondary endpoint: %CfB in femur neck BMD-m12 LS means	Comparison groups	AVT03 - Prolia
		LS mean difference	0.33
		95% CI	-0.95, 0.30
		P-value	Not applicable
	Secondary endpoint: %CfB in femur neck BMD-m18 LS means	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.48
		95% CI	--1.24, 0.28
		P-value	Not applicable

Notes	Therapeutic equivalence was demonstrated in all endpoints since the 95% CI fell entirely within the predefined margins of [-1.45%, 1.45%] for %CfB LS BMD Month 12 AVT03 was considered equivalent to US-Prolia on AUEC of CTX up to month 6 if the 95% confidence interval for the ratio of means laid entirely within the equivalence interval of [0.97; 1.03]. A total of 45 subjects (8.5%) discontinued the study during the Main Treatment Period: 24 subjects (9.0%) in the AVT03 group and 21 subjects (7.9%) in the Prolia group. Reasons for discontinuation from the study were balanced between AVT03 and Prolia groups and included the following categories: Primary reasons for early study treatment discontinuation were withdrawal of (20 subjects; 5 subjects in the AVT03 group and 15 subjects in the Prolia group) and AEs (8 subjects; 6 subjects in the AVT03 group and 2 subjects in the Prolia group). Similarly, the main reasons for early study termination were withdrawal of consent (21 subjects; 6 subjects in the AVT03 group and 15 subjects in the Prolia group) and AEs (8 subjects; 6 subjects in the AVT03 group and 2 subjects in the Prolia group). Dropout rate was considered low.		
Analysis description	**Other: Sensitivity analysis for primary endpoint, MMRM of %CfB in LS BMD to Month 12 – all observed data, without excluding the data that are impacted by ICEs (Full Analysis set)**		
Analysis population and time point description	Multiple Imputation: for AVT03 group under the non-inferiority null (MNAR), for US-Prolia group under MAR		
Descriptive statistics and estimate variability	**Treatment group**	**AVT03**	**Prolia**
	Number of subjects	266	266
	%CfB in lumbar spine BMD-m12 (MI) LS mean	5.06	5.20
	Variability statistic	NA	NA
Effect estimate per comparison	%CfB in lumbar spine BMD-m12 (MI)	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.14
		95% CI	-0.84, 1.12
Notes	Therapeutic equivalence was demonstrated since 95% CI fell entirely within the predefined margins of [-1.45%, 1.45%].		
Analysis description	**Other: Sensitivity analysis: MMRM of %CfB in LS BMD to Month 12 – Multiple Imputation: Without Excluding the Data that are impacted by ICEs (Full Analysis set)**		
Analysis population and time point description	Multiple imputation: for AVT group under the non-inferiority null (MNAR), for US-Prolia group under the MAR		
Descriptive statistics and estimate variability	**Treatment group**	**AVT03**	**Prolia**
	Number of subjects	266	266
	%CfB lumbar spine BMD-m12 LS mean	5.07	5.21
	Variability statistic	NA	NA

Effect estimate per comparison	%CfB lumbar spine BMD-m12	Comparison groups	AVT03 - Prolia
		LS mean difference	-0.14
		95% CI	-0.85, 1.10
		P-value	Not applicable
Notes	Therapeutic equivalence was demonstrated since 95% CI fell entirely within the predefined margins of [-1.45%, 1.45%].		

2.5.5.3. Clinical studies in special populations

Not applicable

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.5.5.6. Supportive study(ies)

Not applicable

2.5.6. Discussion on clinical efficacy

The clinical development programme of AVT03 to demonstrate biosimilarity to the reference product (Xgeva/Prolia) comprised one phase 1 study (AVT03-GL-P01) and one phase 3 study (AVT03-GL-C01). The phase 1 study was a randomised, double-blind, single-dose, parallel study to compare PK/PD, safety and immunogenicity of AVT03 vs. US-Prolia in healthy male volunteers. The phase 3 study is a randomised, double-blind, parallel, multicentre study to compare the efficacy, PK/PD, safety and immunogenicity of AVT03 vs. US-Prolia in postmenopausal women with osteoporosis.

The clinical development plan is acceptable and sufficient to assess the biosimilarity to Prolia.

Design and conduct of clinical studies

<u>AVT03-GL-C01 study design</u>

The study consists of two periods; the two-arm Main Treatment period (Day 0 to Month 12) during which patients received 2 injections of either AVT03 or US-Prolia at 6-month intervals (Day 1 and Month 6); and a three-arm Safety Follow-Up Period (Month 12 to Month 18). Patients who received AVT03 in the Main study period, received again an additional dose of AVT03 at month 12 in the follow up safety period; and patients who received US-Prolia in the Main study period, received either one additional dose of US-Prolia or AVT03 in the Safety period. The duration of the Main Treatment Period of 12 months is considered appropriate for the

evaluation of efficacy based on the percent change from baseline in lumbar spine BMD at Week 52 (primary efficacy endpoint).

The duration of the follow up safety period is another 6 months, and allows assessment of switching from Prolia to AVT03, but also provides additional PK, PD, efficacy and safety data for those patients who continue on the same treatment as initially assigned. The overall study design is deemed acceptable.

The Safety Follow-up Period intends to focus on the safety of AVT03 and EU-Prolia. The final clinical study report (CSR) presents and discusses the results of the Main Treatment Period and Safety Follow up Phase including data after all subjects have had the Month 18 weeks assessments. The duration of the Main Treatment Period of 12 months is considered appropriate for the evaluation of efficacy based on the percent change from baseline in lumbar spine BMD at Week 52 (primary efficacy endpoint).

The study population comprised female patients with postmenopausal osteoporosis (PMO). These are considered the most sensitive population with respect to the approved indications.

Inclusion & exclusion criteria

Inclusion of postmenopausal women with a T-score of ≤-2.5 is in line with the state of art definition and WHO criteria of osteoporosis. The exclusion of patients with T-score ≥-4.0 is also endorsed to reduce inter-subject variability of PMO patients. Lower and upper body mass index (18.5-32.0 kg/m2) have been defined. As body weight may be related to the baseline BMD, and may thus influence the treatment effect of BMD, setting a BMI limit is appropriate.

Medication used prior to the study may have long-term effects on bone metabolism (e.g., bisphosphonates, fluoride, or strontium). Bisphosphonates are recommended and widely used as primary treatment of osteoporosis, excluding these patients might have hampered recruitment of a sufficient number of patients in the study. Patients receiving intravenous bisphosphonates, fluoride, and strontium for osteoporosis within the last 5 years of screening or receiving oral bisphosphonates ≥12 months cumulatively prior to screening have been excluded. Inclusion of patients with prior bisphosphonate use, whether parenteral or oral, is expected to cause heterogeneity in the study population as the inhibition of bone turnover lasts for several years after cessation of bisphosphonates.

However, stratification by prior biologic therapy (Yes vs. No) was applied to control for the potential variability in the treatment response caused by these medications in the statistical analyses. This is acceptable.

Concomitant therapies

Prohibited concomitant medication and accepted washout periods have been described in the study protocol and were part of the exclusion criteria of study AVT03-GL-C01. Any concomitant medication deemed necessary for the welfare of the subject during the study could be given at the discretion of the investigator.

Study assessment

Randomisation and blinding

According to the Protocol and SAP, subject randomisation was stratified by number of years since menopause (≤ 5 years or > 5 years) and prior biologic therapy for osteoporosis (Yes or No). 33 sites randomized subjects. Group of sites (or country) should have been considered as a stratification factor for randomisation as also requested in the follow up SA (EMA/SA/0000084481), but as randomized patients were rather balanced between treatments in each country this is of no further concern. According to the CHMP follow up Scientific Advice (EMA/SA/0000084481), the applicant was in addition recommended to implement stratification for age

(e.g., ≤65 years, >65 years) and according to prior bisphosphonate use instead of prior biologic treatment of osteoporosis, taking in account the long-lasting effect of bisphosphonates on bone tissue. However, according to the CSR, the mean and median age was 65 (or very close to 65) and SD, Min and Max values were also very similar among both groups. This might further infer that age distribution was symmetric at the requested cut-off age of 65, in both groups and no further issue regarding age is raised. In addition, according to Exclusion criteria number 5, previous use of multiple medications including bisphosphonates was prohibited. On the other hand, prior biologic therapy for osteoporosis was considered as a stratification factor. Although "prior biologic therapy for osteoporosis" and "prior bisphosphonate use" may not be completely equivalent, this might explain why only two subjects in each treatment group had used a prior biologic therapy which is rather equivalent to no stratification with respect to this stratification factor. Exclusion of patients with several different previous biologic therapies results in a more homogeneous population and no further issue is raised.

Blinding procedures were adequately described to understand those trial conduct aspects on a reasonable level of detail. In this context, no concerns arise from the methodological perspective regarding potential bias for efficacy and safety evaluations.

Objectives, endpoints and estimands

Primary objective and endpoint

To demonstrate equivalent efficacy of AVT03 vs. US-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12, the applicant chose to evaluate **percent change from baseline in lumbar spine BMD at 12 months and AUEC0-6months of %Cfb sCTX-1** as co-primary efficacy endpoints. Evaluation of these primary efficacy endpoints is acceptable.

Based on the primary efficacy estimand subject's data following any of the ICEs were excluded from the primary efficacy analysis. According to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017), description of an estimand should involve precise specification of certain attributes. Specific conditions under which the treatment effect was intended to be estimated and strategies to handle the ICEs were not explicitly mentioned. Of note, death occurred during the phase 3 trial and should have been foreseen as an ICE and handled e.g., using a composite strategy. However, as there were only few cases (3 deaths in AVT03 and 1 death in US-Prolia groups), this issue is not further pursued.

In the assessment of efficacy and sensitivity analyses in the assessment part of statistical methodology, reference will be made to the following aspects:

Primary efficacy estimand „of interest" should be based on hypothetical strategies for all the ICEs. Such an estimand is sensitive to detect any differences attributable to the pharmacological action. The following two attributes which were not precisely and/or explicitly described by the applicant are relevant for this estimand:

- Treatment condition: Assignment to AVT03 or US-Prolia groups assuming that no subject discontinues from study treatment prior to 6 months without taking prohibited medications prior to 12 months and without additional protocol deviations that impact the assessment of primary endpoint and assuming that no subject receive incorrect study treatment instead of the randomized treatment.
- Strategies to handle the ICEs: hypothetical strategy for all the ICEs.

Treatment policy estimand for efficacy:

Although an estimand based on a hypothetical strategy for all ICEs may be the most sensitive approach to detect differences that are attributable to the pharmacological action, an estimand based on treatment policy

strategy for all the ICEs where ICEs are part of the treatment policies being compared reflects the clinical practice and should be considered. This estimand requires that all data collected after occurrence of the ICEs be used in the analysis. The following attributes that differ from the hypothetical estimand are introduced:

- Treatment condition: Assignment to AVT03 or US-Prolia groups irrespective of study treatment discontinuation prior to 6 months, or taking prohibited medications prior to 12 months, regardless of additional protocol deviations that impact the assessment of primary endpoint or whether or not subjects receive incorrect study treatment instead of the randomized treatment.
- Strategies to handle the ICEs: treatment policy strategy for all the mentioned ICEs.

Estimands based on the treatment policy and hypothetical strategy have equal importance in an equivalence setting and have to lead to similar results for a robust interpretation.

Primary PD estimand

As ICEs were similarly foreseen for the primary efficacy and PD endpoints an estimand framework based on hypothetical strategy for the ICEs „Discontinuation from study treatment prior to 6 months ", "Taking prohibited concomitant medications prior to 6 months", "Additional protocol deviations that impact the assessment of primary PD endpoint" similar to the one described above for the primary efficacy endpoint is relevant for the assessment of the coprimary PD endpoint.

The secondary efficacy endpoints (Percent change from baseline in LS BMD at 6 and 18 months, percent change from baseline in hip and femoral neck BMD at 6, 12 and 18 months, Incidence of new morphometric vertebral fractures at 12 and 18 months, percent change from baseline in sCTX-1 levels at 3, 6, 9, 12, and 18 months) are considered clinically relevant and adequate to support the primary efficacy endpoint. Secondary efficacy endpoints are considered acceptable.

No estimand was explicitly defined for the secondary objectives. However, based on the corresponding analyses a strategy similar to the primary estimand was employed for all the secondary continuous endpoints up to Month 12. This is considered reasonable and no concerns are raised in this regard.

Analysis of the primary efficacy endpoint was based on the FAS, which included all randomized subjects who received at least 1 dose of study treatment. This is considered suitable.

For the main efficacy analysis subjects' data following the ICEs "Treatment discontinuation", "Use of a prohibited medication", "receiving incorrect study treatment instead of the randomized treatment" or "additional protocol" were excluded. All missing data were handled by the MMRM under the MAR assumption. As no subject received incorrect study treatment instead of the randomized treatment, this ICE does not apply. MMRM internally handles missing data and provides unbiased estimates under the MAR assumption. Such a consideration seems to target hypothetical strategies for all the ICEs and is considered appropriate to estimate the primary efficacy estimand of interest.

Sensitivity analysis 1: This sensitivity analysis excluded subjects' data following the ICEs or additional protocol deviations and imputed all missing values whether due to data exclusion or other reasons (e.g., study discontinuation, etc.) under MNAR assumptions by using specified shift parameters to adjust imputed continuous values. The approach is similar to tipping point sensitivity analyses, where only changes in the imputed values of the test group in both directions (one change in each direction) are of interest. This sensitivity analysis is considered suitable to assess the robustness of results to deviations from the MAR assumption in the primary analysis.

Sensitivity analysis 2: According to this sensitivity analysis, subjects' data due to ICEs or additional protocol deviations were not excluded. Treatment discontinuation primarily led to study discontinuation prior to Month 6 and this ICE had the highest frequency among the ICEs. It is understood that this approach applies a treatment policy strategy for few subjects who used prohibited medications prior to Month 12 or had additional protocol deviations, while it considers a hypothetical strategy for all missing values, including those resulting from missing Month 6 and Month 12 doses and therefore produced results very similar to those of the primary analysis rather than targeting the treatment policy estimand for efficacy. However, as the results are well within the margin no concern regarding the treatment policy estimand is raised.

Sensitivity analysis 3 included data from all subjects if observed (treatment policy strategy) and MI assuming MNAR similar to the one applied in the sensitivity analysis 1 if the values were not available (not collected or missing due to exclusion of subjects' data). As few subjects were affected by the treatment policy strategy this sensitivity analysis produced very similar results to sensitivity analysis 1.

The subgroup analysis results of percent change in LS BMD from Baseline up to Month 12 in the subset of subjects by the number of years since menopause (≤ 5 years vs > 5 years), prior biologic therapy for osteoporosis (yes vs no), ADA status (negative vs positive), and neutralizing antibody (nAb) status (negative vs positive) mainly supported the primary analysis unless the sample size was small (≤20) and variability was high.

Secondary analyses of the percent change from Baseline (%Cfb) in LS BMD at 6 months and %Cfb in hip and femoral neck BMD at 6 and 12 months were based on the MMRM which included similar factors as in the primary analysis. Analyses were performed for the observed measurements. This approach is similar to what was considered in the sensitivity analysis 2 and is acceptable as the MMRM assumes MAR for all missing values. The use of the MMRM for Month 6 measurements should be comparable to the use of an ANCOVA model, as there is no visit in between. For Month 18 assessments of %Cfb in LS BMD, hip and femoral neck BMD an ANCOVA model was used. This is acceptable but would have been more prudent to use an MMRM instead.

The equivalence margin for the BMD analysis was set to preserve 70% of the lowest estimate of the originator’s treatment effect as (-1.45%, 1.45%). The margin calculation can be followed and considerations are consistent with the margin derivation proposed in the Follow-up Scientific Advice (EMA/SA/0000084481).

