18 September 2025
EMA/323111/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Degevma

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006239/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

$\%AUC_{ext}$	percentage extrapolated area under the concentration-time curve
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}/AUC_{0\text{-}\infty}$	area under the serum concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	area under the serum concentration-time curve from time 0 to the time of the last measurable drug concentration
$AUC_{0\text{-}tau}$	area under the curve over the dosing period
AUEC	area under the effect curve
BMD	bone mineral density
%cfb	Percent change from baseline
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed serum drug concentration
CPK	creatine phosphokinase
CSR	clinical study report
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	end of study
IgG2	immunoglobulin G2
IMP	investigational medicinal product
LS	least square
LS-BMD	lumbar spine-bone mineral density
mAb	monoclonal antibody
mITT	modified intent-to-treat
P1NP	procollagen type 1 N propeptide
PD	Pharmacodynamic
PFS	prefilled syringe
PK	Pharmacokinetic
RANK	receptor activator of nuclear factor kappa-B
RANKL	receptor activator of nuclear factor kappa-B ligand
SAE	serious adverse events
sc/s.c.	Subcutaneous
sCTX-1	serum C-telopeptide cross-link of type 1 collagen
SD	standard deviation
SmPC	Summary of Product Characteristic

$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed drug concentration
uNTx	urinary N-telopeptide
uNTx/Cr	urinary N-telopeptide corrected for urine creatinine levels
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization
V_Z/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TEVA GmbH submitted on 8 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Degevma, 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.
>
> 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 product.

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 Ponlimsi 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**
28 March 2019	EMEA/H/SA/4069/1/2019/III	Elina Rönnemaa, Kirstine Moll Harboe
30 April 2020	EMEA/H/SA/4069/1/FU/1/2020/II	Juha Kolehmainen, Andrea Laslop
22 April 2021	EMA/SA/0000054656	Andrea Laslop, Kolbeinn Gudmundsson
21 July 2022	EMA/SA/0000089383	Andrea Laslop, Elena Wolff-Holz

The Scientific advice pertained to the following *quality, non-clinical, and clinica*l aspects:

The strategy with regards to the comparability assessment, the suitability of non-clinical study to support the safety evaluation and the demonstration of biosimilarity, the design of the supporting clinical studies and the extrapolation of the study results to all authorised indications of the reference product, and the development of the drug substance and drug product manufacturing process.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Daniela Philadelphy Co-Rapporteur: Frantisek Drafi

The application was received by the EMA on	8 November 2024
The procedure started on	28 November 2024
The CHMP Rapporteur's first Assessment Report was circulated to all	17 February 2025

CHMP and PRAC members on	
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 March 2025
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	13 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 March 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 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	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 July 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2025
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	1 September 2025
The CHMP Rapporteurs circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 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 Degevma on	18 September 2025

2. Scientific discussion

2.1. About the product

TVB-009 (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.

TVB-009 has been developed in 2 forms (TVB-009P and TVB-009X) as a proposed biosimilar candidate to denosumab (trade names Prolia and Xgeva, respectively) in the below 2 configurations:

1. TVB-009P: A single-use prefilled syringe (PFS) with integrated needle safety device (Prolia biosimilar).

2. TVB-009X: A single-use vial (Xgeva biosimilar).

Prolia and Xgeva contain denosumab as active pharmaceutical ingredient but have been authorized for different indications, and consequently they differ in terms of target patient populations, as well as dose and frequency of administration.

In this MAA, the second product (biosimilar of Xgeva) is applied for.

Degevma (TVB-009-X) contains the same amount and concentration of drug substance as the reference medicinal product, Xgeva, and is supplied in a single-dose vial of a 120 mg/1.7mL.

2.2. Type of Application and aspects on development

During the development of denosumab (TVB-009), the applicant sought Scientific advice was obtained from the EMA Scientific Advice Working Party (SAWP) on four occasions. Questions on quality, non-clinical and clinical development were discussed. Most of the advice given in the quality section was considered by the applicant. Details of the clinicals studies were discussed and the advice was followed by the applicant.

2.3. Quality aspects

2.3.1. Introduction

The finished product was developed as a biosimilar to the EU reference medicinal product Xgeva.

The finished product is presented as a solution for injection containing 120 mg of denosumab as active substance.

Other ingredients are: sodium acetate trihydrate; acetic acid, glacial; sorbitol; polysorbate 20; and water for injections.

The product is available in 1.7 mL single use type I glass vials for subcutaneous administration.

2.3.2. Active substance

2.3.2.1. General information

The active substance (AS) denosumab is a fully human IgG2/kappa monoclonal antibody.

The active substance denosumab is comprised of two identical light chains and two identical heavy chains and has a global molecular weight of 147 kDa. Each light chain consists of 215 amino acid residues with a theoretical molecular weight of 23.487 kDa. Each heavy chain contains 448 residues with a theoretical, deglycosylated molecular weight of 48.890 kDa, including the C-terminal lysine. There is a total of 36 cysteine residues in the molecule that form disulfide bonds. The active substance denosumab is a glycosylated molecule containing N-linked oligosaccharide structures on Asn298 of each heavy chain. There is no evidence of O-linked glycosylation.

1Denosumab binds with a high degree of specificity and affinity to RANKL. Denosumab inhibits RANKL binding to RANK, thus preventing the maturation and stimulation of osteoclasts, resulting in reduction of excessive osteoclast-driven bone removal.

2.3.2.2. Manufacture, process controls and characterisation

The biological active substance denosumab is manufactured at Teva Biotech GmbH, Dornierstrasse 10, Donautal, Ulm, Baden-Wuerttemberg, 89079, Germany. Satisfactory proof of GMP compliance and a QP declaration were provided covering manufacturing activities of the active substance and of the cell banks.

Description of manufacturing process and process controls

The denosumab active substance is produced using a CHO cell line. The denosumab active substance manufacturing process has been adequately described and consists of a standard fed-batch process comprised of upstream processing steps followed by a downstream process.

The main steps of the upstream process are vial thaw, inoculum expansion, seed expansion, production, and harvest and clarification. The main steps of the downstream process that follows are protein A affinity chromatography, low pH viral inactivation and depth filtration, anion exchange chromatography, cation exchange chromatography, virus reduction filtration, ultrafiltration/diafiltration, excipient addition, final filtration and filling.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step.

The active substance manufacturing process is considered acceptable.
234
The batch scale was defined for the denosumab active substance. The batch numbering system was described. A unique number consisting of letters and numbers is automatically assigned and traceability is maintained throughout manufacture by an electronic inventory system.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. All raw materials, single-use materials, filters and filter assemblies, cell culture media and solutions, and chromatography resins are listed. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. In particular, specifications are in place for the cell culture media and solutions as well as for the chromatography resins. The applicant confirms that an agreement is in

place with the supplier to notify the applicant in case of changes to these media components. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin.

The denosumab active substance is expressed in the cell line CHO. The host cell line and its origin has been described. The host cell line was confirmed to be free from contamination by mycoplasmas, bacteria, molds, yeasts and to be free from viral contamination. The species of the cell line was confirmed to be of Chinese hamster origin. The construction of the expression vector was described.

5A two-tiered cell banking system is used, and sufficient information is provided regarding preparation, testing, and stability of MCB and WCB and release of future WCBs. Sustainable, viable cultures were obtained from the MCB, and the species of the cell line was confirmed to be of CHO origin. The MCB was confirmed to be free from contamination by mycoplasma, bacteria, moulds, yeasts and adventitious agents. Both cell banks remain stable showing no decreases in viability at thaw and total cells. Long-term stability of the cell banks will be monitored. Future working cell banks will be generated from the current master cell bank once the current working cell bank expires. A qualification protocol was included for the WCB. A revised qualification protocol will be submitted if changes to the specifications are proposed. Minor changes foreseen during the manufacturing and qualification of future working cell banks have been listed and are considered very low risk of impacting cell bank performance or product quality. The limit of in vitro cell age (LIVCA) was investigated.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the denosumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regards to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The denosumab active substance manufacturing process has been validated adequately. Consistency in production has been shown on consecutive full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces denosumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Hold times for process intermediates have been adequately validated under consideration of physicochemical stability and microbial control in small-scale studies and were confirmed at scale.

Impurity clearance studies have been conducted and the results presented.

The shipping process of AS from the AS manufacturing site to the finished product (FP) manufacturers has been adequately qualified. In summary, a profound process validation has been performed and despite the deviations observed it can be concluded that the active substance manufacturing process is capable of consistently producing an active substance of the intended quality.

Manufacturing process development

The manufacturing process development has been described in section 3.2.S.2.6. Critical quality attributes were elucidated based on a risk assessment performed for each identified product quality attribute. The risk classification with determined by 2 factors: impact and uncertainty (or certainty) of that impact. The impact ranking of an attribute was assessed for known or potential consequences on efficacy, pharmacokinetics (PK)/pharmacodynamics (PD), immunogenicity, and safety. The conducted

process characterisation studies have been summarised and include risk assessments on and selection of process parameters and raw materials for characterisation in specific step/stage, the development and qualification of scale-down model for specific process steps/stages, experimental studies on selected process parameters to determine their criticality; to define acceptable ranges for process parameters; and to establish the in-process controls /critical in-process controls based on impact on the outcome of the specific step/stage, worst-case/linkage studies to verify if the acceptance ranges for process parameters and in-process controls are suitable for successive steps in the upstream process, and establishment of process parameter criticality, process parameter acceptance ranges and normal operating ranges (NORs), and in-process controls /critical in-process controls for each specific step/stage. In conclusion the provided process characterisation is acceptable and indicates that the applicant has profound knowledge on the manufacturing process.

Based on product characterisation, process development and process characterisation, impurity clearance studies, stability testing, and scale-up and manufacturing scale experience an integrated control strategy of each critical quality attribute as well as a process control points summary is presented.

In addition, the history of the analytical methods is presented.

The development of the denosumab manufacturing process has been extensively described. Different processes were used throughout development. A summary of the active substance manufacturing history is provided. Apart from the scale up and the transfer of process, the changes are minor and mainly associated with the scale up/facility change or are aiming to improve the process control. In addition, the use of active substance batches manufactured during the development has been indicated. In the first comparability evaluation an in-depth characterisation of relevant physicochemical and biological quality attributes has been presented. In the second comparability evaluation, physicochemical and biological methods were employed to assess product quality attributes with a focus on primary structure, molecular mass, secondary/higher order structure, post-translational modifications (PTM) & heterogeneity, biological activity, and purity & impurities. In addition, release data, in-process data, and finally available stability data under recommended, accelerated, and stressed conditions have been compared. The results of the comparability analyses in section S.2.6 are not considered complete (as not all relevant batches were considered). However, based on the release test results and stability test results provided in the dossier, as well as on the biosimilarity testing results, it can be concluded that the active substance batches from the different active substance process variants can be considered comparable.

Characterisation

The denosumab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG2-type antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterisation of denosumab indicates that this antibody has the ability to bind RANKL with high affinity and to specifically bind to Fc Receptor as expected of an IgG2. In summary, the characterisation is considered appropriate for this type of molecule.

Elucidation of structure and other characteristics

The amino acid sequence was experimentally confirmed with 100% sequence coverage. Biological activity was assessed by adequate potency assay. In conclusion, the provided information is in line with the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 and considered sufficient.

Impurities

Discussion on the potential impurities of the denosumab active substance has been provided. Product-related impurities include size-variants, deamidated and oxidised species and sequence variants. Possible degradation pathways were analysed by applying various stress conditions. All product-related impurities are routinely controlled by in-process tests and release/shelf-life testing to assure consistency in the active substance manufacturing.

Clearance of process-related impurities to acceptable levels was demonstrated.

A nitrosamine risk assessment concluding that there is no risk for nitrosamines contamination originating from the active substance manufacturing process was presented and accepted.

2.3.2.3. Specification

The specification of the denosumab active substance has been adequately justified and includes tests for: Appearance (Ph. Eur.); protein concentration; pH (Ph. Eur.); Osmolality (Ph. Eur.); Identity; Purity size heterogeneity ; Purity charge heterogeneity; Potency; Residual DNA ; Residual Protein A ; Endotoxin (Ph. Eur.); Bioburden (Ph. Eur.); Mycoplasma (Ph. Eur.); In vitro virus test.

The specifications at release cover relevant quality attributes including testing for identity, purity and product-related impurities. The amount of bacterial endotoxin is determined by using the kinetic chromogenic method according to Ph. Eur. 2.6.14, "Bacterial Endotoxins Test" whereas bioburden whereas bioburden is conducted using the membrane filtration method in compliance with Ph. Eur. 2.6.12, Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests. General attributes include appearance - degree of coloration and clarity & degree of opalescence by compendial methods (Ph. Eur. 2.2.2 and 2.2.1), pH according to Ph. Eur. 2.2.3, osmolality according to Ph. Eur. 2.2.35 and protein concentration. It is agreed that relevant structural and functional quality attributes are covered by a panel of state-of the-art and partly orthogonal analytical methods which forms a good basis for the specification testing of a denosumab. A subset of the release assays is also used for stability testing.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Standard methods are conducted according to Ph. Eur. For non-compendial methods, an overview of the method, reagents and equipment, sample preparations, procedure, representative chromatograms, system and sample suitability criteria, and the way of reporting results are included. The analytical methods are adequate for their intended purpose and the implemented system suitability tests, and sample acceptance criteria are suitable to provide adequate control over analytical method performance.

Batch analysis

Batch analysis data on sufficient active substance batches that have been manufactured at the commercial scale were provided. The results are within the specifications and confirm consistency of the manufacturing process.

These batch release data have been used to justify the specification acceptance limits. The strategy for setting acceptance criteria is noted; nevertheless, an important aspect namely clinical justification has not been considered for establishment of the specification acceptance limits. Acceptance criteria should be set in accordance with ICH Q6B, primarily justified from a safety and efficacy point of view, and should also properly reflect the commercial process. Therefore, characterisation results of the

reference product (as obtained by the applicant using their own qualified/validated test methods intended for the proposed biosimilar) may be used for clinical justification of the specification limits of the proposed biosimilar. Result ranges obtained for marketed reference product batches can be assumed to represent a clinically qualified range for the respective quality parameters. Purity specifications have been revised to clinically justified levels.

Reference materials

The applicant has described its reference standards used throughout the development of denosumab. Different classes of reference standards including Interim Reference Standard, Primary Reference Standard, and Working Reference Standard were defined. A two-tiered system with primary and working reference standards has been implemented.

The qualification of future reference standards has been briefly described: A new WRS will be qualified against the current PRS. If a new PRS is required, it will be qualified against the current PRS. Test panel for qualification include stability-indicating methods and extended characterisation methods.

Container closure system

A brief description of the container closure system in use for long-term storage of the active substance has been submitted. A gamma-irradiated 5 L Bottle, with a screw cap is the container closure system for active substance storage. Since no materials of animal origin are used for the product contact materials of the container closure system, the TSE/BSE risk is considered highly unlikely.

Specifications are included and compatibility has been demonstrated. An evaluation of potential leachable components of the active container has been performed. Container closure integrity has been tested and found to be acceptable. The closure container integrity study results confirm that the integrity of the test samples is considered intact, and no leakage has been observed.

2.3.2.4. Stability

Real time, real condition stability data on commercial scale batches of denosumab active substance from the commercial manufacturing process stored in the intended container under long term, and accelerated conditions according to the ICH guidelines were provided.

The recommended storage temperature for the denosumab active substance is -40±10°C. All results obtained at the long-term recommended storage condition were within the specification limits. No trends were observed that could negatively impact the proposed active substance shelf life.

Overall, the active substance is stable and not susceptible to degradation under the recommended storage conditions. Finally, the post-authorisation stability commitment of the applicant in section 3.2.S.7.2 is noted. A forced degradation study was performed to elucidate possible routes of degradation. Two photostability studies were conducted to evaluate the TVB-009 active substance stability upon light exposure in different contexts. Test results from the ICH photostability study, together with the forced degradation study, demonstrate that under worst case conditions, general sensitivity to light is observed, which is expected. Hence during manufacturing and storage appropriate precautions are taken to minimise exposure of the active substance to light.

In conclusion, the proposed shelf-life for the denosumab active substance when stored at -40±10°C in the proposed container is well justified.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and pharmaceutical development

The finished product was developed as a biosimilar to Xgeva.

Denosumab finished product is a 1.7 mL solution for injection containing 120 mg of denosumab that is administered subcutaneously. Denosumab finished product is a sterile, preservative-free, clear to opalescent, colourless to pale yellow aqueous solution supplied in an ISO 2R type I glass vial with serum stopper and aluminium crimp cap.

The qualitative composition for denosumab finished product is the same as the active substance but is diluted with formulation buffer (Sodium acetate trihydrate, Glacial acetic acid, Sorbitol and Polysorbate 20) to achieve the target concentration of 70 mg/mL required to deliver a dose of 120 mg/1.7 mL of denosumab per injection. 1All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There is no novel excipients used in the finished product formulation.

The chosen formulation is sufficiently supported by formulation development. The robustness of the denosumab finished product formulation in its final container closure system (glass vial) was evaluated Compatibility of the finished product formulation with the container closure components was evaluated through stability studies.

The development history from Phase 1 to commercial manufacturing phase of the finished product are presented.

The primary packaging is a 1.7 mL solution in a single use vial (type I glass) with stopper (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Extractables and leachable studies have been performed.

2.3.3.2. Manufacture of the product and process controls

The finished product manufacturing sites and their respective responsibilities are appropriately listed in the dossier. Merckle GmbH, Ulm, Germany, is responsible for batch release. Valid GMP certificates were presented for all sites as a proof of EU-GMP compliance.

Description of manufacturing process and process controls

The finished product solution is formulated by diluting the active substance that has a higher concentration of denosumab using the same formulation buffer solution to meet the target finished product protein concentration of 70 mg/mL.

The denosumab vials are manufactured according to a standard process including the following steps: Thawing of bulk active drug substance (BDS), pooling and mixing of BDS, preparation of denosumab formulation buffer, clarifying filtration of formulation buffer, dilution and mixing of bulk finished product, bioburden reduction filtration, inulin sterile filtration, aseptic filling, 100% visual inspection.

6The operational parameters and the acceptable range (AR) and normal operating range (NOR) for the different manufacturing steps are provided.

The manufacturing process is appropriately described, and process parameters are sufficiently justified based on process characterisation and validation data. Acceptance criteria for process parameters and controls are provided.

No reprocessing is claimed and hence, not allowed. The proposed hold times are sufficiently justified. For identification and traceability of the denosumab vial batches a unique batch number system is necessary. This batch numbering system was provided.2

Control of critical steps and intermediates

The process controls include process inputs (parameters) and process outputs (in-process controls, IPCs) related to finished product manufacturing to ensure that critical quality attributes (CQAs) are controlled and acceptance criteria are met. The classification for each input and output is based upon an assessment of the potential impact on the finished product CQA, as well as the manufacturing process performance.

The control strategy ensures consistent control and monitoring of the finished product. Any deviation to the control strategy will be thoroughly investigated.

A summary of critical steps and corresponding critical process parameters (CPPs) and critical in-process controls (CIPCs) are presented for the manufacturing process of the denosumab vial finished product.

The process controls are adequate, and their respective criticality and limits are sufficiently supported by risk assessments, process characterisation and validation data.

Process validation

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.

The validation of the denosumab finished product commercial manufacturing process was executed. Three consecutive denosumab vial batches were used for the validation of the manufacturing process and all batches met the prospective acceptance criteria and in-process controls, and pre-defined specifications. The minimum and maximum batch sizes are supported by the validation process.

Hold times were validated for each step of the commercial manufacturing process. The denosumab finished product is rendered sterile during the aseptic fill-finish process. In summary, filter validation studies suitability of the sterile filter has been sufficiently demonstrated.

Autoclave validations and media fill qualifications were provided.

The validation summaries for the equipment used to depyrogenate and sterilise the vials are provided.

A shipping validation was performed. Points discussed in former Scientific Advice on the shipping validation are fulfilled.

2.3.3.3. Product specification

The specifications of the finished product are adequate and include tests for: **Appearance** (coloration, clarity, **visible particles**) (Ph. Eur.); protein concentration; pH (Ph. Eur.); **Polysorbate 20 content**; Osmolality (Ph. Eur.); Identity; Purity size heterogeneity; Purity charge heterogeneity; Potency; **Extractable volume** (Ph. Eur.); Endotoxin (Ph. Eur.); **Sterility** (Ph. Eur.); **Sub-visible particles** (Ph. Eur.); **Container closure integrity**. The majority of methods are used to control both the active substance and finished product, except for those in bold that are only tested on the finished product:

appearance (visible particles), polysorbate 20 content, extractable volume, sterility, sub-visible particles, and container closure integrity. Residual DNA, residual protein A, bioburden, mycoplasma, and in vitro virus test are not tested on the finished product.

Specifications were defined in line with ICH Q6B guidance, and Ph. Eur. monograph "Monoclonal Antibodies for Human Use" #2031. The quality of the finished product is not expected to change substantially when stored at the recommended storage condition (2-8°C). Therefore, the acceptance criteria at the end of shelf life for the denosumab vials were set identical to the corresponding release acceptance criteria.

The Ph. Eur. compendial method appearance, pH, osmolality, extractable volume, endotoxin, sterility, have been used at release and stability. Container closure integrity testing is only performed on stability. Sterility is testing in line with Ph. Eur. 2.6.1.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Analytical methods for the finished product release and stability testing are listed. Analytical methods were validated, and adequate method transfer reports were provided.

The validation of the analytical methods specific for the finished product are adequate and in accordance with ICH Q2(R2) and demonstrate the suitability of the analytical procedures for their intended use.

Batch analysis

Batch analysis data from 16 denosumab finished product were provided. All lots met their respective specifications at the time of release. The provided batch data confirm the finished product manufacturing process consistency and the compliance with the finished product specifications.

Impurities

The process-related impurities and product-related impurities and substances in the denosumab finished product are the same as those in the active substance. No new process equipment related leachable were found to be of any safety concern for the finished product.

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. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

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.

Reference materials

The same reference standards as the denosumab active substance are used for testing the finished product.

Container closure system

The finished product container has been described in detail. The commercial finished product container closure system consists of the following: ISO 2R vial (Type I glass), bromobutyl rubber stopper, and aluminium crimp seal with plastic flip-off cap. Secondary packaging for the denosumab vial finished product is a paperboard carton with insert. Vials are sterilised and depyrogenated. Rubber stoppers and aluminium seals are sterilised by the suppliers.

Extractables and leachable studies have been performed, and no compounds of safety concern have been identified.

2.3.3.4. Stability of the product

Real time/real condition stability data of development and clinical, pre-PPQ, and PPQ commercial batches of finished product for up to 36 months under long-term conditions 5°C ± 3°C and for up to 12 months under accelerated conditions at 25°C/60%RH according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Sufficient pharmaceutical/formulation development data to demonstrate that polysorbate levels remain stable over the proposed shelf life of the finished product was submitted by the applicant. Results on all batches stored under long-term conditions showed no significant trend. All results under long-term and accelerated conditions remained within the set acceptance criteria.

Stressed stability data were obtained for up to 6 months at 40°C/75%RH.Finished product vials were tested after 3 freeze-thaw cycles. All quality attributes met the acceptance criteria for the finished product.

A photostability study was performed on denosumab vials in line with ICH Q1B. Test results show light-induced degradation of unprotected vials, and that the secondary packaging is fully protective of degradation from the ICH recommended light exposures. The ICH photostability study together with the manufacturing photostability study support the storage instruction to protect from light and that the secondary packaging sufficiently protects denosumab vials finished product from light exposure.

A stability study was performed to evaluate the impact of potential exposure of denosumab vial finished product to extreme temperatures during patient use remained within the set acceptance criteria. The results from both arms met acceptance criteria with no impactful quality differences observed compared to the 36-month long-term stability data. Therefore, this data supports temperature excursions up to 32 days at 30°C/65%RH.

A temperature excursion study was performed to evaluate the impact of potential exposure of denosumab vial finished product to extreme temperatures during storage and shipping. Results support temperature excursion up to 32 days at 30°C/65%RH showing no substantial differences when compared to long-term stability data.

In addition, a statistical analysis of certain quantitative quality attributes has been performed to further support the shelf-life claim.

The post-authorisation stability commitment of the applicant in section 3.2.P.8.2 is noted.

Based on available stability data on the finished product, a 36-month shelf-life when stored refrigerated at 5°C ± 3°C and protected from light as stated in the SmPC is acceptable.

2.3.3.5. Adventitious agents

The risk of transmissible spongiform encephalopathy (TSE)/bovine spongiform encephalopathy (BSE) agents is minimised by not using any materials of human or animal origin in the active substance manufacturing process and generation of the cell bank system in compliance with the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01).

In addition, viral clearance studies have been performed. A summary document giving a high-level overview and the results of the conducted studies as well as technical reports providing the details of the individual virus clearance studies are included in the dossier. The virus validation studies have been performed on qualified scale-down models which are representative of the commercial manufacturing scale. The provided viral clearance data demonstrate a robust clearance of the model viruses. In summary the applicant's conclusion that the active substance downstream manufacturing process provides an adequate virus clearance capability is agreed.

2.3.3.6. Biosimilarity

Denosumab finished product vial presentation (Degevma) has been developed as a proposed biosimilar to EU-approved reference medicinal product (RMP) Xgeva.

In general, a very comprehensive biosimilarity assessment has been conducted. The analytical similarity assessment consists of a comprehensive side-by-side analytical similarity assessment, comparative stability studies, additional characterisation studies, and demonstration of same strength.

According to guideline on similar biological medicinal products (CHMP/437/04 Rev 1), the applicant needs to show analytical similarity between the denosumab active substance and finished product and EU-sourced RMP. US-sourced comparator may be used as supportive data. Denosumab finished product vial presentation was compared to EU-Xgeva and to pooled EU-/US-Xgeva and the applicant provided a justification and general statistical considerations on pooling EU- and US-Xgeva. The approach by the applicant to demonstrate a scientific bridge between EU- and US-Xgeva seems acceptable.

The analytical similarity assessment is properly described. It is agreed that a sufficient number of batches from both, the proposed biosimilar as well as from the reference product has been included to enable a robust and reliable similarity assessment.

All batches used for similarity evaluation were within the shelf life at the time of testing. No significant differences were observed in the tested parameters, except slight differences, which were also observed in the side-by-side analytical similarity study, which is acceptable.

A range of state-of-the-art, orthogonal methods were used to compare the physicochemical properties including primary structure, molecular mass, post-translational modifications and heterogeneity, secondary/higher order structure and purity/impurities. The functional properties were tested by a range of methods associated with the mechanism of action. All methods were developed as state-of-the-art, scientifically sound, capable of detecting minor differences and qualified as suitable for their intended use.

A quality range approach was used for statistical evaluation of the analytical similarity assessment.

A criticality assessment of the quality attributes (QAs) in the biosimilarity exercise has been provided and all quality attributes were ranked.

To further support the demonstration of biosimilarity between denosumab vial and Xgeva, comparative stability studies including end of shelf-life stability, accelerated stability, and forced degradation was conducted.

Also, additional characterisation studies were conducted. Demonstration of the same strength between denosumab and Xgeva was performed.

In principle, the provided results support, the biosimilarity claim. For most of the quality attributes similarity was demonstrated, observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance of the product. A more detailed discussion on performed similarity studies is given below.

A high-level summary of the analytical similarity results is provided in the table below.