A total planned sample size of 476 for the primary efficacy endpoint followed assumptions made in the follow up Scientific Advice (EMA/SA/0000084481) and was reproducible.

The changes from the protocol-specified analyses are of no concern, as they were decided before the database lock for Month 12.

Results

The original study protocol, version 1.0 dated 15 February 2022 was amended 3 times. Study enrolment was initiated as per protocol version 1.0 at all sites. Local protocol was developed for the sites in the Czech Republic (starting with protocol version 3.1). Overall, the modifications and their reporting for amendments is acceptable. The amendments do not raise concern. In summary, the applicant provided a detailed overview of the protocol amendments.

Participant flow and numbers analysed

There were 532 subjects who were randomized in the study, of whom 266 subjects received AVT03, and 266 subjects received Prolia. Overall, 486 subjects (91.4%) completed treatment up to Month 12 and 46 subjects (8.6%) discontinued treatment (24 [9.0%] in the AVT03 group and 22 [8.3%] in the Prolia group).

A total of 46 subjects (8.6%) terminated the study early (24 [9.0%] in the AVT03 group and 22 [8,3%] in the Prolia group). Overall, 486 subjects received the Month 12 treatment administration. Of these, 242 subjects who completed 12 months on AVT03 continued receiving AVT03. The 244 subjects who up to Month 12 were receiving Prolia, were rerandomized to either continue with Prolia (Prolia/Prolia group; n=122) or start receiving AVT03 as of the Month 12 treatment administration (Prolia/AVT03 group; n=122). 10 subjects discontinued study from Month 12 to Month 18.

Primary reasons for early study treatment discontinuation were withdrawal of (21 subjects; 6 subjects in the AVT03 group and 15 subjects in the Prolia group) and AEs (7subjects in the AVT03 group and 2 subjects in the Prolia group). From Month 12 to Month 18 the most common reason for discontinuations was withdrawal of consent (6 subjects; 3 subjects in the AVT03/AVT03 group, 2 subjects in the Prolia/Prolia group, and 1 subject in the Prolia/AVT03 group). Two subjects (1 subject in AVT03/AVT03 group and 1 subject in Prolia/AVT03 group) were lost to follow up, 1 subject in the AVT03/AVT03 group died (not related to study drug), and 1 subject in the Prolia/AVT03 group discontinued due to other reason.

Number of patients randomized and treated were similar between the treatment groups. Discontinuations were higher in the Prolia group. However, disbalances are considered minor and do not give reason for concern.

Protocol deviations

Up to Month 12, 457 subjects (85.9%) had at least 1 protocol deviation, of which 63 subjects (11.8%) had major and 453 subjects (85.2%) had minor protocol deviations. The most common major protocol deviations were related to subject visits (27 subjects; 5.1%), and study procedures and study procedures – other (14 subjects; 2.6% each). The most common minor protocol deviations were related to subject visits (329 subjects; 61.8%), study procedures related to lab issues (257 subjects; 48.3%) and study procedures - out of window (123 subjects; 23.1%). From Month 12 to Month 18, 364 subjects (74.9%) had at least 1 protocol deviation, of whom 25 subjects (5.1%) had major protocol deviations and 361 subjects (74.3%) had minor protocol deviations. All major protocol deviations were related to study procedures - other (21 subjects; 4.3%) or subject visits (5 subjects; 1.0%). The most common minor protocol deviations were related to subject visits (246 subjects; 50.6%). Overall, the participant flow is comprehensible and described in sufficient detail.

Demographic data

The mean age for AVT03 vs. US-Prolia was 65.2 vs. 64.5 years. Majority of the subjects were White (93.0%), not Hispanic or Latino (99.1%). Most subjects met the postmenopausal criterion of spontaneous amenorrhea (91.5%), while 5.3% and 3.2% had bilateral oophorectomy and met the biochemical criteria of menopause, respectively. Only 0.8% of subjects received prior biologic therapy for osteoporosis 2 subjects in the AVT03 group and 2 subjects in the US-Prolia. 91.5% of the study population met the postmenopausal criterion of spontaneous amenorrhea. 92.5% were more than 5 years postmenopausal. It is agreed that the study population reflects the proposed target population. Most subjects were non-smokers (78.9%). In summary, the demographics indicate that a very balanced population of female patients with a diagnosis of osteoporosis was analysed. This is considered appropriate. The demographics and baseline characteristics were well balanced

across both treatment groups. There were no notable differences between the treatment groups in age and weight. The treatment groups were similar in the time since menopause and prior biologic therapy for osteoporosis. There was a wide range of time from osteoporosis diagnosis to informed consent, resulting in a large difference between the mean and median times. However, both the mean and median times were similar between the groups.

Baseline disease characteristics

Baseline disease characteristics were considered appropriately balanced between treatment groups, facilitating interpretation of the biosimilarity exercise.

Medical history

A total of 285 subjects (53.6%) reported a prior medical/surgical history through Month 12. The most common prior medical/surgical history by SOC were Injury, Poisoning and Procedural Complications (22.6%; which included a large number of fractures), Infections and Infestations (14.1%), Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps) (13.2%), Reproductive System and Breast Disorders (10.5%), Gastrointestinal Disorders (6.6%), and Hepatobiliary Disorders (5.1%). All 532 subjects (100%) reported an ongoing medical/surgical history through Month 12. The most common ongoing medical/surgical history by SOC were Social Circumstances (100%; which included menopause), Injury, Poisoning and Procedural Complications (74.1%; which included fractures), Vascular Disorders (46.4%), Musculoskeletal and Connective Tissue Disorders (44.7%), and Metabolism and Nutrition Disorders (42.9%). A total of 256 subjects (52.7%) reported prior medical/surgical history through Month 12 to End of Study (i.e. Month 18) All 486 subjects (100%) who received their third dose of the study drug reported an ongoing medical/surgical history. The most common prior and ongoing medical/surgical history were generally comparable between the treatment groups.

Prior medication

Overall, 517 subjects (97.2%) reported using a medication prior to the start of their participation in the study up to Month 12. The prior medications reported by the therapeutic main group in at least 10% of subjects included: vitamin D and analogues (67.9%), calcium (33.8%), calcium combinations with vitamin D and/or other drugs (33.8%), hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (i.e., statins) (26.1%), selective beta-blocking agents (17.9%), thyroid hormones (15.6%), proton pump inhibitors (11.1%), plain angiotensin-converting enzyme (ACE) inhibitors (11.1%), and COVID-19 vaccines (10.0%). This is plausible. The influence on the biosimilarity exercise is considered negligible.

(Prohibited) concomitant medication in the main treatment period

In the AVT03 group, 263 subjects (98.9%) received at least 1 concomitant therapy during the study up to Month 12 and in the Prolia group 264 subjects (99.2%) received concomitant therapy. The most common therapies in the AVT03 and Prolia group, respectively, were: vitamin D and analogues (69.5% and 74.4%), calcium combinations with vitamin D and/or other drugs (56% and 54.9%), calcium (37.2% and 39.8.6%), HMG-CoA reductase inhibitors (31.2% and 25.6%), selective beta-blocking agents (20.7% and 18.4%), thyroid hormones (18.4% and 13.9%), proton pump inhibitors (13.9% and 11.7%), plain ACE inhibitors (14.7% and 12.8%), and dihydropyridine derivatives (11.3% and 11.3%). There were no notable changes in concomitant medication after rerandomisation and up to Month 18 compared with the first 12 months of treatment. Calcium supplements continued to be the most common concomitant medication. For the Calcium supplementation it is 93.9% and the AVT03 and 97.5% in the Prolia group. With this high percentages no influence on the biosimilarity is expected. Vitamin D supplementation was administered, except in 52

participants (31 [11.7%] in the AVT03 group and 21 [7.9%] in the Prolia group). However, there was no imbalance between the treatment groups. All non-supplemented participants had a baseline Vitamin D level above 20 ng/ml, as required by study protocol and in alignment with international guidelines recommendation on Vitamin D supplementation. The use of other concomitant medication was also balanced between the treatment groups, therefore no negative effect on the biosimilarity assessment is expected.

Primary efficacy endpoint

The co-primary efficacy endpoints of the study were the percent change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 and percent change from baseline in the AUEC of s-CTX at Month 6. The results and assessment of the co-primary endpoint percent change from baseline in the AUEC of s-CTX are included in Section on clinical pharmacology. In brief, PD similarity of AUEC0-6months for percent change from Baseline of sCTX-1 was demonstrated as the 95% CIs of GMR between the two treatment arms (0.97, 1.03) was entirely within the pre-specified margin (0.80, 1.25).

The least squares mean (SE) for percent change from Baseline in LS BMD to Month 12 were 5.30% (0.870) in the AVT03 group and 5.18% (0.872) in the Prolia group, with the least square mean (SE) difference of 0.12 (0.356). The 90% and 95% CIs for the difference of the least square means between test and reference groups at Month 12 were -0.47, 0.71 and -0.58, 0.82, respectively, and were contained within the predefined range (-1.45%, 1.45%). Thus, the primary efficacy endpoint data support the claim for biosimilarity.

Secondary efficacy endpoints

Percent change from baseline in the LS BMD at month 6 and 18

The mean (SD) percent change in LS BMD from Baseline to Month 6 was 3.96% (0.863) in the AVT03 group and 3.88% (0.863) in the Prolia group. The mean percent change in LS BMD from Baseline to Month 18 was 5.86% (1.260) in the AVT03/AVT03 group, 6.16% (1.290) in the Prolia/AVT03 group, and 5.58% (1.310) in the Prolia/Prolia group These results were in line with the percent change in LS BMD at Month 12, showing that the change in LS BMD from Baseline to Month 6 and Baseline to Month 18 was comparable between the two treatment arms.

Percent change from baseline in Hip and femoral neck BMD at months 6 and 12

The mean (SD) percent change in the hip BMD from Baseline to Month 6 was comparable between the AVT03 group and the Prolia group, with a least squares mean difference (SE) of -0.45 (0.253) (95% CI -0.95, 0.05). Similarly, the mean (SD) percent change from Baseline to Month 12 was also comparable between the groups (-0.08 [0.247], 95% CI -0.56, 0.41).

The mean percent change in hip BMD from Month 12 to Month 18 was comparable among the treatment groups, with a least squares mean difference (SE) of -0.21 (0.314) (95% CI -0.83, 0.41) between the AVT03/AVT03 and Prolia/AVT03 groups, 0.29 (0.313) (95% CI -0.33, 0.90) between the AVT03/AVT03 and Prolia/Prolia groups, and 0.50 (0.362) (95% CI -0.21, 1.21) between the Prolia/AVT03 and Prolia/Prolia groups.

Change in femoral neck BMD

The mean (SD) percent change in the femoral neck BMD from Baseline to Month 6 was comparable between the AVT03 group and the Prolia group, with least squares mean difference (SE) of -0.30 (0.337) (95% CI -0.96, 0.36). Similarly, the mean (SD) percent change from Baseline to Month 12 was also comparable between the groups (-0.33 [0.316], 95% CI -0.95, 0.30). The mean percent change in the femoral neck BMD from Month 12 to EoS was comparable among the treatment groups, with a least squares mean difference

(SE) of 0.58 (0.430) (95% CI 0.27, 1.42) between the AVT03/AVT03 and Prolia/AVT03 groups, 0.43 (0.430) (95% CI -0.41, 1.28) between the AVT03/AVT03 and Prolia/Prolia groups, and -0.15 (0.496) (95% CI -1.12, 0.83) between the Prolia/AVT03 and Prolia/Prolia groups.

Incidence of new morphometric vertebral fractures at month 12

In the AVT03 group 8 subjects (3.3%) experienced a new vertebral fracture and in the Prolia group 6 subjects (2.5%) experienced a new vertebral fracture. The number of subjects with new fractures is comparable between the 2 treatment groups. In the AVT03/AVT03 group, from Month 12 to Month 18, 4 subjects (1.7%) experienced a new vertebral fracture, in the Prolia/AVT03 group, 1 subject (0.9%) experienced a new vertebral fracture, and in the Prolia/Prolia group, 1 subject (0.9%) experienced a new vertebral fracture. The number of subjects with new fractures is comparable among AVT03 and Prolia treatment groups. The applicant clarified that the number of a new vertebral fractures was comparable between both groups throughout the study.

Generally, the results for the secondary BMD endpoints support biosimilarity of the IP to the reference product.

In study AVT03-GL-C01, the co-primary efficacy analysis based on the percent change from baseline in LS-BMD at week 52 was met as the 95% CI of the difference between the AVT03 and the US-Prolia group was within the pre-specified and accepted equivalence criteria. This was further supported by secondary endpoint results and subgroup/sensitivity analyses. Thus, the provided efficacy data support the biosimilarity of AVT03 and Prolia.

2.5.7. Conclusions on the clinical efficacy

The provided efficacy data support the biosimilarity of Zvogra and the reference product.

2.5.8. Clinical safety

Safety data on AVT03 is available from Study AVT03-GL-P01 and Study AVT03-GL-C01, where safety was assessed as part of the secondary study objectives.

Because Study AVT03-GL-P01 was conducted in healthy male participants following single dose administration of AVT03 or Prolia and Study AVT03-GL-C01 in postmenopausal women with osteoporosis following multiple dose administration of AVT03 or Prolia, a single pooled safety analysis of these studies was not considered meaningful, and safety results are discussed below per individual study.

Study AVT03-GL-C01 comprised a 4-week screening period, 12 months treatment period upon rerandomisation of the US-Prolia group and a safety follow up until the end of the study visit at Month 18, including a third dose of the study treatment at Month 12. With the initial submission, a preliminary CSR1 with data up to Month 12 + 2 weeks was provided and the full safety data were submitted later in the procedure.

2.5.8.1. Patient exposure

Study AVT03-GL-P01

A total of 99 (98.0%) healthy participants received a single s.c. dose (60 mg/mL) of AVT03 on Day 1 and 107 (99.1%) participants received a single s.c. dose (60 mg) of US-Prolia on Day 1. The mean administered injection weight of the study treatment was comparable in the AVT03 and the US-Prolia groups (1.06 grams and 1.05 grams, respectively).

Study AVT03-GL-C01

All 532 randomized participants received their first study treatment administration on Day 1 (266 in each treatment group) and after 6 months, 252 (94.7%) and 251 (94.4%) participants received their second AVT03 or US-Prolia injections, respectively. Overall, 486 participants (91.4%) completed treatment up to Month 12 (242 in the AVT03 group and 244 in the US-Prolia group). Of those, 242 participants initially randomized to AVT03 continued receiving AVT03 and all (100%) received their full third dose. Participants who received US-Prolia for their first 2 injections were re-randomized in a 1:1 ratio to either continue with US-Prolia (US-Prolia/US-Prolia group; n=122) or to receive AVT03 (US-Prolia/AVT03 group; n=122) and all of them received their third injection (100% in both treatment arms). Thus, overall, 388 postmenopausal women with osteoporosis received at least one dose of AVT03.

Demographics and baseline data for the two study populations are described in the pharmacology and efficacy sections of this report.

2.5.8.2. Adverse events

The analysis of AEs focused on treatment-emergent adverse events (TEAEs), which included all TEAEs, serious TEAEs, fatal TEAEs, TEAEs leading to discontinuation of study treatment or withdrawal from the study, all TEAEs by severity, and treatment related TEAEs. Special attention was paid to treatment-emergent AEs of special interest (AESIs), encompassing all relevant warnings and precautions from the Prolia product information, as well as ISRs. Further, routine laboratory safety parameters, vital sign, physical examination measurements and 12-lead electrocardiogram (ECG) results were analyzed. The immunogenicity assessments included the frequency and titres of ADAs and frequency of nAbs to denosumab and their impact on safety and tolerability.

In all individual clinical studies, safety analyses were carried out using the Safety Population, which was defined as all randomized participants who received any amount (Study AVT03-GL-P01 or at least one dose (Study AVT03-GL-C01) of the randomly allocated study treatment, with treatment assignment based on the actual treatment received.

Study AVT03-GL-P01

Of the 206 dosed participants, 74.8% of participants reported at least 1 TEAE during the study. The frequency of participants with TEAEs was similar between treatment groups; however, the number of events in US-Prolia group (230 events) were slightly higher compared with the AVT03 group (208 events).

Overall, 38.3% of participants had at least 1 study treatment-related TEAE. The frequency of participants who reported study treatment-related TEAEs in the AVT03 group (43.4%) was higher than the US-Prolia group (33.6%). The majority of participants (73.3%) experienced mild TEAEs and 19.9% experienced moderate TEAEs. No severe TEAEs were reported during the study.

Overall, 22.3% of participants had study treatment-emergent AESIs, with no notable differences between groups. The majority of AESIs were considered study treatment-related (reported by 16% of participants), with no notable differences between groups.

Overall, 6.3% of participants had local administration site reactions that were also considered as AESI; the frequency of participants with these events was higher in the US-Prolia group (9.3%) as compared with the AVT03 group (3.0%). All the administration site reactions were mild, except for 1 event (AVT03 group) that was moderate in severity.

The frequency of Grade ≥3 laboratory abnormalities was low (18.0% of participants overall), and similar between groups. Overall, 6.8% of these Grade ≥3 laboratory abnormalities were considered IP-related (9.1% in the AVT03 group and 4.7% in the US-Prolia group).

One participant (0.9%) in the US-Prolia group had a serious TEAE of drug hypersensitivity. This event was considered to be study treatment-related.

No fatal TEAEs or TEAEs leading to study discontinuation occurred during the study.

Table 33: AVT03-GL-P01: Overview of Treatment-Emergent Adverse Events (Safety Population)

Category	Statistic	AVT03 (N=99)	US-Prolia (N=107)	Overall (N=206)
At least one TEAE	n (%) E	75 (75.8) 208	79 (73.8) 230	154 (74.8) 438
At least one IP-related TEAE	n (%) E	43 (43.4) 70	36 (33.6) 55	79 (38.3) 125
At least one TEAE of special interest	n (%) E	21 (21.2) 30	25 (23.4) 34	46 (22.3) 64
At least one IP-related TEAE of special interest	n (%) E	16 (16.2) 21	17 (15.9) 22	33 (16.0) 43
At least one TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	17 (17.2) 20	20 (18.7) 23	37 (18.0) 43
At least one IP-related TEAE of laboratory abnormality of at least CTCAE Grade 3	n (%) E	9 (9.1) 11	5 (4.7) 5	14 (6.8) 16
At least one local administration site reaction	n (%) E	3 (3.0) 4	10 (9.3) 13	13 (6.3) 17
At least one serious TEAE	n (%) E	0	1 (0.9) 1	1 (0.5) 1
At least one serious IP-related TEAE	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Any TEAE leading to death	n (%)	0	0	0
Any TEAE leading to discontinuation from the study	n (%)	0	0	0
At least one TEAE by severity	n (%)	75 (75.8)	79 (73.8)	154 (74.8)
Mild	n (%)	73 (73.7)	78 (72.9)	151 (73.3)
Moderate	n (%)	22 (22.2)	19 (17.8)	41 (19.9)
Severe	n (%)	0	0	0
At least one IP-related TEAE by severity	n (%)	43 (43.4)	36 (33.6)	79 (38.3)
Mild	n (%)	40 (40.4)	33 (30.8)	73 (35.4)
Moderate	n (%)	9 (9.1)	8 (7.5)	17 (8.3)
Severe	n (%)	0	0	0
At least one TEAE of special interest by severity	n (%)	21 (21.2)	25 (23.4)	46 (22.3)
Mild	n (%)	21 (21.2)	21 (19.6)	42 (20.4)
Moderate	n (%)	1 (1.0)	4 (3.7)	5 (2.4)
Severe	n (%)	0	0	0
At least one IP-related TEAE of special interest by severity	n (%)	16 (16.2)	17 (15.9)	33 (16.0)
Mild	n (%)	16 (16.2)	14 (13.1)	30 (14.6)
Moderate	n (%)	1 (1.0)	3 (2.8)	4 (1.9)
Severe	n (%)	0	0	0
At least one local administration site reaction by severity	n (%)	3 (3.0)	10 (9.3)	13 (6.3)
Mild	n (%)	3 (3.0)	10 (9.3)	13 (6.3)
Moderate	n (%)	1 (1.0)	0	1 (0.5)
Severe	n (%)	0	0	0

AE : adverse event; CTCAE : Common Terminology Criteria for AE; E : number of TEAEs in each category; IP : investigational product; n: Number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N: total number of subjects in the relevant population; TEAE: treatment-emergent AE; %: percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. A related TEAE is defined as any TEAE reported as having a possible, probable or highly probable relationship to IP and includes events with a missing relationship. A serious TEAE is defined as any TEAE for which 'Serious event' is indicated as 'Yes'. A TEAE of special interest is defined as any AE considered to be of special interest per protocol. A local administration site reaction is defined as any AE for which the high-level group term is coded to 'Administration site reactions'.
For the summary of TEAEs by severity, subjects could appear in more than 1 severity category. Subjects were only counted once within each severity category. AEs with missing severity were classified as 'severe'.

The most frequently reported TEAEs (≥20% of participants in any group) were under the following SOCs:

- Infections and infestations: 28.3% in the AVT03 group and 21.5% in the Prolia group.
- Musculoskeletal and connective tissue disorders: 20.2% in the AVT03 group and 23.4% in the US-Prolia group.
- Nervous system disorders: 22.2% in the AVT03 group and 20.6% in the Prolia group.
- General disorders and administration site conditions lower in the AVT03 group than the US- US-Prolia group: 13.1% in the AVT03 group and 23.4% in the US-Prolia group.

At the PT level, the most frequently reported TEAEs (≥5% of participants in any group are listed in the following table.

Table 34: AVT03-GL-P01: Incidence of TEAEs Occurring in ≥5% of Participants in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	Statistic	AVT03 (N=99)	US-Prolia (N=107)	Overall (N=206)
At least one TEAE	n (%) E	75 (75.8) 208	79 (73.8) 230	154 (74.8) 438
Infections and infestations	n (%) E	28 (28.3) 34	23 (21.5) 27	51 (24.8) 61
Upper respiratory tract infection	n (%) E	7 (7.1) 7	6 (5.6) 8	13 (6.3) 15
COVID-19	n (%) E	7 (7.1) 7	3 (2.8) 3	10 (4.9) 10
Musculoskeletal and connective tissue disorders	n (%) E	20 (20.2) 32	25 (23.4) 31	45 (21.8) 63
Arthralgia	n (%) E	6 (6.1) 7	6 (5.6) 6	12 (5.8) 13
Rhabdomyolysis	n (%) E	5 (5.1) 6	4 (3.7) 4	9 (4.4) 10
Pain in extremity	n (%) E	3 (3.0) 3	6 (5.6) 6	9 (4.4) 9
Nervous system disorders	n (%) E	22 (22.2) 31	22 (20.6) 30	44 (21.4) 61
Headache	n (%) E	18 (18.2) 24	17 (15.9) 22	35 (17.0) 46
General disorders and administration site conditions	n (%) E	13 (13.1) 21	25 (23.4) 34	38 (18.4) 55
Influenza like illness	n (%) E	8 (8.1) 12	14 (13.1) 16	22 (10.7) 28
Injection site pain	n (%) E	1 (1.0) 1	6 (5.6) 8	7 (3.4) 9
Gastrointestinal disorders	n (%) E	14 (14.1) 18	21 (19.6) 31	35 (17.0) 49
Toothache	n (%) E	3 (3.0) 3	6 (5.6) 7	9 (4.4) 10
Investigations	n (%) E	12 (12.1) 12	9 (8.4) 11	21 (10.2) 23
Blood creatine phosphokinase increased	n (%) E	8 (8.1) 8	7 (6.5) 9	15 (7.3) 17
Metabolism and nutrition disorders	n (%) E	9 (9.1) 9	6 (5.6) 6	15 (7.3) 15
Vitamin D deficiency	n (%) E	7 (7.1) 7	3 (2.8) 3	10 (4.9) 10
Blood and lymphatic system disorders	n (%) E	4 (4.0) 6	6 (5.6) 6	10 (4.9) 12
Neutropenia	n (%) E	4 (4.0) 6	6 (5.6) 6	10 (4.9) 12

Source: Module 5.3.3.1, CSR AVT03-GL-P01, Table 14.3.1.2.2

AE : adverse event; E : number of TEAEs in each category; IP : investigational product; MedDRA : Medical Dictionary for Regulatory Activities; n : number of subjects with at least one TEAE in each category (subjects with multiple events in each

category are counted only once in each category); N: total number of subjects in the relevant population; TEAE: treatment-emergent AE; %: percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration.
The AEs were coded using MedDRA Version 25.0.

Treatment-Emergent Adverse Events by ADA Status

All subjects in this study were ADA positive and there were no participants who were ADA negative. Thus, the analysis of TEAE by ADA status is futile.

Treatment-Emergent Adverse Events by nAb Status

There were 80 nAb (neutralizing Antibody) positive participants in this study (AVT03 = 39, US- Prolia = 41) and 126 nAb negative participants (AVT03 = 60, US-Prolia = 66).

The proportion of participants with a TEAE was comparable between the two groups in the nAb positive (AVT03 vs US-Prolia - 82.1% vs 73.2%) subgroup and nAb negative (AVT03 vs US- Prolia: 71.7% vs 74.2%) subgroup. Most of the TEAEs were mild in severity in nAb positive (AVT03 vs US-Prolia: 82.1% vs 73.2%) and nAb negative (AVT03 vs US-Prolia: 68.3% vs 72.7%) subgroups. One serious TEAE was reported in one participant (1.5%) in the US-Prolia treatment group of the nAb negative subgroup.

Study AVT03-GL-C01

Up to Month 12, 178 participants (66.9%) reported 515 TEAEs in the AVT03 group and 178 participants (66.9%) reported 436 TEAEs in the US-Prolia group. Most participants experienced TEAEs that were mild or moderate in the AVT03 treatment arm (22.9% and 41.0%, respectively) and in the US-Prolia arm (24.4% and 39.8%, respectively).

From Month 12 to Month 18/EoS, 99 participants (40.9%) reported 154 TEAEs in the AVT03/AVT03 group, 39 participants (32.0%) reported 63 TEAEs in the US-Prolia/AVT03 group, and 39 participants (32.0%) reported 63 TEAEs in the US-Prolia/US-Prolia group. Most of the TEAEs were mild or moderate. Severe TEAE were reported in 5 (2.1%) participants from the AVT03/AVT03 group, 3 (2.5%) participants from the US-Prolia/AVT03 group, and 1 participant from the US-Prolia/US-Prolia group.

Treatment-Related TEAEs

Up to Month 12, 59 participants (22.2%) reported 92 treatment-related TEAEs in the AVT03 group and 50 participants (18.8%) reported 68 treatment-related TEAEs in the US-Prolia group.

From Month 12 to Month 18/EoS, 16 participants (6.6%) in the AVT03/AVT03 group experienced a total of 19 TEAEs, 4 participants (3.3%) in the US-Prolia/AVT03 group experienced 4 TEAEs and 5 participants (4.1%) in the US-Prolia/US-Prolia group experienced a total of 7 TEAEs that were related to study drug.

Serious TEAEs

Up to Month 12, 9 participants (3.4%) in the AVT03 group had 14 serious TEAEs and 10 participants (3.8%) in the US-Prolia group had 10 serious TEAEs. None of the serious TEAEs were considered related to study treatment.

From Month 12 to Month 18/EoS, 6 serious TEAEs were reported in 6 participants (2.5%) in the AVT03/AVT03 group, 3 serious TEAEs in 3 participants (2.5%) in the US-Prolia/AVT03 group and 3 serious TEAEs in 2 participants (1.6%) in the US-Prolia/US-Prolia group.

TEAEs that led to Study Treatment Discontinuation

Up to Month 12, treatment-related TEAEs that led to study treatment discontinuation were reported in 2 participants (0.8%; 2 TEAEs) in the AVT03 group.

No TEAEs that led to study drug discontinuation were reported in participants during the period from Month 12 to Month 18/EoS.

TEAEs that led to Early Termination

Up to Month 12, 10 participants (3.8%) reported 11 TEAEs that led to early termination in the AVT03 group, and 3 participant (1.1%) experienced 3 TEAEs that led to early termination in the US-Prolia group.

A TEAE was reported in 1 participant (0.4%) in the AVT03/AVT03 group that led to early termination from Month 12 to Month 18/EoS.

AESIs

Up to Month 12, 60 TEAEs of special interest were reported in 43 participants (16.2%) in the AVT03 group and 48 TEAEs of special interest were reported in 38 participants (14.3%) in the US-Prolia group.

From Month 12 to Month 18/EoS, 17 participants (7.0%) experienced 18 TEAEs of special interest in the AVT03/AVT03 group, 5 participants (4.1%) experienced 5 TEAEs of special interest in the US-Prolia/AVT03 group, and 5 participants (4.1%) in the US-Prolia/US-Prolia group experienced 5 TEAEs of special interest.

Deaths

Up to Month 12, 3 participants died in the AVT03 group and 1 participant in the US-Prolia group. None of the deaths were considered to be related to study drug.

A death (sudden death) was reported in a participant in the AVT03/AVT03 group from Month 12 to Month 18/EoS. None of the deaths were considered to be related to study drug.

Table 35: AVT03-GL-C01: Overview of Treatment Emergent Adverse Events – Baseline to Month 12 (Safety Analysis Set)

	AVT03 (N=266)		US-Prolia (N=266)	
	Subjects n (%)	**Events n**	**Subjects n (%)**	**Events n**
Any TEAE	178 (66.9)	515	178 (66.9)	436
Maximum severity of TEAEs				
Mild	61 (22.9)	102	65 (24.4)	112
Moderate	109 (41.0)	200	106 (39.8)	161
Severe	8 (3.0)	12	7 (2.6)	8
Treatment-related TEAEs	59 (22.2)	92	50 (18.8)	68
Serious TEAEs	9 (3.4)	14	10 (3.8)	10
Treatment-related serious TEAEs	0	0	0	0
TEAEs leading to discontinuation from study treatment	8 (3.0)	8	3 (1.1)	3

Treatment-related TEAEs leading to discontinuation from study treatment	2 (0.8)	2	0	0
TEAEs leading to early termination from study	10 (3.8)	11	3 (1.1)	3
Treatment-related TEAE leading to early termination from study	2 (0.8)	3	0	0
Serious TEAE leading to early termination from study	4 (1.5)	4	1 (0.4)	1
Treatment-related serious TEAE leading to early termination from study	0	0	0	0
TEAEs of special interest	43 (16.2)	60	38 (14.3)	48
Death	3 (1.1)	3	1 (0.4)	1

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.1.1
TEAE: treatment-emergent adverse event
Notes: N = number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the first dose of study drug (Day 1) but before the Month 12 dose. Subjects were counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity were counted as severe. A subject is presented only once in the respective subject count by strongest relationship. Events with unknown relationship to study drug were counted as drug-related.