Table 1: Summary of analytical similarity results

Product attribute	**Test method**			**Evaluation**
Primary structure	Peptide mapping	Profiling		Similar
		Sequence coverage (%)[a]	LC HC	Similar
		N-terminal sequence		Identical
		C-terminal peptide		Identical
	Free thiol (Ellman) (mol SH/mol protein)			Similar
Molecular mass	Intact mass (Da)	G0F/G0F		Similar
		Deglycosylated		Similar
	Reduced mass (Da)	HC (G0F)		Similar
		HC (G1F)		Similar
		HC (G2F)		Similar
		HC (deglycosylated)		Similar
		LC		Similar
	Subunit mass (Da)	Fc/2 (G0F)		Similar
		Fc/2 (G1F)		Similar
		Fc/2 (deglycosylated)		Similar
		Fd’		Similar
Post-translational modifications and heterogeneity	Peptide mapping	Deamidation – HC N385, 390 (%)		Similar
		Oxidation M253 (%)		Lower in TVB-009
		Oxidation M359 (%)		Similar
		Oxidation M398 (%)		Similar
		Oxidation M429 (%)		Similar
		Oxidation M106 (%)		Similar
		Aglycosylation (%)		Similar
	icIEF	Main peak (%)		Higher in TVB-009
		Acidic species (%)		Lower in TVB-009
		Basic species (%)		Similar
	HILIC	G0F-GlcNAc (%)		Similar

Product attribute	Test method		Evaluation
		G0 (%)	Higher in TVB-009
		G0F (%)	Similar
		Man5 (%)	Lower in TVB-009
		G1F (1,6) (%)	Similar
		G1F (1,3) (%)	Similar
		G2F (%)	Similar
		Afucosylation	Similar
		Agalactosylation	Similar
	RP-HPLC	Isoform B (%)	Lower in TVB-009
		Isoform A/B (%)	Higher in TVB-009 based on EU QR
		Isoform A (%)	Higher in TVB-009
Secondary / higher-order structure	CD	Far-UV	Similar
		Near-UV	Similar
	FTIR		Similar
	DSC		Similar
Purity and impurities	SE-HPLC	Monomer (%)	Higher in TVB-009
		Dimer (%)	Lower in TVB-009
		Fragments (%)	Similar
	NR-CGE	Intact IgG (%)	Similar
		HHL (%)	Similar
		Fragments (%)	Similar
	R-CGE	HC+LC (%)	Higher in TVB-009 based on EU QR
		NGHC (%)	Similar
		Fragments (%)	Similar
Fab domain associated functions	Inhibition of RANKL induced TRAP induction in pre-osteoplastic cells (%RP)[b]		Similar
	RANKL binding – competitive ELISA (%RB)		Similar
	RANKL binding affinity – by KinExA: K_D [pM]; (%RA)		Similar
	Inhibition RANKL-induced IkB/NFkB reporter (%RP)		Similar
	Binding to transmembrane RANKL by FACS (%RB)		Similar
Fc domain associated functions	Binding to FcRn by SPR: K_D [nM] (%RA)		Similar
	Binding to FcγRIIA-Arg by SPR: K_D [nM] (%RA)		Similar
	Binding to FcγRIIA-His by SPR: K_D [nM] (%RA)		Similar
	Binding to FcγRIIB by SPR: K_D [nM] (%RA)		Similar

Product attribute	Test method	Evaluation
	Binding to FcγRIIIA-Val by SPR: K_D [nM] (%RA)	Lower K_D in TVB-009 based on EU QR and higher %RA in TVB-009 based on pooled QR
	Binding to C1q by ELISA (%RB)	Similar

Conclusion

A comprehensive assessment of biosimilarity between denosumab vial finished product (Degevma) and Xgeva has been presented. The analytical similarity assessment was performed with orthogonal state-of-the-art methods including analysis of primary and higher order structure, purity/impurity, post-translational modifications, charge variants, glycan profile, and biological activity. The observed differences have been adequately discussed and justified and shown not to impact biological function related to mechanism of action.

Overall, the presented quality data support the biosimilarity of denosumab vial finished product (Degevma) to EU-Xgeva. In addition, a suitable scientific bridge has been established to show that US-Xgeva is representative of the EU RMP.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

In general, a well-established Quality dossier has been provided. No major objection and a limited number of other concerns have been raised during the procedure. The applicant has received several scientific advices where the quality development has been extensively discussed. The recommendations given in these advices as well as the relevant EMA/ICH guidance have been in large parts taken into consideration. In summary, from a quality point of view the marketing authorisation application is approvable.

The denosumab vial presentation (Degevma) was developed as a biosimilar to the EU reference medicinal product Xgeva. A comprehensive biosimilarity assessment was provided and the provided results support the biosimilarity claim. Similarity was demonstrated for most quality attributes considered and the observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance of the product. In addition, a suitable scientific bridge has been established to show that US-Xgeva is representative of the EU RMP.

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. 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 safety. The presented data support the biosimilarity of denosumab vial finished product (Degevma) to EU-Xgeva. In addition, a suitable scientific bridge has been established to show that US-Xgeva is representative of the EU RMP.

2.4. Non-clinical aspects

2.4.1. Introduction

For the overall testing strategy, publicly available information on reference product and current guidance as outlined in the ICH M3(R2), ICH S6(R1), and EMA Guidance (similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues, July 2015), were considered.

2.4.2. Pharmacology

2.4.2.1. Pharmacodynamic studies

Characterization of TVB-009 structural and functional parameters, and additional biosimilarity assessment to evaluate the similarity between TVB-009 and US and EU Prolia and Xgeva was performed in vitro (for details reference is made to the Quality section).

For detailed assessment of in vitro characterization of TVB-009 please refer to the Quality section of the AR.

Assessment of secondary pharmacodynamics was incorporated into a single-dose GLP comparative SC study with 1 mg/kg TVB-009 and Prolia (US) in cynomolgus monkeys (n = 4 animals/sex/group), with a 43-day follow-up period. PD was determined by serum cross-linked N-telopeptide type I (NTx), ALP and serum calcium measurement. NTx was determined by a validated enzyme-linked immunosorbent assay (ELISA). NTx values from all animals that were treated with TVB-009 or Prolia (US) were below the lower limit of quantitation at all time points. Consequentially, this PD endpoint could not be assessed. Indirect assessment of bone turnover was determined by evaluating total ALP and serum calcium levels. Following administration, ALP as well as calcium levels of animals from both treatment groups decreased in a comparable manner after the administration of 1 mg/kg TVB-009 and Prolia (US).

For in vivo comparison, data using Prolia rather than Xgeva as the RMP was submitted. In vivo data to show comparability between biosimilar candidate and RMP is regarded of supportive value only as animal models are deemed insensitive to show minor differences. Thus, the submitted data is not regarded relevant for overall assessment of similarity.

2.4.2.2. Safety pharmacology programme

Dedicated Safety pharmacology studies have not been performed with TVB-009 in accordance with EMA Guideline.

2.4.2.3. Pharmacodynamic drug interactions

Dedicated drug-drug interaction studies have not been performed with TVB-009 in accordance with EMA Guideline.

2.4.3. Pharmacokinetics

In accordance with the relevant guidance, dedicated pharmacokinetics studies were not performed for TVB-009. However, toxicokinetic (TK) parameters were estimated as part of the supportive single dose sc toxicology study in cynomolgus monkey.

The described assays for detection of denosumab and ADA in monkey serum were validated accordingly and are generally regarded fit-for-purpose.

PK data was generally comparable between the originator and the biosimilar product. Minor differences were observed during elimination phase, with TVB-009 treated animals showing fast elimination than after Prolia treatment. These findings appear to correlate inversely with median ADA titres which were increased in TVB-009 treated animals, suggested to result in more rapid elimination. Generally, immunogenicity in animals is not regarded representative of the human situation and high ADA titres were not observed in clinical trials. Together with the insensitivity of animal data with regard to showing biosimilarity, these differences are difficult to interpret and thus not further pursued.

Tissue distribution studies are generally not required for biosimilar medicinal products. Hence, no comparative distribution studies have been performed with TVB-009 and Prolia/Xgeva. Volume of distribution (Vz/F) values for both TVB-009 and originator were estimated from the GLP-compliant single-dose comparative study in cynomolgus monkeys and did not indicate significant differences. This approach is regarded acceptable.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

In a GLP single-dose comparative study with TVB-009 and Prolia (US), cynomolgus monkeys (n = 4 animals/sex/group) were treated with a single sc dose of 1 mg/kg of TVB-009 or Prolia (US). Animals were followed for a 43-day period based on PK data generated by Amgen, indicating that 43 days is the time period required to characterize the elimination phase. The study was conducted in the cynomolgus monkey as a relevant species since denosumab recognizes and neutralizes receptor activator of nuclear factor kappa B ligand (RANKL) in non-human primate (NHP), but does not recognize rodent RANKL. The sc route is the clinical route of administration.

Denosumab was highly immunogenic in NHP after single administrations (FDA Pharmacology Reviews 2010; EMA EPAR Assessment Report 2010). Based on these data, a single-dose regimen was selected for the study to reduce the expected inter-individual variability in exposure due to immunogenicity.

The objective of the study was to characterize the safety, TK, PD, and immunogenicity profile of TVB-009 compared to Prolia (US). Safety assessments included clinical observations, body weight, food consumption, clinical pathology and urinalysis. Pathologic examination was performed at termination with histopathology being conducted on selected tissues. TK parameters were assessed to evaluate exposure (ie, C_{max}, AUC), and elimination parameters for TVB-009 versus Prolia (US). Anti-denosumab antibodies were monitored for both TVB-009 and Prolia. PD was determined by cross-linked N-telopeptide (NTx), ALP and serum calcium measurement.

2.4.4.2. Repeat dose toxicity

No repeat-dose toxicity studies have been performed with TVB-009 in accordance with currently effective guidance.

2.4.4.3. Genotoxicity

No genotoxicity studies have been conducted with TVB-009.

2.4.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with TVB-009.

2.4.4.5. Reproductive and developmental toxicity

Comparative reproductive and developmental toxicological studies between TVB-009 and Prolia/Xgeva have not been conducted in agreement with EMA Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical issues, 2015.

2.4.4.6. Toxicokinetic data

Toxicokinetics were evaluated as part of the single-dose toxicity study conducted in cynomolgus monkey, please see above.

2.4.4.7. Local Tolerance

Local tolerance was evaluated as part of the single-dose sc comparability study in cynomolgus monkey. Data did not indicate signs of local intolerance at the injection site with either TVB-009 or RMP.

2.4.4.8. Other toxicity studies

No other toxicity studies have been performed with TVB-009 as these were deemed unnecessary in accordance with EMA Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical issues, 2015.

2.4.5. Ecotoxicity/environmental risk assessment

The use of medicinal product TVB-009 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.

2.4.6. Discussion on non-clinical aspects

The functional in vitro assay panel covered activities associated with the mechanism of action and pharmacodynamics. For detailed assessment of in vitro characterization of TVB-009 please refer to the Quality section of the AR.

A single-dose GLP comparative sc toxicology study with 1 mg/kg TVB-009 and Prolia (US) in cynomolgus monkeys (n = 4 animals/sex/group), with a 43-day follow up period was nevertheless conducted. Generally, such in vivo data are not recommended in the EU for biosimilarity assessment as animal data is generally deemed insensitive to show similarity between test and reference product. For reference, in vivo studies were also not recommended to be conducted in the CHMP scientific advice

(EMA/CHMP/SAWP/180678/2019) for TVB-009. Therefore, these data is regarded of supportive value only.

PD parameters were evaluated as part of the in vivo toxicity study in Cynomolgus monkey. Although these PD endpoints are generally in accordance with the current guidelines, they are not sensitive enough to provide relevant information about biosimilarity to the RMP. In addition, the validation of the NTx method is incomplete. However, as all NTx values were under the lower limit of quantitation and this data is of little relevance, this will not be pursued further. Circulating ALP serum calcium levels showed comparable reduction compared to the RMP. Thus, these data overall support the proposed similarity approach as no significant differences were noted between TVB-009 and Prolia. Please refer to the in vitro part of the similarity exercise in the quality section for detailed assessment of biosimilarity between TVB-009 and the reference product.

Dedicated Safety pharmacology and drug-drug interaction studies have not been performed with TVB-009 in accordance with EMA Guideline.

In accordance with relevant guidance, no dedicated pharmacokinetics studies were performed for TVB-009. Instead, TK parameters were estimated as part of the supportive single dose sc toxicology study in cynomolgus monkey. The assays for detection of denosumab and ADA in monkey serum were validated accordingly and are generally regarded fit-for-purpose.

PK data were generally comparable between the originator and the biosimilar product, with Minor differences were observed during elimination phase i.e. with TVB-009 treated animals showing faster elimination than Prolia treated animals. These findings appear to correlate inversely with median ADA titres. Considering that generally immunogenicity in animals is not regarded representative of the human situation, high ADA titres were not observed in clinical trials, and the insensitivity of animal data with regard to showing biosimilarity, these differences were not further pursued.

Tissue distribution studies are generally not required for biosimilar medicinal products; accordingly none were performed. Volume of distribution (Vz/F) values estimated from the comparative study did not indicate significant differences. This approach is regarded acceptable.

According to the C_{max} and AUC values, the selected dose 1 mg/kg seems to be adequate to reach clinical exposures.

No additional pharmacokinetic studies were performed and included in Module 4, which is in line with EMA guidelines.

Safety assessments included clinical observations, body weight, food consumption, clinical pathology and urinalysis. Pathologic examination was performed at termination and histopathology was conducted on selected tissues.

Overall, this single dose sc toxicology study in cynomolgus monkey (males and females) demonstrated that TVB-009 was well tolerated and provided an appropriate safety profile in cynomolgus monkeys. In general, comparability between TVB-009 and Prolia (US) was supported with respect to clinical observations, local tolerance at the injection sites, changes in body weights, food consumption, clinical pathology, urinalysis, bone turnover blood chemistry parameters, organ weights, gross pathology, histopathology of selected organs, and TK exposure.

Minor differences were observed between TVB-009 and RMP treated animals in the histopathological assessment of lymph nodes. However, these findings of active prominent follicles and lymphoid hyperplasia of the paracortex in some animals generally indicate an immune-mediated effect, which appears reasonable when treating cynomolgus monkeys with denosumab. As the sample size is small and interindividual variation large, no statistically relevant conclusions can be drawn from this study.

Furthermore, animals are generally not regarded sensitive models to show similarity/differences between the biosimilar candidate and the RMP. Thus, overall, these findings are not further pursued as the non-clinical similarity exercise between TVB-009 and the RMP should be based on in vitro characterisation submitted in Module 3 and discussed in the quality section of this report

Dedicated studies on repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity have not been performed with TVB-009. This is in accordance to currently effective guidance.

Local tolerance was evaluated as part of the single-dose sc comparability study in cynomolgus monkey. Data did not indicate signs of local intolerance at the injection site with either TVB-009 or RMP.

Information related to relevant findings in the originator (e.g. reproductive and developmental toxicity of the reference medicinal product (Xgeva)) has been adequately reflected in SmPC sections 4.6 and 5.3 of the proposed biosimilar. The SmPC is in accordance with the originator with all relevant information included.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, TVB-009 denosumab is not expected to pose a risk to the environment. The applicant provided a valid justification for the absence of ERA studies on the aforementioned grounds, which is deemed acceptable.

2.4.7. Conclusion on the non-clinical aspects

Nonclinical in vivo data in the context of a biosimilar development are regarded of supportive value only and no conclusions on similarity can be drawn due to general lack of sensitivity of in vivo (animal) models in regard to biosimilarity assessment.

For a detailed assessment of in vitro characterization of TVB-009 please refer to the Quality section of the AR.

No other concerns are raised on the provided nonclinical developmental data.

2.5. Clinical aspects

2.5.1. Introduction

All clinical studies described below have been conducted with the Prolia biosimilar candidate (Ponlimsi/TVB-009P) and using Prolia as a reference product. No clinical studies have been conducted with the Xgeva biosimilar candidate (Degevma/TVB-009X) using Xgeva as a reference product. The CHMP agreed that, if biosimilarity is demonstrated between TVB-009 and Prolia US and Prolia EU, this can be bridged to Xgeva (or the other way around), since EU Prolia and EU Xgeva share the same composition and there is only a difference in denosumab concentration and a minor difference the concentration of the excipients. It was agreed that it is not required also to demonstrate comparable PK/PD with the Xgeva product (EMEA/H/SA/4069/1/2019/III).

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.

Table 2: Tabular overview of clinical studies

Study identifier	Study design and type of control	Test Product(s); Dosage Regimen; Route of Administration	No. of patients	Primary Objectives and endpoints
TVB009-BE-10157	Phase 1, randomized, double-blind, single-dose, parallel-group, 3-arm study in healthy participants (male and female). Active control	Single SC injection of TVB-009 60mg OR Single SC injection of EU-Prolia 60mg OR Single SC injection of US-Prolia 60mg	345 subjects entered (115 in each arm)	To demonstrate the pharmacokinetic similarity of TVB-009P with EU-Prolia The co-primary endpoints were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$
TVB009-IMB-30085	Phase 3, randomized, double-blind, multi-dose, multinational, multicenter in postmenopausal women with osteoporosis (PMO) Active control	In total 3 SC injections of denosumab (TVB-009 60 mg or US-Prolia 60 mg) every 26 weeks	332 entered (166 in each arm)	To demonstrate that there are no clinically meaningful differences in efficacy between TVB-009P and Prolia US administered sc in patients with PMO The co-primary endpoints were %change from baseline in bone mineral density at the lumbar spine (LS-BMD) at Week 52, and % change from baseline in the PD marker serum C-telopeptide cross-link of type 1 collagen (sCTX-1) at Week 26

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

The analytical methods have been validated according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). All measured parameters were acceptable.

Bioequivalence

Study TVB009-BE-10157

2.5.2.1.1. Study design

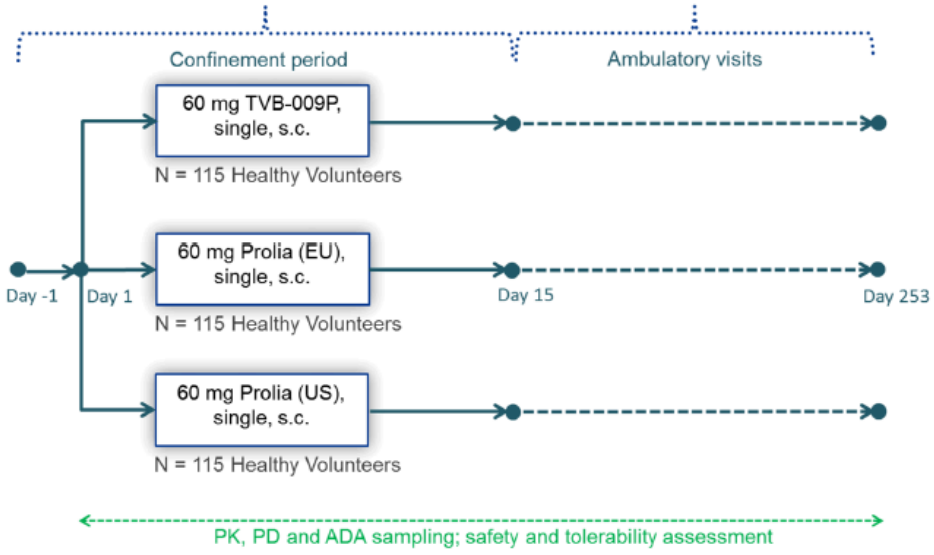
Study TVB009-BE-10157 was a randomized, double-blind, single-dose, 3-arm parallel-group study of TVB-009P, Prolia (US), and Prolia (EU) in healthy subjects. The study evaluated the PK and PD similarity of TVB-009P versus Prolia (US), and Prolia (EU) in healthy subjects.

The study consisted of a screening period (between Day -30 to Day -2), a confinement period (from Day-1 to Day 15), ambulatory visits (Day 17- Day 225), and an end of study (EoS) visit on Day 253.

Subjects were randomly assigned in a ratio of 1:1:1 to receive a single injection of either 60 mg of TVB009 or 60 mg of EU-Prolia or 60 mg of US-Prolia. The injections were administered sc via a single-dose prefilled syringe (PFS).

All subjects were to received calcium 1000 mg daily and at least 400 IU vitamin D daily from Day 1 to Day 253 (EoS) as supplemental treatment.

Figure 1: Overall study schematic diagram



ADA=anti-drug antibody; EU=European Union; N=subjects; PD=pharmacodynamics; PK=pharmacokinetic; sc=subcutaneous; US=United States

2.5.2.1.2. Study participants - Key eligibility criteria:

Healthy male or female subjects between 28 and 55 years of age with a Body mass index (BMI) of 18.5 to 29.9 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.

2.5.2.1.3. Objectives, Endpoints

The primary objective was to demonstrate the pharmacokinetic similarity of TVB-009P with EU-Prolia.

The co-primary endpoints were maximum observed serum drug concentration (C_{max}), area under the serum concentration-time curve (AUC) from time 0 to the time of the last quantifiable measurement (AUC_{0-t}), and area under the serum concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$).

The secondary objectives of the study were to evaluate the PK similarity of EU-Prolia and US-Prolia; and to evaluate the PK similarity of TVB-009P and Prolia (EU and US) based on secondary PK parameters.

The secondary endpoints were the time to maximum observed serum drug concentration (t_{max}), apparent serum terminal elimination rate constant (λz), the apparent total body clearance (CL/F), the apparent volume of distribution during the terminal phase (Vz/F), AUC from pre-dose to 14, 28, 56, and 84 days post-dose.

PK sampling time points

Blood samples for PK analyses were collected on Day 1 (pre-dose and 6 and 12 hours post-dose), Days 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 22, 29 (±1 day), 43 (±1 day), 57(±1 day), 71(±1 day), 85 (±1 day), 99 (±2 days), 113 (±2 days), 141 (±2 days), 169 (±2 days), 197 (±2 days), 225 (±2 days), 253 (±2 days, End of Study or Early Termination).

2.5.2.1.4. Randomisation and blinding

Randomisation

Subjects were planned to be enrolled sequentially into cohorts. The first 9 subjects were planned toll be randomized per study treatment (TVB-009P, Prolia [US] or Prolia [EU]) in a ratio of 1:1:1; 72 hours after study drug administration and a positive safety assessment, enrolment of the remaining subjects was planned to commence in a 1:1:1 ratio. The randomisation was stratified by ethnicity (Hispanic or Latino; not Hispanic or Latino) and weight category (<70 kg; ≥70 kg through ≤90 kg; >90 kg).

Blinding

At the investigational centre, only the pharmacist or designee who was supposed to dispense the study drug and the study drug administrator were planned to be unblinded; they were not supposed to participate in safety assessments. The study drug was planned to be prepared in a separate room by the non-blinded pharmacist. In order to ensure additional subject blinding, measures were taken during the study drug injection to shield the study drug from the subject.

The pharmacy staff at the investigational centre who dispensed the IMP knew the treatment given to each subject. In addition, assigned dose administrators and 2 other individuals from the investigational centre knew the treatment assignments since they provided necessary quality assurance and oversight of IMP preparation and administration. These individuals were not involved in the conduct of any study procedures or assessment of any adverse events. The sponsor assigned an unblinded monitor to reconcile study supplies and review dosing documentation during the course of the study.

2.5.2.1.5. Sample size

A sample size of 345 randomized subjects (115 subjects per arm) was chosen to provide 291 subjects (97 subjects per arm) in the PK Analysis Set, assuming a 15% drop-out rate. This number was considered sufficient to provide 90% power for similarity tests of the three co-primary endpoints $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} between TVB-009P and Prolia US and Prolia EU respectively from the following considerations: Bioequivalence was considered shown if the geometric mean ratio (GMR) of the two treatment groups fell within the standard PK bioequivalence margin of [0.8, 1.25] assuming a Type I error rate of 5%, a maximum of 5% true difference between treatment groups (TVB-009P vs the respective originator), a maximum coefficient of variation of 36.6% for the PK primary endpoints ($AUC_{0-\infty}$ and AUC_{0-t}; 32.4% CV was assumed for C_{max}), and a minimum correlation of 0.75 between the endpoints ($AUC_{0-\infty}$ and C_{max}; other correlations assumed to be 1).

2.5.2.1.6. Analysis sets

The *randomized analysis set* was to include all randomized subjects. In this analysis set, treatment was to be assigned based on the treatment to which subjects were randomized, regardless of which treatment they actually received.

The *safety analysis set* was to include all subjects who received a dose of IMP. In this analysis set, treatment was to be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomized. The safety analysis set was planned to be used for all safety and immunogenicity analyses, unless stated otherwise.

The *PK analysis set* was to include those subjects from the safety analysis set who had sufficient data to calculate at least 1 PK parameter for IMP and had no events or protocol deviations which could

adversely affect the calculation of PK parameters. Subjects with pre-dose values >5% of individual C_{max} were to be excluded. The PK analysis set was to be used for all PK summaries and analyses.

The *PD analysis set* was to include those subjects from the PK analysis set who had sufficient data to calculate at least 1 PD parameter and had no events or deviations that would affect calculation of parameters. The PD analysis set was planned to be used for all PD summaries and analyses.

2.5.2.1.7. Statistical methods

Serum concentration data were to be individually listed and summarized using descriptive statistics by nominal time point and treatment group. Mean concentration-time profiles for each treatment group were to be presented by nominal time point on linear and semi-logarithmic scales. In addition, individual concentration-time profiles (on linear and semi-logarithmic scales) by actual sampling time were to be provided individually and on the same graph (spaghetti plot).

The PK parameters listed previously were to be calculated for TVB-009P or denosumab serum levels from individual concentration-time data using appropriate validated software (Phoenix® WinNonlin Version 6.2.1 or higher) using non-compartmental methods.

Concentration values below the limit of quantitation (BLQ) of the assay were to be treated as 0 when calculating summary statistics for serum drug concentrations. For calculating PK parameters and individual subject concentration-time profiles, a BLQ value at time 0, at a sampling time before the 1st quantifiable serum drug concentration, or at a sampling time between 2 quantifiable concentrations were to be treated as 0. All other BLQ values were to be set to missing. Missing values were planned to be ignored when calculating PK parameters (except for partial AUCs).

Primary analyses of PK endpoints

In order to evaluate the similarity of PK response of TVB-009P vs Prolia EU and US respectively, as well as the similarity of Prolia EU vs US, analysis of variance (ANOVA) models were planned for and performed on each of the ln-transformed co-primary endpoints C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$; with treatment as a fixed effect and a factor of body weight category (weight <70 kg; weight ≥70 kg through ≤90 kg; weight >90 kg) as a covariate. Per PK-parameter, all three treatment-arm comparisons were carried out within one ANOVA model. For each parameter, the least-squares (LS) means, differences between the LS means, and the 90% confidence intervals (CIs) associated with these differences were to be determined based on the ln-transformed values, and exponentiated to obtain the LS geometric means (GMs), LS geometric mean ratios (GMRs), and 90% CIs for the LS GMRs on the original scale.

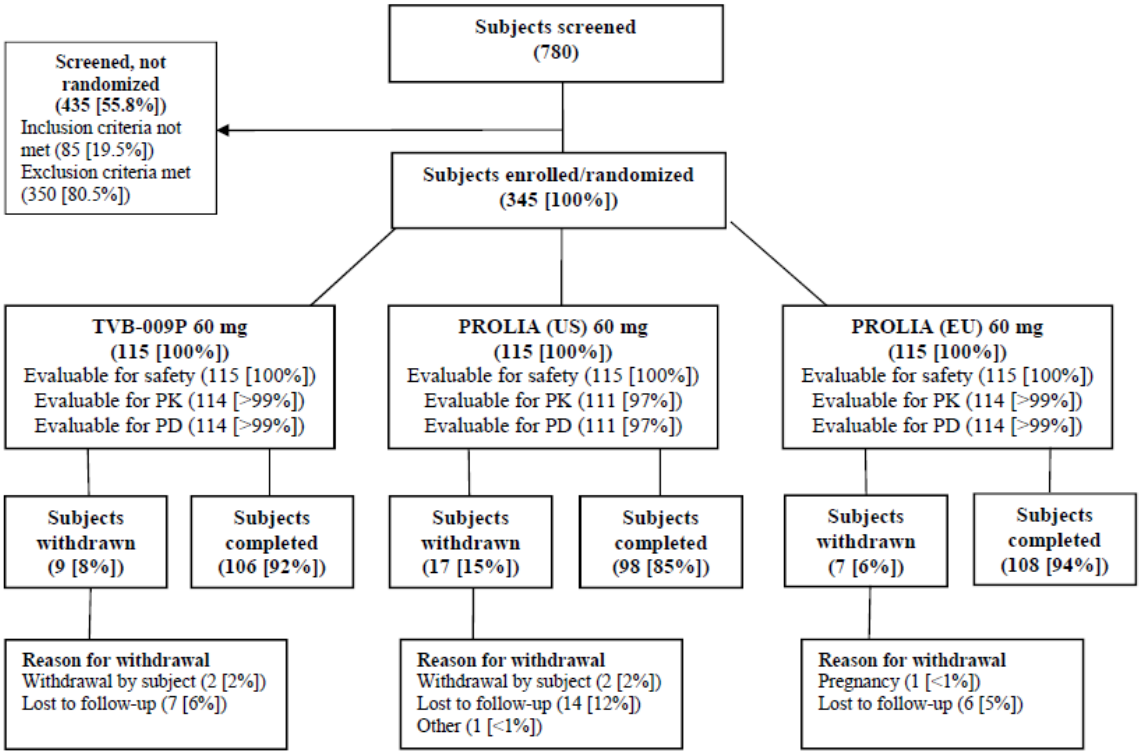
The PK outcome of two products was considered similar if the 90% CIs of the LS GMRs for all co-primary PK endpoints fell entirely within the pre-defined bounds of the standard bioequivalence margin, which was 0.80 to 1.25.

In the SAP, the applicant outlined plans for two specific *sensitivity analyses for the co-primary PK endpoints:* The first involved re-running the previously described primary analyses with ethnicity ('Hispanic' or 'Latino' vs other) as an additional covariate. The second involved re-running the previous analyses without covariates. The applicant further planned that if sensitivity analysis for missing data due to COVID-19 was required, this would have been planned prior to the first database lock and specifics included in an addendum to the analysis plan.

The *secondary and exploratory (ln-transformed) PK endpoints* were to be summarized by treatment group using descriptive statistics (GM and %CV except for t_{max} (median, and min/max), $t_{1/2}$ (mean and SD), and $\%AUC_{ext}$ (median and min/max); no formal hypothesis testing was planned.

2.5.2.1.8. Participant flow

Figure 2: Subject disposition (all subjects)



Source: Summary 15.1.
Numbers in parentheses are numbers of subjects.
The denominator for calculating percentages is the number of subjects in the Randomized Analysis Set.
EU=European Union; PD=pharmacodynamics; PK=pharmacokinetics; US=United States.