Table 36: AVT03-GL-C01: Overview of Treatment Emergent Adverse Events – From Month 12 to End of Study (Safety Analysis Set)

	AVT03 / AVT03 (N=242)		US-Prolia / AVT03 (N=122)		US-Prolia / US-Prolia (N=122)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	99 (40.9)	154	39 (32.0)	63	39 (32.0)	63
Maximum severity of TEAEs						
Mild	45 (18.6)	56	19 (15.6)	22	23 (18.9)	34
Moderate	49 (20.2)	69	17 (13.9)	18	15 (12.3)	19
Severe	5 (2.1)	5	3 (2.5)	3	1 (0.8)	1
Treatment-related TEAEs	16 (6.6)	19	4 (3.3)	4	5 (4.1)	7
Serious TEAEs	6 (2.5)	6	3 (2.5)	3	2 (1.6)	3
Treatment-related serious TEAEs	0	0	0	0	0	0
TEAEs leading to discontinuation from study treatment	0	0	0	0	0	0
Treatment-related TEAEs leading to discontinuation from study treatment	0	0	0	0	0	0
TEAEs leading to early termination from study	1 (0.4)	1	0	0	0	0

Treatment-related TEAE leading to early termination from study	0	0	0	0	0	0
Serious TEAE leading to early termination from study	1 (0.4)	1	0	0	0	0
Treatment-related serious TEAE leading to early termination from study	0	0	0	0	0	0
TEAEs of special interest	17 (7.0)	18	5 (4.1)	5	5 (4.1)	5
Death	1 (0.4)	1	0	0	0	0

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.1.3
TEAE: treatment-emergent adverse event.
N = number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the Month 12 dose up to End of Study. Subjects were counted only once at the maximum severity in the following order: severe, moderate, and mild. Events with unknown severity were counted as severe. A subject is presented only once in the respective subject count by strongest relationship. Events with unknown relationship to study drug were counted as drug-related.

Up to Month 12

A total of 178 participants (66.9%) reported 515 TEAEs in the AVT03 group and 178 participants (66.9%) reported 436 TEAEs in the US-Prolia group.

Most commonly reported TEAEs by SOC were Infections and Infestations (37.6% in the AVT03 group; 33.8% in the US-Prolia group), Metabolism and Nutrition Disorders (13.9% in the AVT03 group; 12.8% in the US-Prolia group) and Musculoskeletal and Connective Tissue Disorders (16.5% in the AVT03 group; 13.2% in the US-Prolia group).

By PT, the most commonly reported TEAEs in the AVT03 group were upper respiratory tract infection (11.7%), hypocalcaemia (10.5%), and nasopharyngitis (8.6%).

By PT, the most commonly reported TEAEs in the US-Prolia group were upper respiratory tract infection (12.8%), hypocalcaemia (8.3%), and nasopharyngitis (7.5%).

From Month 12 to Month 18/EoS

A total of 99 participants (40.9%) reported 154 TEAEs in the AVT03/AVT03 group, 39 participants (32.0%) reported 63 TEAEs in the US-Prolia/AVT03 group, and 39 participants (32.0%) reported 63 TEAEs in the US-Prolia/US-Prolia group.

Treatment-Emergent Adverse Events by ADA Status

All but two patients in this study were ADA positive. There were two participants who were ADA negative, one in each group (AVT03, US Prolia). Thus, the analysis of TEAE by ADA status is futile.

Treatment-Emergent Adverse Events by nAb Status

The incidence of TEAEs by nAb status up to Month 12 is presented below.

Table 37: AVT03-GL-C01: TEAEs by nAb Status – Up to Month 12 (Safety Analysis Set)

	AVT03 N=266		US-Prolia N=266	
	nAb-Positive (N=13) n (%)	nAb-Negative (N=253) n (%)	nAb-Positive (N=20) n (%)	nAb-Negative (N=246) n (%)
Any TEAE	10 (76.9)	168 (66.4)	14 (70.0)	163 (66.3)
Maximum severity of TEAEs				
Mild	5 (38.5)	56 (22.1)	6 (30.0)	60 (24.4)
Moderate	5 (38.5)	104 (41.1)	6 (30.0)	98 (39.8)
Severe	0	8 (3.2)	2 (10.0)	5 (2.0)
Treatment-related TEAEs	2 (15.4)	57 (22.5)	6 (30.0)	45 (18.3)
Serious TEAEs	0	9 (3.6)	2 (10.0)	8 (3.3)
Treatment-related serious TEAEs	0	0	0	0
TEAE leading to discontinuation from study treatment	0	6 (2.4)	0	3 (1.2)
Treatment-related TEAE leading to discontinuation from study treatment	0	2 (0.8)	0	1 (0.4)
TEAE leading to early termination	0	9 (3.6)	0	3 (1.2)
Treatment-related TEAE leading to early termination	0	2 (0.8)	0	1 (0.4)
Serious TEAE leading to early termination	0	4 (1.6)	0	1 (0.4)
Treatment-related serious TEAE leading to early termination	0	0	0	0
TEAEs of special interest	3 (23.1)	36 (14.2)	2 (10.0)	34 (13.8)
Death	0	3 (1.2)	0	1 (0.4)

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.11.2.1
nAb: neutralizing antibody
N=Number of subjects treated in the relevant Safety Analysis Set and NAb group and is used as the denominator for percentage calculations.
n (%) represents number and % of subjects with events starting on or after the first dose of study drug (Day 1) but before the Month 12 dose. Subjects are counted only once at the maximum severity in the following order: severe, moderate, and mild.
Events with unknown severity are counted as severe. Subject is presented only once in the respective subject count by strongest relationship. Events with unknown relationship to study drug are counted as drug-related.
nAb Positive if any positive nAb result observed before Month 12 dose; nAb Negative otherwise.

2.5.8.3. Adverse drug reactions

Study AVT03-GL-P01

The percentage of participants who reported IP-related TEAEs in the AVT03 group (43.4%) was higher than that in the US-Prolia group (33.6%). The IP-related TEAEs were most frequently reported (≥10% of participants in any group) under the SOC of musculoskeletal and connective tissue disorders (13.1% in the AVT03 group and 9.3% in the US-Prolia group). For this frequently reported SOC, the percentage of participants who reported study treatment-related TEAEs in the AVT03 group was comparable to that observed in the US-Prolia group.

At the PT level, the most frequently reported related TEAEs (≥5% of participants in any group) were pain in extremity, injection site pain, vitamin D deficiency, and headache.

Table 38: AVT03-GL-P01: Incidence of Study Treatment-Related TEAEs Occurring in ≥5% of Participants in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	Statistic	AVT03 (N=99)	US-Prolia (N=107)	Overall (N=206)
At least one IP-related TEAE	n (%) E	43 (43.4) 70	36 (33.6) 55	79 (38.3) 125
Musculoskeletal and connective tissue disorders	n (%) E	13 (13.1) 17	10 (9.3) 11	23 (11.2) 28
Pain in extremity	n (%) E	5 (5.1) 6	2 (1.9) 2	7 (3.4) 8
General disorders and administration site conditions	n (%) E	7 (7.1) 8	8 (7.5) 11	15 (7.3) 19
Injection site pain	n (%) E	1 (1.0) 1	6 (5.6) 8	7 (3.4) 9
Metabolism and nutrition disorders	n (%) E	7 (7.1) 7	3 (2.8) 3	10 (4.9) 10
Vitamin D deficiency	n (%) E	6 (6.1) 6	2 (1.9) 2	8 (3.9) 8
Nervous system disorders	n (%) E	7 (7.1) 7	3 (2.8) 3	10 (4.9) 10
Headache	n (%) E	7 (7.1) 7	3 (2.8) 3	10 (4.9) 10

Source: Module 5.3.3.1, CSR AVT03-GL-P01, Table 14.3.1.3.2
AE: adverse event; IP: investigational product; MedDRA: Medical Dictionary for Regulatory Activities;
TEAE: treatment-emergent AE
n = number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N = total number of subjects in the relevant population; E = number of TEAEs in each category; % = percentage of subjects in each category calculated relative to the total number of subjects in the relevant population.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. A related TEAE is defined as any TEAE reported as having a possible, probable or highly probable relationship to IP and includes events with a missing relationship.
AEs were coded using MedDRA Version 25.0.

Study AVT03-GL-C01

Up to Month 12

A total of 59 participants (22.2%) reported 92 treatment-related TEAEs in the AVT03 group and 50 participants (18.8%) reported 68 treatment-related TEAEs in the US-Prolia group. None of the treatment-related TEAEs in either treatment group were serious.

The most common treatment-related TEAEs in the treatment groups were:

- AVT03 group: hypocalcaemia (28 events in 24 participants [9.0%]) and Adjusted calcium decreased (12 events in 11 participants [4.1%]).
- US-Prolia group: hypocalcaemia (21 events in 18 participants [6.8%]) and ISR (10 events in 8 participants [3.0%]).

Table 39: AVT03-GL-C01: Treatment-Related TEAEs (in at Least 1% of Participants in Any Treatment Group) by Primary System Organ Class and Preferred Term – Up to Month 12 (Safety Analysis Set)

SOC PT	AVT03 (N=266)		US-Prolia (N=266)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any Reported	59 (22.2)	92	50 (18.8)	68
Metabolism and nutrition disorders	24 (9.0)	28	19 (7.1)	22
Hypocalcaemia	24 (9.0)	28	18 (6.8)	21
Musculoskeletal and connective tissue disorders	13 (4.9)	20	17 (6.4)	21
Musculoskeletal pain	6 (2.3)	7	7 (2.6)	7
Arthralgia	3 (1.1)	5	4 (1.5)	5
Pain in extremity	3 (1.1)	3	2 (0.8)	2
Investigations	18 (6.8)	21	9 (3.4)	11
Adjusted calcium decreased	11 (4.1)	12	3 (1.1)	3
Activated partial thromboplastin time prolonged	6 (2.3)	6	2 (0.8)	2
Calcium ionised decreased	3 (1.1)	3	3 (1.1)	4

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.3.2.1.
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class. N=number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the first dose of study drug (Day 1) but before the Month 12 dose. Subject was presented only once in the respective subject count by strongest relationship. Events with unknown relationship to study drug were counted as drug-related.
Adverse events were coded using MedDRA version 27.0.

From Month 12 to Month 18/EoS

From Month 12 to Month 18/EoS, a total of 16 participants (6.6%) reported 19 treatment-related TEAEs in the AVT03/AVT03 group, 4 participants (3.3%) reported 4 treatment-related TEAEs in the US-Prolia/AVT03 group, and 5 participants (4.1%) reported 7 treatment-related TEAEs in the US-Prolia/US-Prolia group.

Table 40: AVT03-GL-C01: Treatment-Related TEAEs (in at Least 1% of Participants in Any Treatment Group) by Primary System Organ Class and Preferred Term – From Month 12 to End of Study (Safety Analysis Set)

***SOC* PT**	**AVT03/AVT03 (N=242)**		**US-Prolia/AVT03 (N=122)**		**US-Prolia/US-Prolia (N=122)**	
	Subjects n (%)	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Subjects with any treatment-related TEAEs						
Any Reported	16 (6.6)	19	4 (3.3)	4	5 (4.1)	7
Investigations	11 (4.5)	13	3 (2.5)	3	3 (2.5)	3
Adjusted calcium decreased	8 (3.3)	8	2 (1.6)	2	0	0
Calcium ionised decreased	5 (2.1)	5	1 (0.8)	1	2 (1.6)	2

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.3.2.3.
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class.
N = number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the Month 12 dose up to End of Study. Subject was presented only once in the respective subject count by strongest relationship. Events with unknown relationship to study drug were counted as drug-related.
Adverse events were coded using MedDRA version 27.0.

2.5.8.4. Serious adverse event/deaths/other significant events

Study AVT03-GL-P01

No fatal TEAEs or TEAEs leading to study discontinuation occurred during the study.

One participant (0.9%) in the US-Prolia group had a serious TEAE of drug hypersensitivity during the study. The event was moderate in severity, was considered to be possibly related to the study treatment and had an outcome of recovered/resolved. This event was also considered as an AESI.

Overall, 46 participants (22.3%) experienced at least 1 AESI. No AESIs of serious dermatological reactions, diverticulitis, or bone conditions were reported during the study. The most frequently reported AESIs were related to musculoskeletal and connective tissue disorders, reported by 15.5% of participants overall.

The majority of AESIs were considered study treatment-related (reported by 16% of participants). The percentage of participants who reported study treatment-related AESIs in the AVT03 group (16.2%) was similar to the US-Prolia group (15.9%).

Table 41: Incidence of TEAEs of Special Interest (Safety Population)

System Organ Class Preferred Term	Statistic	AVT03 (N=99)	US-Prolia (N=107)	Overall (N=206)
At least one TEAE of special interest	n (%) E	21 (21.2) 30	25 (23.4) 34	46 (22.3) 64
Musculoskeletal and connective tissue disorders	n (%) E	16 (16.2) 22	16 (15.0) 19	32 (15.5) 41
Arthralgia	n (%) E	4 (4.0) 4	4 (3.7) 4	8 (3.9) 8
Pain in extremity	n (%) E	5 (5.1) 5	2 (1.9) 2	7 (3.4) 7
Back pain	n (%) E	2 (2.0) 2	4 (3.7) 4	6 (2.9) 6
Musculoskeletal chest pain	n (%) E	2 (2.0) 2	2 (1.9) 2	4 (1.9) 4
Myalgia	n (%) E	2 (2.0) 2	2 (1.9) 2	4 (1.9) 4
Neck pain	n (%) E	2 (2.0) 2	2 (1.9) 2	4 (1.9) 4
Musculoskeletal pain	n (%) E	0	2 (1.9) 2	2 (1.0) 2
Costochondritis	n (%) E	1 (1.0) 2	0	1 (0.5) 2
Muscle spasms	n (%) E	1 (1.0) 1	0	1 (0.5) 1
Pain in jaw	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Rotator cuff syndrome	n (%) E	1 (1.0) 1	0	1 (0.5) 1
Tendonitis	n (%) E	1 (1.0) 1	0	1 (0.5) 1
General disorders and administration site conditions	n (%) E	3 (3.0) 4	7 (6.5) 9	10 (4.9) 13
Injection site pain	n (%) E	1 (1.0) 1	6 (5.6) 8	7 (3.4) 9
Injection site erythema	n (%) E	2 (2.0) 2	0	2 (1.0) 2
Injection site pruritus	n (%) E	1 (1.0) 1	0	1 (0.5) 1
Non-cardiac chest pain	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Injury, poisoning and procedural complications	n (%) E	2 (2.0) 3	2 (1.9) 2	4 (1.9) 5
Muscle strain	n (%) E	2 (2.0) 2	1 (0.9) 1	3 (1.5) 3
Ligament sprain	n (%) E	1 (1.0) 1	1 (0.9) 1	2 (1.0) 2
Metabolism and nutrition disorders	n (%) E	1 (1.0) 1	1 (0.9) 1	2 (1.0) 2
Hypocalcaemia	n (%) E	1 (1.0) 1	0	1 (0.5) 1
Hypophosphataemia	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Immune system disorders	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Drug hypersensitivity	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Infections and infestations	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Cellulitis	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Skin and subcutaneous tissue disorders	n (%) E	0	1 (0.9) 1	1 (0.5) 1
Sensitive skin	n (%) E	0	1 (0.9) 1	1 (0.5) 1

Source: Module 5.3.3.1, CSR AVT03-GL-P01, Table 14.3.1.6.1
% : percentage of subjects in each category calculated relative to the total number of subjects in the relevant population; AE : adverse event; E : number of TEAEs in each category; IP : investigational product; MedDRA : Medical Dictionary for Regulatory Activities; n : number of subjects with at least one TEAE in each category (subjects with multiple events in each category are counted only once in each category); N : total number of subjects in the relevant population; TEAE : treatment-emergent AE.
A TEAE is defined as any AE which commenced or worsened in severity on or after the start of IP administration. A TEAE of special interest is defined as any AE considered to be of special interest per protocol. AEs with missing severity were classified as 'severe'. Maximum severity is defined as the most severe occurrence within each subject, system organ class and preferred term.
AEs were coded using MedDRA Version 25.0.