2.5.2.1.9. Protocol deviations

No subject had any important protocol deviation or important COVID-19 protocol deviation during the study.

2.5.2.1.10. Numbers analysed

Table 3: Subjects analysed

Analysis group, n (%)	TVB-009P 60 mg	Prolia (US) 60 mg	Prolia (EU) 60 mg	Total
Randomized analysis set	115 (100)	115 (100)	115 (100)	345 (100)
Randomized analysis set, not treated	0	0	0	0
Safety analysis set	115 (100)	115 (100)	115 (100)	345 (100)
Pharmacokinetic analysis set	114 (>99)	111 (97)	114 (>99)	339 (98)
Pharmacodynamic analysis set	114 (>99)	111 (97)	114 (>99)	339 (98)
Completed study	106 (92)	98 (85)	108 (94)	312 (90)

Source Data: Listing 16.2.1.1

Of the 345 subjects who received the study drug, 6 subjects were excluded from the PK and PD analyses. Five of these 6 subjects were excluded due to early termination that did not allow for characterization of the absorption and elimination phases. One subject in the TVB-009P treatment group was excluded because their pre-dose denosumab concentration was >5% of the C_{max} value.

For 3 additional subjects (1 Prolia US, 2 Prolia EU) the exclusion of individual parameters was decided in the blinded data review meeting prior to database lock and unblinding of the study. AUC_{0-t} and $AUC_{0-\infty}$ were excluded but C_{max} was included for these subjects.

The terminal rate constant and therefore $AUC_{0-\infty}$ were not calculated for 8 additional subjects (3 TVB-009P, 3 Prolia US and 2 Prolia EU) following the predefined rules in the SAP.

2.5.2.1.11. Baseline data

Table 4: Demographic information (randomised analysis set)

Demographic variables	TVB-009P 60 mg (N=115)	PROLIA (US) 60 mg (N=115)	PROLIA (EU) 60 mg (N=115)	Total (N=345)
Age, years				
n	115	115	115	345
Mean	40.9	41.0	40.5	40.8
SD	8.33	7.38	7.89	7.85
Median	41.0	42.0	40.0	41.0
Min, max	28, 55	28, 55	28, 55	28, 55
Sex, n (%)				
Male	50 (43)	62 (54)	62 (54)	174 (50)
Female	65 (57)	53 (46)	53 (46)	171 (50)
Race, n (%)				
White	103 (90)	97 (84)	107 (93)	307 (89)
Black or African American	12 (10)	18 (16)	8 (7)	38 (11)
Ethnicity, n (%)				
Not Hispanic or Latino	0	0	1 (<1)	1 (<1)
Hispanic or Latino	115 (100)	115 (100)	114 (>99)	344 (>99)
Weight, kg				
n	115	115	115	345
Mean	74.4	73.8	73.8	74.0
SD	10.98	10.82	11.19	10.97
Median	74.0	74.0	73.2	74.0
Min, max	52, 105	52, 97	51, 106	51, 106
Weight category, n (%)				
<70 kg	43 (37)	44 (38)	43 (37)	130 (38)
≥70 kg to ≤90 kg	64 (56)	63 (55)	62 (54)	189 (55)
>90 kg	8 (7)	8 (7)	10 (9)	26 (8)
Height, cm				
n	115	115	115	345
Mean	166.8	167.3	166.3	166.8
SD	8.91	7.75	9.06	8.58
Median	166.0	167.0	166.0	166.0
Min, max	149, 189	148, 185	148, 192	148, 192

Demographic variables	TVB-009P 60 mg (N=115)	PROLIA (US) 60 mg (N=115)	PROLIA (EU) 60 mg (N=115)	Total (N=345)
BMI, kg/m^2				
n	115	115	115	345
Mean	26.67	26.29	26.59	26.52
SD	2.472	2.836	2.724	2.679
Median	26.96	26.73	27.21	26.96
Min, max	20.1, 29.8	18.6, 29.9	18.9, 29.9	18.6, 29.9

Source: Summary 15.2.
BMI=body mass index; EU=European Union; min=minimum; max=maximum; N=total number of subjects; SD=standard deviation; US=United States.

Overall, 16 subjects out of the 339 subjects in the pharmacokinetic analysis set (4.7%) had non-zero pre-dose denosumab concentrations (7 subjects in the TVB-009P group, 4 subjects in the Prolia [US] group and 5 subjects in the Prolia [EU] group); all these subjects were included in the PK analysis as their predose denosumab concentrations were ≤5% of the C_{max}.

2.5.2.1.12. Treatment administered

Table 5: Batch information for each treatment

Compound	Lot#	Source	Expiry/ Retest Date	Manufacturer	Nominal Conc. (mg/mL)	Measured Protein Conc. (mg/mL)[1]	Storage Conditions
Prolia®	1091465	US	31.01.2021	Amgen	60	**61.0**	2-8°C or (<-56°C)
Prolia®	1096043B	EU	31.03.2021	Amgen	60	**61.7**	2-8°C or (<-56°C)
TVB-009	3-FIN-3251	Teva	25.04.2020[2]	Teva	59.4	**59.4**	2-8°C or (<-56°C)

[1] Measured Protein concentration based on results obtained from Drug Product Development & Operations, Biologics CMC, West Chester - US
[2] Manufacturer lot 3-FIN-3251 corresponds to Teva lot No. P200513-0001L001 (supporting documentation are provided in Appendix 7). 25-Apr-2020 corresponds to 12M stability data. The stability assessment is ongoing to 36M.

2.5.2.1.13. Outcomes

Primary Pharmacokinetic Analysis

Table 6: Statistical Analysis of Pharmacokinetic Parameters - Pharmacokinetic Analysis Set

Parameter	Treatment Group	N	LS Geometric Mean	Comparison	LS Geometric Mean Ratio	90% CI of LS Geometric Mean Ratio
Cmax (ng/mL)	TVB-009P 60 mg	114	6422			
	PROLIA (EU) 60 mg	114	7116			
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.902	0.8337, 0.9769
AUC[0-t] (ug*day/mL)	TVB-009P 60 mg	114	275			
	PROLIA (EU) 60 mg	112	298			
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.924	0.8522, 1.0021
AUC[0-inf] (ug*day/mL)	TVB-009P 60 mg	113	283			
	PROLIA (EU) 60 mg	112	303			
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.936	0.8655, 1.0129

$AUC_{[0-t]}$=area under the serum concentration-time curve from time 0 to the time of the last measurable drug concentration; $AUC_{[0-inf]}$=area under the serum concentration-time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed serum drug concentration; LS=least squares; N=number of participants; Prolia (EU) European Union sourced Prolia

Sensitivity analyses

- No covariates

Table 7: Statistical Analysis of Pharmacokinetic Parameters - Pharmacokinetic Analysis Set – Sensitivity analysis: no covariates

Parameter	Treatment Group	N	LS Geometric Mean	Comparison	LS Geometric Mean Ratio	90% CI of LS Geometric Mean Ratio
Cmax (ng/mL)	TVB-009P 60 mg	114	6873			
	PROLIA (US) 60 mg	111	7183			
	PROLIA (EU) 60 mg	114	7584			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	0.957	0.8795, 1.0407
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.906	0.8336, 0.9852
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.056	0.9705, 1.1484
AUC[0-t] (ug*day/mL)	TVB-009P 60 mg	114	291			
	PROLIA (US) 60 mg	110	290			
	PROLIA (EU) 60 mg	112	314			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	1.005	0.9214, 1.0959
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.928	0.8511, 1.0115
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.083	0.9927, 1.1816
AUC[0-inf] (ug*day/mL)	TVB-009P 60 mg	111	300			
	PROLIA (US) 60 mg	107	294			
	PROLIA (EU) 60 mg	110	319			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	1.019	0.9351, 1.1110
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.940	0.8625, 1.0235
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.085	0.9951, 1.1827

- Excluding subjects with incomplete Pk profiles

Table 8: Statistical Analysis of Pharmacokinetic Parameters - Pharmacokinetic Analysis Set – Sensitivity analysis: excluding subjects with incomplete pharmacokinetic profiles

Parameter	Treatment Group	N	LS Geometric Mean	Comparison	LS Geometric Mean Ratio	90% CI of LS Geometric Mean Ratio
Cmax (ng/mL)	TVB-009P 60 mg	108	6355			
	PROLIA (US) 60 mg	102	6593			
	PROLIA (EU) 60 mg	109	7106			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	0.964	0.8853, 1.0493
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.894	0.8226, 0.9722
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.078	0.9901, 1.1731
AUC[0-t] (ug*day/mL)	TVB-009P 60 mg	108	272			
	PROLIA (US) 60 mg	102	269			
	PROLIA (EU) 60 mg	109	297			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	1.011	0.9291, 1.1009
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.916	0.8427, 0.9957
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.104	1.0145, 1.2016
AUC[0-inf] (ug*day/mL)	TVB-009P 60 mg	106	279			
	PROLIA (US) 60 mg	101	271			
	PROLIA (EU) 60 mg	109	299			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	1.030	0.9474, 1.1188
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.933	0.8602, 1.0126
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	1.103	1.0156, 1.1981

Pharmacokinetic Parameters

Table 9: Pharmacokinetic parameters by treatment group

Parameter	Statistic	TVB-009P 60 mg (N=114)	PROLIA (US) 60 mg (N=111)	PROLIA (EU) 60 mg (N=114)
C_{max} (ng/mL)	GM (%CV)	6872.6 (45.17)	7183.4 (41.14)	7583.7 (31.98)
AUC_{0-t} (µg*day/mL)	GM (%CV)	291.1 (47.03)	289.7 (41.42)	313.8 (33.34)
AUC_{0-inf} (µg*day/mL)	GM (%CV)	299.6 (45.08)	293.9 (41.82)	318.9 (32.44)
t_{max} (day)	Median (min, max)	12.0 (2, 84)	10.0 (2, 28)	8.0 (1, 28)
$t_{½}$ (day)	Mean (SD)	14.1 (5.26)	13.1 (4.89)	14.0 (5.41)
CL/F (mL/day)	GM (%CV)	200.3 (45.08)	204.1 (41.82)	188.2 (32.44)
V_z/F (mL)	GM (%CV)	3810.9 (52.59)	3613.5 (46.06)	3545.4 (50.61)
λ_z (1/day)	GM (%CV)	0.1 (39.78)	0.1 (37.35)	0.1 (39.02)
$\%AUC_{ext}$ (%)	Median (min, max)	0.6 (0, 9)	0.5 (0, 14)	0.5 (0, 7)
AUC_{0-14d} (µg*day/mL)	GM (%CV)	64.9 (51.13)	70.7 (47.88)	76.4 (34.80)
AUC_{0-28d} (µg*day/mL)	GM (%CV)	133.6 (45.86)	141.2 (39.14)	150.1 (31.14)
AUC_{0-56d} (µg*day/mL)	GM (%CV)	224.2 (40.23)	228.5 (37.44)	246.9 (29.41)
AUC_{0-84d} (µg*day/mL)	GM (%CV)	272.5 (40.87)	271.1 (38.57)	293.7 (30.46)

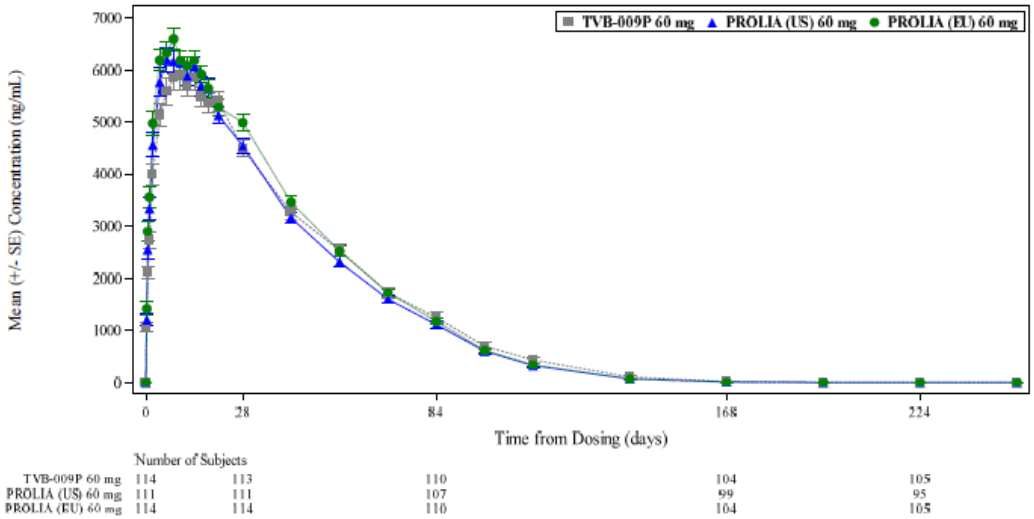
Source: Summary 15.10

AUC=area under the concentration-time curve; AUC_{0-14d}=AUC from time 0 to 14 days; AUC_{0-28d}=AUC from time 0 to 28 days; AUC_{0-56d}=AUC from time 0 to 56 days; AUC_{0-84d}=AUC from time 0 to 84 days; AUC_{0-inf}=AUC from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable concentration; $\%AUC_{ext}$=percentage extrapolated AUC; CL/F=apparent total body clearance; C_{max}=maximum observed drug concentration; CV=(geometric) coefficient of variation; GM=geometric mean; N=number of subjects; $t_{½}$=terminal elimination half-life; t_{max}=time to maximum observed drug concentration; V_z/F=apparent volume of distribution; λ_z=terminal elimination rate constant.

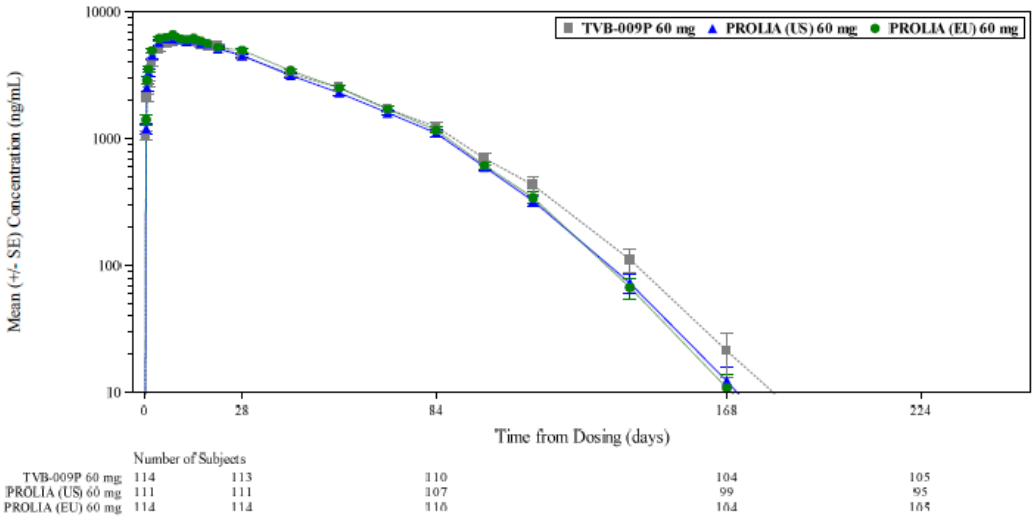
Mean denosumab serum concentration-time profiles

Figure 3: Mean concentration-time profiles of denosumab

a) Linear Scale



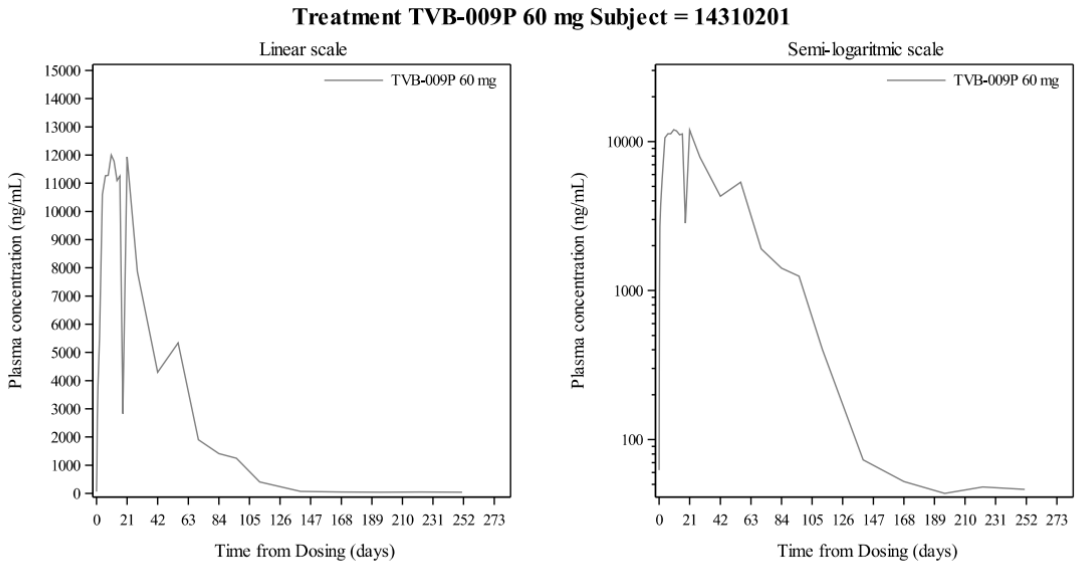
b) Semi-logarithmic Scale

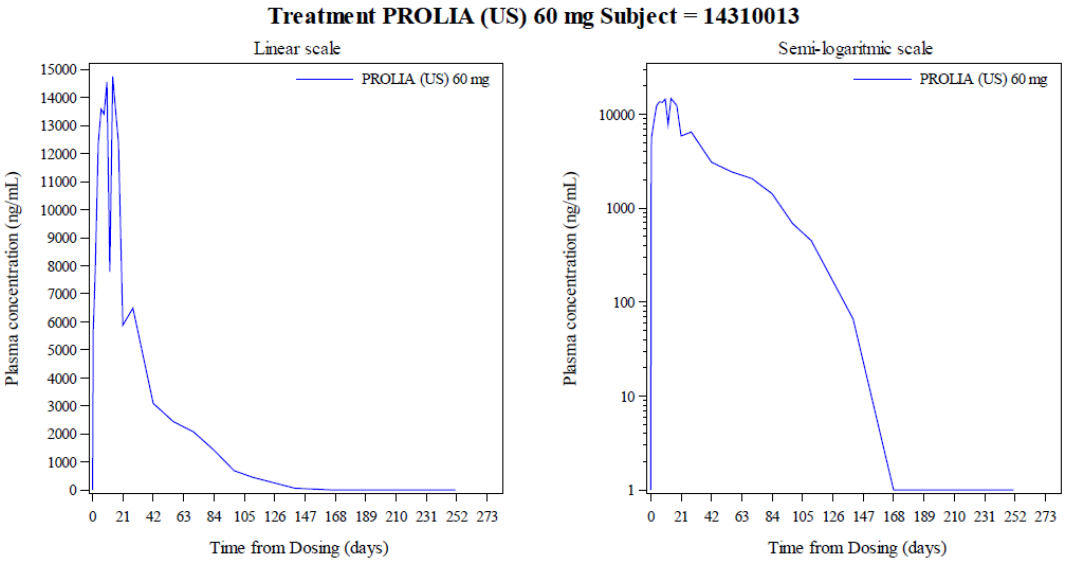


Source: Figure 15.1
SE=standard error.

Individual denosumab serum concentration-time profiles

Figure 4: Example of individual denosumab serum concentration-time profiles





Pharmacokinetics in the target population

Study TVB009-IMB-30085

For a detailed assessment of the study design, please refer to the efficacy section.

The comparison of pharmacokinetics between TVB-009P and Prolia US was an exploratory objective of the study in post-menopausal women with osteoporosis.

The pharmacokinetic endpoints were:

- serum concentration before next dose (C_{trough}), before 2nd and 3rd dose, and 6 months after 3rd dose

- serum concentration at 2 weeks post-dose (C_{2weeks})

Pharmacokinetic sampling

Table 10: Sampling schedule

Study period	Screen-ing	Base-line	Main treatment period								Transition period		
Visit number	V1	V2	V3[a]	V4[a]	V5[a]	V6[a]	V7	V8[a]	V9[b]		V10[a]	V11[a]	V12
									EOM	SOT			EOS/ET
Day/week and allowed time windows	Up to 4 weeks before V2	Day 1	Day 15 ±3 days	Week 4 ±3 days	Week 8 ±5 days	Week 12 ±7 days	Week 26 ±7 days	Week 39 ±14 days	Week 52 ±14 days		Week 54 2 weeks ±3 days after V9	Week 65 13 weeks ±14 days after V9	Week 78 26 weeks ±14 days after V9
Pharmacokinetics sampling (serum concentration of IMP)		X	X	X	X	X	X	X	X		X	X	X

Results

Table 11: Pharmacokinetic parameters in main treatment period (Safety analysis set)

Visit Statistic	TVB-009P (N=166)	PROLIA US (N=165)
C_{2weeks}: Day 15		
n	163	164
Mean (SD)	4172.16 (1791.203)	4481.88 (1567.986)
Geometric Mean	3853.64	4272.75
Geometric CV%	51.2	37.6
Median (Min, Max)	3945.65 (0, 8738.9)	4458.30 (0, 8848.8)
Missing	3	1
C_{trough} before the second dose: Week 26		
n	158	152
Mean (SD)	39.67 (148.522)	42.30 (159.335)
Geometric Mean	96.98	88.94
Geometric CV%	143.1	129.7
Median (Min, Max)	0 (0, 1579.2)	0 (0, 1749.2)
Missing	8	13
C_{trough} before the third dose: Week 52		
n	152	147
Mean (SD)	51.51 (131.878)	66.93 (208.665)
Geometric Mean	106.61	100.38
Geometric CV%	145.1	157.0
Median (Min, Max)	0 (0, 746.4)	0 (0, 1936.3)
Missing	14	18

Source: Excerpt from Summary 14.2.5.1, Listing 16.2.5.2
BLQ = below limit of quantitation; C_{2weeks} = serum concentration at 2 weeks post-dose; C_{trough} = serum concentration before next dose; CV% = coefficient of variation; max = maximum; min = minimum; SD = standard deviation; US = United States.
Concentrations BLQ were treated as zero.

Table 12: Pharmacokinetic parameters in transition period (Transition safety analysis set)

Visit Statistic	TVB-009P/TVB-009P (N=148)	PROLIA US/PROLIA US (N=72)	PROLIA US/TVB-009P (N=71)
Week 54			
n	146	68	70
Mean (SD)	4539.78 (1923.641)	4519.92 (1559.614)	4525.18 (1891.446)
Geometric Mean	4056.54	4354.49	4103.09
Geometric CV%	70.9	34.1	75.2
Median (Min, Max)	4387.45 (0.0, 9479.5)	4317.23 (0.0, 9136.8)	4526.21 (0.0, 8516.4)
Missing	2	4	1
Week 65			
n	143	69	69
Mean (SD)	1051.97 (826.363)	1215.45 (820.500)	1282.95 (854.116)
Geometric Mean	753.60	941.09	998.85
Geometric CV%	124.7	109.1	111.3
Median (Min, Max)	895.85 (0.0, 3812.7)	1001.73 (0.0, 4837.9)	1162.86 (0.0, 3763.0)
Missing	5	3	2
C_{trough} 6 months after the third dose: Week 78			
n	140	67	69
Mean (SD)	61.20 (161.136)	58.31 (114.174)	71.64 (124.253)
Geometric Mean	110.02	104.56	107.62
Geometric CV%	144.9	119.7	130.2
Median (Min, Max)	0.00 (0.0, 1164.0)	0.00 (0.0, 588.3)	0.00 (0.0, 529.3)
Missing	8	5	2

Source: Excerpt from Summary 14.2.5.2, Listing 16.2.5.2
BLQ = below limit of quantitation; C_{trough} = serum concentration before next dose; CV% = coefficient of variation; max = maximum; min = minimum; SD = standard deviation; US = United States.
Concentrations BLO were treated as zero.

Overall, of the 331 participants, 7 participants had non-zero pre-dose denosumab concentrations (4 participants in the TVB-009P group and 3 participants in the Prolia US group).

2.5.2.2. Pharmacodynamics

Mechanism of action

Denosumab is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor. Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, receptor activator of nuclear factor kappa-B (RANK), on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. This mechanism of action of denosumab is the same across all approved indications.

Primary and Secondary pharmacology

Study TVB009-BE-10157

The pharmacodynamic (PD) objective of the study was to evaluate the PD similarity of TVB-009P and Prolia (EU and US).

The PD endpoints were:

- serum C-telopeptide cross-link of type 1 collagen (sCTX-1)
- urinary N-telopeptide (uNTx) corrected for urine creatinine levels (uNTx/Cr)
- procollagen type 1 N-terminal propeptide (P1NP)

For all 3 PD parameters the following was calculated:

- percent (%) change from baseline to each timepoint;
- suppression at each timepoint (levels BLQ based on the LLOQ of the respective assay);
- the time to reach maximal reduction, i.e time to first instance of BLQ or to the lowest measured value;
- the area under the effect curve (AUEC)

Specifically, similarity was explored for sCTX-1 using:

- percent change of sCTX-1 from baseline at 24 weeks (168 days) post-dose
- sCTX-1 suppression at 4 weeks (28 days) post-dose

and, for uNTx using:

- uNTx suppression at 4 weeks (28 days) post-dose

PD sampling

Blood samples (4 mL) for the measurement of sCTX-1 and P1NP were obtained pre-dose and up to 252 days after IMP administration.

Urine samples (20 mL) for the measurement of uNTx and uNTx/Cr were collected pre-dose and up to 252 days after IMP administration.

Analysis methods

sCTX-1 Percent Change from Baseline at Day 169

The analysis model for comparing TVB-009P to Prolia (US), TVB-009P to Prolia (EU), and Prolia (EU) to Prolia (US) for sCTX-1 percent change from baseline at day 169 (or week 24) was an ANOVA with treatment as a fixed effect and with sCTX-1 level at baseline and body weight category (<70 kg; ≥70 kg through ≤90 kg; >90 kg) as covariates. All comparisons were included in the same model. The LS means, differences between the respective LS means, and the 95% CI associated with these differences were determined.

sCTX-1 and uNTx Suppression at Day 29

The binary outcome variables sCTX-1 suppression and uNTX suppression were compared between the two treatment groups using the 90% CI of the difference between the proportions of subjects with suppression at week 4. In addition, the values and the percent changes from baseline up to each timepoint of sampling of sCTX-1, uNTx/Cr and P1NP, as well as the time to maximal reduction and the value of the AUEC for each of these endpoints was to be summarized by treatment group and presented using descriptive statistics.

PD results

Table 13: Statistical analysis of sCTX-1 Percent change from Baseline at Day 169

Treatment Group	N	LS GM	95% CI of LS Mean	Comparison	LS GM Ratio	95% CI of LS GM Ratio
TVB-009P 60 mg	104	-77.5	-80.7, -74.2			
PROLIA (US) 60 mg	99	-77.2	-80.5, -73.8			
PROLIA (EU) 60 mg	104	-78.6	-81.9, -75.4			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	-0.3	-4.4, 3.8
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	1.1	-2.9, 5.2
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	-1.5	-5.6, 2.6

Source: Summary 15.17
Percent change values were analyzed using an ANOVA with treatment group as a fixed effect, and weight category and the baseline value as a covariate.
LLOQ for sCTX-1 is 0.033 ng/mL.
For calculation of inferential statistics, results <LLOQ are assigned the LLOQ value.
ANOVA=analysis of variance; GM=geometric mean; LLOQ=lower limit of quantification; LS=least square; sCTX-1=serum C-telopeptide cross-link of type 1 collagen; vs=versus.

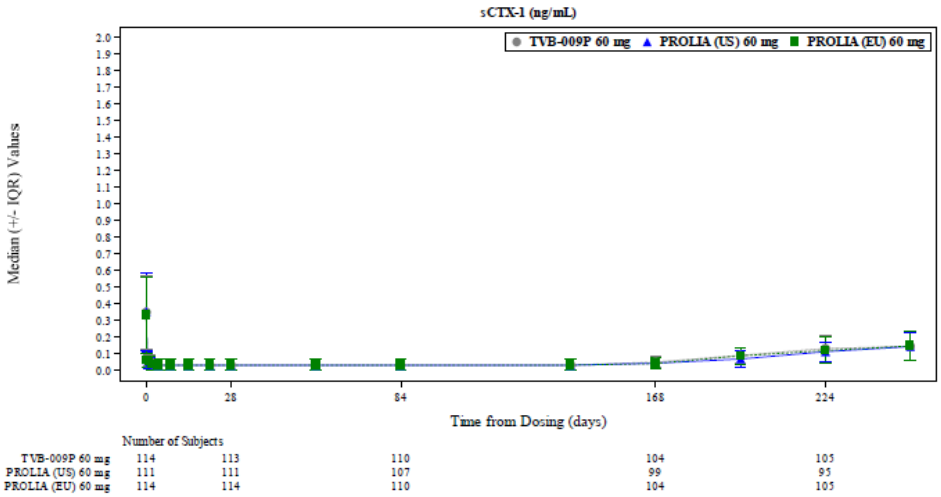
Table 14: Statistical analysis of sCTX-1 and uNTx suppression at Day 169

Parameter	Treatment Group	N	Suppression Proportion	Comparison	Proportion Difference	90% CI of Proportion Difference
sCTX-1 at Day 29	TVB-009P 60 mg	113	0.95			
	PROLIA (US) 60 mg	111	0.92			
	PROLIA (EU) 60 mg	114	0.96			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	0.03	-0.082, 0.140
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	-0.01	-0.118, 0.100
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	0.04	-0.074, 0.145
uNTx at Day 29	TVB-009P 60 mg	113	0.30			
	PROLIA (US) 60 mg	111	0.36			
	PROLIA (EU) 60 mg	114	0.27			
				TVB-009P 60 mg vs PROLIA (US) 60 mg	-0.06	-0.167, 0.052
				TVB-009P 60 mg vs PROLIA (EU) 60 mg	0.03	-0.083, 0.135
				PROLIA (EU) 60 mg vs PROLIA (US) 60 mg	-0.09	-0.198, 0.022

Source: Summary 15.19
BLQ=below the limit of quantitation; CI=confidence interval; sCTX-1=serum C-telopeptide cross-link of type 1 collagen; LLOQ=lower limit of quantification; uNTX=urinary N-telopeptide; vs=versus.
LLOQ for sCTX-1 is 0.033 ng/mL and for uNTx is 20 nM.
Suppression is defined as a BLQ result.
CIs based on exact test for difference in proportions.