More participants in the US-Prolia (10 [9.3%]) group reported at least 1 local administration site reaction (ASR) compared with the AVT03 (2 [2.0%]) group. The most frequent reactions were injection site pain

(reported in 6 (5.6%) of participants in US-Prolia group and 1 (1.0%) of participants in AVT03 group) and vessel puncture site bruise (reported in 4 [3.7%] of participants in the US-Prolia group and none of the participants in the AVT03 group). Based on the injection site reaction assessments, 7 (3.4%) participants reported at least 1 local ISR (with a worst postdose severity of Grade ≥1). The percentage of participants with these events was comparable in both the groups: 2 participants (2.0%) in the AVT03 group and 5 participants (4.7%) in the US-Prolia group. All reported reactions were Grade 1 or Grade 2 in severity; no Grade ≥3 reactions were reported.

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Up to Month 12, 3 participants died in the AVT03 group and 1 participant in the US-Prolia group. None of the deaths were considered to be related to study drug. Causes of death were pneumonia, metastatic lung carcinoma and unknown cause in the AVT03 group, and sudden death due to unknown cause in the US-Prolia group. One participant in the AVT03 group died due to sudden death during the period from Month 12 to end of study.

Up to Month 12, 9 participants (3.4%) in the AVT03 group had 14 serious TEAEs and 10 participants (3.8%) in the US-Prolia group had 10 serious TEAEs. None of the serious TEAEs were considered related to study treatment.

Table 42: AVT03-GL-C01: Serious TEAEs by Primary System Organ Class and Preferred Term – Up to Month 12 (Safety Analysis Set)

System Organ Class **Preferred Term**	**AVT03 (N=266)**		**US-Prolia (N=266)**	
	Subjects n (%)	**Events n**	**Subjects n (%)**	**Events n**
Any serious TEAE	**9 (3.4)**	**14**	**10 (3.8)**	**10**
Gastrointestinal disorders	*3 (1.1)*	*3*	*1 (0.4)*	*1*
Abdominal pain	0	0	1 (0.4)	1
Chronic gastritis	1 (0.4)	1	0	0
Erosive duodenitis	1 (0.4)	1	0	0
Pancreatitis	1 (0.4)	1	0	0
Infections and infestations	*2 (0.8)*	*3*	*1 (0.4)*	*1*
Appendicitis	0	0	1 (0.4)	1
Infective myositis	1 (0.4)	1	0	0
Pneumonia	1 (0.4)	1	0	0
Soft tissue infection	1 (0.4)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*1 (0.4)*	*1*	*2 (0.8)*	*2*
Breast cancer female	0	0	1 (0.4)	1
Haemangioma of bone	0	0	1 (0.4)	1
Lung cancer metastatic	1 (0.4)	1	0	0

Cardiac disorders	1 (0.4)	*2*	*0*	*0*
Chronic coronary syndrome	1 (0.4)	1	0	0
Ventricular arrhythmia	1 (0.4)	1	0	0
General disorders and administration site conditions	1 (0.4)	*1*	1 (0.4)	*1*
Death	1 (0.4)	1	0	0
Sudden death	0	0	1 (0.4)	1
Psychiatric disorders	*0*	*0*	*2 (0.8)*	*2*
Depressed mood	0	0	1 (0.4)	1
Schizoaffective disorder	0	0	1 (0.4)	1
Vascular disorders	*0*	*0*	*2 (0.8)*	*2*
Hypertension	0	0	1 (0.4)	1
Iliac artery occlusion	0	0	1 (0.4)	1
Endocrine disorders	*1 (0.4)*	*1*	*0*	*0*
Hyperparathyroidism primary	1 (0.4)	1	0	0
Injury, poisoning and procedural complications	*0*	*0*	*1 (0.4)*	*1*
Craniocerebral injury	0	0	1 (0.4)	1
Metabolism and nutrition disorders	*1 (0.4)*	*1*	*0*	*0*
Dehydration	1 (0.4)	1	0	0
Renal and urinary disorders	*1 (0.4)*	*1*	*0*	*0*
Renal failure	1 (0.4)	1	0	0
Reproductive system and breast disorders	*1 (0.4)*	*1*	*0*	*0*
Genital prolapse	1 (0.4)	1	0	0

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.4.1.1
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event
N = number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the first dose of study drug (Day 1) but before the Month 12 dose. Subjects were counted once within a SOC and once for each unique PT.
Adverse events were coded using MedDRA version 27.0.

From Month 12 to Month 18/EoS, serious TEAEs were reported in 6 participants (2.5%; 6 serious TEAEs) in the AVT03 group and 3 participants (2.5%; 3 serious TEAEs) in the US-Prolia/AVT03 groups and 2 participants (1.6%; 3 serious TEAEs) in the Prolia/Prolia group. All the PTs of SAEs did not occur in more than 1 participant in either of the groups.

Up to Month 12, 60 TEAEs of special interest were reported in 43 participants (16.2%) in the AVT03 group and 48 TEAEs of special interest were reported in 38 participants (14.3%) in the US-Prolia group.

The most common AESIs were hypocalcaemia (13 participants, 4.9%), adjusted calcium increased (12 participants, 4.5%), musculoskeletal pain (6 participants, 2.3%), and arthralgia (8 participants, 3.0%) in the

AVT03 group; hypocalcaemia (14 participants, 5.3%), musculoskeletal pain (7 participants, 2.6%), and arthralgia (5 participants, 1.9%) in the US-Prolia group.

From Month 12 to Month 18/EoS, 17 participants (7.0%) in the AVT03/AVT03 group experienced 18 AESIs, 5 participants (4.1%) in the US-Prolia/AVT03 group and in the US-Prolia/US-Prolia group, experienced 5 AESIs each.

Table 43: AVT03-GL-C01: TEAEs of Special Interest by Primary System Organ Class and Preferred Term – Up to Month 12 (Safety Analysis Set)

SOC PT	AVT03 (N=266)		US-Prolia (N=266)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any Reported	43 (16.2)	60	38 (14.3)	48
Musculoskeletal and connective tissue disorders	22 (8.3)	31	20 (7.5)	26
Arthralgia	8 (3.0)	10	5 (1.9)	6
Musculoskeletal pain	6 (2.3)	7	7 (2.6)	7
Pain in extremity	5 (1.9)	6	2 (0.8)	2
Spinal pain	2 (0.8)	3	3 (1.1)	4
Myalgia	1 (0.4)	1	2 (0.8)	3
Back pain	1 (0.4)	1	2 (0.8)	2
Groin pain	0	0	1 (0.4)	1
Joint swelling	1 (0.4)	1	0	0
Muscle spasms	0	0	1 (0.4)	1
Neck pain	1 (0.4)	1	0	0
Pain in jaw	1 (0.4)	1	0	0
Metabolism and nutrition disorders	13 (4.9)	14	14 (5.3)	16
Hypocalcaemia	13 (4.9)	14	14 (5.3)	16
Investigations	12 (4.5)	13	4 (1.5)	4
Adjusted calcium decreased	12 (4.5)	13	4 (1.5)	4
Gastrointestinal disorders	1 (0.4)	1	0	0
Abdominal pain upper	1 (0.4)	1	0	0
Immune system disorders	0	0	1 (0.4)	1
Hypersensitivity	0	0	1 (0.4)	1
Nervous system disorders	0	0	1 (0.4)	1
Sciatica	0	0	1 (0.4)	1
Skin and subcutaneous tissue disorders	1 (0.4)	1	0	0
Dermatitis allergic	1 (0.4)	1	0	0

Source: Module 5.3.5.1, CSR1 AVT03-GL-C01, Table 14.3.1.9.1
MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event.
N = number of subjects treated in the relevant Safety Analysis Set and was used as the denominator for percentage calculations. n (%) represents number and percent of subjects with events starting on or after the first dose of study drug (Day 1) but before the Month 12 dose. Subjects were counted once within a SOC and once for each unique PT.

Adverse events were coded using MedDRA version 27.0

Up to Month 12, injection site reactions were reported as a TEAE by 11 participants (4.1%) in the AVT03 group and by 8 participants (3.0%) in the US-Prolia group. All ISRs were mild in severity, except for 1 participant who experienced a single incidence of a moderate reaction (erythema and itching) after AVT03 administration.

From Month 12 to Month 18/EoS, among all participants, ISRs were reported as a TEAE by 2 participants in the AVT03/AVT03 group and 1 participant each in US-Prolia/AVT03 group, and US-Prolia/US-Prolia group. All the ISRs were mild in severity and transient.

2.5.8.5. Laboratory findings

Clinical Laboratory Evaluations

Study AVT03-GL-P01

There were no clinically meaningful changes in mean values for haematology, coagulation, or clinical chemistry over time, and no treatment group differences were noted.

AVT03 had a comparable clinical laboratory test profile to US-Prolia, with similar mean values of these parameters over time in both the groups. An increase in the calcium levels over time and a decrease in the PTH levels over time were observed in both the groups.

Shifts in haematology, coagulation, or clinical chemistry parameters from normal at baseline to either low or high at Day 252 (EOS visit) were generally infrequent. The shifts were not considered to be clinically meaningful, were not associated with clinical symptoms, and were resolved without intervention.

There were no abnormal clinically significant findings in urinalysis parameters at any visit based on the Investigator's assessment.

TEAEs of laboratory abnormalities were reported in 47 participants (25 participants in the AVT03 group and 22 participants in the US-Prolia group). Thirty-seven participants (18.0% of participants in the Safety Population) reported 43 TEAEs of Grade ≥3 laboratory abnormality, 17 (17.2%) in the AVT03 group and 20 (18.7%) in the US-Prolia group. All of these reported Grade ≥3 events were mild in severity and most of the events had resolved by the end of the study.

Fourteen participants (6.8%) had study treatment-related TEAEs of Grade ≥3 laboratory abnormality: 9 participants (9.1%) in the AVT03 group and 5 participants (4.7%) in the US-Prolia group. The most frequently reported study treatment-related Grade ≥3 laboratory abnormality was neutropenia, reported in 7 participants. All of these events had resolved by the end of the study.

Study AVT03-GL-C01

Up to Month 12, 50 TEAEs were reported under the SOC of Investigations in 39 participants (14.7%) in the AVT03 group. 21 TEAEs in 18 participants (6.8%) were considered related to the study treatment. These included 12 events of adjusted calcium decreased in 11 participants, 6 events of activated partial thromboplastin time prolonged in 6 participants and 3 events of calcium ionized decreased in 3 participants. Most TEAEs related to laboratory values were mild or moderate and 1 participant in the AVT03 group experienced events of ALT increased and AST increased that were considered severe.

In the US-Prolia group 44 TEAEs were reported under the SOC of Investigations in 37 participants (13.9%); 11 TEAEs in 9 participants (3.4%) were considered related to study treatment. These included 2 events of activated partial thromboplastin time prolonged in 2 participants, 3 events of adjusted calcium decreased in 3

participants, 1 event of adjusted calcium increased in 1 participant, 4 events of calcium ionized decreased in 3 participants, and 1 event of INR increased in 1 participant. All events were mild or moderate in severity.

Under the investigations SOC, from Month 12 to Month 18/EoS, there were 29 TEAEs reported in 24 participants (9.9%) in the AVT03/AVT03 treatment group, 15 TEAEs were reported in 8 participants (6.6%) in the US-Prolia/AVT03 treatment group, and 14 TEAEs were reported in 9 participants (7.4%) US-Prolia/US-Prolia group.

Vital Signs, Physical Findings, Observations Related to Safety

Study AVT03-GL-P01

There were no clinically meaningful changes in mean values for vital signs parameters from baseline over the course of the study and no meaningful differences between both the treatment groups were noted. Shifts in vital signs from normal at baseline to abnormal not clinically significant or clinically significant at EOS (Day 252) were infrequent, reported in <10% of participants.

There were no clinically meaningful changes in mean values for ECG parameters over the course of the study and no meaningful differences between the treatment groups. There were no abnormal clinically significant findings in ECG parameters based on the Investigator's evaluation.

Any abnormal clinically significant findings were appropriately reported as AEs or TEAEs.

Study AVT03-GL-C01

Up to Month 12, 2 participants in the AVT03 group had 3 vital sign measurements and 2 participants in the US-Prolia group had 3 measurements that were considered TEAEs. None were related to study drug. No other clinically meaningful changes from Baseline over time were observed across the treatment groups in vital signs up to Month 18/EoS.

No differences were seen in ECG findings up to Month 12 and from Month 12 to Month 18/EoS. Most ECG interpretations were normal or abnormal not clinically significant at all the timepoints, with 1 participant in the AVT03 group having an abnormal clinically significant ECG that was reported as a TEAE. The event was not related to study drug.

No notable differences were seen in physical examinations across the treatment groups in the study from baseline to Month 12. From Month 12 to the Month 18/EoS, 1 physical examination finding was considered as a TEAE (cardiac murmur) reported in 1 participant in the AVT03/AVT03 group.

2.5.8.6. In vitro biomarker test for patient selection for safety

Not applicable

2.5.8.7. Safety in special populations

Not applicable

2.5.8.8. Immunological events

The applicant has adopted an electrochemiluminescence immunoassay (ECLIA) bridging assay to screen, confirm and quantify denosumab specific antibodies in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed and is considered state of the art.

Further, the applicant presented a qualitative assay for the detection of neutralising ADA's in human serum. The presented assay was well described and established.

Study AVT03-GL-P01

The incidence of ADAs and nAbs to denosumab was observed over time during the complete study period of Study AVT03-GL-P01. The trend of onset and development of ADAs and nAbs over time were similar in both the treatment groups. At baseline (i.e., predose on Day 1), 1 participant in the US-Prolia group was positive for binding ADAs; none of the participants in the AVT03 group were ADA positive at baseline. Post-baseline, the frequency of participants with at least 1 positive ADA result at any time point was 100% in both the treatment groups. ADA formation progressively increased, with the highest positivity rates seen at Day 71 (80.8% in the AVT03 group) and Day 112 (82.2% in the US-Prolia group). The positivity rates decreased thereafter until the EoS (Day 252) in both the treatment groups in a comparable manner.

The level of the ADA titres indicated a generally low quantity of ADA in the serum samples. There was a similar trend observed in the incidence of ADA and titres of AVT03 to Prolia.

In all the nAb positive participants, the frequency of participants who tested positive for nAbs also increased over the duration of the study, with the highest frequency of nAb positivity reported at Day 112 in the AVT03 and US-Prolia groups (11.1% and 11.2%, respectively). The nAb positivity rates decreased thereafter until the EoS (Day 252). The percentage of participants with at least 1 positive nAb result in the AVT03 group (39.4%) was comparable to the US-Prolia group (38.3%).