Figure 5: Median concentration-time profiles of biomarkers of bone turnover

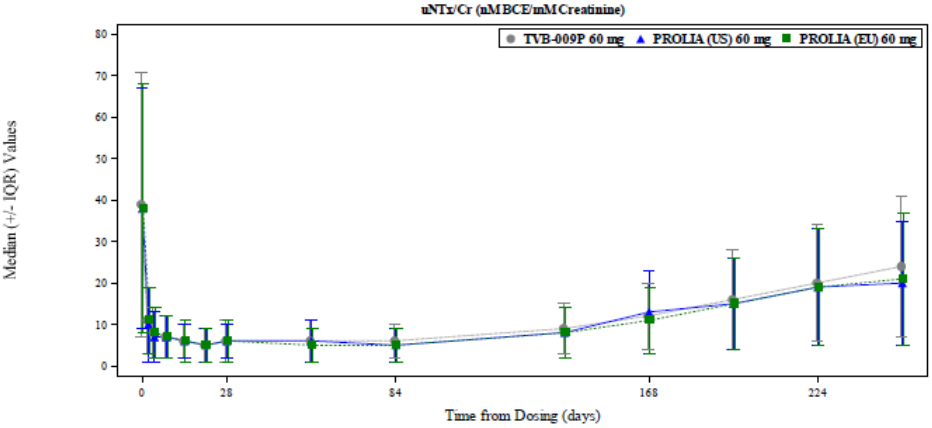
sCTX-1



Number of Subjects

TVB-009P 60 mg	114	113	110	104	105
PROLIA (US) 60 mg	111	111	107	99	95
PROLIA (EU) 60 mg	114	114	110	104	105

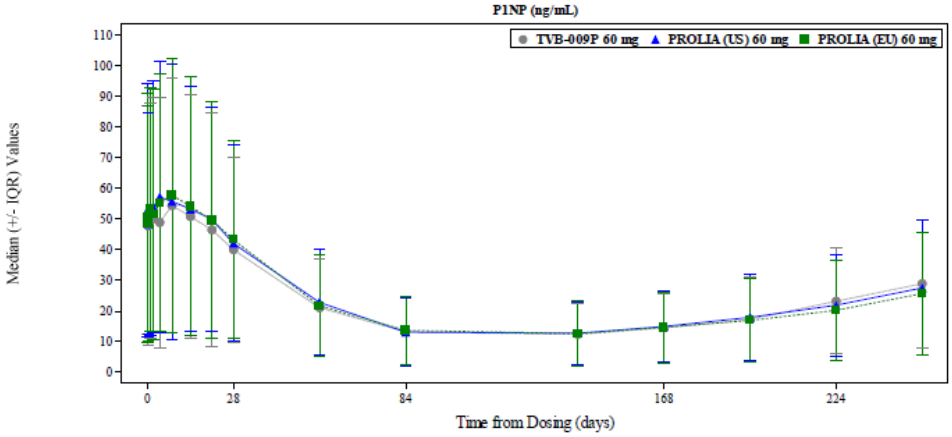
uNTX/Cr



Number of Subjects

TVB-009P 60 mg	114	113	110	104	105
PROLIA (US) 60 mg	111	111	107	99	95
PROLIA (EU) 60 mg	114	114	110	104	105

P1NP



Number of Subjects

TVB-009P 60 mg	114	113	110	104	105
PROLIA (US) 60 mg	111	111	107	99	95
PROLIA (EU) 60 mg	114	114	110	104	105

Source: Ad Hoc Figure 1

IQR=interquartile range; P1NP=procollagen type 1 N-terminal propeptide; sCTX-1=serum C-telopeptide cross-link of type 1 collagen; uNTX/Cr=urinary N-telopeptide corrected for urine creatinine levels.

Table 15: Median time to maximum reduction

Variable	Statistic	TVB-009P 60 mg (N=114)	PROLIA (US) 60 mg (N=111)	PROLIA (EU) 60 mg (N=114)
sCTX-1 time to maximal reduction (days)	n	106	98	108
	Median	4.0	4.0	4.0
	Min, max	0, 28	0, 28	0, 28
uNTx/Cr time to maximal reduction (days)	n	106	98	108
	Median	21.0	24.5	21.0
	Min, max	2, 141	2, 224	2, 168
P1NP time to maximal reduction (days)	n	106	98	108
	Median	140.0	140.0	140.0
	Min, max	55, 224	56, 196	84, 197

TVB009-IMB-30085

Two markers of bone turnover were assessed in study TVB009-IMB-30085: sCTX-1 and P1NP. sCTX-1 was assessed as a co-primary endpoint in this study.

Primary PD endpoint was percent Change from Baseline in Serum C-telopeptide Cross-link of Type 1 Collagen (sCTX-1) at Week 26

Secondary PD endpoints during the Main Treatment period were:

- percent change from baseline in sCTX-1 at all time-points
- sCTX-1 suppression at week 4 (defined as sCTX-1 level below the limit of quantitation)
- percent change from baseline in procollagen type 1 N propeptide (P1NP) at week 26 and week 52

Additionally, PD markers were assessed in the transition period as well.

PD sampling

Blood samples (4 mL) for assessment of sCTX-1 and P1NP were collected via venipuncture or indwelling catheter before and up to 78 weeks after administration of first IMP dose at visit 2 (baseline), visit 3 (Day 15), visit 4 (Week 4), visit 5 (week 8), visit 6 (week 12), visit 7 (week 26), visit 8 (week 39), visit 9 (week 52, EOM), visit 10 (week 54), visit 11 (week 65), visit 12 (week 78, EOS/ET).

Blood sampling for sCTX-1 and P1NP assessment was taken in the morning hours after overnight fasting. Samples were collected consistently at the same time of the day for an individual participant at all visits. Vigorous exercise was to be avoided the day prior to sampling.

Results

Co-primary endpoint: Percent Change from Baseline in Serum C-telopeptide Cross-link of Type 1 Collagen (sCTX-1) at Week 26

Table 16: Analysis of the Percent Change from Baseline to Week 26 in Serum C-telopeptide cross-link of Type 1 collagen (sCTX-1) (modified intent-to-treat analysis set)

Statistic	TVB-009P (N=157)	PROLIA US (N=152)
LS mean	-56.05	-65.13
95% CI for LS mean	-64.99, -47.12	-74.09, -56.17
LS mean difference TVB-009P – PROLIA US	9.07	
95% CI for the difference	-0.14, 18.29	

Source: Summary 14.2.1.2, Listing 16.2.6.3
ANCOVA = analysis of covariance; BLQ = below limit of quantitation; CI = confidence interval; LS = least squares; LLOQ = lower limit of quantitation; sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; US = United States.
LS means, differences and CIs from the ANCOVA model with percent change from baseline to week 26 in sCTX-1 as the outcome, treatment group, region and previous use of bisphosphates as fixed effects, baseline sCTX-1 and baseline weight as covariates.
Missing outcomes were not imputed. Results BLQ were imputed as the LLOQ = 0.033 ng/mL
Biosimilarity was to be demonstrated if the 95% CI for the difference fell entirely within the equivalence margin of (-20, +20).

Sensitivity/supplementary analyses of the co-primary PD endpoint

ITT analysis set

Table 17: Analysis of the Percent Change from Baseline to Week 26 in Serum C-telopeptide cross-link of Type 1 collagen (sCTX-1) (Intent-to-treat analysis set)

Statistic	TVB-009P (N=166)	PROLIA US (N=166)
LS mean	-56.49	-65.21
95% CI for LS mean	-65.28, -47.69	-74.08, -56.33
LS mean difference TVB-009P – PROLIA US	8.72	
95% CI for the difference	-0.36, 17.81	

Source: Summary 14.2.3.7, Listing 16.2.6.3
ANCOVA = analysis of covariance; BLQ = below limit of quantitation; CI = confidence interval; LS = least squares; LLOQ = lower limit of quantitation; sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; US = United States.
LS means, differences and CIs from the ANCOVA model with percent change from baseline to week 26 in sCTX-1 as the outcome, treatment group, region and previous use of bisphosphates as fixed effects, baseline sCTX-1 and baseline weight as covariates.
Missing outcomes were not imputed. Results BLQ were imputed as the LLOQ = 0.033 ng/mL
Biosimilarity was to be demonstrated if the 95% CI for the difference fell entirely within the equivalence margin of (-20, +20)

Per-protocol (PP) analysis set

Table 18: Supplementary analysis of the percent change from Baseline to Week 26 in sCTX-1 per protocol analysis set

Statistic	TVB-009P (N=138)	PROLIA US (N=133)
LS Mean	-56.10	-70.60
95% CI for LS Mean	-65.29, -46.91	-79.93, -61.27
LS Mean Difference TVB-009P - PROLIA US	14.50	
95% CI for the Difference	4.88, 24.12	

Secondary PD endpoints (Main Treatment period)

- Percent Change from Baseline in Serum C-telopeptide Cross-link of Type 1 Collagen (sCTX-1) at All Time-Points

Table 19: Summary of serum C-telopeptide cross-link of type 1 collagen (sCTX-1, ng/mL) in the main treatment period (Modified intent-to-treat analysis set)

Visit	TVB-009P	PROLIA US
Mean (SD) percent change from baseline to:		
Day 15	-84.27 (17.649)	-85.29 (17.785)
Week 4	-85.22 (16.284)	-85.24 (17.878)
Week 8	-85.18 (15.895)	-85.44 (17.466)
Week 12	-85.20 (15.837)	-85.59 (17.540)
Week 26	-60.03 (49.389)	-70.30 (30.874)
Week 39	-84.61 (17.498)	-84.72 (21.340)
Week 52	-57.91 (44.161)	-68.80 (35.846)

Source: Excerpt from Summary 14.2.4.4.1, Listing 16.2.6.3
BLQ = below limit of quantitation; LLOQ = lower limit of quantitation; sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; SD = standard deviation; US = United States.
Baseline was defined as the last assessment prior to the first administration of the trial drug. Missing values were not imputed. sCTX-1 levels BLQ were imputed as the LLOQ = 0.033 ng/mL.

- Serum C-telopeptide Cross-link of Type 1 Collagen (sCTX-1) Suppression at Week 4

Table 20: Summary of serum C-telopeptide cross-link of type 1 collagen (sCTX-1) suppression at Week 4 (Modified intent-to-treat analysis set)

Statistic	TVB-009P (N=157)	PROLIA US (N=152)
n/M (%)	146/155 (94.2)	142/151 (94.0)
Difference in % (95% CI) TVB-009P – PROLIA US	0.2 (-5.1, 5.4)	

Source: Summary 14.2.4.7, Listing 16.2.6.3
BLQ = below limit of quantitation; CI = confidence interval; M = total number of participants with any sCTX-1 assessment at week 4; n = number of participants with sCTX-1 suppression at week 4; US = United States.
sCTX-1 suppression was defined as sCTX-1 level BLQ.
Percent was calculated as n/M*100%.

- Percent Change from Baseline in Procollagen Type 1 N Propeptide (P1NP) at all time-points

Table 21: Summary of procollagen type 1 N propeptide (P1NP, ng/mL) in the main treatment period (Modified intent-to-treat analysis set)

Visit	TVB-009P (N=157)	PROLIA US (N=152)
Mean (SD) percent change from baseline to:		
Day 15	2.20 (29.023)	6.07 (38.974)
Week 4	-20.62 (26.375)	-16.82 (42.774)
Week 8	-58.33 (21.796)	-55.93 (25.074)
Week 12	-69.27 (22.799)	-68.69 (22.841)
Week 26	-59.81 (27.330)	-64.01 (21.779)
Week 39	-72.53 (18.105)	-73.08 (20.714)
Week 52	-56.43 (35.431)	-62.03 (33.712)

Source: Excerpt from Summary 14.2.4.5.1, Listing 16.2.6.3
BLQ = below limit of quantitation; LLOQ = lower limit of quantitation; max = maximum; min = minimum; SD = standard deviation; US = United States.
Baseline was defined as the last assessment prior to the first administration of the trial drug.
Missing values were not imputed. P1NP levels BLQ were imputed as the LLOQ = 2 ng/mL.

2.5.3. Discussion on clinical pharmacology

Assays

The presented Pharmacokinetic assay to measure TVB-009/Denosumab in human serum was well described and established. All reagents, matrices and antibodies and used lot numbers were provided. The assay was validated according to the guideline on bioanalytical method validation and validated for its accuracy/precision, selectivity, specificity, interference, dilutional linearity, hook effect, stability, and robustness. All measured parameters were acceptable. Analytical comparability between standard curves including 8 non-zero concentrations for TVB-009, EU-Prolia and US-Prolia was confirmed. Performance of the assay during clinical studies is considered acceptable. All calibration standards and QCs met the acceptance criteria, and all samples were tested within the validated storage time. Incurred sample reanalysis was performed according to the guideline on bioanalytical method validation.

For pharmacodynamic measurement, validated commercially available kits were used. They were well described and set up correctly and they are considered valid for their intended use. The applicant performed partial validations including denosumab interference, carry-over, stability, and parallelism. Performance of the assays during clinical studies is acceptable.

The methods to determine immunogenicity (ADA, nAB assay) were well described and developed. The assays were validated and established according to the guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). All critical reagents, drugs, matrices and antibodies and used lot numbers were provided. The assays were validated with respect to cut-points (screening, confirmatory), sensitivity, drug tolerance, target interference, assay precision, selectivity, haemolytic/lipemic interference, robustness, and the analyte was tested for stability (short-term, freeze/thaw).

Studies with Pharmacokinetic and Pharmacodynamic data

Similarity in PK and PD between TVB-009 and the reference product (Prolia) was investigated in a phase 1 PK/PD trial in healthy subjects (TVB009-BE-10157) and in a phase 3 efficacy and safety trial in patients with postmenopausal osteoporosis (TVB009-IMB-30085). Both trials are completed.

Study TVB009-BE-10157 was a randomized, double-blind, single-dose, 3-arm parallel-group study, with an aim to demonstrate the PK and PD similarity of TVB-009P versus US-Prolia, and EU-Prolia in healthy subjects. The study design is considered appropriate for the characterization of the PD profile of the investigated products.

The study population comprised healthy male and female subjects aged 28-55 years with a BMI of 18.5-29.9 kg/m² (inclusive) and a body weight of ≥50 kg. Healthy volunteers are considered a sensitive population for a bioequivalence study. Inclusion of subjects >28 years of age to ensure bone maturity is agreed too. Subjects with a prior history of bone disease or conditions affecting bone metabolism were excluded, as well as subjects with any previous exposure to any anti-RANKL therapy and any other osteoporosis treatment and subjects with exposure to any biologic therapy in the last 3 months before screening or within 5 half-lives, whichever was longer. In addition, subjects with notable alcohol and cigarette consumption were excluded from the study. The overall eligibility criteria are acceptable.

Subjects were randomized in a 1:1:1 ratio to receive a single s.c. injection of either 60 mg of TVB009/EU-Prolia/US-Prolia. Randomisation was stratified by ethnicity and weight category. There is no concern regarding noteworthy bias related to allocation issues. The study was double-blind. Only the pharmacist or designee who was supposed to dispense the study drug and the study drug administrator were planned to be unblinded; these staff members were not supposed to participate in assessments. According to the descriptions provided in the study documentation, adequate blinding methods were planned and applied.

The primary objective of the study was to demonstrate the pharmacokinetic similarity of TVB-009P with EU-Prolia.

The co-primary endpoints were C_{max}, $AUC_{0-\infty}$ and AUC_{0-t}. C_{max} and $AUC_{0-\infty}$ are in line with requirements for demonstration of similarity after sc administration of a single dose monoclonal antibody (EMA/CHMP/BMWP/403543/2010), while AUC_{0-t} is not needed for EU MAA but is not objected to. Additional PK parameters are standard PK parameters in a bioequivalence study and are acceptable. The secondary endpoints were t_{max}, the apparent serum terminal elimination rate constant (λz), the apparent total body clearance (CL/F) the apparent volume of distribution during the terminal phase (Vz/F), AUC from pre-dose to several time points post-dose.

For the primary data analyses of the AUC parameters, initially single observations had been excluded based on pre-defined criteria which were not considered reasonable in this assessment. As those data exclusions affected primary analyses outcome, the applicant was requested to provide new analyses including all participants from the PK set, ignoring the pre-defined exclusion criteria. Compared to the analysis excluding subjects, the reanalysis data showed the AUC_{0-t} did not change (neither in PE nor in CIs), while AUC_{0-ext} changed minimally. The confidence intervals were contained within the pre-specified margins, therefore the results of these analyses do not change the conclusion on PK equivalence.

The study also evaluated pharmacodynamic similarity of TVB-009 and Prolia (EU and US). The PD endpoints comprised serum C-telopeptide cross-link of type 1 collagen (sCTX-1) and urinary N-telopeptide (uNTx) corrected for urine creatinine levels (uNTx/Cr) as biomarkers of bone resorption and procollagen type 1 N-terminal propeptide (P1NP) as a biomarker of bone formation.

A sample size of 345 randomized subjects (115 subjects per arm) was chosen to provide 291 subjects (97 subjects per arm) in the PK Analysis Set. Sample size calculations can be followed from the computational perspective. No issues are raised in relation to power and sample size.

Statistical methods and analysis sets

Analysis sets were defined to form the basis of the statistical analyses of different endpoints; these sets generally conform to standard definitions.

The PK outcome of two products was considered similar if the 90% CIs of the LS GMRs for all co-primary PK endpoints fell entirely within the pre-defined bounds of the standard bioequivalence margin [0.80 to 1.25]. An ANOVA was applied for analysis of the co-primary PK endpoints C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, which is considered adequate.

The supportive descriptive analyses of the co-primary PK endpoints, as well as those of the secondary and exploratory endpoints is acceptable.

Two interim analyses were carried out without relevant impact on trial outcome interpretation.

Study TVB009-IMB-30085 was a randomized, double-blind, multinational, multicenter study to demonstrate similar efficacy and safety of TVB-009P compared to Prolia US administered in 3 sc doses of 60 mg every 26 weeks (3 injections) in postmenopausal women with osteoporosis. The study design is described in the discussion on clinical efficacy.

In the study, the comparison of PK between TVB-009P and Prolia US was an exploratory objective. The PK endpoints were serum concentration at 2 weeks post-dose (C_{2weeks}), C_{trough} before the second dose, C_{trough} before the third dose and C_{trough} 6 months after the third dose.

The study also evaluated PD similarity of TVB-009 and Prolia-US in terms of sCTX and P1NP. The Percent Change from Baseline (%cfb) in Serum C-telopeptide Cross-link of Type 1 Collagen (sCTX-1) at Week 26 was a co-primary endpoint, together with the percent change from baseline at Week 52 in LS-BMD. Both endpoints are of importance, s-CTX for having a better dynamic response and therefore being more sensitive, and BMD for being of greater clinical relevance. For more information, including the estimand, margins, analysis sets, statistical methods for estimation and sensitivity analysis etc. please refer to the discussion on clinical efficacy.

The secondary PD endpoints during the main treatment period included %cfb in sCTX-1 at all time-points, sCTX-1 suppression at week 4 and percent change from baseline in P1NP at week 26 and week 52. sCTX and P1NP were also assessed in the transition period.

Overall, the design of both studies is considered adequate and sufficient to investigate bioequivalence of TVB-009 to Prolia.

Results

Study TVB009-BE-10157

All 345 subjects enrolled received at least 1 dose of the study drug. In total, 312 (90%) subjects completed the study. A total of 33 (10%) subjects withdrew. The most frequent reason for withdrawal was loss to follow-up. No concerns are raised regarding the subject who withdrew.

The treatment groups were balanced regarding age, body weight and BMI. Overall, the percentages of men and women were the same (50% men and 50% women), but there were more men than women in the EU-Prolia and US-Prolia groups compared to the TVB-009P group. This imbalance is slight and numerically within what would be expected by chance and is not expected to have a notable influence on the results. The protein concentration in batches used in the study was similar for all three products (61 mg/mL, 61.7 mg/mL and 59.4 mg/mL for US-Prolia, EU-Prolia and TVB009, respectively).

PK outcomes

The concentration-time curves for the whole study population were comparable between the treatment groups following administration of a single s.c. dose of the respective product. Nonetheless, a tendency for under-availability of TVB-009P compared to EU-Prolia is observed, which is reflected in lower estimates of C_{max} as well as $AUC_{0-\infty}$ and AUC_{0-t} for TVB-009P compared to EU-Prolia.

The apparent total body clearance (CL/F) was somewhat larger for TVB-009 compared to EU-Prolia (200.3 mL/day and 188.2 ml/Day, respectively). Similarly, the apparent volume of distribution (Vz/F) was somewhat larger for TVB-009 compared to EU-Prolia (3810.9 mL and 3545.4 mL, respectively). Both CL/F and Vz/F estimates are in line with general under-availability of TVB-009P.

T_{max} for TVB-009 was reached later (median t_{max} 12 days) compared to EU-Prolia (median t_{max} 8 days). Since the dosing of Prolia is one injection every 6 months, this difference is unlikely to have a relevant impact on the efficacy.

The primary analysis

The geometric LS mean ratios (TVB-009P/EU-Prolia) for C_{max}, $AUC_{0-\infty}$ and AUC_{0-t}, were 0.902 (90% CI [0.8337, 0.9769]), 0.936 (90%CI [0.8665, 1.0129]) and 0.924 (90%CI [0.8522, 1.0021]), respectively. The 90% CIs around the geometric LS mean ratio (TVB-009P/EU-Prolia) for all three co-primary endpoints fell entirely within the [80.00%, 125.00%] equivalence range. Based on these results, the equivalence was demonstrated. However, individual concentration-time curves raise doubts regarding the validity of raw concentration data and the study results in general.

In several subjects' individual serum concentration profiles, a sudden drop in concentration at a single evaluation time point was observed, followed by recovery to previous concentration levels at the subsequent evaluation time point. Additionally, some subjects exhibited multiple peaks in concentration levels interspersed with less drastic declines. These results occurred in a substantial number of subjects. Since many of these irregular concentration values were observed close to t_{max}, this was considered to have potential implications for estimation of both AUC as well as on C_{max}. It is of note that these patterns occur across all treatment groups.

The applicant was asked to meticulously investigate any potential causes for fluctuations in the denosumab blood serum concentration-time curves. The applicant conducted a comprehensive investigation encompassing blood sampling procedures, shipping and handling conditions, sample haemolysis/lipemia, assay performance, freeze/thaw cycles, sample splitting, incurred sample reanalysis inclusion, anomalous investigations, analyst training, dilution factors, laboratory operations, and data management activities. No root cause related to methodological, procedural, technical, human-related, or laboratory-related aspects could be identified for the sudden drops in concentration followed by recovery to higher levels.

Further, the applicant provided a literature-backed rationale for how the fluctuations in denosumab concentrations in the blood plasma serum could occur through the interplay of the formation of different denosumab–RANKL complexes and the compensatory upregulation of RANKL in response to treatment. While this biological explanation for the irregular PK curves could indeed be plausible, it is not well-established or testable.

Since this phenomenon had been observed in several denosumab biosimilar candidates, the CHMP called on the Methodology Working Party (MWP) to consult a pharmacokinetic Operational Expert Group (PK OEG) on this matter. In the MWP response to CHMP, the PK OEG concludes that "several possible justifications were provided in the literature but those seem speculative at this time and we cannot fully present any definitive root cause in the denosumab cases."

In summary, neither the applicant nor the MWP were able to identify a (single) definitive reason for denosumab fluctuations in PK concentration data. Hence, uncertainty in relation to this phenomenon needs to be accounted for in the current assessment and PK equivalence needs to be assessed based on the available data.

Fluctuations were observed with both the biosimilar candidate and the reference product. The applicant has sufficiently demonstrated that the distribution of concentration-time profiles that deviate notably from the average profile estimated using the PopPK model is comparable between treatment arms.

Assuming the observed phenomenon is real, and the data are therefore valid, and further considering that the non-compartmental model is considered the gold standard for analysing PK profiles with intense sampling schemes, and no alternative model is currently deemed more suitable, no relevant concerns would remain as regards the conclusion on PK-equivalence. It could even be argued that the potential for such fluctuations would make it more challenging for the biosimilar candidate to show similarity. On the other hand, some uncertainty in relation to data validity persist, and it cannot be entirely ruled out from the methodological perspective that the observed phenomenon could bias the equivalence testing towards too liberal similarity conclusion (making the compared groups more similar that they actually are).

The primary analysis based on the full dataset, including subjects with large fluctuations, demonstrated PK similarity of the biosimilar candidate to the reference product. The value of post- hoc analyses that exclude extreme values/subjects is questionable, as such an approach requires defining a cut-off for determining which concentrations at a single time point or which PK profiles as a whole are considered impacted, which can only be arbitrary. These analyses are therefore not requested.

In conclusion, despite the largely unexplained nature of the observed phenomenon, further pursuit of the issue is not considered necessary and PK equivalence PK can be concluded.

It is also of note that the estimated coefficient of variation for all co-primary endpoints as well as the estimated percentage difference in treatment effect from the complete trial exceeded the anticipated values that were provided in the SAP and used for sample size calculations. This phenomenon might also be seen as indicator of data errors and may change towards formerly expected magnitudes of variability once issues regarding the serum individual concentration profiles have been addressed.

A total of 4.7% subjects in the PK analysis set had non-zero pre-dose denosumab concentrations (7, 5 and 4 participants in the TVB-009P, EU-Prolia, and US-Prolia group, respectively). Although the applicant could not identify a reason for non-zero pre-dose denosumab concentrations, analyses both including and excluding these subjects fell within standard equivalence margins.

PD outcomes

Three biomarkers of bone turnover were assessed in the study TVB009-BE-10157: sCTX-1, uNTX/Cr and P1NP.

For each biomarker of bone turnover, all 3 treatment groups had a similar concentration-time profile over the course of the study.

sCTX decreased in a similar manner in all 3 treatment groups. The LS geometric mean for the %cfb to Day 169 (Week 25) was -77.5, -77.2 and -78.6 for TVB-009P, US-Prolia and EU-Prolia, respectively. The LS GM ratio (TVB-009 vs. EU-Prolia) was 1.1 (95% CI [-2.9, 5.2]). The other two comparisons (TVB-009P and US-Prolia and US-Prolia and EU-Prolia) yielded similar results. At Day 85, the percentage of subjects with suppression was high (>95%) and similar between all groups. From day 141 onwards, sCTX-1 levels started increasing again, similarly in all treatment groups, reflecting the known reversibility of denosumab effects on bone remodelling once serum levels diminish.

Since the PD endpoints are secondary endpoints in this Phase I study, the assessment of formal analyses of equivalence is of minor importance. Nonetheless, analyses carried out provide supportive evidence for a biosimilarity claim.

Median time to reach maximal reduction, of sCTX-a, uNTX/Cr and P1NP was similar in all 3 treatment groups for each biomarker. For sCTX-1, median time to maximal reduction was 4 days in all treatment groups. This is in line with the information given in the Prolia SmPC, according to which a nadir for s-CTX-1 was reached by 3 days. Similarly, for each biomarker of bone turnover, all 3 treatment groups had comparable AUEC values.

The PD results in healthy subjects supported biosimilarity of TVB-009 to Prolia (EU and US).

Study TVB009-IMB-30085

For changes in the planned conduct of study, participant flow, baseline data and protocol deviations, please see discussion on efficacy section.

PK outcomes

At Day 15, denosumab concentration (C_{2weeks}) in the TVB-009 group was about 10% lower compared to the US-Prolia group, similar to the difference of 10% in C_{max} between TVB-009 and EU-Prolia observed in the Phase 1 study. C_{trough} before second and third dose was low in both groups, and most participants had denosumab concentrations BLQ. Following second administration, denosumab concentrations increased again, also in the transition period.

Similar to the observations made in the Phase 1 study, individual concentration-time curves showed irregular concentration-time profiles. The distribution of concentration-time profiles that deviate notably from the average profile estimated using the PopPK model is comparable between treatment arms.