Table 44: Summary of Detection of Anti-Drug Antibodies and Neutralizing Antibodies to Denosumab (Study AVT03-GL-P01, Safety Population)

Treatment Group	Statistics	Day 1 Predose	Day 7	Day 8	Day 15	Day 29	Day 57	Day 71	Day 112	Day 141	Day 196	Day 224	EOS /Day 252	Any Positive
Antidrug Antibody (ADA) Positivity														
AVT03 (N=99)	n (%)	0	44 (44.4)	46 (46.5)	60 (60.6)	67 (67.7)	76 (76.8)	80 (80.8)	77 (77.8)	74 (74.7)	44 (44.4)	22 (22.2)	6 (6.1)	99 (100.0)
Prolia (N=107)	n (%)	1 (0.9)	41 (38.3)	45 (42.1)	57 (53.3)	74 (69.2)	80 (74.8)	80 (74.8)	88 (82.2)	80 (74.8)	47 (43.9)	21 (19.6)	9 (8.4)	107 (100.0)
Neutralizing Antibody (nAb) Positivity														
AVT03 (N=99)	n (%)	0	7 (7.1)	6 (6.1)	8 (8.1)	6 (6.1)	11 (11.1)	10 (10.1)	11 (11.1)	10 (10.1)	4 (4.0)	5 (5.1)	1 (1.0)	39 (39.4)
Prolia (N=107)	n (%)	0	6 (5.6)	4 (3.7)	2 (1.9)	9 (8.4)	9 (8.4)	8 (7.5)	12 (11.2)	12 (11.2)	4 (3.7)	3 (2.8)	0	41 (38.3)

Source: Module 5.3.3.1 CSR AVT03-GL-P01, Table 14.2.3.1 and Table 14.2.3.2
ADA : anti-drug antibodies; EOS: End of Study; nAb: neutralizing antibody; N: total number of participants in the relevant population; n: number of participants with an assessment available at the relevant time point; %: percentage of participants in each category calculated relative to the total number of participants in the relevant population.
For nAb positivity rates, percentages of participants at each timepoint who are positive to nAb divided by total number of participants with any ADA positive result are presented.

Note: nAb test is only performed when ADA titre is 'Positive'.

A summary of PK parameters by ADA and nAb positive/negative subgroups is presented below. All participants in the PK Population were ADA positive postbaseline, and therefore the PK results for this subgroup were identical to those for the overall PK Population. There were no participants in the ADA

negative subgroup. In the immunogenicity subgroups, the point estimates of the GMRs for the exposure PK parameters were contained entirely within 80.00% to 125.00%.

Table 45: Summary of Serum Denosumab PK Parameters by Anti-Drug Antibodies and Neutralizing Antibodies Status (Study AVT03-GL-P01, PK Population)

		Test		Reference		Ratio of Geometric LS Means (%)	90% Confidence Interval for Ratio of LS Means	
Comparison (Test/Reference)	Parameter (Units)	n	Geometric LS Mean	n	Geometric LS Mean	Test/ Reference	Lower 5% CL (%)	Upper 5% CL (%)
ADA Positive								
AVT03 60 mg / Prolia 60 mg	C_{max} (ng/mL)	99	7,192.87	106	6,673.32	107.79	102.231	113.642
	$AUC_{0\text{-}inf}$ (h·ng/mL)	98	7,528,147.75	103	6,669,757.41	112.87	107.169	118.874
	$AUC_{0\text{-}last}$ (h·ng/mL)	99	7,457,574.92	106	6,547,992.79	113.89	107.719	120.416
nAb Positive								
AVT03 60 mg / Prolia 60 mg	C_{max} (ng/mL)	39	7,181.30	40	6,584.30	109.07	100.744	118.077
	$AUC_{0\text{-}inf}$ (h·ng/mL)	39	7,482,193.59	40	6,854,569.35	109.16	101.120	117.831
	$AUC_{0\text{-}last}$ (h·ng/mL)	39	7,480,082.71	40	6,834,319.56	109.45	101.334	118.213
nAb Negative								
AVT03 60 mg / Prolia 60 mg	C_{max} (ng/mL)	60	7,178.21	66	6,746.77	106.39	99.105	114.221
	$AUC_{0\text{-}inf}$ (h·ng/mL)	59	7,524,875.98	63	6,582,584.03	114.31	106.640	122.543
	$AUC_{0\text{-}last}$ (h·ng/mL)	60	7,406,846.18	66	6,408,623.24	115.58	107.072	124.755

Source: Module 5.3.3.1 CSR AVT03-GL-P01, Table 14.2.2.2.1
ADA: anti-drug antibody; AUC0-inf: area under the concentration-curve after extrapolation from time t to time infinity; AUC0-last: area under the serum concentration-curve from time zero to time t, where t is the last time point with concentrations above the LLOQ, calculated by linear up/log down trapezoidal summation; CL: confidence limit; Cmax: maximum serum concentration; LS: least Square; nAb: neutralizing antibody.
n: Number of participants used in calculation.
Treatment Comparison by analysis of covariance of log-transformed parameters with model: log(parameter) = Treatment + body weight at baseline as the covariate. 90% confidence interval for ratio of LS mean is constructed from the one-sided lower 5% CL and one-sided upper 5% CL. PK similarity is determined if, for each pairwise comparison, the 90% confidence intervals for the ratios of geometric LS means are entirely contained with the equivalence margin 80% to 125%. It is noted that the parameters of Cmax and AUC0-last are presented for US FDA and Japanese PMDA, and Cmax and AUC0-inf are presented for EMA.

Note: There are no participants who were ADA Negative. Thus, the stratum for these participants is not presented.

All participants in the PD Population were ADA-positive postbaseline, and therefore the PD results for this subgroup were identical to those for the overall PD Population. There were no participants in the ADA-negative subgroup. The observed trend in the PD data based on immunogenicity subgroups was consistent in both the treatment groups, AVT03 and Prolia.

Study AVT03-GL-C01

From baseline to Month 12, the overall frequency of ADAs was similar in both treatment groups (99.6% vs 99.6%, respectively), as was the treatment-emergent ADA incidence (100.0% vs 100.0%, respectively). The overall frequency of nAbs was 7.5% in the US-Prolia group and 4.9% in the AVT03 group, and the treatment-emergent nAb incidence was 7.6% and 5.1%, respectively. After the first treatment administration, the ADA titres were detectable at Day1 post-dose and reached the peak levels between Day 60 (Month 2) and Day 90 (Month 3), and then decreased up to Day 180 (Month 6). A similar time course with generally lower titres was observed after the second administration. The median ADA titre values in the AVT03 and US-Prolia groups were comparable up to Month 12 (Module 5.3.5.1 CSR1 AVT03-GL-C01, Table 14.6.3.1).

Table 46: Confirmed Positive Antibody Incidence and Anti-drug Antibody by Visit (Safety Analysis Set) – From Baseline to Month 12

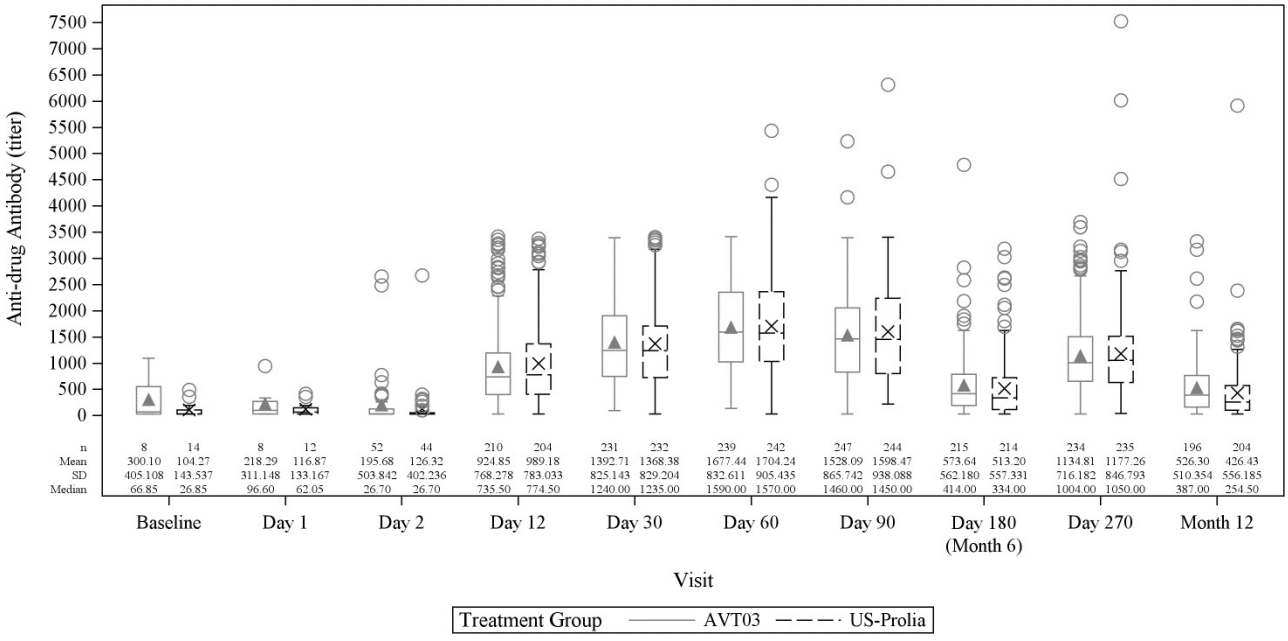
Results	AVT03 (N=266) n (%)	US-Prolia (N=266) n (%)
Total antibody incidence [1]	m=266	m=266
Binding (ADA) [A]	265 (99.6)	265 (99.6)
Neutralizing antibodies [B]	13 (4.9)	20 (7.5)
Baseline (preexisting antibody incidence) [2]	m=266	m=266
Binding (ADA) [A]	9 (3.4)	14 (5.3)
Neutralizing antibodies [B]	0	0
Treatment-emergent ADA incidence up to Month 12 [3]	m1=256	m1=251
Binding (ADA) [C]	256 (100.0)	251 (100.0)
Treatment-emergent nAb incidence up to Month 12 [3]	m2=256	m2=251
Neutralizing antibodies [D]	13 (5.1)	19 (7.6)
ADA by Visit		
Baseline (Pre-existing Antibody Incidence)	m=263	m=263
Binding (ADA)	9 (3.4)	14 (5.3)
Neutralizing antibodies	0	0
Day 1	m=262	m=264
Binding (ADA)	8 (3.1)	13 (4.9)
Neutralizing antibodies	0	1 (0.4)
Day 2	m=263	m=261
Binding (ADA)	56 (21.3)	46 (17.6)
Neutralizing antibodies	0	0
Day 12	m=250	m=262
Binding (ADA)	215 (86.0)	207 (79.0)
Neutralizing antibodies	0	0
Day 30	m=257	m=258
Binding (ADA)	235 (91.4)	240 (93.0)
Neutralizing antibodies	1 (0.4)	1 (0.4)
Day 60	m=258	m=256
Binding (ADA)	246 (95.3)	250 (97.7)
Neutralizing antibodies	0	1 (0.4)
Day 90	m=262	m=257
Binding (ADA)	251 (95.8)	249 (96.9)
Neutralizing antibodies	2 (0.8)	5 (1.9)
Day 180 (Month 6)	m=251	m=250
Binding (ADA)	222 (88.4)	221 (88.4)
Neutralizing antibodies	5 (2.0)	9 (3.6)
Day 270	m=240	m=246

Binding (ADA)	237 (98.8)	240 (97.6)
Neutralizing antibodies	7 (2.9)	3 (1.2)
Month 12	m=235	m=243
Binding (ADA)	203 (86.4)	207 (85.2)
Neutralizing antibodies	3 (1.3)	0

Source: Module 5.3.5.1 CSR1 AVT03-GL-C01, Table 14.6.1.1 and Table 14.6.2.1
ADA: anti-drug antibody; nAb: neutralizing antibody [1] Positive result at any visit before Month 12 dose.
[2] Baseline is defined as the last non-missing assessment prior to first dose (Day 1).
[3] Negative result or no result at Baseline and positive result post-dose but before Month 12 dose.
[A] % = n/m, where m is the total number of subjects with ADA assessed in the specified time period.
[B] % = n/ADA+, where ADA+ is the total number of subjects with positive ADA status in the specified time period.
[C] % = n/m1, where m1 is the number of subjects with ADA assessed post-dose up to Month 12 dose. Subjects with ADA positive at Baseline are not included in m1.
% = n/m2, where m2 is the number of subjects with treatment-emergent ADA Incidence up to Month 12 dose. Subjects with ADA / nAb positive at Baseline are not included in m2

Median titre levels for positive ADAs in both treatment groups increased from baseline to Day 90, then decreased on Day 180 (Month 6), increased after second dose administration, then decreased on Month 12. The median ADA titre values in the AVT03 and Prolia groups were comparable up to Month 12.

Figure 14: Box Plot of Titres for Positive Anti-drug Antibody (ADA) Results by Visit (Safety Analysis Set) - From Baseline to Month 12



Sources: Module 5.3.5.1 CSR1 AVT03-GL-C01, Figure 14.6.1.1 SD: standard deviation
Line: median, Symbol: mean, Box: upper and lower quartiles, Whiskers: 1.5 x Interquartile Range (IQR) or Min- Max (If all observations are within 1.5xIQR then whiskers represent Min/Max; otherwise whiskers represent the highest/lowest observations within 1.5xIQR and observations outside 1.5xIQR are marked as outliers), Circles: Outliers

Impact of ADAs and nAbs on Serum Concentrations

From Baseline to Month 12 in ADA positive participants, the mean denosumab serum levels of both AVT03 and US-Prolia treatment groups increased from Day 1 to Day 12, then decreased from Day 30 till Month 12.

Only one participant was ADA negative in the study. Mean denosumab serum levels were comparable between AVT03 and Prolia in the ADA positive subgroup population.

The mean denosumab serum levels of both AVT03 and US-Prolia in participants who were nAb positive were comparable to those who were nAb negative. The mean denosumab serum levels of both AVT03 and US-Prolia treatment groups increased from Day 1 to Day 12, then decreased from Day 30 till Month 12 in participants with or without nAb. Mean denosumab serum levels were comparable between AVT03 and Prolia in the nAb positive and nAb negative subgroup populations.

Impact of ADAs and nAbs on PD Characteristics

In total, 263 participants from the PD Analysis Set in each AVT03 and US-Prolia group were ADA positive postbaseline, and therefore the PD profiles in terms of AUEC0-6 months of %Cfb sCTX-1 were identical to those for the overall PD Population. The AUEC0-6 months in the nAb positive or nAb negative subgroup were comparable to the overall population. In the immunogenicity subgroups, the point estimates of the GMRs for the AUEC0-6 months were contained entirely within 0.80 to 1.25.

2.5.8.9. Safety related to drug-drug interactions and other interactions

Not applicable

2.5.8.10. Discontinuation due to adverse events

None of the participants discontinued the study or study treatment due to a TEAE in Study AVT03-GL-P01.

Study AVT03-GL-C01

In the AVT03 group, 8 participants (3.0%) had 8 TEAEs that led to early termination or treatment discontinuation up to Month 12. An additional TEAE that led to study treatment discontinuation (but not early termination), glomerular filtration rate decreased, was reported in 1 participant. In the US-Prolia group, 3 participants (1.1%) had 3 TEAEs that led to early termination up to Month 12.

Most of the events occurred in single participants, except for TEAEs under SOC *Musculoskeletal and connective tissue disorders,* which occurred in 3 participants in the AVT03 group as compared to 0 in the US-Prolia group.

No TEAEs leading to treatment discontinuation was reported from Month 12 to Month 18/EoS discontinuation. One TEAE of sudden death in a participant in the AVT03/AVT03 group led to the early termination Month 12 to Month 18/EoS.

2.5.8.11. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

Safety data on AVT03 is available from Study AVT03-GL-P01 and Study AVT03-GL-C01, where safety was assessed as part of the secondary study objectives.

Safety data are reported separately for each study as they were conducted in different populations (healthy male subjects and female subjects with PMO, respectively). The SAF of each study consisted of all subjects, who received at least one dose of study drug. The safety assessments performed during these studies were designed to capture the known safety issues listed in the originator label and are considered appropriate. The overall design of the clinical studies is considered adequate for a comprehensive safety assessment of AVT03.

At the time of the initial submission Study AVT03-GL-C01 was ongoing and a preliminary CSR1 with data up to Month 12 + 2 weeks was provided. The final CSR of that study and the full safety dataset were provided with the responses to the Day 120 List of Questions. Minor numerical differences in the safety data from baseline to Month 12 were reported between CSR versions dated 24-AUG-2024 and 07-JAN-2025, respectively. This results from updates to the safety data between the initial database freeze on 20-Jun-24 (two weeks after the last participant completed Month 12 visit) and the final database lock on 18-Nov-24. Between database freeze and final database lock, participants continued protocol scheduled activities resulting in ongoing data entry, monitoring activities and data cleaning, as per corresponding study plans. According to the applicant, no further updates were made to the data after final database lock.

In total, 99 healthy male subjects received a single s.c. dose (60 mg) of AVT03 and 388 postmenopausal women with osteoporosis received up to three s.c. doses (60 mg) AVT03 throughout the clinical development programme. The reference product (US-Prolia, 60 mg) was administered to 107 healthy males; 266 female patients received up to two doses of US-Prolia, and, as a result of the study design, 122 patients received three s.c. doses of US-Prolia. The percentages of subjects who received the scheduled number of doses were comparable between groups in each of the studies.

The size of the safety database and the treatment duration are considered sufficient.

Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by primary System Organ Class (SOC) and Preferred Term (PT). The analysis of AEs focused on treatment-emergent adverse events (TEAEs), which included all TEAEs, serious TEAEs, fatal TEAEs, TEAEs leading to discontinuation of study treatment or withdrawal from the study, all TEAEs by severity, and treatment related TEAEs. Special attention was paid to treatment-emergent AEs of special interest (AESIs), encompassing all relevant warnings and precautions from the Prolia product information, as well as ISRs. Further, routine laboratory safety parameters, vital sign, physical examination measurements and 12-lead electrocardiogram (ECG) results were analysed. The immunogenicity assessments included the frequency and titres of ADAs and frequency of nAbs to denosumab and their impact on safety and tolerability.

In the phase 1 PK trial (Study AVT03-GL-P01), overall, approximately 75% of participants experienced at least one TEAE with comparable frequencies between treatment groups. The numbers for IP-related TEAEs, however were higher in the AVT03 group compared to the reference group: 43 (43.4%) patients experienced 70 IP-related TEAE in the AVT03 group and 36 (33.6%) participants experienced 55 IP-related events in the reference group. The most frequently IP-related TEAEs reported during AVT03-GL-P01 study, based on the number of adverse events reported, are mainly driven by four SOCs: *Musculoskeletal and Connective tissue Disorders, Metabolism and Nutrition Disorders, Nervous system Disorders and Investigations*. Regarding *Musculoskeletal and Connective tissue Disorders*, the highest number of events reported were *Pain in extremity* (6 events in 5 participants in AVT03 group vs. 2 events in 2 participants in Prolia group). All were considered mild, had a short duration and most resolved without medical intervention except in one participant in whom the AE resolved after administration of paracetamol. *Pain in extremity* is classified as a very common undesirable effect in the product information of the reference product (Prolia, EPAR – Product Information).

Within SOC *Nervous system Disorder, Headache* was the only PT reported. Most of these events were mild, except for 2 which were assessed as moderate. All were transient, with a short duration and resolved without sequelae.

There was a notable difference in treatment-related TEAEs of Grade ≥3 laboratory abnormality, which were reported for 9 participants (9.1%) in the AVT03 group and 5 participants (4.7%) in the US-Prolia group in the phase 1 study. The most frequently reported study treatment-related Grade ≥3 laboratory abnormality was neutropenia, reported in 7 participants. All reported events of "neutropenia" as well as of "white blood cell count decreased" had no accompanying symptoms, no actions were taken, and events were resolved without interventions. Most of the events were isolated and did not pertain throughout the course of the study.

Vitamin D deficiency was observed in approximately 5% of participants overall, with a higher incidence in the AVT03 group compared to the reference group (7 (7.1%) subjects and 3 (2.8%) subjects in the AVT03 and the reference group, respectively). One of the participants in the AVT03 group had a medical history of Vitamin D deficiency. There were 4 participants with Vitamin D concentration <20 ng/ml at baseline, two in each group. Vitamin D supplementation was administered to all participants according to protocol requirements, so neither medical history nor Vitamin D supplementation can explain potential differences between groups. Most events were mild and only one event was considered moderate in severity. In all except two participants calcium levels were within normal range across all study visits. In those two participants one isolated, transient and slight decrease in serum calcium was reported. However, none of the TEAEs of Vitamin D deficiency had any accompanying clinical manifestations. Overall, it is concurred that the differences described are not considered to be clinically meaningful.

No fatal TEAEs or TEAEs leading to study discontinuation occurred during the phase 1 PK study. Only one serious TEAE occurred in that study, this being an event of drug hypersensitivity of moderate severity in the US-Prolia group. AEs of special interest (AESI) were recorded in approximately 22% of subjects with a similar incidence between groups in the PK study. Injection site reactions were overall low (experienced by <5% of participants) and numerically higher in the US-Prolia group compared to the AVT03 group.

In the Phase 3 efficacy and safety study (Study AVT03-GL-C01), up to Month 12, the numbers of patients with at least one TEAE was comparable between groups (178 (66.9%) in the AVT03 group and 178 (66.9%) in the US-Prolia group), although the number of events was higher in the AVT03 group compared to the reference group (515 and 436, respectively).

The incidence of IP-related TEAEs as well as the incidences of TEAEs leading to discontinuation from study treatment and/or early termination from study, including serious TEAEs, were more frequent in the AVT03 group compared to the reference group. Calcium deficiency (PTs "*Hypocalcaemia"* and "*Adjusted calcium decreased"*) was a driver for the numerically higher incidence of IP related TEAEs in AVT03 treated patients compared to the control with 24 (9.0%) patients and 19 (7.1%) patients having "*Hypocalcaemia"* in the AVT03 and control group, respectively, up to Month 12. During the same period 11 (4.1%) and 3 (1.1%) patients presented with "*Adjusted calcium decreased"* in the AVT03 and control group, respectively. From Month 12 to Month 18/End of Study, 19 IP-related TEAEs in 16 participants [6.6%] were reported in the AVT03 group and 11 related-TEAEs in 9 participants [3.7%] were reported in the Prolia group. The differences were mainly driven by PTs *"Adjusted calcium decreased"* and *"Calcium ionized decreased"*. All these events were mild or moderate and all were asymptomatic, i.e., without any clinical manifestation.

Hypocalcaemia is a known adverse event for denosumab and the safety profile described in the submitted study is aligned with the safety profile described for the reference product. As the study was not designed for statistical comparison of selected adverse events, no firm conclusion can be drawn on the significance of the

observed differences. However, a certain degree of uncertainty remains whether denosumab AVT03 could lead to more cases of hypocalcaemia than the reference product.

Differences unfavourable for AVT03 were also noted in the SOCs Musculoskeletal and connective tissue disorders and Metabolism and nutrition disorders, the latter being driven by vitamin D deficiency, which was 3-times as frequent in the AVT03 group compared to the reference group.

The safety data show that the tendency towards more frequent incidences of vitamin D deficiency and hypocalcaemia in the AVT03 group compared to the reference group that was observed until Month 12 also continued until the end of study. Baseline calcium levels were within required protocol ranges (>8.6 mg/dl and <10.5 mg/dl) for all study participants as well as baseline Vitamin D levels (>20 ng/ml). Vitamin D deficiency as a prior and ongoing medical condition was comparable between groups, therefore this does not offer an explanation. The applicant explained that despite all patients having Vitamin D values >20 ng/ml, a higher percentage of participants in the Prolia group had baseline Vitamin D levels ≥30 ng/ml, which is considered a threshold for a proper calcium balance. Therefore, participants in the AVT03 group, with a lower percentage of participants with Vitamin D levels ≥30ng/ml at baseline, were at higher risk of hypocalcaemia. However, this was not substantiated with detailed data.

Nevertheless, none of the participants had any clinically significant impact of hypocalcaemia on vital signs and ECG results up to Month 12. From Month 12 to EOS, 1 participant reported a clinically significant increase in Systolic Blood pressure, but this participant had a medical history of "Hypertension" since 2006 which was ongoing at study entry. Overall, no clinically significant impact on ECG parameters was reported for any participant.

There were five fatal TEAEs in study AVT03-GL-C01. Four participants died in the AVT03 group and 1 participant in the US-Prolia group. None of the deaths are considered IP-related, thus no concern is raised. Serious TEAEs were reported in <4% of patients overall and were comparable between treatments. None of the serious TEAEs were considered IP-related. Up to Month 12, the incidences of TEAEs of special interest (AESI) were reported in approximately 15% of participants overall and were comparable between group. The most common AESIs were hypocalcaemia, musculoskeletal pain and arthralgia.

Injection site reactions were reported in 11 participants (4.1%) in the AVT03 group and 7 participants (2.6%) in the US-Prolia group, up to Month 12. Most of these events were mild in severity except for one event of moderate grade in the AVT03 group. Considering the overall incidences of injection site reactions reported across both studies to date, no concern is raised.

Immunogenicity

Evaluation of binding (ADA) and neutralizing (nAb) anti-drug antibodies has been carried out over time in both, the phase 1 PK/PD study in healthy subjects and the phase 3 efficacy and safety study in postmenopausal women with osteoporosis.

ADA were observed in almost all individuals in both studies and nAb formation occurred in up to 39.4% and 7.6% of participants in the phase 1 and the phase 3 study, respectively. This is striking, as it is not in line with data established with the originator denosumab. ADA formation has been reported to be present in <1% of subjects in the clinical development programme of Prolia and Xgeva. It is a common phenomenon that more sensitive immunogenicity assays are available during the development of similar biological medicinal products, leading to more frequent detection of ADA as compared to the development of the originator. However, the presence of ADA in up to 100% of subjects and the high incidence of nAb are unexpected. On request, the applicant referred to the highly sensitive test methods for ADA and nAb determination as an

explanation for the high incidence of ADA and nAb positive subjects across both clinical trials. This is acknowledged.

Despite the high immunogenicity response for ADA in the two clinical studies, not all samples were positive across all time points. In both clinical studies, ADA formation progressively increased to similar levels in both groups up to Day 112 and then decreased with comparable rates. So, although the overall immunogenicity response was at 100% the immunogenicity rates were lower at individual sampling days and allowed a comparison of the immunogenicity response between the different treatment groups of AVT03 and Prolia. Furthermore, the results of the ADA titre analysis showed that the antibody levels in studies AVT03-GL-P01 and AVT03-GL-C01 were of low range and confirmed the statement that the ADA assay used in the clinical studies was highly sensitive and able to detect anti-denosumab antibodies at low concentrations, thus explaining the high immunogenicity response.

Importantly, ADA formation as well as ADA titre levels were comparable between treatment groups in both studies. The incidence of nAb was lower in the phase 3 study in PMO patients as compared to the phase 1 study in healthy subjects. Within both studies, comparable incidences were observed between treatments. Furthermore, the key PK parameters in the phase 1 study as well as mean denosumab serum levels in the phase 3 study were comparable between AVT03 and Prolia treatment by ADA and nAb subgroups. Also, the proportion of participants with a TEAE was comparable between nAb positive and nAb negative participants in the phase 1 PK study and there was no evident impact of nAb formation on safety.

Thus, overall, comparable immunogenicity was demonstrated between AVT03 and its reference product.

2.5.10. Conclusions on the clinical safety

Based on the provided data, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the denosumab reference product. Of note, incidences of vitamin D deficiency and hypocalcaemia were overall more frequent in AVT03 treated subjects compared to subjects in the reference group. However, all related TEAEs were mild or moderate and all were asymptomatic, i.e., without any clinical manifestation.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 47: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	Cardiovascular events Malignancy Delay in diagnosis of primary malignancy in giant cell tumour of bone Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.6.3. Risk minimisation measures

Table 48: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.1. PIL sections 2 and 4. Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire. Additional pharmacovigilance activities: None.
Atypical femoral fracture	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	
Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of denosumab treatment are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL sections 2 and 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Cardiovascular events	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	None.	
Malignancy	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 5.1. PIL section 4. Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in SmPC Section 4.4. In order to inform patients of this risk, corresponding text is also present in the PIL section 4. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures: None. Legal status: Restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities:

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	Additional risk minimisation measures: None.	None.
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures: SmPC sections 4.5 and 5.1. PIL section 2. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk minimisation measures: None. Legal status: Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xgeva. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zvogra (Denosumab) is included in the additional monitoring list as it is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Zvogra (AVT03) was developed as a biosimilar product to Xgeva (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation (Xgeva: 120 mg/1.7mL single use vial).

The proposed indications are the same as approved for the reference product Xgeva that is indicated for:

- Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

For this MAA, the applicant intends to claim all of the indications of the reference product.

Quality

The applicant performed a comprehensive analytical biosimilarity exercise. It was shown that EU-Prolia and EU-Xgeva are comparable and therefore data from EU-Prolia and EU-Xgeva can be pooled to establish the EU-reference product quality range for comparative analytical similarity assessment. This was also shown for US-Prolia and US-Xgeva batches. Furthermore, the EU-reference product quality range can be regarded comparable to US-reference product quality ranges, which supports the extrapolation of clinical data generated with US-Prolia to EU-Prolia and EU-Xgeva.

In the head-to-head (H2H) comparative analytical similarity assessments a number of batches of the two presentations (vial and PFS), as well as bridging between Prolia and Xgeva marketed in EU and US were compared. The AVT03 batches used in the analytical biosimilarity exercise have been manufactured according to the clinical or intended commercial process. Overall, the number of lots is expected to reflect variability sufficiently and is deemed acceptable for evaluation of similarity.

For the evaluation of the analytical similarity data, the applicant used a quality range approach (mean RMP ± X SD). The multiplier "X" was assessed and justified for each analytical method. Overall, the applicant appropriately discussed the statistical approach as recommended in the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development.

The relevant quality attributes of the denosumab molecule were assessed using a broad panel of orthogonal state-of-the art analytical techniques that cover primary structure, higher order structure, post-translational modifications, physicochemical attributes, process related impurities, potency and Fc related attributes. Two cell-based assays have been applied to characterise the RANKL related mechanism of action (potency). The osteoclast differentiation assay, directly address the mechanism of action of denosumab, complemented by the validated cell-based reporter gene assay in Saos-2 cells This is complemented by the validated cell-based reporter gene assay in Saos-2 cells that is used for release testing. In addition, RANKL binding is tested by surface plasmon resonance (SPR). The validation or qualification status of all analytical methods are indicated, and short descriptions of characterisation assays provided. Overall, the analytical methods used for the analytical comparability exercise are considered sufficient and are suitable for the intended use.

These complementary studies are adequately designed to support the conclusion drawn.

The totality of analytical data from the main analytical similarity study, the supportive bridging studies, and the comparative forced degradation study demonstrate that AVT03 is highly similar to the RMPs EU-Prolia and EU-Xgeva. The minor differences observed for various physico-chemical attributes are in principle not expected to impact clinical performance of AVT03. Observed difference have been discussed and justified with data to confirm high similarity between biosimilar and reference product. Characterisation data for IgG2 isoforms in AVT03 and reference product has been provided (potency, PTMs, SEC profile).

Clinical aspects

AVT03 is a biosimilar product for Amgen denosumab, intended to be marketed with two different brand names, Kefdensis and Zvogra, similarly to the innovator (EU-Prolia, EU-Xgeva) containing the same active substance,

but with separate indications, strengths and presentations. In the current clinical development, the applicant has used only US-licenced Prolia as a control treatment.