PD outcomes

The change from baseline in sCTX-1 at Week 26 was -56.05% and -65.13% in the TVB-009 and Prolia group, respectively. The LS mean difference (TVB009 – Prolia) for %cfb in sCTX-a at Week 26 (mITT) was 9.07 with the 95% CI falling within the pre-specified equivalence margin of ±20%. Though meeting the pre-specified margin, TVB-009 had approximately 9% lower effect on the decrease of sCTX-1 compared to Prolia. Additionally, the upper bound of the 95% was near the upper limit of the margin (95% CI [-0.14, 18.29]).

While biosimilarity between TVB-009P and Prolia US was demonstrated for both co-primary endpoints (see efficacy results) using the mITT analysis set, the analysis based on the PP analysis set for sCTX-1 failed i.e. the upper limit of the 95% CI was outside the pre-specified margin (95% CI [4.88, 24.12]). The results of sensitivity and supplementary analyses for sCTX-1 yielded similar results as the primary analysis.

sCTX-1 levels decreased by 56.05% in the TVB-009 group and 65.13% in the Prolia group from baseline to Week 26. However, an analysis of individual response data revealed that some patients experienced either a much smaller decrease or even a marked increase in sCTX-1 levels at Week 26 compared to baseline. These patients are considered outliers that strongly impact the primary analysis of sCTX-1 in terms of the mean value and the position/width of the confidence interval. The applicant was asked to visualize the distribution of observed sCTX-1 %cfb values per study arm for week 26 and explore the sensitivity of the primary analysis to outliers. It appears the original biosimilarity assessment on the PP analysis set was impacted by a single outlier. An analysis excluding this participant in the TVB-009 treatment group with a value >300 yielded 95% CIs of the estimated mean differences that were completely contained within the usual equivalence range of +/-20%.

As opposed to the phase 3 study, the difference in mean % change from baseline in sCTX-1 in the phase 1 study was very small, providing reassurance that, without extreme values, the results between treatments are more similar.

The %cfb in sCTX-1 was similar between treatment arms over time. At Week 4, the percentage of patients with sCTX-a suppression was high (94%) and similar between the groups. This is consistent with finding from the phase 1 study, where at Day 29, the number of participants with suppression of sCTX-a (levels BLQ) was >90% in all 3 treatment groups.

Following the first denosumab dose, levels of sCTX-1 decreased from baseline to Week 26 in both treatment groups and remained suppressed until approximately Week 26, after which they increased again. This is in line with observations made for the reference product and aligns with the timing of the second dose administration according to the Prolia SmPC. This is also consistent with the observations in the phase 1 study in healthy subjects (TVB009-BE-10157). In the phase 3 study, up to Week 26, the percentage of patients with sCTX-1 suppression was very high (up to 96%) and similar between the treatment arms. At Week 26, prior to administration of the second dose, the percentage of patients with sCTX-a suppression was lower in the TVB-009 arm compared to the Prolia arm (26.9% vs. 35.6%), which suggests that the effect of TVB-009 wanes off earlier. Following administration of the second dose, the suppression was again very high and comparable between the treatments.

The results for P1NP were comparable between treatments over time.

2.5.4. Conclusions on clinical pharmacology

Although the reasons for fluctuations in denosumab concentrations remain elusive, based on the provided data, the PK similarity is considered to be demonstrated. The PD equivalence is also considered to be established.

2.5.5. Clinical efficacy

Table 22: Description of clinical efficacy studies with TVB-009

Number of Trial Centers, Locations	Trial Start Date Enrollment Status and Date Total Enrollment/ Planned	Trial Design Trial Duration	Treatments (Dose, Route, Regimen)	Trial Objective	Diagnosis Inclusion Criteria	Number of Participants Entered/ Completed Gender M/F Age: Mean ± SD	Primary Efficacy Endpoint Other Efficacy Assessments
Trial TVB009-IMB-30085							
71 trial sites (71 sites screened participants and 58 sites randomized participants) across 10 countries	Started: 22 March 2021 Completed 19 June 2023 332/326	Randomized, double-blind, multinational, multicenter trial. 82 weeks	TVB-009P: 60 mg/mL (1 mL) PFS PROLIA US: 60 mg/mL (1 mL) PFS sc injection 3 sc doses of 60 mg/mL; 26 weeks apart First dose of TVB-009P or PROLIA US following randomization; second dose 26 weeks after the first dose; third dose at week 52	To demonstrate that there were no clinically meaningful differences in efficacy between TVB-009P and PROLIA US administered sc in patients with postmenopausal osteoporosis	Female postmenopausal[a] patients with osteoporosis at age ≥60 and ≤90 years, body weight ≥50 kg and ≤90 kg (≥110 lb and ≤198 lb) at screening, BMD measurement T score of less than -2.5 but not less than -4.0 by DXA at the lumbar spine at screening, at least 3 vertebrae in the L1-L4 region that were evaluable by DXA, serum 25 (OH) vitamin D level >20 ng/mL at screening and no current hyper- or hypocalcemia, agreed to be supplemented with 1000 mg calcium and at least 400 IU	Randomized/ Enrolled: 332 Completed: 276[b] 332 F Age[c]: 68.1 ± 5.63 years	Percent change from baseline in LS-BMD at week 52 based on centrally assessed DXA measurements, percent change from baseline in sCTX-1 at week 26; percent change from baseline in P1NP at week 26 and week 52; total hip and femoral neck BMD by DXA measurement, assessment of lateral spine X-ray vertebral fracture, assessment of non-vertebral fractures.

			(26 weeks after the second dose)		vitamin D daily from screening until the last visit		

Source: Clinical Study Report (CSR) of Trial TVB009-IMB-30085

[a] The postmenopausal status was defined as: spontaneous amenorrhea for >12 months, or spontaneous amenorrhea >6 months and serum FSH and E2 in menopausal range, or surgical menopause at least 6 weeks before the start of screening.

[b] Number of participants who completed the entire trial.

[c] Reported for all randomized participants.

BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; E2 = estradiol; EU = European Union; F = female; FSH = follicle stimulating hormone; L1 = lumbar vertebra1; L4 = lumbar vertebra4; LS-BMD = lumbar spine-bone mineral density; M = male; PFS = prefilled syringe; P1NP = procollagen type 1 N propeptide; sc = subcutaneous; sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; SD = standard deviation; US = United States.

2.5.5.1. Dose response study(ies)

Not applicable for biosimilars

2.5.5.2. Main study(ies)

TVB009-IMB-30085

Methods

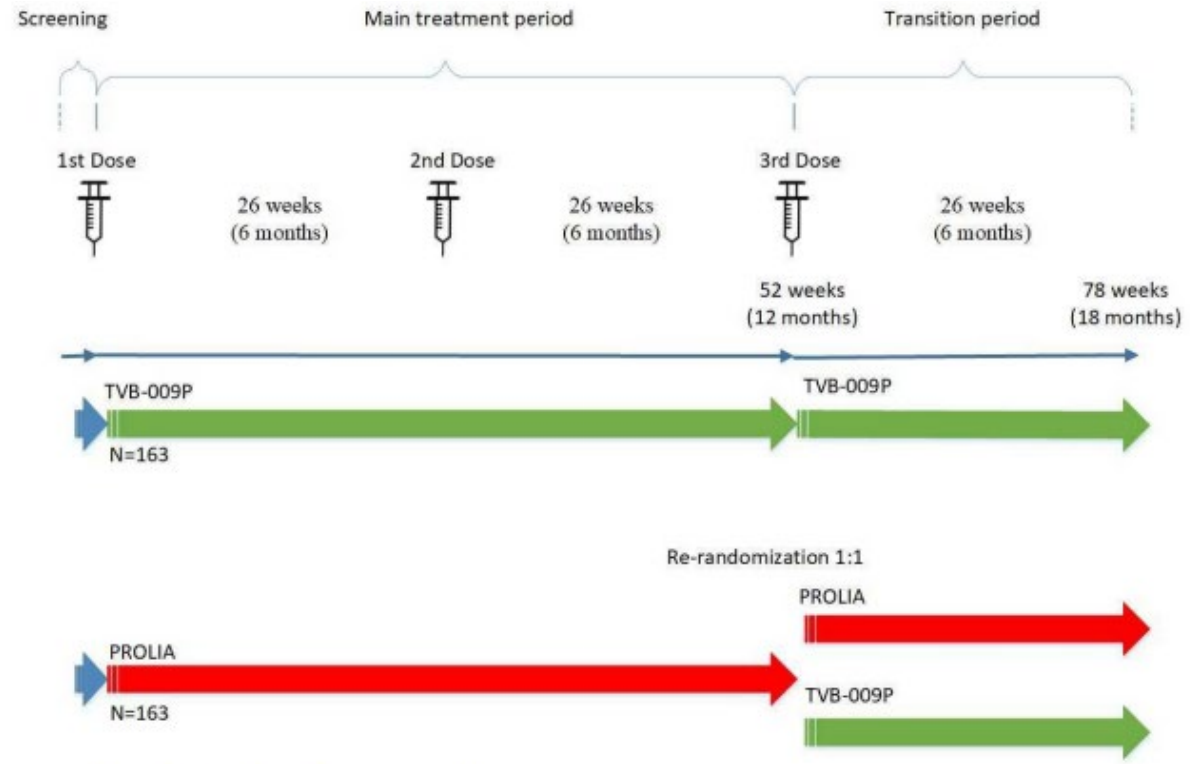
This was a randomized, double-blind, multinational, multicenter study to demonstrate similar efficacy and safety of TVB-009P compared to Prolia US administered in 3 sc doses of 60 mg every 26 weeks (3 injections) in patients with PMO. This study consisted of a screening period (up to 4 weeks) and a 52-week double-blind main treatment period (2 arms), followed by a 26-week double-blind transition period (3 arms).

At baseline, participants were randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or Prolia US ("main treatment period"). The first dose of TVB-009P or Prolia US was administered following randomization. The second dose was administered 26 weeks after the first dose.

At week 52 (26 weeks after the second dose and prior to receiving their third dose), participants in the Prolia US arm were re-randomized in a 1:1 ratio to either continue with a third dose of Prolia US or transition to TVB-009P and receive a single dose of TVB-009P in the transition period to primarily assess immunogenicity and safety after a transition from Prolia US to TVB-009P until week 78. All participants who did not terminate the trial before the third dose were followed for 26 weeks after the third dose of trial drug until week 78.

Final procedures and assessments were performed at the end of study (EOS) visit, at the end of the 78-week trial period. Participants who withdrew from the trial before completing the 78-week trial period had the early termination (ET) procedures and assessments performed at their final visit. The EOS was defined as the last visit of the last participant of the transition period.

Figure 6: Study schema



Source: Protocol Amendment 2 (Section 16.1.1)

- **Study Participants**

The study population comprised women with postmenopausal osteoporosis.

Main inclusion criteria

a. clinically stable, ambulatory, female postmenopausal adults (≥60 and ≤90 years) with a diagnosis of osteoporosis

b. postmenopausal status, defined as:

– spontaneous amenorrhea for >12 months, or

– spontaneous amenorrhea >6 months and serum follicle stimulating hormone (FSH) and estradiol in menopausal range, or

– surgical menopause at least 6 weeks before the start of screening

c. body weight ≥50 kg and ≤90 kg (≥110 lb and ≤198 lb) at screening

d. agreed to be supplemented with 1000 mg calcium and at least 400 IU vitamin D daily from screening until the last visit

e. a bone mineral density (BMD)-measurement T-score of less than -2.5 but not less than -4.0 by dual-energy X-ray absorptiometry (DXA) at the lumbar spine at screening based on central reader assessment

f. at least 3 vertebrae in the first lumbar vertebra (L1) - fourth lumbar vertebra (L4) region that were evaluable by DXA

g. serum 25-hydroxy vitamin D level >20 ng/mL at screening and no current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range, as assessed by the central laboratory. Vitamin D and calcium supplements were provided, and participants were to be rescreened once to re-evaluate calcium and/or vitamin D level post repletion.

Main exclusion criteria

a. known malabsorption of calcium or vitamin D supplements
b. metabolic or bone disease (except osteoporosis) such as Paget's disease, Cushing's disease, rheumatoid arthritis, sclerosteosis, osteomalacia, osteogenesis imperfecta, osteopetrosis, ankylosing spondylitis, hyperprolactinemia, malabsorption syndrome, osteomyelitis, multiple myeloma or related lymphoproliferative disorder, or bone metastases
c. current, uncontrolled hyperthyroidism or hypothyroidism, per participant report or chart review
d. hypoparathyroidism or hyperparathyroidism (irrespective of current controlled or uncontrolled status)
e. history and/or presence of risk factors of osteonecrosis of the jaw, as determined by the principal investigator (eg, unhealed open soft tissue lesions in the mouth, poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, recent or planned invasive dental procedures such as tooth extractions within the next 18 months), presence of anemia or coagulopathy at screening, and/or inability to maintain oral hygiene during the trial
f. history and/or presence of 1 severe or more than 2 moderate vertebral fractures (as determined by central reading of lateral spine X-ray during the screening period)
g. history and/or presence of hip fracture or atypical femur fracture
h. known hypersensitivity to any components of the investigational medicinal products (IMPs) stated in the protocol or to calcium or vitamin D
i. renal impairment manifested with an estimated glomerular filtration rate (eGFR) <45 mL/min
j. cardiac disease as per investigator's discretion, including electrocardiogram (ECG) abnormalities at screening indicating significant risk of safety for participants participating in the trial
k. malignancy or past malignancy (except for local non-melanoma skin cancer fully resected)
l. current skin infection(s)
m. infectious disease:

   – acute infection and/or antibiotic treatment had to be resolved 28 days prior to the first dose of IMP

   – any relevant chronic infection

   – ongoing hepatitis B, hepatitis C, human immunodeficiency virus (HIV) Types 1 or 2 infection

   – positive test for coronavirus disease 2019 (COVID-19) during screening or participant reporting a recent history of confirmed COVID-19 which had not fully recovered more than 14 days before screening

n. used intravenous bisphosphonates within less than 5 years prior to screening
o. used oral bisphosphonates within the 12 months prior to start of screening and/or cumulative use >3 years before the start of screening

p. ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements). The following rules for prior use of osteoporosis treatments had to be adhered to:

   – drugs being investigated for osteoporosis, eg, romosozumab: dose received at any time

   – strontium or fluoride (for osteoporosis): dose received at any time

   – teriparatide or any parathyroid hormone analogs: dose received within 12 months before the start of screening

   – calcitonin: dose received within 6 months before the start of screening

   – cinacalcet: dose received within 3 months before the start of screening

q. ongoing use of any bone active drugs which can affect BMD including:

   – heparin (except topical), anti-convulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, or anabolic steroids; dose received within 3 months before the start of screening

   – systemic glucocorticosteroids: total cumulative dose of ≥50 mg within 3 months prior to randomization

   – systemic oral or transdermal estrogen, or selective estrogen receptor modulators: more than 1 month of cumulative use within 6 months prior to randomization.

- **Treatments**

Patients received in total 3 injections of TVB-009 and/or Prolia US at a dose of 60 mg, administered at an interval of 26 weeks. During the main treatment period, patients received the first 2 injections of either TVB-009P or US-Prolia (on Day 1 and Week 26). At the start of the Transition period, at week 52 patients received the third dose. Patients initially randomised to the US-Prolia arm were re-randomized in a 1:1 ratio to either continue with a third dose of US-Prolia or transition to TVB-009P and receive a single dose of TVB-009P. The participants initially randomised to TVB-009 arm received a third dose of TVB-009P.

Participants were administered TVB-009P or US-Prolia as a single sc injection over >5 seconds in the abdomen.

Participants also received vitamin D and calcium supplements, as per Prolia SmPC. Participants were instructed to take 1000 mg calcium daily and at least 400 IU vitamin D daily from screening to week 78 (EOS). If hypocalcaemia was detected, and there was no additional underlying reason, this was to be further monitored and corrective treatment with calcium were to be considered.

Any osteoporosis treatment (other than calcium and vitamin D supplements) or ongoing use of any bone active drugs were prohibited during trial, such as: denosumab (other than the trial drug), romosozumab, strontium, fluoride (for treatment of osteoporosis), intravenous or oral bisphosphonates, teriparatide or any parathyroid hormone analogs, tibolone or any systemic oral or transdermal estrogen or selective estrogen receptor modulators, calcitonin, cinacalcet, prolonged (i.e.,>2 months) systemic glucocorticoid therapy, heparin (except topical), anti-convulsives (exception: benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, gonadotropin releasing hormone agonists, or anabolic steroids, lithium.

- **Objectives**

The primary objective of the study was to demonstrate that there are no clinically meaningful differences in efficacy between TVB-009P and Prolia US administered subcutaneously (sc) in patients with postmenopausal osteoporosis.

The primary equivalence testing included:

- the analysis of LS-BMD percent change from baseline at week 52. Similarity was supposed to be demonstrated if the 95% confidence interval (CI) for the least squares (LS) mean difference between TVB-009P and US-Prolia fell entirely within the similarity margin of ±1.45%. This similarity margin of ±1.45% was assumed to preserve 70% of the treatment effect of denosumab based on the lower bound of the 95% CI for the pooled denosumab treatment effect in placebo-controlled trials (Bone, 2008; Cummings, 2009; McClung, 2006).
- the analysis of sCTX-1 percent change from baseline at week 26. Similarity was demonstrated if the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±20%. The similarity margin of ±20% for this endpoint preserves 68% of the treatment effect of denosumab based on the lower bound of the 95% CI for the pooled denosumab treatment effect in previously reported placebo-controlled trials (Amgen 2020; Amgen 2010; Amgen 2018).

Secondary objectives of this study were:

- To compare further efficacy and PD parameters between TVB-009P and Prolia US
- To compare efficacy and PD parameters between TVB-009P and Prolia US after a single transition from Prolia US to TVB-009
- To compare the safety and tolerability, including device-related events, between TVB-009P and Prolia US
- To compare the safety and tolerability, including device-related events, between TVB-009P and Prolia US after a single transition from Prolia US to TVB-009
- to assess the immunogenicity of TVB-009P in comparison with Prolia US
- to assess the immunogenicity of TVB-009P in comparison with Prolia US after a single transition from Prolia US to TVB-009

An exploratory objective of this study was to compare pharmacokinetics between TVB-009P and Prolia US.

- **Outcomes/endpoints**

Percent change in LS-BMD from baseline at week 52 and percent change in sCTX-1 from baseline at week 26 were co-primary endpoints.

The LS-BMD co-primary estimand was the difference in mean percent change in LS-BMD from baseline at week 52 between TVB-009P and Prolia US treatment arms, regardless of intercurrent events in the

target population of patients with postmenopausal osteoporosis who received at least one dose of IMP and had both, a baseline and at least 1 post-baseline assessment of LS-BMD.

The sCTX-1 co-primary estimand was the difference in mean percent change in sCTX-1 from baseline at week 26 between TVB-009P and Prolia US treatment arms, regardless of intercurrent events in the target population of patients with postmenopausal osteoporosis.

Secondary efficacy endpoints in the main treatment period:

- percent change from baseline in LS-BMD at week 26 based on centrally assessed DXA measurements
- percent change from baseline in femoral neck BMD by DXA at week 26 and at week 52
- percent change from baseline in total hip BMD by DXA at week 26 and at week 52
- incidence of fractures up to week 52

Efficacy endpoints in the transition period:

- percent change from week 52 in LS-BMD by DXA at week 78
- percent change from week 52 in femoral neck BMD by DXA at week 78
- percent change from week 52 in total hip BMD by DXA at week 78
- incidence of fractures up to week 78

Efficacy Measurements

Lumbar Spine-Bone Mineral Density was measured by Dual-Energy X-Ray Absorptiometry. The lumbar spine scans included vertebrae L1 through L4. The vertebrae on which the measurement was based was consistent throughout the trial on an individual participant level. The same DXA machine was to be used for all trial procedures for a particular participant for the duration of the trial. All LS-BMD DXA scans were submitted to and analysed by the central imaging vendor.

Total Hip and Femoral Neck Bone Mineral Density were also measured by Dual-Energy X-Ray Absorptiometry. These scans were unilateral only. For each participant, the same hip was to be scanned throughout the trial and the same machine was to be used for all trial procedures for the duration of the trial. All hip and femoral neck bone DXA scans were submitted to and analysed by the central imaging vendor.

Participants underwent a lateral spine X-ray for the assessment of vertebral fractures by the central imaging vendor. Nominally, the vertebral fracture was assessed in all vertebrae from the fourth thoracic vertebra (T4) to the L4. Any new fracture was reported as an AE. The assessment was performed at visit 1 (baseline), visit 9 (Week 52, EOM), and visit 12 (Week 78, EOS/ET).

For PD endpoints, see pharmacodynamics section.

- **Sample size**

A sample size of 292 evaluable patients (146 patients per arm in a 1:1 randomization ratio) was planned to provide 80% power to detect similarity based on difference in mean percent change in LS-BMD at week 52, assuming a true difference of 0 and an SD of 3.8% in each treatment arm. Similarity was planned to be demonstrated if the 95% CI for the mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±1.45%.

Assuming a true mean difference of 5% and an SD of 21% in each arm for sCTX-1 percent change from baseline at week 26, the proposed sample size of 292 evaluable patients (146 per arm) was

supposed to result in a power of close to 100% for testing this endpoint. Similarity was to be demonstrated if the 95% CI for the mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±20%.

Assuming a drop-out rate of 10%, approximately 326 patients (163 per arm) were planned to be randomized to achieve approximately 292 evaluable patients (146 per arm). For the case that assessment of LS-BMD was missing or not evaluable from more than 10% of the patients at the week 26 visit, the sponsor might have decided to continue recruiting patients in order to increase the number of evaluable patients.

- **Randomisation and Blinding (masking)**

Randomisation

At baseline, participants were planned to be randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or Prolia US ("main treatment period"). The randomization was planned stratified by region (US/non-US) and any use of previous bisphosphonates (yes/no). At week 52, prior to receiving their third dose of trial drug, participants in the Prolia US treatment group were to be re-randomized in a 1:1 ratio to receive a third dose of Prolia US or switch to TVB-009P ("transition period") to receive a single dose of TVB-009P. The re-randomization was to be stratified by region (US/non-US) and any use of previous bisphosphonates (yes/no). All participants in the TVB-009P group were planned to receive a third dose of TVB-009P at week 52. Individual randomization codes, indicating the IMP assignment for each randomized participant, was planned to be available to the investigator(s) or pharmacist(s) at the investigational centre.

Blinding

This was a double-blind trial. Participants and investigators were planned to remain blinded to IMP assignment during the trial. At the investigational centre, only the unblinded pharmacist or the unblinded designee was supposed to manage the trial drug at the sites and to administer them to the participants. These unblinded personnel did not participate in any efficacy, PK, PD, immunogenicity, and safety assessments. The unblinded pharmacist or unblinded designee prepared the trial drugs in a separate room and transferred them to the dosing room in a neutral container to maintain the blind. In the dosing room, prior to and during dose administration, there were only the participant and the unblinded site personnel. In order to ensure additional participant blinding during the administration, since the syringes of the reference and test products looked different, a blindfold with an additional pillow at chest level (or similar device) was planned to be used during the trial drug administration to shield the view of the syringe from the participant.

Before the database lock (DBL), staff responsible for efficacy and safety analysis, PK and immunogenicity bioanalysis, population PK analysis, and/or PK/PD analysis did not have access to the participant treatment randomization. After last participant last visit and DBL of the main treatment period, the sponsor was to unblind the treatments for the analysis of the main treatment period (up to and including week 52; not including third IMP dose and assessments following the third dose). After completion of the trial (after week 78), the second DBL was planned to occur, and the transition period was fully unblinded and analysed.

- **Statistical methods**

Data for disposition, demography, medical history, drug exposure and treatment compliance were planned to be summarised making use of appropriate descriptive statistical methods.

Primary Efficacy analysis

The primary analysis was planned to be based on the mITT Analysis Set. The mITT Analysis Set included all randomized participants who received at least 1 dose of trial drug and had at least 1 post-baseline evaluation of LS-BMD. Participants who withdrew from the trial prior to week 26 would not have a post-baseline LS-BMD measurement and were therefore not to be included in the mITT Analysis Set. Treatment was assigned based on the treatment to which participants were randomized, regardless of which treatment they actually received.

The same analysis set was to be used for both estimands and therefore participants who terminated before week 26 were not to be included in the sCTX-1 analysis.

The planned primary analysis of LS-BMD percent change from baseline at week 52 was an analysis of covariance (ANCOVA) model with treatment, region (US/non-US), and previous use of bisphosphates (yes/no) as a fixed effects and baseline LS-BMD value and body weight at baseline as covariates. If the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±1.45, similarity was to be concluded.

Missing values for LS-BMD at week 52 were to be imputed under the assumption that these were missing at random (MAR); this was considered a valid assumption given that both treatment arms were active. The first step in the imputation procedure involved imputing intermittent missing values at week 26 (i.e., missing value at week 26, but non-missing at week 52) 50 times using a Markov Chain Monte Carlo (MCMC) method for each treatment arm separately. The imputation model was to include factors for baseline LS-BMD value, body weight at baseline, and week 52 LS-BMD. Note that region and previous use of bisphosphates were not to be included, as the MCMC methods did not support classification factors. The resulting dataset with monotone missing pattern was used in the next step, in which trailing missing values were imputed using the monotone regression predictive mean matching multiple imputation method (Heitjan and Little, 1991; Schenker and Taylor, 1996), for each treatment arm separately. The imputation model was to include factors for baseline LS-BMD value, body weight at baseline, region (US/non-US), previous use of bisphosphates (yes/no) as well as last available post-baseline LS-BMD percent change from baseline value (obtained from week 26 or ET visit measurement). This was considered a conservative approach for similarity testing, as missing data was to be imputed within each treatment group separately. This imputation method was considered reliable as long as the percentage of participants with missing LS-BMD at week 52 was low.

The planned analysis of the co-primary endpoint sCTX-1 percent change from baseline at week 26 was an ANCOVA model with treatment, region (US/non-US), and previous use of bisphosphates (yes/no) as a fixed effects and baseline sCTX-1 value and body weight at baseline as covariates. If the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±20%, similarity was to be concluded.

As only very few missing sCTX-1 assessments at Week 26 were expected in the mITT analysis set, no imputation for missing values of this endpoint were planned/performed. However, sCTX-1 values that fell below the limit of quantification (BLQ) were imputed as the low limit of quantification (LLOQ).

The resulting datasets, completed with imputed values, were to be analysed using the model specified above, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).

Sensitivity analysis for the primary analysis

To evaluate the primary analysis models for both primary efficacy endpoints, they were planned to be re-run on the multiple-imputed dataset with only the treatment group as a covariate

Sensitivity analysis for the BLQ imputation in the primary analysis of sCTX-1 percent change from baseline at week 26 was also planned: Specifically, a two-dimensional tipping point analysis approach was designed wherein the primary analysis of this endpoint was repeated using different imputed values for patients in the TVB-009P group and the Prolia US group, in the range of 0 to LLOQ (0.033 ng/mL). Values of 0, 0.011, 0.022 and 0.033 were used for each treatment groups separately, for a total of 16 combinations.

Supplementary analyses for the primary analysis

Supplementary analyses were planned and conducted to evaluate the effect of assumptions on missing data on the results:

1. In order to assess the sensitivity of the primary analysis to the MAR assumption on missing data for patients that have at least 1 post-baseline value, supplementary analyses for the primary analysis were conducted using multiple imputation under MNAR assumption. In these analyses, missing LSB- MD percent change from baseline at week 52 were imputed using the same imputation method as in the primary analysis except that first the percent change from baseline in LS-BMD at week 52 in patients randomized to TVB-009P with missing LS-BMD at week 52 were imputed assuming the treatment effect had worsened by δ1 compared to the patients who had no missing value (where δ1 = 0 to 2% or estimated treatment effect the TVB-009P group, whichever is higher, in steps of 0.5%), and then his was repeated assuming the treatment effect of Prolia US had worsened according to the same system. The resulting complete, imputed datasets were each again analysed using the same model as the primary analysis model, and the resulting statistics combined using methodology provided by Rubin (1987) and Little and Rubin (2002).

2. To further alleviate the concern on the uncertainty introduced by missing data, the following two separate one-sided tests of alpha=0.05 with missing data imputed under the corresponding null model using a multiple imputation method were conducted:

- In the first test, missing values for the TVB-009P group were imputed assuming the treatment effect had worsened (i.e. LS-BMD percent change from baseline decreased) by the equivalence margin value of 1.45%, while the missing values for the Prolia US group were imputed without penalization. Non-inferiority was then tested by checking that the lower 95% confidence limit for the mean difference TVB-009P – Prolia US was greater than the margin value of -1.45%.

- In the second test, missing values for the TVB-009P group were imputed assuming the treatment effect was improved (i.e. LS-BMD percent change from baseline increased) by the equivalence margin value of 1.45%, while the missing values for the Prolia US group were imputed without penalization. Non-superiority was then be tested by checking that the upper 95% confidence limit for the mean difference TVB-009P – Prolia US was less than the margin value of 1.45%.

Again, the resulting datasets were analysed as per the primary analysis model and the results combined using Rubin’s rules.

3a. The primary analyses, including the multiple imputation approach, were repeated on the ITT analysis set.

3b. The two-dimensional tipping point analysis was repeated on the ITT analysis set.

4. The primary analyses were repeated for the PP analysis set without imputation.

5. The primary analyses were repeated in the mITT analysis set. This time excluding patients who received IMP not as randomised at baseline and/or at week 26.

Secondary Efficacy analysis

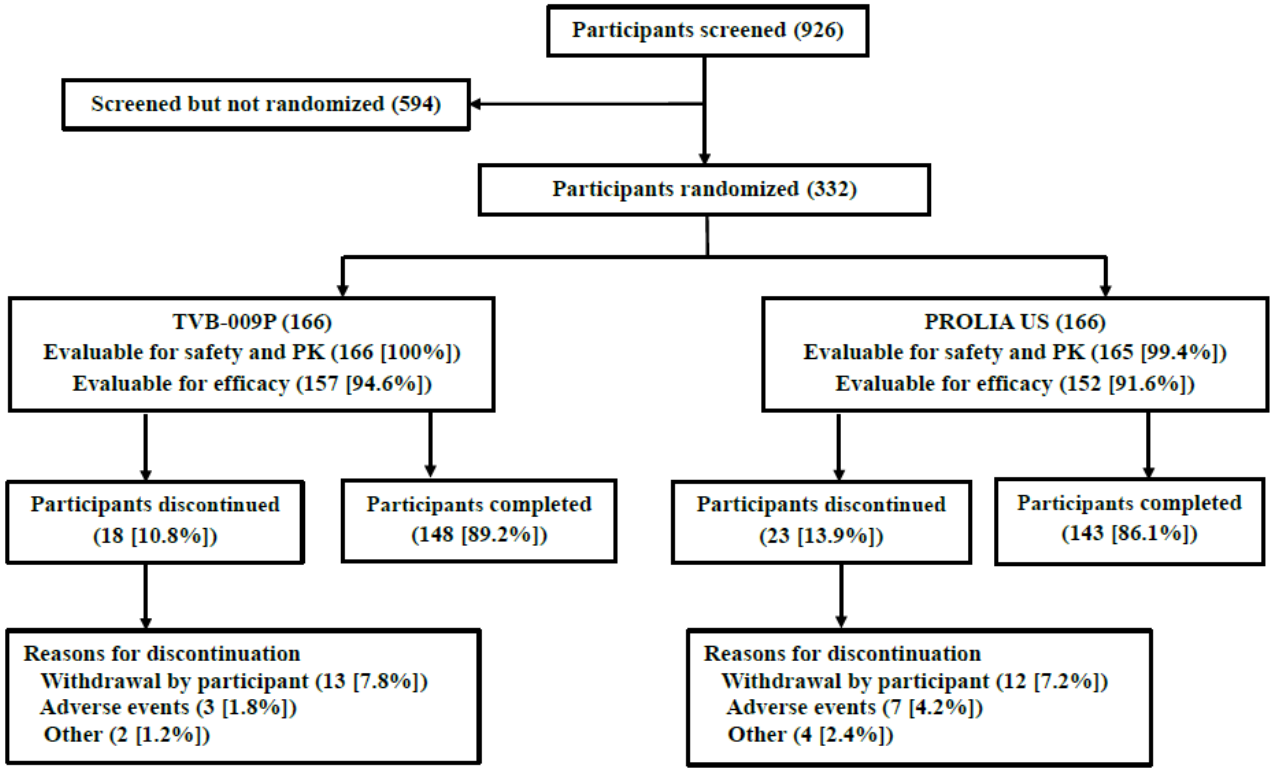
No formal hypothesis testing was planned for the secondary efficacy endpoints. For continuous endpoints such as percent change from baseline in LS-BMD, femoral neck BMD, total hip BMD, sCTX-1, and P1NP at weeks 26 and 52 (as applicable), descriptive statistics were presented by treatment group and visit. For binary endpoints such as sCTX-1 suppression or incidence of fractures, number and percentage of participants achieving the endpoint was presented by treatment group. For descriptive purposes, 95% CIs for the differences in percentages between treatment groups was presented. Vertebral fractures reported by sites in the electronic case report form (eCRF), vertebral fractures identified by the central reader of X-rays (new fractures not found at screening), and non-vertebral fractures reported by sites in the eCRF were summarized separately. Vertebral fractures identified by the central reader and non-vertebral fractures were also summarized together. For safety data analyses and reporting, standard statistical methodology was applied.

Results

- **Participant flow**

Main treatment period

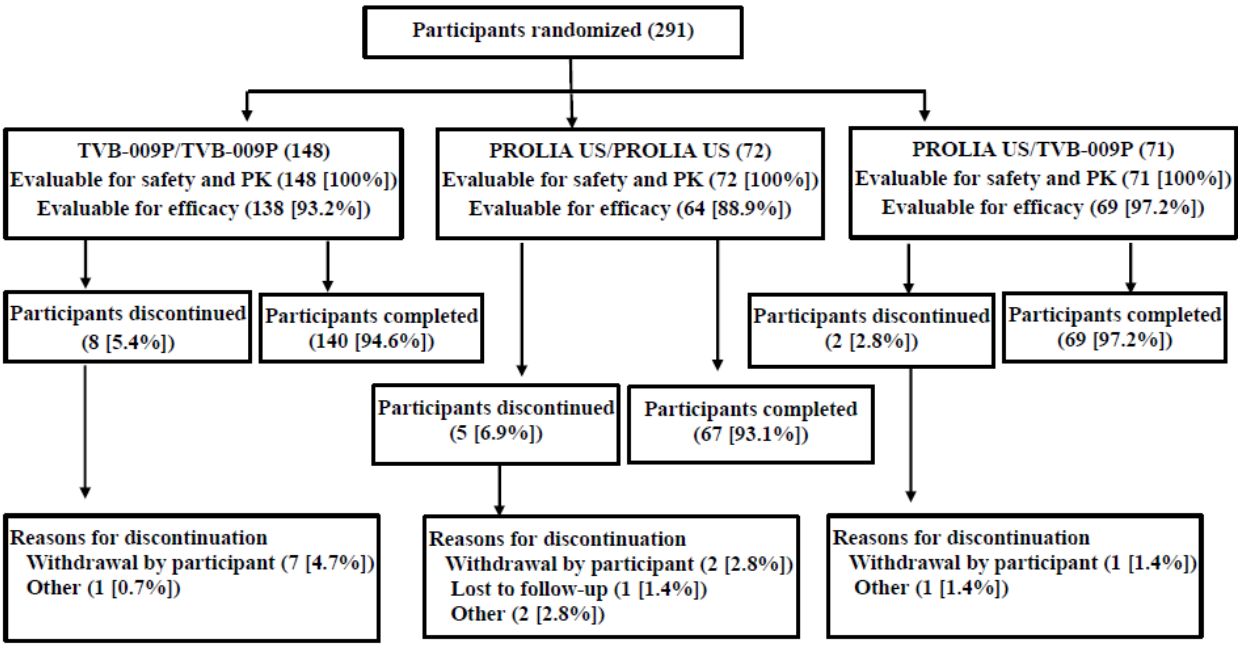
Figure 7: Participant disposition in the main treatment period (all screened participants)



Source: Summary 14.1.1.1, Listing 16.2.1.1, Listing 16.2.1.2, Listing 16.2.3
PK = pharmacokinetics; US = United States.
Numbers in parentheses are numbers of participants.

Transition period

Figure 8: Participant disposition in the transition period (transition intent-to-treat analysis set)



Source: Summary 14.1.1.2, Listing 16.2.1.2, Listing 16.2.3
PK = pharmacokinetics; US = United States.
Numbers in parentheses are numbers of participants.

- **Recruitment**

Trial Initiation Date (first participant enrolled): 22 March 2021

Trial Completion Date (last participant completed): 19 June 2023

- **Conduct of the study**

Protocol amendments

The original protocol (dated 09 December 2020) was amended twice. In addition, 8 protocol administrative letters were issued during the trial to document changes to process and to enable the collection of additional information.

Protocol amendment 1 (dated 03 February 2021) added the coordinating investigator details, explained the definition of term MNAR to missing not at random, updated the legal representative of the sponsor in the EU. No patients were enrolled up to that date.

Protocol amendment 2 (dated 29 June 2021) added a sentence specifying minimum time of 3 months between two DXA scans, included examples for events leading to trial discontinuation and provided instructions for the management of BMD reduction of more than 7% from baseline, corrected statement in Section 4.5 (per inclusion criterion h participants could have a serum 25-(OH) vitamin D level >20 ng/mL at screening), included instructions for the management of hypocalcaemia and hypercalcemia, clarified that staff involved in trial drug preparation/administration will not be involved in any trial assessments, clarified that DXA results after start of treatment will be provided to the investigator after trial completion, specified that total hip and femoral neck BMD will be measured by unilateral DXA, clarified that any new fracture should be reported as an AE, added a new sub section for pregnancy test (urine dipstick) on day 1, added additional supplementary analyses to further

alleviate the concern on the uncertainty introduced by missing data, deleted a statement about difficulty in transmitting the form in Appendix A, updated the contact details for Interactive Voice Recognition System in Appendix A. Up to this point 14 patients have been included in the trial.

Administrative Letters were all issued after the Protocol 2 amendment.

Protocol deviations

Table 23: Summary of major protocol deviations in the main treatment period (intent-to-treat analysis set)

Deviation	TVB-009P (N=166) n (%)	PROLIA US (N=166) n (%)	Total (N=332) n (%)
Participants with at least one major deviation	28 (16.9)	33 (19.9)	61 (18.4)
Early termination occurred prior to week 52[a]	16 (9.6)	20 (12.0)	36 (10.8)
Week 26 visit out of window	3 (1.8)	7 (4.2)	10 (3.0)
LS-BMD assessment at week 52 is out of window by >4 weeks	0	4 (2.4)	4 (1.2)
sCTX-1 is not assessed at week 26 visit	1 (0.6)	3 (1.8)	4 (1.2)
LS-BMD is not assessed at week 52 visit	2 (1.2)	1 (0.6)	3 (0.9)
Other	2 (1.2)	1 (0.6)	3 (0.9)
Prohibited medications	3 (1.8)	0	3 (0.9)
Assessment not performed per protocol	2 (1.2)	0	2 (0.6%)
Different machine manufacturers were used for LS-BMD assessment	1 (0.6)	1 (0.6)	2 (0.6)
Did not receive trial drug injection at baseline or week 26	0	1 (0.6)	1 (0.3)
Major inclusion/exclusion criteria not met	0	1 (0.6)	1 (0.3)
Unblinding of treatment	1 (0.6)	0	1 (0.3)

Source: Summary 14.1.4, Listing 16.2.2

[a] Included participants who were considered discontinued as per 'End of Main Treatment' form and had missed either week 26 or week 52.

ITT = intent-to-treat; LS-BMD = lumbar spine-bone mineral density; sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; US = United States

Percentages were based on the number of participants in the treatment group in the ITT Analysis Set.

A participant was counted once under each applicable deviation type.

- **Baseline data**

Table 24: Demographic characteristics (intent-to-treat analysis set)

Characteristic Statistic	TVB-009P (N=166)	PROLIA US (N=166)	Total (N=332)
Age (years)			
n	166	166	332
Mean (SD)	68.5 (5.69)	67.7 (5.56)	68.1 (5.63)
Median (Min, Max)	67.5 (60, 84)	67.0 (60, 84)	67.0 (60, 84)
Ethnicity, n (%)			
Hispanic or Latino	23 (13.9)	18 (10.8)	41 (12.3)
Not-Hispanic No Latino	143 (86.1)	148 (89.2)	291 (87.7)
Race, n (%)			
White	165 (99.4)	164 (98.8)	329 (99.1)
Black/African American	1 (0.6)	1 (0.6)	2 (0.6)
Not Reported/Unknown	0	1 (0.6)	1 (0.3)
Height (cm)			
n	166	166	332
Mean (SD)	158.96 (5.451)	159.90 (6.131)	159.43 (5.811)
Median (Min, Max)	159.00 (144.0, 174.0)	159.20 (145.0, 177.0)	159.00 (144.0, 177.0)
Weight (kg)			
n	166	166	332
Mean (SD)	65.97 (10.103)	64.64 (9.159)	65.30 (9.651)
Median (Min, Max)	65.00 (50.0, 89.9)	63.55 (49.9, 90.3)	64.86 (49.9, 90.3)
Body mass index (kg/m^2)			
n	166	166	332
Mean (SD)	26.137 (3.9595)	25.344 (3.7359)	25.740 (3.8639)
Median (Min, Max)	26.020 (17.30, 37.76)	24.630 (17.27, 35.58)	25.360 (17.27, 37.76)

Table 25: Baseline characteristics (intent-to-treat analysis set)

Characteristic Statistic	TVB-009P (N=166)	PROLIA US (N=166)	Total (N=332)
Baseline LS-BMD (g/cm^2)			
n	166	166	332
Mean (SD)	0.7683 (0.07507)	0.7630 (0.07755)	0.7657 (0.07625)
Median (Min, Max)	0.7605 (0.608, 0.920)	0.7485 (0.609, 0.944)	0.7580 (0.608, 0.944)
Baseline sCTX-1 (ng/mL)			
n	166	165	331
Mean (SD)	0.4969 (1.39927)	0.4077 (0.26239)	0.4524 (1.00757)
Median (Min, Max)	0.3570 (0.033, 18.162)	0.3760 (0.033, 2.337)	0.3660 (0.033, 18.162)
Missing	0	1	1
Previous use of bisphosphonates, n (%)			
Yes	21 (12.7)	21 (12.7)	42 (12.7)
No	145 (87.3)	145 (87.3)	290 (87.3)
Prior fractures, n (%)			
Yes	37 (22.3)	38 (22.9)	75 (22.6)
No	129 (77.7)	128 (77.1)	257 (77.4)
Taking calcium and vitamin D supplement, n (%)[a]			
Yes	28 (75.7)	28 (73.7)	56 (74.7)
No	9 (24.3)	10 (26.3)	19 (25.3)

Source: Excerpt from Summary 14.1.2.1, Listing 16.2.4.3, Listing 16.2.6.1, Listing 16.2.6.3

[a] Osteoporosis status details form was completed only if participant experienced any fracture prior to trial start.

LS-BMD = lumbar spine-bone mineral density; Max = maximum; Min = minimum;
sCTX-1 = serum C-telopeptide cross-link of type 1 collagen; SD = standard deviation; US = United States.
Percentages were based on the number of participants with non-missing values in the treatment group in the analysis set.

Medical history

Overall, 300 (90.6%) participants had at least one medical history condition (148 [89.2%] participants in the TVB-009P group and 152 [92.1%] participants in the Prolia US group). The most frequently reported medical history SOCs (>30% participants) were vascular disorders in 57.1% participants, musculoskeletal and connective tissue disorders in 43.5% participants, surgical and medical procedures in 38.7% participants, and metabolism and nutritional disorders in 32.3% participants.

Prior Therapy

13.3% of patients in the TVB-009P group and 10.8% of patients in the Prolia US group were previously treated with bisphosphonates.

Concomitant therapy

All patients were to be treated with calcium and vitamin D supplements. 97.6% of subjects in the TVB-009 group and 98.2% in the Prolia-US group received vitamin D and analogues. 75.3% of subjects in the TVB-009 group and 78.8% in the Prolia-US group received calcium, whereas 25.3% and 23.0% of subjects in TVB-009 and Prolia group, respectively received calcium combinations with vitamin D and/or other drugs.

- **Numbers analysed**

Main treatment period

Table 26: Analysis population – main treatment period (all screened participants)

	TVB-009P n (%)	PROLIA US n (%)	Total n (%)
Randomized (ITT Analysis Set)	166	166	332
mITT Analysis Set	157 (94.6)	152 (91.6)	309 (93.1)
PP Analysis Set	138 (83.1)	133 (80.1)	271 (81.6)
Safety Analysis Set	166 (100.0)	165 (99.4)	331 (99.7)

Source: Excerpt from Summary 14.1.1.1, Listing 16.2.3
ITT = intent-to-treat; mITT = modified intent-to-treat; PP = per-protocol; US = United States
Percentages were based on the number of randomized participants in each treatment group.

Transition period

Table 27: Analysis population – transition period (transition intent-to-treat analysis)

	TVB-009P/ TVB-009P n (%)	PROLIA US/ PROLIA US n (%)	PROLIA US/ TVB-009P n (%)	Total n (%)
Randomized for transition period (TITT Analysis Set)	148	72	71	291
TmITT Analysis Set	138 (93.2)	64 (88.9)	69 (97.2)	271 (93.1)
Transition Safety Analysis Set	148 (100.0)	72 (100.0)	71 (100.0)	291 (100.0)

Source: Excerpt from Summary 14.1.1.2, Listing 16.2.3
TITT = transition intent-to-treat; TmITT = transition modified intent-to-treat; US = United States
Percentages were based on the number of participants for the treatment period in each treatment group.

- **Outcomes and estimation**

Co-primary endpoint: Percent Change from Baseline in Lumbar Spine Bone Mineral Density (LS-BMD) at Week 52

Table 28: Analysis of percent change from baseline to week 52 in Lumbar Spine Bone Mineral Density (LS-BMD) (modified intent-to-treat analysis set): DBL1 Data

Statistic	TVB-009P (N=157)	PROLIA US (N=152)
LS mean	4.76	4.54
95% CI for LS mean	3.82, 5.69	3.62, 5.47
LS mean difference TVB-009P – PROLIA US	0.21	
95% CI for the difference	-0.73, 1.15	

Source: Summary 14.2.1.1 (DBL1 data, Table Generation Date: 04 May 2023), Listing 16.2.6.1 (DBL1 data, Table Generation Date: 04 May 2023)
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares, LS-BMD = lumbar spine-bone mineral density; MAR = missing at random; US = United States.
LS means, differences and CIs from the ANCOVA model with percent change from baseline to week 52 in LS-BMD as the outcome, treatment group, region and previous use of bisphosphates as fixed effects, baseline LS-BMD and baseline weight as covariates.
Missing outcomes were imputed using multiple imputation methods under the MAR assumption.
Biosimilarity was to be demonstrated if the 95% CI for the difference fell entirely within the equivalence margin of (-1.45, +1.45).

Sensitivity/supplementary analyses of the efficacy co-primary endpoint LS-BMD

ITT analysis set

Table 29: Analysis of percent change from baseline to week 52 in Lumbar Spine Bone Mineral Density (LS-BMD) (intent-to-treat analysis set): DBL1 Data

Statistic	TVB-009P (N=166)	PROLIA US (N=166)
LS mean	4.76	4.55
95% CI for LS mean	3.84, 5.69	3.65, 5.46
LS mean difference TVB-009P – PROLIA US	0.21	
95% CI for the difference	-0.70, 1.13	

Source: Summary 14.2.3.4 (DBL1 data, Table Generation Date: 04 May 2023), Listing 16.2.6.1 (DBL1 data, Table Generation Date: 04 May 2023)
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; LS-BMD = lumbar spine-bone mineral density; MAR = missing at random; US = United States.
LS means, differences and CIs from the ANCOVA model with percent change from baseline to week 52 in LS-BMD as the outcome, treatment group, region and previous use of bisphosphates as fixed effects, baseline LS-BMD and baseline weight as covariates. Missing outcomes imputed using multiple imputation methods under the MAR assumption. Biosimilarity was to be demonstrated if the 95% CI for the difference falls entirely within the equivalence margin of (-1.45, +1.45).

PP analysis set

Table 30: Supplementary analysis of percent change from baseline to week 52 in LS-BMD (per protocol analysis set)

Supplementary Analysis of Percent Change from Baseline to Week 52 in LS-BMD
Per Protocol Analysis Set

Statistic	TVB-009P (N=138)	PROLIA US (N=133)
LS Mean	5.06	4.62
95% CI for LS Mean	4.10, 6.01	3.66, 5.57
LS Mean Difference TVB-009P - PROLIA US	0.44	
95% CI for the Difference	-0.54, 1.42	

Secondary endpoints

Main treatment period

- **Secondary EP: Percent Change from Baseline to Week 26 and Week 52 in Lumbar Spine Bone Mineral Density (LS-BMD)**

Table 31: Summary Lumbar Spine Bone Mineral Density (LS-BMD) in the mean treatment period (modified intent-to-treat analysis set): DBL1 Data

Visit Statistic	TVB-009P (N=157)	PROLIA US (N=152)
Percent change from baseline to week 26		
n	157	151
Mean (SD)	3.70 (4.294)	3.62 (3.815)
Median (Min, Max)	3.35 (-22.5, 19.3)	3.44 (-6.2, 15.8)
Missing	0	1
Percent change from baseline to week 52		
n	150	145
Mean (SD)	5.40 (4.266)	5.07 (3.896)
Median (Min, Max)	5.41 (-4.1, 20.3)	4.76 (-3.9, 19.0)
Missing	7	7

Source: Excerpt from Summary 14.2.4.1.1, Listing 16.2.6.1
max = maximum; min = minimum; SD = standard deviation; US = United States.
Baseline was defined as the last assessment prior to the first administration of the trial drug.
Missing values were not imputed.

- **Percent Change from Baseline to Week 26 and Week 52 in Femoral Neck Bone Mineral Density**

Table 32: Summary of femoral neck bone mineral density in the main treatment period (modified intent-to-treat analysis set)

Visit Statistic	TVB-009P (N=157)	PROLIA US (N=152)
Percent change from baseline to week 26		
n	156	150
Mean (SD)	1.87 (4.877)	2.01 (3.611)
Median (Min, Max)	1.83 (-11.4, 43.1)	2.04 (-11.4, 15.5)
Missing	1	2
Percent change from baseline to week 52		
n	150	145
Mean (SD)	2.39 (5.795)	2.34 (3.780)
Median (Min, Max)	1.99 (-19.5, 45.5)	2.18 (-10.3, 21.5)
Missing	7	7

Source: Excerpt from Summary 14.2.4.2.1, Listing 16.2.6.2
max = maximum; min = minimum; SD = standard deviation; US = United States.
Baseline was defined as the last assessment prior to the first administration of the trial drug.
Missing values were not imputed.

- **Percent Change from Baseline to Week 26 and Week 52 in Total Hip BMD**

Table 33: Summary of total hip bone mineral density in the main treatment period (modified intent-to-treat analysis set)

Visit Statistic	TVB-009P (N=157)	PROLIA US (N=152)
Percent change from baseline to week 26		
n	156	150
Mean (SD)	1.89 (3.488)	2.02 (2.526)
Median (Min, Max)	1.85 (-13.0, 28.9)	2.08 (-3.7, 12.5)
Missing	1	2
Percent change from baseline to week 52		
n	150	145
Mean (SD)	2.67 (3.981)	3.00 (2.768)
Median (Min, Max)	2.77 (-11.9, 29.9)	2.83 (-3.3, 11.8)
Missing	7	7

Source: Excerpt from Summary 14.2.4.3.1, Listing 16.2.6.2
max = maximum; min = minimum; SD = standard deviation; US = United States.
Baseline was defined as the last assessment prior to the first administration of the trial drug.
Missing values were not imputed.

- **Incidence of fractures**

Table 34: Summary of fractures in the main treatment period (modified intent-to-treat analysis set)

Endpoint Statistic	TVB-009P (N=157)	PROLIA US (N=152)
Vertebral fracture (per local site), n (%)	0	2 (1.3)
Vertebral fracture (per central reader)[a]		
Evaluable subjects	148	144
n (%)	1 (0.7)	3 (2.1)
Maximum grade:		
Grade 1	0	2 (1.4)
Grade 2	1 (0.7)	0
Grade 3	0	1 (0.7)
Non-vertebral fracture, n (%)	2 (1.3)	2 (1.3)
Any fracture (vertebral fractures per central reader and non-vertebral fractures), n (%)	3 (1.9)	5 (3.3)

Source: Excerpt from Summary 14.2.4.6.1, Listing 16.2.6.4.1
[a] Percentages were based on the number of participants in the treatment group in the mITT analysis set with available assessment at screening and week 52 or early termination.
CI = confidence interval; mITT = modified intent-to-treat; n = the number of participants with any fraction of the specified type; US = United States.
Percentages were based on the number of participants in the treatment group in the mITT Analysis Set, unless otherwise specified. Difference in percentage was defined as ([% in TVB-009P group] – [% in PROLIA US group]).

Transition period

- **Percent Change from Week 52 in LS-BMD to Week 78**

Table 35: Summary of Lumbar Spine Bone Mineral Density (LS-BMD) in the transition period (transition modified intent-to-treat analysis set)

Visit Statistic	TVB-009P/TVB-009P (N=138)	PROLIA US/PROLIA US (N=64)	PROLIA US/TVB-009P (N=69)
Percent change from week 52 to week 78			
n	137	62	68
Mean (SD)	0.82 (3.120)	1.15 (3.440)	1.24 (3.069)
Median (Min, Max)	1.15 (-11.2, 7.4)	1.09 (-7.0, 8.1)	1.26 (-7.6, 7.8)
Missing	1	2	1

Source: Excerpt from Summary 14.2.4.1.2, Listing 16.2.6.1
max = maximum; min = minimum; SD = standard deviation; US = United States.
Missing values were not imputed.

- **Percent Change from Week 52 to Week 72 in Femoral Neck BMD**

Table 36: Summary of femoral neck bone mineral density in the transition period (transition modified intent-to-treat analysis set)

Visit Statistic	TVB-009P/TVB-009P (N=138)	PROLIA US/PROLIA US (N=64)	PROLIA US/TVB-009P (N=69)
Percent change from week 52 to week 78			
n	137	62	68
Mean (SD)	0.38 (3.525)	0.80 (3.560)	0.94 (3.082)
Median (Min, Max)	0.32 (-12.2, 14.0)	0.57 (-9.8, 9.8)	0.50 (-5.4, 10.4)
Missing	1	2	1

Source: Excerpt from Summary 14.2.4.2.2, Listing 16.2.6.2
max = maximum; min = minimum; SD = standard deviation; US = United States.
Missing values were not imputed.

- **Percent Change from Week 52 to Week 78 in Total Hip BMD**

Table 37: Summary of total hip bone mineral density in the transition period (transition modified intent-to-treat analysis set)

Visit Statistic	TVB-009P/TVB-009P (N=138)	PROLIA US/PROLIA US (N=64)	PROLIA US/TVB-009P (N=69)
Percent change from week 52 to week 78			
n	137	62	68
Mean (SD)	0.01 (2.089)	0.66 (2.109)	0.27 (2.264)
Median (Min, Max)	0.00 (-6.2, 7.5)	0.41 (-4.6, 5.7)	0.12 (-3.7, 6.6)
Missing	1	2	1

Source: Excerpt from Summary 14.2.4.3.2, Listing 16.2.6.2
max = maximum; min = minimum; SD = standard deviation; US = United States.
Missing values were not imputed.

- **Incidence of fractures**

In the TVB-009P/TVB-009P treatment group, 1 (0.8%) participant suffered grade 2 vertebral fracture per central reader and none of the participants had non-vertebral fractures.

In the Prolia US/TVB-009P treatment group, 1 (1.4%) participant suffered non-vertebral fracture and none of the participants had vertebral fractures.

- **Ancillary analyses**

After the DBL for the main treatment period, corrections were made to data for assessment of LS-BMD following cross-validation of the scanner by the central reader. Corrections were applied to all participant data from those scanners that had calibration corrections identified after DBL1 resulting in changes to the corrected values but not of the original values. The analysis including corrected values is presented in the table below.

Table 38: Analysis of percent change from baseline to week 52 in Lumbar Spine Bone Mineral Density (LS-BMD) (modified intent-to-treat analysis set): DBL2 Data

Statistic	TVB-009P (N=157)	PROLIA US (N=152)
LS mean	4.98	4.67
95% CI for LS mean	4.08, 5.89	3.76, 5.57
LS mean difference TVB-009P – PROLIA US	0.32	
95% CI for the difference	-0.60, 1.23	

Source: Summary 14.2.1.1, Listing 16.2.6.1
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares, LS-BMD = lumbar spine-bone mineral density; MAR = missing at random; US = United States.
LS means, differences and CIs from the ANCOVA model with percent change from baseline to week 52 in LS-BMD as the outcome, treatment group, region and previous use of bisphosphates as fixed effects, baseline LS-BMD and baseline weight as covariates.
Missing outcomes were imputed using multiple imputation methods under the MAR assumption.
Biosimilarity was to be demonstrated if the 95% CI for the difference fell entirely within the equivalence margin of (-1.45, +1.45).

sCTX-1 Suppression at Each Visit (mITT Analysis Set)

Table 39: sCTX-1 Suppression at Each Visit (mITT Analysis Set)

Visit, n/M (%)	TVB-009P (N=157)	PROLIA US (N=152)
Baseline	3/157 (1.9%)	3/152 (2.0%)
Day 15	143/155 (92.3%)	139/151 (92.1%)
Week 4	146/155 (94.2%)	142/151 (94.0%)
Week 8	146/157 (93.0%)	145/152 (95.4%)
Week 12	146/155 (94.2%)	144/150 (96.0%)
Week 26	42/156 (26.9%)	53/149 (35.6%)
Week 39	147/154 (95.5%)	145/151 (96.0%)
Week 52	30/151 (19.9%)	47/146 (32.2%)

Percent change from baseline to week 52 in LS-BMD, Per-Protocol Analysis Set - Excluding Patients with PK Non-Zero at Baseline (post-hoc): 95% CI for the difference [-0.66, 1.30].