The clinical development program of AVT03 included two clinical studies to demonstrate similarity in PK, PD, efficacy, safety and immunogenicity of AVT03 and the reference product.

Study AVT03-GL-P01 was a double-blind, randomized, 2-arm, single-dose, parallel-group study to demonstrate pharmacokinetic (PK) equivalence and to compare pharmacodynamics (PD), safety, tolerability, and immunogenicity of AVT03 with US-Prolia in healthy male subjects. The study was conducted at multiple investigational sites in New Zealand, Australia and South Africa. Subjects were randomised in a 1:1 ratio to one of the treatments groups and stratified by body weight (≤ 75 kg versus > 75 kg). The study had a duration of up to 40 weeks, including a screening period of up to 4 weeks prior to IP administration on Day 1 and a follow-up until the end of the study visit at day 252. The EOS visit was at Day 252. Overall, the design of study AVT03-GL-P01 is acceptable and is generally in agreement with previous Scientific Advice received from EMA (EMA/SA/0000084481 and EMA/SA/0000061798).

Study AVT03-GL-C01 was a randomized, double-blind, multicentre, 2-arm, multiple-dose, parallel-group, phase III study in postmenopausal women with osteoporosis to compare the efficacy, safety, tolerability, immunogenicity, pharmacodynamics and pharmacokinetics of AVT03 and US-authorized Prolia. The study was conducted in 5 countries (Bulgaria, Czech Republic, Georgia, Poland and Sout Africa). Subjects were randomized in a 1:1 ratio for the main treatment period (52 weeks). In the follow up/transition period (week 52-78) subjects receiving US-Prolia were re-randomized to receive either AVT03 or US-Prolia. The subjects received in total three s.c. doses of AVT03 or US-Prolia on day 1, month 6 and month 12. Overall, the design of study AVT03-GL-C01 is acceptable and is generally in agreement with previous Scientific Advice received from EMA (EMA/SA/0000084481 and EMA/SA/0000061798).

3.2. Results supporting biosimilarity

Quality

For many quality attributes including those related to the MoA analytical similarity between AVT03 and the reference products EU-Prolia and EU-Xgeva was demonstrated. The observed minor analytical differences have been adequately evaluated and justified regarding their impact on clinical performance of the product.

A detailed characterisation of charge variants revealed the presence of similar variants for both AVT03 and EU-Prolia and EU-Xgeva. Additional studies investigating the impact of glycosylation on biological activities show comparable results for both products.

Similar degradation profiles and kinetics were determined for AVT03 and the reference products under thermal, photolytic, low/high pH and oxidative stress further supporting biosimilarity.

Clinical

PK/PD

Study AVT03-GL-P01

Biosimilarity in PK of AVT03 and US-Prolia was shown in healthy male subjects.

The mean serum denosumab PK parameters in the AVT03 group were comparable with those in the Prolia group. The geometric mean Cmax value in the AVT03 group (7382.1 ng/mL) was comparable to that in the

Prolia group (6513.4 ng/mL). The geometric mean AUC values in the AVT03 group (AUC0-inf: 7637731.8 h·ng/mL; AUC0-last: 7559695.8 h·ng/mL) were also comparable to those in the Prolia group (AUC0-inf: 6578675.2 h·ng/mL; AUC0-last: 6465342.9 h·ng/mL). The median Tmax was around 168 hours in both the treatment groups, with values ranging from 48 to 602.42 hours in the AVT03 group and from 47.90 to 1677.70 hours in the Prolia group. There was no significant difference in the time to attain maximum serum concentrations of denosumab (Tmax) between the treatment groups. The means of the secondary PK parameters (i.e., $t_{1/2}$, Vz/F, CL/F, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}24}$) were comparable between the treatments supporting the PK similarity.

The ratio (AVT03/US-Prolia) of the geometric LS mean for C_{max} was 107.79% with the corresponding 90% CI being (102.231% and 113.642%). The ratio of the geometric mean for $AUC_{0\text{-inf}}$ was 112.87% with the 90% CI being (107.169% and 118.874%). The ratio of the geometric mean for $AUC_{0\text{-last}}$ was 113.89% with the corresponding 90% CI being (107.719% and 120.416%). Thus, all primary PK endpoints were met as all results were within the pre-defined equivalence margin of (0.80% and 1.25%).

The mean denosumab serum concentration time-profiles within the PK-analysis set were overall comparable between AVT03 and US-Prolia groups.

The evidence for the PD equivalence stems from study AVT03-GL-C01, while the PD results in study AVT03-GL-P01 are considered in support of these primary results. Overall, the secondary PD endpoint from study AVT03-GL-P01, AUEC over the study period of s-CTX were comparable between AVT03 and US-Prolia.

The median percent change from baseline of s-CTX at each study visit showed practically overlapping curves for the s-CTX parameter throughout the treatment period.

Study AVT03-GL-C01

The PK endpoint Serum trough concentration of AVT03 and Prolia was assessed as PK endpoint in the target population. The mean serum concentrations increased to a similar extent, peaking around Day 12. The two concentration curves then decreased in parallel by Day 180 (Month 6). By Day 180, prior to second study drug administration, the geometric mean (GEO CV%) trough concentration was 10.52 ng/mL (599.4%) in the AVT03 group and 7.46 ng/mL (401.2%) in the Prolia group. The geometric mean (GEO CV%) trough concentrations at Month 12 prior to the third dose, were 10.23 ng/mL (642.3%) in the AVT03 group and 7.09 ng/mL (392.9%) in the Prolia group. From Month 12 to Month 18, the serum concentrations of AVT03 and Prolia decreased to levels similar to those observed at Month 12 before study drug administration.

In summary, the mean serum trough concentrations prior to Month 6 and Month 12 dosing were almost comparable between the treatment groups supporting biosimilarity supporting pharmacokinetic similarity of the test and reference product.

Biosimilarity in pharmacodynamics was also demonstrated in osteoporosis patients in study AVT03-GL-C01. The co-primary PD endpoint "$AUEC_{0\text{-}6months}$ of serum CTX" was met. The point estimate of the geometric LS means ratio (AVT03/US-Prolia) for AUEC was 1.016 with the corresponding 95% CI being (0.97; 1.03). Thus, the 95% CI was within the pre-specified and accepted equivalence range of [0.89, 1.12].

Efficacy

Study AVT03-GL-C01

The biosimilarity of AVT03 and US-Prolia in terms of efficacy was demonstrated in osteoporosis patients. The percent change from baseline in LS-BMD at Week 52 was the co-primary efficacy endpoint in this study. The statistical analysis on the hypothetical estimand revealed that the difference between the AVT03 and the US-

Prolia group was 0.356% with the corresponding 95% CI being 0.58% and 0.82%. Thus, the 95% CI was within the pre-specified and accepted equivalence range of [-1.45%, 1.45%] and the co-primary efficacy endpoint was met.

Similarity in efficacy was further supported by the secondary efficacy endpoints. The percent change from baseline in bone mineral density at femoral neck at Month 6, 12 and 18 was comparable between the groups. Similarly, the percent change from baseline in bone mineral density at total femoral neck at Month 6, 12 and 18 was also comparable between the groups. Additionally, the incidence of new morphometric vertebral fractures at month 12 and month 18 was comparable between the treatment groups.

Safety

The overall design of the clinical studies is considered adequate for a comprehensive safety assessment of AVT03. The size of the safety database, the posology and treatment duration are considered appropriate. Study completion rates and baseline characteristics were overall comparable between groups in each of the studies, as were medical history and concurrent illnesses.

Based on the provided data, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the denosumab reference product.

3.3. Uncertainties and limitations about biosimilarity

Quality

Compared to EU- and US-Prolia and Xgeva, AVT03 contains different levels of A and A/B isoforms and thus a lower level of B disulfide isoform. It was shown that disulfide isoform distribution seems to have a minimal effect on biological activity. The applicant notes that IgG2 disulfide isoforms interconvert to the B isoform in vitro and in vivo and therefore differences in this quality attribute have little to no effect on safety or efficacy. Overall, considering the extent or location of the modifications, and the MoA of denosumab an impact on clinical performance in the targeted indications is not expected.

Clinical

PK/PD

In study AVT-03-P01 in some of the PK profiles, a sudden drop in concentration at a single evaluation time point followed by recovery to previous concentration levels at the subsequent evaluation time point was observed. The applicant performed a systematic and thorough root cause analysis regarding the validity of the PK concentration read outs. 19 individual PK samples have been identified as outliers. However, no root cause could be determined. In order to understand the impact of the identified implausible datapoints sensitivity analyses have been performed.

For the majority of cases this issue occurred in the absorption phase at early time points around Cmax. While these cases – potentially resulting from intercurrent events of unknown origin – occurred with comparable frequency in both treatment arms, such is not considered reassuring to result in robust and conservative conclusions in general, as such patterns contribute to arms looking more similar than they actually are. Nevertheless, in the present application these cases occurred with a sufficiently low frequency such that given the otherwise clear results, this anticonservative behaviour of the strategy did not relevantly manifest in the data, such that a conclusion of equivalent PK between the two treatment arms is possible. In these, the way of handling the unexpected PK profiles and minimal impact on the comparison of AVT03 vs Prolia. Despite the lack of a root cause for the PK phenomenon, there is no impact of the implausible datapoints on

the overall conclusion of PK similarity. The sensitivity analyses support a conclusion on PK equivalence between AVT03 and Prolia.

Safety and Immunogenicity

In the phase 1 PK trial (Study AVT03-GL-P01), the numbers for IP-related TEAEs were higher in the AVT03 group compared to the reference group. This was mainly driven by events falling under the SOC of *Musculoskeletal and Connective tissue Disorders,* which conforms to the safety profile of the reference product. Further, vitamin D deficiency was observed in approximately 5% of participants overall, with a higher incidence in the AVT03 group compared to the reference group. Overall, the differences described are not considered to be clinically meaningful.

In the Phase 3 efficacy and safety study (Study AVT03-GL-C01), numerical differences unfavourable for AVT03 were noted in TEAEs related to *Metabolism and nutrition disorders*, including vitamin D deficiency and hypocalcaemia/decreased calcium. As pointed out by the applicant, hypocalcaemia is a well-known adverse event for denosumab and the safety profile described in this study is aligned with the safety profile described for the reference product. As the study was not designed for in depth comparison of selected adverse events, no firm conclusion can be drawn on the significance of the observed differences. However, a certain degree of uncertainty remains whether denosumab AVT03 could lead to more cases of hypocalcaemia/calcium decrease than the reference product.

3.4. Discussion on biosimilarity

Quality

At the quality level similarity between AVT03 and EU-Prolia and EU-Xgeva could be demonstrated for many quality attributes in a comprehensive analytical similarity exercise. In particular, two cell based assays directly or indirectly reflecting the mechanism of action of denosumab were demonstrated being highly similar between both products alongside the RANKL binding assay. The observed analytical differences have been adequately evaluated and are not expected to impact clinical performance of the product in the targeted indications. Observed difference have been discussed and justified with data to confirm high similarity between biosimilar and reference product. Characterisation data for IgG2 isoforms in AVT03 and reference product has been provided (potency, PTMs, SEC profile).

Clinical

In *study AVT03-GL-P01* conducted in healthy male volunteers, PK similarity was formally demonstrated between AVT03 and US-Prolia as the 90% CIs for the GLSM of the ratio test/reference for the primary PK parameters (AUC0-inf, AUC0-last, and Cmax) were fully contained within the predefined bioequivalence limits of [80.00% to 125.00%]. Furthermore, no notable treatment differences were observed in the secondary PK parameters tmax, t1/2, Vz/F, CL/F, AUC_{0-24} and AUC_{0-last}.

All individual concentration PK curves were provided by the applicant. In some of the PK profiles, a sudden drop in concentration at a single evaluation time point followed by recovery to previous concentration levels at the subsequent evaluation time point was observed. For the majority of cases, this issue occurred in the absorption phase at early time points around Cmax. While these cases – potentially resulting from intercurrent events of unknown origin - occurred with comparable frequency in both treatment arms, such is not considered reassuring to result in robust and conservative conclusions in general, as such patterns contribute to arms looking more similar than they actually are. Nevertheless, in the present application these

cases occurred with a sufficiently low frequency such that given the otherwise clear results, this anticonservative behaviour of the strategy did not relevantly manifest in the data, such that a conclusion of equivalent PK between the two treatment arms is possible.

The applicant performed a systematic and thorough root cause analysis regarding the validity of the PK concentration read outs. 19 individual PK samples have been identified as outliers. However, no root cause could be determined. In order to understand the impact of the identified implausible datapoints sensitivity analyses has been performed. In these analyses, the way of handling these unexpected PK profiled had minimal impact on PK similarity. Despite the lack of a root cause for the PK phenomenon, there is no impact of the implausible datapoints on the overall PK similarity conclusion. Therefore, these sensitivity analyses support a conclusion on PK equivalence between AVT03 and Prolia.

PK data from *study AVT03-GL-C01* conducted in female osteoporosis patients further support PK similarity of the test and reference product. The mean denosumab concentration-time profiles for the whole study period were similar for the treatment groups. The exposure was overall similar between the treatment groups, supporting the PK similarity of the test and reference product in the osteoporosis patients.

PD similarity is supported by both clinical studies and is specifically demonstrated in study *AVT03-GL-C01*. In *study AVT03-GL-C01*, biosimilarity in pharmacodynamics was demonstrated in female osteoporosis patients. The co-primary PD endpoint "AUEC(0-6months) of serum CTX" was met as the geometric LS means ratio (AVT03/US-Prolia) for AUEC with the corresponding 95% CI was within the pre-specified and accepted acceptance range of 0.97 to 1.03.

Similarity regarding efficacy was shown in *study AVT03-GL-C01*. The co-primary efficacy analysis on the percent change from baseline in LS-BMD at Week 52 was met, as the difference between the AVT03 and the US-Prolia group with the corresponding 95% CI was within the pre-specified and accepted acceptance range [-1.45%, 1.45%]. The statistical analysis on the hypothetical estimand revealed that the difference between the AVT03 and the US-Prolia group was 0.356% with the corresponding 95% CI being 0.58% and 0.82%. Efficacy analyses of the bone mineral density at femoral neck and total hip at month 6 month 12 and month 18 further support the similarity in efficacy between the test and reference product.

Regarding safety evaluation, incidences of vitamin D deficiency and hypocalcaemia/calcium decrease were overall more frequent in AVT03 treated subjects compared to subjects in the reference group. However, all related TEAEs were mild or moderate and without any clinical manifestation. Based on the provided data, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the denosumab reference product.

3.5. Extrapolation of safety and efficacy

AVT03 was developed as a biosimilar product to Prolia/Xgeva. The mechanism of action is identical to the reference products. The monoclonal antibody denosumab targets and binds to RANKL, thus preventing interaction of RANKL with RANK. Block of interaction of RANKL with RANK leads to reduced osteoclast formation and function. Thus, bone resorption and cancer induced bone destruction is decreased.

The mechanism of action is identical across all indications, i.e. binding to RANKL and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalized bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Thus, based on the same mechanism of action, extrapolation to all indications might be allowed.

The extrapolation is further supported by the fact that the known PK, safety and immunogenicity profile of denosumab as summarized in the product information for Prolia/Xgeva is comparable across the approved indications and patient populations.

Furthermore, the clinical data were derived from healthy male volunteers and female osteoporosis patients. These are regarded sensitive populations in terms of evaluating biosimilarity of AVT03 and the reference product.

Based on the above, the safety and efficacy profile of AVT03 as assessed in the PMO indication can be extrapolated to all indications applied for Zvogra.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Zvogra is considered biosimilar to Xgeva. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zvogra is favourable in the following indication(s):

> Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).
>
> Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The CHMP therefore recommends the granting of the marketing authorisation to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.