Percent change from baseline to week 26 in sCTX-1 - Per-Protocol Analysis Set - Excluding Patients with PK Non-Zero at Baseline (post-hoc): 95% CI for the difference [5.25, 24.19].

- **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 40: Summary of efficacy for trial TVB009-IMB-30085

Title: A Randomized, Double-Blind, Multinational, Multicenter Study to Compare Efficacy, Safety, and Immunogenicity of TVB-009P and Denosumab (Prolia) in Patients with Postmenopausal Osteoporosis		
Study identifier	TVB009-IMB-30085	
Design	A randomized, double-blind, multinational, multicenter trial to demonstrate similar efficacy and safety of TVB-009P compared to Prolia US administered sc, in 3 doses of 60 mg every 26 weeks (3 injections) in patients with postmenopausal osteoporosis. This trial consisted of a screening period (up to 4 weeks) and a 52-week double blind main treatment period, followed by a 26-week double-blind transition period. Participants were randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or Prolia US ("main treatment period"). At week 52, participants in the Prolia US arm were re-randomized in a 1:1 ratio to either continue with a third dose of Prolia US or transition to TVB-009P and receive a single dose of TVB-009P in the transition period to primarily assess immunogenicity and safety after a transition from Prolia US to TVB-009P until week 78. Final procedures and assessments were performed at the end of study (EOS) visit, at the end of the 78-week trial period. The EOS was defined as the last visit of the last participant of the transition period.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks Not applicable 26 weeks transition period
Hypothesis	Equivalence	
Treatments groups (randomized)	Test IMP: TVB-009P 60 mg every 26 weeks	N = 166

	Reference IMP: Prolia 60 mg every 26 weeks		N = 166
Endpoints and definitions	Primary endpoint	Lumbar spine bone mineral density (LS-BMD)	Percent change from baseline to week 52 in LS-BMD
	Co-Primary Endpoint	Serum C telopeptide cross-link of type 1 collagen (sCTX-1)	Percent change from baseline in sCTX-1 at week 26
	Secondary endpoint	LS-BMD	Percent change from baseline in LS-BMD at week 26
	Secondary endpoint	Femoral neck BMD	Percent change from baseline in femoral neck BMD by DXA at week 26 and at week 52
	Secondary endpoint	Total hip BMD	Percent change from baseline in total hip BMD by DXA at week 26 and at week 52
	Secondary endpoint	sCTX-1	Percent change from baseline in sCTX-1 at all time-points
	Secondary endpoint	sCTX-1	sCTX-1 suppression at week 4 (defined as sCTX-1 level below the limit of quantitation)
	Secondary endpoint	procollagen type 1 N propeptide (P1NP)	Percent change from baseline in P1NP at week 26 and week 52
	Secondary endpoint	Fractures	Incidence of fractures up to week 52
Database lock	DBL1 (main treatment phase): 02 May 2023; DBL2 (transition phase): 16 August 2023		
Results and Analysis			
Primary Endpoint			
Analysis population and time point description	Modified Intent-to-Treat (mITT) analysis set, week 52 The mITT analysis set included all randomized participants who received at least 1 dose of trial drug and had at least 1 post baseline evaluation of LS-BMD. Participants who withdrew from the trial prior to week 26 would not have a post-baseline LS-BMD measurement and were therefore not to be included in the mITT analysis aet.		
Percent Change from Baseline to Week 52 in LS-BMD Biosimilarity was demonstrated as the 95% CI for the difference fell entirely within the equivalence margin of ±1.45%.	**Treatment group**	**TVB-009P**	**Prolia US**
	Number of Participants	157	152
	LS mean	4.76	4.54
	95% CI for LS mean	3.82, 5.69	3.62, 5.47
	LS mean difference TVB-009P – Prolia US	0.21	
	95% CI for the difference	**-0.73, 1.15**	
Co-Primary PD Endpoint			
Analysis population and time point description	Modified Intent-to-Treat (mITT) analysis set, week 26		
Percent change from baseline to Week 26 in sCTX-1 Biosimilarity was demonstrated as the 95% CI for the	**Treatment group**	**TVB-009P**	**Prolia US**
	Number of Participants	157	152
	LS mean	-56.05	-65.13
	95% CI for LS mean	-64.99, -47.12	-74.09, -56.17

difference fell entirely within the equivalence margin of ±20%.	LS mean difference TVB-009P – Prolia US	9.07	
	95% CI for the difference	-0.14, 18.29	
Secondary efficacy endpoints			
Analysis population	Modified Intent-to-Treat (mITT) analysis set		
Percent change from baseline in LS-BMD at week 26 (mITT)	**Treatment group**	**TVB-009P**	**Prolia US**
	Mean (SD)	3.70 (4.294)	3.62 (3.815)
Percent change from baseline in femoral neck BMD by DXA at week 26 and at week 52	**Treatment group**	**TVB-009P**	**Prolia US**
	Mean (SD) W26	1.87 (4.877)	2.01 (3.611)
	Mean (SD) W52	2.39 (5.795)	2.34 (3.780)
Percent change from baseline in total hip BMD by DXA at week 26 and at week 52	**Treatment group**	**TVB-009P**	**Prolia US**
	Mean (SD) W26	1.89 (3.488)	2.02 (2.526)
	Mean (SD) W52	2.67 (3.981)	3.00 (2.768)
Percent change from baseline in total hip BMD by DXA at week 26 and at week 52	**Treatment group**	**TVB-009P**	**Prolia US**
	Mean (SD) W26	1.89 (3.488)	2.02 (2.526)
	Mean (SD) W52	2.67 (3.981)	3.00 (2.768)
Any fracture (vertebral fractures per central reader and non-vertebral fractures) up to week 52	**Treatment group**	**TVB-009P**	**Prolia US**
	Any fracture up to week 52, n (%)	3 (1.9)	5 (3.3)
Supplementary Analysis for the Primary Endpoint			
Analysis population and time point description	Intent-to-Treat (ITT) analysis set, week 52		
Percent Change from Baseline to Week 52 in LS-BMD	**Treatment Group**	**TVB-009P**	**Prolia US**
	Number of Participants	166	166
	LS mean	4.76	4.55
	95% CI for LS mean	3.84, 5.69	3.65, 5.46
	LS mean difference TVB-009P – Prolia US	0.21	
	95% CI for the difference	-0.70, 1.13	
Analysis population and time point description	Per Protocol analysis set, week 52		
Percent Change from Baseline to Week 52 in LS-BMD	**Treatment Group**	**TVB-009P**	**Prolia US**
	Number of Participants	138	133
	LS mean	5.06	4.62
	95% CI for LS mean	4.10, 6.01	3.66, 5.57
	LS mean difference TVB-009P – Prolia US	0.44	
	95% CI for the difference	-0.54, 1.42	
Supplementary Analysis for the Co-Primary Endpoint			
Analysis population and time point description	Intent-to-Treat (ITT) analysis set, week 26		
Percent change from baseline to Week 26 in sCTX-1	**Treatment Group**	**TVB-009P**	**Prolia US**
	Number of Participants	166	166
	LS mean	-56.49	-65.21
	95% CI for LS mean	-65.28, -47.69	-74.08, -56.33

	LS mean difference TVB-009P – Prolia US	8.72	
	95% CI for the difference	-0.36, 17.81	
Analysis population and time point description	Per Protocol analysis set, week 26		
Percent change from baseline to Week 26 in sCTX-1	**Treatment Group**	**TVB-009P**	**Prolia US**
	Number of Participants	138	133
	LS mean	-56.10	-70.60
	95% CI for LS mean	-65.29, -46.91	-79.93, -61.27
	LS mean difference TVB-009P – Prolia US	14.50	
	95% CI for the difference	4.88, 24.12	

2.5.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

In agreement with scientific advice received by the EMA (EMEA/H/SA/4069/1/2019/III, EMEA/H/SA/4069/1/FU/1/2020/II), the assessment of comparable efficacy and safety of TVB009 and reference product Prolia has been performed in a single phase III study (TVB009-IMB-30085).

Trial TVB009-IMB-30085 was a randomized, double-blind, multinational, multicentre trial with an objective to demonstrate similar efficacy and safety of TVB-009 compared to Prolia US administered subcutaneously (sc) in women with postmenopausal osteoporosis (PMO). Participants were randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or Prolia US ("main treatment period") administered in a 26-week interval. At week 52, participants in the Prolia US arm were re-randomized in a 1:1 ratio to either continue with a third dose of Prolia US or transition to TVB-009 and receive a single dose of TVB-009 ("transition period").

The **study design** is considered adequate for a comparability exercise. The 52-week duration of the main period is sufficiently long to evaluate comparability of the co-primary endpoints s-CTX and LS-BMD as well as safety and immunogenicity. The re-randomisation and switch at Week 52 are not a requirement for an EU MA and lead to a decrease a number of evaluable patients who remain in Prolia treatment arm for a long-term comparison of efficacy and safety. Nonetheless, this provides some additional information on immunogenicity and safety after a transition from Prolia to TVB-009 and is acceptable.

The **study population** comprised women with postmenopausal osteoporosis. The reference product Prolia is approved in several different indications. Among these, women with postmenopausal osteoporosis (PMO) represent the most sensitive population for measuring comparative efficacy, safety and immunogenicity of denosumab. The heterogeneity of the study population was reduced, and consequently, the chance of detecting differences between treatments increased by the combination of eligibility criteria and stratification at randomisation.

A US-sourced reference product Prolia was used as a **comparator**. The use of a US-sourced instead of an EU-sourced reference product is acceptable on the condition that analytical comparability between TVB-009, US-Prolia and EU-Prolia has been demonstrated (as mandated in CHMP/437/04 Rev 1). The

posology (dose 60 mg every 6 months) and route of administration (subcutaneous, in the abdomen) are in line with those approved for Prolia for the treatment of postmenopausal osteoporosis.

The **primary objective** of the study was to demonstrate that there are no clinically meaningful differences in efficacy between TVB-009P and Prolia US administered subcutaneously (sc) in patients with postmenopausal osteoporosis. The **co-primary endpoints**, percent change from baseline (%cfb) in LS-BMD at week 52 and percent change from baseline(%cfb) in sCTX-1 at week 26, have been agreed to during a scientific advice procedure (EMEA/H/SA/4069/1/FU/1/2020/II). Both endpoints are of importance, s-CTX for having a better dynamic response and therefore being more sensitive, and BMD for being of greater clinical relevance. Evaluation of both endpoints as co-primary increases the totality of evidence in the process of demonstrating similarity.

The primary **estimand** was the difference in mean percent change in LS-BMD from baseline at week 52 between TVB-009P and Prolia US treatment arms, regardless of intercurrent events in the target population of patients with postmenopausal osteoporosis who received at least one dose of IMP and had both, a baseline and at least 1 post-baseline assessment of LS-BMD. The sCTX-1 co-primary estimand was the difference in mean percent change in sCTX-1 from baseline at week 26 between TVB-009P and Prolia US treatment arms, regardless of intercurrent events in the target population of patients with postmenopausal osteoporosis. The attempt to use the estimand framework to define the analysis setting falls short of adding clarity for assessment. A "treatment policy"-like strategy was foreseen for primary equivalence testing, without providing a justification for this choice and also without any specifications for intercurrent events. In the planning documents, there were no estimand considerations concerning secondary-, sensitivity or supportive analyses. Those aspects were preplanned outside the estimand framework and are assessed further below.

Secondary efficacy endpoints included %cfb in BMD in femoral neck and total hip as well as LS-BMD at different time points and incidence of fractures. The selected secondary endpoints are clinically relevant and in line with relevant EMA guidelines on the treatment of osteoporosis.

The co-primary efficacy parameter BMD was assessed by Dual-energy X-ray absorptiometry (DXA) scans using Hologic and GE Lunar DXA machines. The lumbar spine scans included vertebrae L1 through L4. The vertebrae on which the measurement was based was consistent throughout the trial on an individual participant level. The same DXA machine was to be used for all trial procedures for a particular participant for the duration of the trial. All LS-BMD DXA scans were centrally adjudicated. Assessments were performed equally between arms. The assessment of the primary efficacy is adequate.

The co-primary PD parameters, sCTX-1 was quantified in human serum using an assay based on chemiluminescence technology. Performance of the assays during clinical studies is acceptable. For details, see discussion on clinical pharmacology.

Generally, the **primary analyses** were conducted on the mITT analysis set, which included all randomized participants who received at least 1 dose of the trial drug and had at least 1 post-baseline evaluation of LS-BMD. The same analysis set was to be used for both estimands and therefore participants who terminated before week 26 were not to be included in the sCTX-1 analysis.

The planned primary analysis of LS-BMD %cfb at week 52 was an analysis of covariance (ANCOVA) model with treatment, region (US/non-US), and previous use of bisphosphates (yes/no) as a fixed effects and baseline LS-BMD value and body weight at baseline as covariates. Similarity was to be concluded if the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±1.45. The similarity margin of ±1.45% was assumed to preserve 70% of the treatment effect of denosumab based on the lower bound of the 95% CI for the pooled denosumab treatment effect based on a meta-analysis of 3 placebo-controlled trials (Bone, 2008;

Cummings, 2009; McClung, 2006). The equivalence margin is considered justified from a statistical perspective. Missing values for LS-BMD at week 52 were to be imputed under the assumption that these were missing at random (MAR). The intermittent missing values at week 26 were imputed via an MCMC method, and a monotone regression predictive mean matching multiple imputation method was applied to impute the trailing missing values; both imputations were performed separately for each treatment arm.

The planned analysis of sCTX-1 %cfb at week 26 was an ANCOVA model with treatment, region (US/non-US), and previous use of bisphosphates (yes/no) as a fixed effects and baseline sCTX-1 value and body weight at baseline as covariates. If the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±20%, similarity was to be concluded. The similarity margin of ±20% for this endpoint preserves 68% of the treatment effect of denosumab based on the lower bound of the 95% CI for the pooled denosumab treatment effect in previously reported placebo-controlled trials (Amgen 2020; Amgen 2010; Amgen 2018). This margin is also considered acceptable from the methodological perspective. As only very few missing sCTX-1 assessments at Week 26 were expected in the mITT analysis set, no imputation for missing values of this endpoint were planned/performed. However, sCTX-1 values that fell below the limit of quantification (BLQ) were imputed as the low limit of quantification (LLOQ).

A number of sensitivity/supplementary analyses was planned for both co-primary endpoints.

The definition of analysis sets is not well aligned with the sparse description of estimands. However, the spectrum of analysis models eventually applied – including a variety of sensitivity analyses – is considered reasonable to evaluate the robustness of primary equivalence results, in particular with regard to MAR/MNAR assumptions and missing data imputation strategies.

The prespecified ANCOVA modelling is considered adequate to determine estimates for group differences which can serve as basis for equivalence evaluation. According to the descriptions of the trial outcome provided, the data collection process resulted only in a small number of missing data for the co-primary endpoints, which makes the potential influence of the chosen imputation strategies on equivalence conclusions rather small. The pre-specified imputation methods, in combination with the set of sensitivity and supportive analyses, are considered sufficient to provide a basis for assessment of similarity in the primary outcome variables.

A **sample size** of 292 evaluable patients (146 patients per arm in a 1:1 randomization ratio) was planned to provide 80% power to detect similarity based on difference in mean percent change in LS-BMD at week 52, assuming a true difference of 0 and an SD of 3.8% in each treatment arm. Assuming a true mean difference of 5% and an SD of 21% in each arm for sCTX-1 percent change from baseline at week 26, the proposed sample size of 292 evaluable patients (146 per arm) was supposed to result in a power of close to 100% for testing this endpoint. Assuming a drop-out rate of 10%, approximately 326 patients (163 per arm) were planned to be randomized to achieve approximately 292 evaluable patients (146 per arm). Power/Sample size calculations can be followed from the computational perspective based on the assumptions made. There are no multiplicity issues in connection to primary equivalence testing.

Efficacy data and additional analyses

Of the 332 randomized participants, 291 (87.7%) participants completed the main treatment period and 41 (12.3%) participants discontinued from the main treatment period. The discontinuation rate was relatively low and comparable between the two treatment groups. The primary reasons of discontinuation in the main treatment period were similar between treatment arms.

Important covariates such as age, body weight/BMI, baseline LS-BMD, previous use of bisphosphonates and prior fractures were comparable between the treatment groups at baseline. The

median baseline sCTX was comparable between the groups, but the mean baseline sCTX was higher in the TVB-009 group, influenced by the extreme maximum value in the TVB-009 group (18.162 ng/mL). Elevated sCTX levels up to 2 ng/mL indicate a moderate elevation which can be seen in PMO patients. However, sCTX values >10 ng/mL are considered extreme and are typically associated with aggressive bone diseases, including malignancies. The sCTX value was not a part of eligibility criteria for the study. Whether this value reflects a measurement error or indicates the presence of another underlying bone disease that should have led to exclusion of this patient from the study remains unclear. Regardless of the reason, this value is considered an outlier, which may significantly impact the equivalence testing of the co-primary PD endpoint. This is further discussed in the clinical pharmacology section.

Outcomes

Following two doses of denosumab, bone mineral density in lumbar spine (LS-BMD) increased from baseline to Week 52 in both treatment groups. The change from baseline in LS-BMD at Week 52 was 4.76% and 4.54% in the TVB-009 and Prolia group, respectively. The results for Prolia are comparable to the performance of denosumab in the FREEDOM trial at Month 12. The LS mean difference (TVB009 – Prolia) for the percent change from baseline to week 52 in LS-BMD (mITT) was 0.21 and the 95% CI for the difference [-0.73, 1.15] fell entirely within the equivalence margin of ±1.45%. Sensitivity and supplementary analyses for %cfb to Week 52 in LS-BMD supported the primary analysis.

Biosimilarity between TVB-009P and Prolia US was demonstrated for both co-primary efficacy endpoints.

Femoral neck BMD increased from the baseline to Week 26 and Week 52 by about 1-2% in both treatment arms, but the increase was slightly lower in the TVB-009 group (about 10% point difference), based on median values at both time points. These results should be interpreted with caution due to the overall smaller effect compared to LS-BMD.

Total hip BMD increased from the baseline to Week 26 and Week 52 about 2-3% in both treatment arms, but the increase was slightly lower in the TVB-009 group (about 10% point difference at Week 26, which decreased at Week 52), based on median values at both time points. These results should be interpreted with caution due to the overall smaller effect compared to LS-BMD.

In the TVB-009P/TVB-009P treatment group, 1 (0.8%) participant suffered grade 2 vertebral fracture per central reader and none of the participants had non-vertebral fractures. In the Prolia US/TVB-009P treatment group, 1 (1.4%) participant suffered non-vertebral fracture and none of the participants had vertebral fractures. The incidence of fractures is too low and not sensitive to detect differences between treatments.

Based on the overall low incidence of ADA and nABs, with a tendency towards less immunogenicity after treatment with TVB-009 as compared to the reference product, there are no concerns regarding the relevant impact on efficacy.

2.5.7. Conclusions on the clinical efficacy

The efficacy results overall support biosimilarity between Ponlimsi and Prolia.

2.5.8. Clinical safety

The safety of TVB-009P has been evaluated in two clinical trials.

Trial TVB009-BE-10157 was a Phase 1, randomized, double-blind, single-dose, 3-arm parallel-group trial that evaluated the PK and PD similarity of TVB-009P versus Prolia US, and Prolia EU in healthy participants. The trial consisted of a screening period (4 weeks), a confinement period and ambulatory visits (i.e., 36 weeks of treatment/observation), and an end of study (EOS) visit (on day 253). Eligible participants were randomly assigned in a ratio of 1:1:1 to receive TVB-009P, Prolia US, or Prolia EU as a single 60 mg sc administration under fasted conditions. Safety and tolerability were assessed by adverse events (AEs), results of clinical laboratory tests (haematology, clinical chemistry, and urinalysis), vital signs, electrocardiogram (ECG) findings, physical examination findings, injection site findings, and concomitant medication usage.

Trial TVB009-IMB-30085 was a randomized, double-blind, multinational, multicentre trial with an objective to demonstrate similar efficacy and safety of TVB-009P compared to Prolia US administered sc in patients with postmenopausal osteoporosis. The trial consisted of a screening period (up to 4 weeks) and a 52-week double-blind main treatment period, followed by a 26-week double-blind transition period. Participants received 3 sc injections of TVB-009P and/or Prolia US at a dose of 60 mg, administered by a qualified healthcare provider (according to local regulations). The first dose of TVB-009P or Prolia US was administered following randomization, the second dose was administered 26 weeks after the first dose, and third dose at week 52 (26 weeks after the second dose). Participants in the Prolia US arm either continued with a third dose of Prolia US or transitioned to TVB-009P and received a single dose of TVB-009P in the transition period. This was to primarily assess immunogenicity and safety after a transition from Prolia US to TVB-009P until week 78. The safety of TVB-009P and Prolia US was assessed throughout the trial by evaluating AEs, device related AEs and malfunctions, clinical laboratory test results, vital signs measurements, ECG findings, physical examination results, local tolerability at the injection site, and concomitant medication usage.

All statistical analyses for safety data were performed with the Safety Analysis Sets of the respective trial, where the safety population included all participants who received at least 1 dose of the trial treatment.

For Trial TVB009-IMB-30085, the analyses during main treatment period and transition period were performed with the Safety Analysis Set and Transition Safety Analysis Set, respectively. The Transition Safety Analysis Set included all participants who received the third dose of the investigational medicinal product (IMP). The analyses of data on participant disposition, demographic and baseline characteristics were performed with the intent-to-treat (ITT) Analysis Set that included all randomized participants. Descriptive statistics were used to summarize AEs and safety results.

2.5.8.1. Patient exposure

A total of 352 participants received at least 1 dose of TVB-009P across the two clinical trials.

In Trial TVB009-BE-10157, 115 healthy participants received a single sc dose of 60 mg TVB-009P.

In Trial TVB009-IMB-30085, 166 participants with postmenopausal osteoporosis received at least 1 dose of TVB-009P (60 mg sc) in the main treatment period; 8 participants received a single dose and 158 participants received 2 doses. Overall, in the entire trial, 148 participants received 3 doses of TVB-009P in the TVB-009P/TVB-009P treatment group and an additional 71 participants received 1 dose of TVB-009P (60 mg sc) in the transition period after previously receiving 2 doses of Prolia US (60 mg sc) in the main treatment period.

Overall, across the two trials, the duration of exposure to TVB-009P (i.e., participants who received at least 1 dose of TVB-009P) can be summarized as follows:

- <6 months = 194 participants (115 participants in Trial TVB009-BE-10157 and in Trial TVB009-IMB-30085; 8 participants who received a single dose of TVB-009P in the main treatment period and 71 participants who received a single dose of TVB-009P in the transition period after previously receiving 2 doses of Prolia US in the main treatment period)
- ≤12 months = 10 participants (158 participants who received 2 doses of TVB-009P in the main treatment period minus 148 participants who received 3 doses of TVB-009P in the TVB-009P/TVB-009P treatment group in Trial TVB009-IMB-30085)
- >12 months = 148 participants (overall 148 participants received 3 doses of TVB-009P in the TVB-009P/TVB-009P treatment group in the entire Trial TVB009-IMB-30085).

2.5.8.2. Adverse events

In Trial TVB009-BE-10157, overall, 106 (31%) participants reported at least 1 AE: 31 (27%) participants in the TVB-009P treatment group, 38 (33%) participants in the Prolia US treatment group, and 37 (32%) participants in the Prolia EU treatment group. Adverse events considered by the investigator to be related to trial drug (i.e., reasonable possibility) were reported for 6 (5%) participants in the TVB-009P treatment group, 11 (10%) participants in the Prolia US treatment group, and 14 (12%) participants in the Prolia EU treatment group. Overall, 3 (<1%) participants experienced AEs considered to be severe. There were no deaths, serious adverse events (SAEs), or AEs leading to discontinuation.

The most frequently occurring AEs in all treatment groups were blood creatine phosphokinase (CPK) increase and alanine aminotransferase (ALT) increase, which were reported more commonly in the Prolia US and Prolia EU treatment groups than in the TVB-009P treatment group. The majority of participants experiencing blood CPK and ALT elevations were male (28/34 participants [82%] and 11/19 participants [58%], respectively). The elevations were asymptomatic, mostly transient, and observed throughout the trial (including at pre-dose in some instances).

Table 41: Adverse Events Occurring in >2% of Participants Overall by System Organ Class and Preferred Term (Trial TVB009-BE-10157)

System Organ Class **MedDRA Version 23.0 preferred term**	**Number (%) of Participants**			
	TVB-009P (N = 115)	**Prolia US (N = 115)**	**Prolia EU (N = 115)**	**Total (N = 345)**
Participants with at least 1 adverse event	31 (27)	38 (33)	37 (32)	106 (31)
Gastrointestinal disorders	**5 (4)**	**5 (4)**	**5 (4)**	**15 (4)**
Constipation	3 (3)	3 (3)	4 (3)	10 (3)
General disorders and administration site conditions	**6 (5)**	**4 (3)**	**2 (2)**	**12 (3)**
Influenza like illness	5 (4)	4 (3)	2 (2)	11 (3)
Infections and infestations	**3 (3)**	**1 (<1)**	**3 (3)**	**7 (2)**
Investigations	**15 (13)**	**22 (19)**	**24 (21)**	**61 (18)**
Blood CPK increased	8 (7)	11 (10)	15 (13)	34 (10)
Blood triglycerides increased	3 (3)	4 (3)	4 (3)	11 (3)
ALT increased	2 (2)	9 (8)	8 (7)	19 (6)

Musculoskeletal and connective tissue disorders	**3 (3)**	**5 (4)**	**5 (4)**	**13 (4)**
Pain in extremity	1 (<1)	3 (3)	2 (2)	6 (2)
Nervous system disorders	**4 (3)**	**4 (3)**	**1 (<1)**	**9 (3)**
Skin and subcutaneous tissue disorders	**3 (3)**	**3 (3)**	**3 (3)**	**9 (3)**

Source: Clinical Study Report (CSR) of Trial TVB009-BE-10157, Table 19
ALT = alanine aminotransferase; CPK = creatine phosphokinase; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of participants; SOC = system organ class; US = United States
Preferred terms were sorted by descending order of incidence within SOC for the TVB-009P 60 mg treatment group. Participants were counted only once in each preferred term category, and only once in each SOC category.

The comparison of ADRs across three treatment groups (TVB-009P, Prolia US, and Prolia EU) revealed that the Prolia EU group had the highest incidence of ADRs (12%), followed by Prolia US (10%), and TVB-009P (5%). The most reported TEAEs assessed as related by investigator were elevated liver enzymes, particularly ALT, and musculoskeletal and connective tissue disorders. At the SOC level, the Prolia EU and Prolia US groups had higher incidences of increased ALT (6% each) compared to TVB-009P (2%). Additionally, musculoskeletal and connective tissue disorders were more frequently reported in the Prolia US and Prolia EU groups (3% each) compared to TVB-009P (0%).

In the TVB-009P treatment group, the investigator-assessed treatment-related adverse events were reported from following System Organ Class (SOC): gastrointestinal disorders, investigations, nervous system disorders, and skin and subcutaneous tissue disorders. The treatment-related AEs were reported in a maximum of 2 subjects per event in the TVB-009P group.

Study TVB009-IMB-30085

In Trial TVB009-IMB-30085, in the main treatment period, 231 (69.8%) participants experienced 730 treatment-emergent adverse events (TEAEs); 123 (74.1%) participants in the TVB-009P treatment group experienced 374 TEAEs and 108 (65.5%) participants in the Prolia US treatment group experienced 356 TEAEs. Of the TEAEs, overall, 32 (9.7%) participants reported 61 trial drug-related TEAEs; 19 (11.4%) participants with 27 trial drug-related TEAEs in the TVB-009P treatment group and 13 (7.9%) participants with 34 trial drug-related TEAEs in the Prolia US treatment group. Overall, 14 (4.2%) participants experienced serious TEAEs; 8 (4.8%) participants in the TVB-009P treatment group and 6 (3.6%) participants in the Prolia US treatment group. The TEAEs leading to discontinuation of the IMP were reported for 4 (2.4%) participants in the TVB-009P treatment group and 6 (3.6%) participants in the Prolia US treatment group.

In the transition period, the treatment groups presented were based on the participant's treatment in the main treatment period and transition period among those participants who received the third dose of the IMP. A total of 96 (33.0%) participants experienced 191 TEAEs in the transition period; 50 (33.8%) participants experienced 115 TEAEs in the TVB-009P/TVB-009P treatment group, 20 (27.8%) participants experienced 40 TEAEs in the Prolia US/Prolia US treatment group, and 26 (36.6%) participants experienced 36 TEAEs in the Prolia US/TVB-009P treatment group. A total of 3 TEAEs related to trial drug were reported for 2 (1.4%) participants in TVB-009P/TVB-009P treatment group. No trial drug-related TEAEs were reported in the Prolia US/Prolia US and Prolia US/TVB-009P treatment groups. Overall, 6 (2.1%) participants experienced serious TEAEs; 5 (3.4%) participants in the TVB-009P/TVB-009P treatment group and 1 (1.4%) participant in the Prolia US/TVB-009P treatment group. No TEAEs leading to discontinuation of trial drug were reported during the transition period.

In the overall treatment period (entire trial), the treatment groups included those randomized participants who received at least 1 dose of the IMP and stayed on the same treatment throughout the trial. A total of 130 (78.3%) participants in the TVB-009P/TVB-009P treatment group experienced 489

TEAEs and 64 (68.1%) participants in the Prolia US/Prolia US treatment group experienced 247 TEAEs. The TEAEs considered by the investigator to be related to trial drug were reported in 19 (11.4%) participants in the TVB-009P/TVB-009P treatment group and 9 (9.6%) participants in the Prolia US/Prolia US treatment group. Overall, in the entire trial, 12 (7.2%) participants in the TVB-009P/TVB-009P treatment group and 3 (3.2%) participants in the Prolia US/Prolia US treatment group experienced serious TEAEs. The TEAEs leading to discontinuation of the IMP were reported for 4 (2.4%) participants in the TVB-009P/TVB-009P treatment group and 6 (6.4%) participants in the Prolia US/Prolia US treatment group.

No deaths were reported during the trial.

Table 42: Overview of Treatment-Emergent Adverse Events (Trial TVB009-IMB-30085)

	Main Treatment Period Safety Analysis Set			Transition Period Transition Safety Analysis Set				Overall Treatment Period Safety Analysis Set	
	TVB-009P (N = 166) n (%) m	PROLIA US (N = 165) n (%) m	Total (N = 331) n (%) m	TVB-009P/ TVB-009P (N = 148) n (%) m	PROLIA US/ PROLIA US (N = 72) n (%) m	PROLIA US/ TVB-009P (N = 71) n (%) m	Total (N = 291) n (%) m	TVB-009P/ TVB-009P (N = 166) n (%) m	PROLIA US/ PROLIA US (N = 94)[a] n (%) m
Number of participants; n (percentage of participants; %) number of events; m:									
Any TEAE	123 (74.1) 374	108 (65.5) 356	231 (69.8) 730	50 (33.8) 115	20 (27.8) 40	26 (36.6) 36	96 (33.0) 191	130 (78.3) 489	64 (68.1) 247
TEAE related to trial drug	19 (11.4) 27	13 (7.9) 34	32 (9.7) 61	2 (1.4) 3	0	0	2 (0.7) 3	19 (11.4) 30	9 (9.6) 28
TEAE related to medical device	0	0	0	0	0	0	0	0	0
Serious TEAE	8 (4.8) 8	6 (3.6) 7	14 (4.2) 15	5 (3.4) 6	0	1 (1.4) 1	6 (2.1) 7	12 (7.2) 14	3 (3.2) 3
TEAE leading to discontinuation of the trial drug	4 (2.4) 5	6 (3.6) 11	10 (3.0) 16	0	0	0	0	4 (2.4) 5	6 (6.4) 11
TEAE leading to death	0	0	0	0	0	0	0	0	0

Source: Clinical Study Report (CSR) of Trial TVB009-IMB-30085, Table 41, Table 43, Table 44
eCRF = electronic case report form; IMP = investigational medicinal product; m = the number of events; n = the number of participants with events; TEAE = treatment-emergent adverse event; US = United States.
[a] N = participants randomized to Prolia US who received at least 1 dose of the Prolia US and stayed on Prolia US throughout the trial, irrespective of discontinuation after the first dose.
Safety Analysis Set included all randomized participants who received at least 1 dose of the IMP. Transition Safety Analysis Set included all participants who received the third dose of the IMP. Percentages were based on the number of participants in the treatment group in the respective Analysis Set.
The TEAEs related to trial drug were the events with relationship to trial drug recorded as "reasonable possibility" on the eCRF.

During the main treatment period, overall, 231 (69.8%) participants experienced at least 1 TEAE. The most frequently occurring TEAEs reported in ≥5% participants in either treatment group (TVB-009P vs. Prolia US, respectively) were vitamin D deficiency (20.5% vs.12.7%), coronavirus disease 2019 (COVID-19) (10.2% vs. 13.3%), headache (9.6% vs. 9.1%), hypercalcaemia (8.4% vs. 11.5%), arthralgia (8.4% vs. 7.9%), vitamin D decreased (6.0% vs. 3.0%), back pain (5.4% vs. 3.6%), nasopharyngitis (4.2% vs. 5.5%) and pain in extremity (3.6% vs. 6.1%).

The higher incidence of participants with vitamin D deficiency/vitamin D decreased in the TVB-009P treatment group could be possibly due to the higher number of participants with low 25-(OH) vitamin D3 levels at baseline in the TVB-009P treatment group (22.4%) as compared with the Prolia US treatment group (14.3%).

During the transition period, overall, 96 (33.0%) participants experienced at least 1 TEAE. The most frequently occurring TEAEs reported in ≥5% participants in either treatment group (TVB-009P/TVB-009P vs. Prolia US/Prolia US, respectively) were back pain (5.4% vs. 2.8%), nasopharyngitis (2.7% vs. 6.9%), and arthralgia (2.7% vs. 5.6%). No TEAEs in ≥5% participants were reported in the Prolia US/TVB-009P treatment group.

2.5.8.3. Serious adverse event/deaths/other significant events

Study TVB009-BE-10157

There were no SAEs, AEs leading to discontinuation or deaths in Trial TVB009-BE-10157.

Local tolerability at the injection site (erythema, ecchymosis, induration, tenderness, warmth, and swelling, and pain) was reported in less than 5% of the participants. The most common injection site finding was erythema. At 20 minutes post-dose, 12 (3%) participants had mild erythema: 5 (4%) participants in the TVB-009P treatment group, 4 (3%) participants in the Prolia US treatment group, and 3 (3%) participants in the Prolia EU treatment group. Of these participants, 1 participant in the TVB-009P treatment group also had mild erythema at 1 hour and 2 hours post-dose and 2 participants in the Prolia EU treatment group also had mild erythema at 1-hour post-dose. The only other injection site findings were 1 mild case of ecchymosis and 1 mild case of tenderness, both in participants in the TVB-009P treatment group. All injection site findings were mild and transient.

Study TVB009-IMB-30085

No deaths occurred in Study TVB009-IMB-30085.

In the main treatment period, 14 (4.2%) participants experienced serious TEAEs; 8 (4.8%) participants in the TVB-009P treatment group and 6 (3.6%) participants in the Prolia US treatment group.

The serious TEAEs experienced by participants in the TVB-009P treatment group included adrenal mass, bile duct stone, cholelithiasis, hepatitis C, infective periostitis, gastric neoplasm, ureterolithiasis and peripheral arterial occlusive disease in 1 participant each. Of these, serious TEAEs of hepatitis C, infective periostitis, and gastric neoplasm were of mild intensity; serious TEAEs of bile duct stone, ureterolithiasis and peripheral arterial occlusive disease were of moderate intensity; and serious TEAEs of adrenal mass and cholelithiasis were of severe intensity. None of the serious TEAEs had a reasonable possible relationship to the trial drug.

The serious TEAEs experienced by participants in the Prolia US treatment group included cholecystitis acute, COVID-19 pneumonia, osteonecrosis, osteonecrosis of jaw, splenic marginal zone lymphoma in 1 participant each, and atrial flutter and myocardial ischaemia (1 participant). Of these, all were of moderate intensity and considered with no reasonable possible relationship to the trial drug or medical device except for 2 serious TEAEs of osteonecrosis of jaw that was mild in intensity and osteonecrosis that was moderate in intensity, both with reasonable possible relationship to the trial drug.

In the main treatment period, 4 participants from the Prolia US treatment group experienced non-serious TEAEs that led to discontinuation from the trial. The TEAEs included tooth infection, pain in extremity, pulpitis dental, and Factor II mutation in 1 participant each. Four (2.4%) participants in the TVB-009P treatment group experienced TEAEs leading to discontinuation of IMP that included hepatitis C, infective periostitis, gastric neoplasm in 1 participant each; and fibula fracture and foot fracture (1 participant). Of these TEAEs in the TVB-009P treatment group, all TEAEs were of mild intensity with no reasonable possible relationship to the trial drug or medical device except for the TEAE of fibula fracture that was moderate in intensity with a reasonable possible relationship to the IMP. In the Prolia US treatment group, 6 (3.6%) participants experienced TEAEs leading to discontinuation of the IMP that included osteonecrosis of jaw, pain in extremity, pulpitis dental in 1 participant each; cholecystitis acute, nasal congestion, pollakiuria and cough (1 participant); arthralgia, bursitis and osteonecrosis (1 participant), and Factor II mutation (1 participant). Of these, TEAEs of osteonecrosis of jaw, pain in extremity, cough, nasal congestion, pollakiuria, bursitis, and Factor II mutation were of mild intensity and TEAEs of pulpitis dental, cholecystitis acute, arthralgia, and osteonecrosis were of moderate intensity. None of the TEAEs had a reasonable possible relationship to the trial drug or medical device

except for the TEAEs of pain in extremity, osteonecrosis, and osteonecrosis of jaw that had a reasonable possible relationship to the IMP.

The incidence of injection site reactions (ISR) was comparable between both treatment groups (TVB-009P, 8.4% vs. Prolia US, 9.1%) in the main treatment period. All ISR were mild except for 2 events in the Prolia US group which were moderate in severity. No severe injection site tolerability signs were reported and the mean pain numerical response scale (NRS) for local tolerability and pain was comparable in both treatment groups (TVB-009P vs. Prolia US, respectively) on day 1 (0.5 vs. 0.4) and at week 26 (0.3 vs. 0.4).

In the transition period, 6 (2.1%) participants experienced serious TEAEs; 5 (3.4%) participants in the TVB-009P/TVB-009P treatment group and 1 (1.4%) participant in the Prolia US/TVB-009P treatment group. There were no serious TEAEs reported in the Prolia US/Prolia US treatment group. The serious TEAEs experienced by participants in the TVB-009P/TVB-009P treatment group included bone cancer, chronic obstructive pulmonary disease, urinary incontinence, COVID-19 pneumonia, helicobacter infection, and malaise in 1 participant each. Of these, bone cancer, chronic obstructive pulmonary disease, and urinary incontinence were of severe intensity and COVID-19 pneumonia, helicobacter infection, and malaise were of moderate intensity. In the Prolia US/TVB-009P treatment group, the serious TEAE experienced by 1 (1.4%) participant was cholelithiasis that was mild in intensity. None of the serious TEAEs present in the transition period had a reasonable possible relationship to the trial drug.

In the transition period, none of the participants experienced any non-serious TEAEs that led to discontinuation from the trial.

The incidence of ISR was higher in the Prolia US/Prolia US group (9.7%) compared to the TVB-009P/TVB-009P group (4.7%) and the Prolia US/TVB-009P group (5.6%). No moderate or severe injection site tolerability signs were reported in the transition period and the mean pain NRS for local tolerability and pain was comparable between the treatment groups.

2.5.8.4. Laboratory findings

Haematology Parameters

In Trial TVB009-BE-10157, there were no apparent trends in mean changes from baseline, throughout the trial, to EOS for any haematology variable after administration of TVB-009P, Prolia US or Prolia EU. Overall, the incidence of potentially clinically significant (PCS) haematology abnormalities was low (3% overall) and similar across the 3 treatment groups, with the exception of decreased haemoglobin, which was only observed in the TVB-009P (3 participants) and Prolia US (2 participants) treatment groups. No participant reported changes in haematology values that were reported as an AE.

In Trial TVB009-IMB-30085, there were no clinically meaningful changes from baseline at any timepoint for any haematology parameter in either treatment groups in the main treatment period, transition period, and overall treatment period. A summary of potentially clinically significant haematology values is presented in the table below. The majority of participants had normal results for the haematology parameters.

Table 43: Potentially Clinically Significant Hematology Values (Trial TVB009-IMB-30085)

Parameter Criterion	Main Treatment Period Safety Analysis Set		Transition Period Transition Safety Analysis Set			Overall Treatment Period Safety Analysis Set	
	TVB-009P (N = 166) n (%)	PROLIA US (N = 165) n (%)	TVB-009P/ TVB-009P (N = 148) n (%)	PROLIA US/ PROLIA US (N = 72) n (%)	PROLIA US/ TVB-009P (N = 71) n (%)	TVB-009P/ TVB-009P (N = 166) n (%)	PROLIA US/ PROLIA US (N = 94) n (%)
Eosinophils/Leukocytes, N1	165	162	141	68	69	165	91
>10%	3 (1.8)	6 (3.7)	2 (1.4)	0	1 (1.4)	4 (2.4)	2 (2.2)
Hematocrit, N1	165	162	144	69	69	165	91
Male: <0.37 L/L, Female: <0.32 L/L	2 (1.2)	1 (0.6)	1 (0.7)	0	0	3 (1.8)	1 (1.1)
Hemoglobin, N1	165	162	144	69	69	165	91
Male: ≤115 g/L, Female: ≤95 g/L	1 (0.6)	0	1 (0.7)	0	0	2 (1.2)	0
Platelets count, N1	165	162	144	69	69	165	91
≤75 × 10^9/L	0	1 (0.6)	0	0	0	0	1 (1.1)
≥700 × 10^9/L	0	0	0	0	0	0	0
Leukocytes, N1	165	162	143	69	69	165	91
≤3 × 10^9/L	10 (6.1)	6 (3.7)	5 (3.5)	0	1 (1.4)	11 (6.7)	2 (2.2)
≥20 × 10^9/L	0	0	0	0	0	0	0

Source: Clinical Study Report (CSR) of Trial TVB009-IMB-30085, Table 53, Summary 14.3.2.3.1.3, Summary 14.3.2.3.1.2
n = the number of participants meeting the criterion at least once in the respective Analysis Set; N1 = the number of participants with any assessment of the parameter in the in the respective Analysis Set.
Percentage was n/N1*100%.

In the main treatment period, majority of the TEAEs were mild and did not have a reasonable possible relationship to the trial drug. One event of white blood cell (WBC) count decreased in the TVB-009P treatment group was considered to have a reasonable possible relationship to the trial drug. This event started on Day 381 and was resolved by Day 402.

In the transition period, the individual clinically significant haematology abnormalities that were reported as TEAEs were mild and had no reasonable possible relationship to the trial drug.

Clinical Chemistry Parameters

In Trial TVB009-BE-10157, overall, there were no apparent trends in mean changes from baseline, throughout the trial, to EOS for any clinical chemistry variable after administration of TVB-009P, Prolia US or Prolia EU with the following exceptions:

1. Slight decreases in mean values for calcium and phosphate compared to baseline were observed for all 3 treatment groups from day 5 to day 113 and day 169, respectively.
2. Slight increases in mean values for ALT were observed for all 3 treatment groups at day 11 and day 15.
3. There were isolated increases in mean values for CPK (ie, increase from mean baseline >300 U/L) in the Prolia (EU) treatment group due to individual CPK elevations at day 85 and day 253.

No meaningful differences were seen between the treatment groups in the number of participants with PCS clinical chemistry abnormalities, with the exception of increased transaminases (ALT, aspartate aminotransferase [AST], and gamma-glutamyl transferase [GGT]) which were observed more frequently in the Prolia US and Prolia EU treatment groups than in the TVB-009 treatment group. These elevations were transient, mostly observed on day 11 and day 15, but also observed later in the

trial (day 85 and day 169). Most of the PCS abnormalities were single occurrences and/or occurred in participants with intermittent abnormalities (some of which were present prior to IMP dosing).

The ALT and AST elevations were further analysed post-hoc based on the Food and Drug Administration (FDA) toxicity grades. The highest toxicity grade for any participant with multiple abnormal values for the same test is summarized below. The majority of abnormal ALT and AST post-baseline values (137 [40%] participants and 50 [14%] participants, respectively) were considered Grade 1 according to the FDA toxicity grading scale. Abnormal ALT and AST post-baseline Grade 2 and above values were observed at higher frequencies in the Prolia US and Prolia EU treatment groups compared to the TVB-009P treatment group.

Table 44: ALT and AST Post-Baseline Grading per FDA Toxicity Grade for Healthy Volunteers by Treatment Group (Trial TVB009-BE-10157)

Test	Grade	Number (%) of Participants			
		TVB-009P (N = 115)	Prolia US (N = 115)	Prolia EU (N = 115)	Total (N = 345)
ALT	Grade ≥1	44 (38)	42 (37)	51 (44)	137 (40)
ALT	Grade ≥2	4 (3)	11 (10)	13 (11)	28 (8)
ALT	Grade ≥3	0	2 (2)	5 (4)	7 (2)
AST	Grade ≥1	12 (10)	17 (15)	21 (18)	50 (14)
AST	Grade ≥2	0	3 (3)	2 (2)	5 (1)
AST	Grade ≥3	0	1 (<1)	2 (2)	3 (<1)
ALT or AST	Grade ≥1	45 (39)	42 (37)	52 (45)	139 (40)
ALT or AST	Grade ≥2	4 (3)	11 (10)	14 (12)	29 (8)
ALT or AST	Grade ≥3	0	2 (2)	6 (5)	8 (2)

Source: Clinical Study Report (CSR) of Trial TVB009-BE-10157, Table 21
ALT = alanine aminotransferase; AST = aspartate aminotransferase; EU = European Union; FDA = Food and Drug Administration; ULN = upper limit of the normal range; US = United States.
Grade 1 = 1.1 to 2.5 × ULN; Grade 2 = 2.6 to 5 × ULN; Grade 3 = 5.1 to 10 × ULN
Participants with greatest post-baseline toxicity grade were counted.

The clinical chemistry abnormalities reported as AEs in Trial TVB009-BE-10157 included the following:

- Liver function test (LFT) abnormalities: 27 events were reported for 21 participants (ALT increased; AST increased; LFT increased; LFT abnormal). These AEs were reported more frequently in the Prolia EU (10 participants) and Prolia US (9 participants) treatment groups compared to the TVB-009P treatment group (2 participants). Most of the events (20/27 [74%] events) were mild and transient. All events resolved with the exception of an event reported at the last assessment with an unknown status. In total, 17/27 (62%) events were assessed as possibly related to trial drug by the investigator.
- CPK increases: 39 events were reported for 34 participants. These AEs were reported more frequently in the Prolia EU (15 participants) and Prolia US (11 participants) treatment groups compared to the TVB-009P treatment group (8 participants). Most events (38/39 [97%] events) were mild or moderate and transient. All events resolved with the exception of 2 events reported at the last assessment with an unknown status. All events were considered not related to IMP by the investigator.
- Triglyceride increases: 11 events were reported for 11 participants, with a similar incidence across all 3 treatment groups. Most events (9/11 [82%] events) were mild and

10 of 11 participants reporting these events had elevated triglycerides prior to IMP dosing. All events were assessed as not related to IMP by the investigator.

- Additionally, in the TVB-009P treatment group, 1 event of blood glucose increased (value of 9.45 mmol/L [reference range: 3.6 - 5.5 mmol/L]) was reported for a participant that had intermittent elevated glucose levels from screening onwards and 1 event of blood calcium increased (value of 2.96 mmol/L [reference range: 2.18 - 2.56 mmol/L]) was reported on day 252. Both events were mild and considered not related to IMP by the investigator.

In Trial TVB009-IMB-30085, there were no clinically meaningful changes from baseline at any timepoint for any clinical chemistry parameter in either treatment groups in the main treatment period, transition period, and overall treatment period. A summary of potentially clinically significant chemistry values is presented below. The majority of the participants had normal results for the clinical chemistry parameters in both the treatment groups. No clinically meaningful differences were seen between the treatment groups in the number of participants with clinically significant clinical chemistry abnormalities or types of abnormalities.

Table 45: Potentially Clinically Significant Chemistry Values (Trial TVB009-IMB-30085)

Parameter Criterion	Main Treatment Period Safety Analysis Set		Transition Period Transition Safety Analysis Set			Overall Treatment Period Safety Analysis Set	
	TVB-009P (N=166) n (%)	PROLIA US (N=165) n (%)	TVB-009P/ TVB-009P (N=148) n (%)	PROLIA US/ PROLIA US (N=72) n (%)	PROLIA US/ TVB-009P (N=71) n (%)	TVB-009P/ TVB-009P (N=166) n (%)	PROLIA US/ PROLIA US (N=94) n (%)
Alkaline phosphatase, N1	165	162	144	70	70	165	91
≥3 × ULN	0	0	0	0	0	0	0
Alanine aminotransferase, N1	165	162	144	70	70	165	91
≥3 × ULN	0	0	0	0	0	0	0
Aspartate aminotransferase, N1	165	162	144	70	70	165	91
≥3 × ULN	1 (0.6)	0	0	0	0	1 (0.6)	0
Bilirubin, N1	165	162	144	70	70	165	91
≥34.2 µmol/L	2 (1.2)	1 (0.6)	0	0	1 (1.4)	2 (1.2)	0
Creatinine, N1	165	162	144	70	70	165	91
≥177 µmol/L	0	0	0	0	0	0	0
Gamma-glutamyl transferase; N1	165	162	142	69	70	165	91
≥3 × ULN	5 (3.0)	4 (2.5)	1 (0.7)	1 (1.4)	0	5 (3.0)	2 (2.2)
Lactate dehydrogenase, N1	165	162	144	70	69	165	91
≥3 × ULN	0	0	0	0	0	0	0
Urate, N1	165	162	144	70	70	165	91
Male: ≥625 µmol/L, Female: ≥506 µmol/L	3 (1.8)	1 (0.6)	1 (0.7)	0	0	3 (1.8)	0

Source: Clinical Study Report (CSR) of Trial TVB009-IMB-30085, Table 50, Summary 14.3.2.3.2.3, Summary 14.3.2.3.2.2
n = the number of participants meeting the criterion at least once in the respective Analysis Set; N1 = the number of participants with any assessment of the parameter in the respective Analysis Set; ULN = upper limit of normal range; US = United States
Percentage was n/N1*100%.

In the main treatment period, the majority of TEAEs were mild with no reasonable possible relationship to the trial drug. The following clinical chemistry abnormalities reported as TEAEs were considered to have a reasonable possible relationship to the trial drug:

- 3 events of hypocalcaemia, 2 events of vitamin D deficiency, and 1 event each of vitamin D decreased and blood calcium increased in the TVB-009P treatment group.
- 1 event of blood creatine phosphokinase increased in the Prolia US treatment group.

In the transition period, the majority of individual clinically significant clinical chemistry abnormalities that were reported as TEAEs were mild with no reasonable possible relationship to the trial drug, except for 1 event of LDL increased in the TVB-009P/TVB-009P treatment group that was considered to have a reasonable possible relationship to the trial drug.

Urinalysis Parameters

In Trial TVB009-BE-10157, there were no apparent trends in mean changes from baseline, throughout the trial, to EOS for either urinalysis variable (pH or specific gravity) after administration of TVB-009P, Prolia US and Prolia EU. No relevant differences were observed between the 3 treatment groups. Approximately one-quarter of participants had PCS occult blood during the trial (4 male participants), the rest being female participants. For some female participants, occult blood occurred in association with menstruation; the proportion of participants was similar across the 3 treatment groups.

One participant (TVB-009P) reported an AE of haematuria on day 149. The event was mild in severity, considered by the investigator as unrelated to trial treatment, and resolved at visit 15 (day 198).

In Trial TVB009-IMB-30085, there were no clinically meaningful changes from baseline at any timepoint for any numeric urinalysis parameter in both treatment groups, in the main treatment period and overall treatment period. In the main treatment period, majority of the TEAEs were mild and did not have a reasonable possible relationship to the trial drug. The following urinary abnormalities reported as TEAEs were considered to have a reasonable possible relationship to the trial drug:

- 1 event of urinary tract infection and 1 event of haematuria in the TVB-009P treatment group.
- 2 events of urinary tract infection in the Prolia US treatment group.

In the transition period, individual clinically significant urinalysis parameters that were reported as TEAEs did not have a reasonable possible relationship to the trial drug.

Electrocardiography Findings

One participant had an ECG finding reported as an AE (abnormal atrial rhythm per ECG at day 255) in Trial TVB009-BE-10157. The event was mild in severity, asymptomatic, considered by the investigator as not related to trial drug and resolved on day 263. Overall, no clinically meaningful trends were observed in mean changes from baseline, throughout the trial, to EOS for ECG parameters (mean heart rate, PR interval, QRS duration, QT interval, QTc interval [Fridericia], and RR interval results) after administration of TVB-009P, Prolia US and Prolia EU. No relevant differences were observed across the 3 treatment groups in Trial TVB009-BE-10157.

In Trial TVB009-IMB-30085, in the main treatment period, none of the participants had any abnormal clinically significant ECG result in both treatment groups. In the transition period and overall treatment period, 2 (1.4%) participants in the TVB-009P/TVB-009P treatment group had abnormal clinically significant ECG result at week 78.

2.5.8.5. Safety in special populations

Not applicable for biosimilars

2.5.8.6. Immunological events

Immunogenicity Results from Trial TVB009-BE-10157 in Healthy Participants

Trial TVB009-BE-10157 assessed the immunogenicity of drug product of TVB-009 as proposed biosimilar to Prolia (TVB-009P) in comparison with Prolia EU and Prolia US in a total of 345 healthy participants.

There were no severe hypersensitivity reactions (e.g., anaphylaxis) in Trial TVB009-BE-10157 that would have required additional samples for immunogenicity assessment according to the protocol. Therefore, only the scheduled blood samples as described in TVB009-BE-10157 Clinical Study Protocol with Amendment 02, Section 3.4 were assessed for ADA.

The ADA in serum samples were analysed using the same validated assays for all products, employing a 3-tiered approach as described further above.

No participants who received TVB-009 had detectable ADAs against denosumab.

A total of 3 participants (<1%) who received Prolia had detectable ADAs against denosumab. Two of these participants (1 in the Prolia EU group and 1 in the Prolia US group) were ADA positive before and after trial drug administration. These participants were not among the group of participants with measurable pre-dose denosumab concentrations. Their ADA titres were low and did not increase after trial drug administration. The third participant with detectable ADAs against denosumab was in the Prolia US group and had a treatment-emergent ADA response after trial drug administration with a very low ADA titer at 2 time points (log10 titres of 1.6 and 1.5 for Day 15 and Day 29, respectively; the participant discontinued [lost to follow-up] from the trial after Day 29). Because of the very low response, samples were not analysed for the detection of NAb response. For reference, participants considered as treatment-emergent ADA were those who initially screened as ADA negative at baseline but tested positive for ADA at later time points after drug administration or already ADA positive from baseline but showed an increase in OD signal or in percent inhibition signal in the confirmatory tier at time points after drug administration.

Participants in the reference groups, who tested positive for ADAs, did not show any evidence of PK/PD effects or safety concerns, such as hypersensitivity reactions.

Immunogenicity Results from Trial TVB009-IMB-30085 in Patients with Postmenopausal Osteoporosis

Trial TVB009-IMB-30085 assessed the immunogenicity of TVB-009P in comparison with Prolia US and after a single switch from Prolia US to TVB-009P. This study included a total of 331 participants with PMO.

Blood samples for the assessment of ADA were collected throughout Trial TVB009-IMB-30085 at the timepoints shown in Table 1 of the TVB009-IMB-30085 Clinical Study Protocol with Amendment 02, Section 3.5. Additional samples were to be collected if any severe hypersensitivity reaction (e.g., anaphylaxis), serious adverse or immunogenicity-related adverse event were observed.

The assessment of ADA and neutralizing potential used the same validated analytical methods that were used for the assessment in trial TVB009-BE-10157 in healthy volunteers. Participants that were screened to be ADA positive from baseline with no change or increase in OD signal and in percent inhibition signal in the confirmatory tier at further tested time points were marked as not treatment-emergent ADA and therefore not further characterized for titre and neutralizing activity. Participants with treatment-emergent ADA were counted as ADA positive. Overall, 11 (6.6%) participants in the TVB-009P treatment group and 25 (15.2%) participants in the Prolia US treatment group were ADA positive (any time in period) in the main treatment period. One (0.6%) participant in the TVB-009P treatment group (n=166) and 2 (1.21%) participants in the Prolia US treatment group (n=165) had positive neutralizing ADA status. A comparable number of participants (8 participants in the TVB-009P treatment group and 11 participants in the Prolia US treatment group) were ADA positive (not treatment-emergent ADA).

A summary of ADA incidence, titre, and neutralizing potential for the main treatment is presented below.

Table 46: Trial TVB009-IMB-30085: Summary of Immunogenicity in the Main Treatment Period (Safety Analysis Set)

Assessment Statistic	TVB-009P (N=166)									PROLIA US (N=165)								
	D1	D15	W4	W8	W12	W26	W39	W52	Any Time in Period	D1	D15	W4	W8	W12	W26	W39	W52	Any Time in Period
ADA status																		
N1	166	163	163	164	160	157	155	152	166	165	164	161	162	160	152	153	147	165
Positive, n (%)	3 (1.8)	9 (5.5)	5 (3.1)	7 (4.3)	4 (2.5)	3 (1.9)	5 (3.2)	5 (3.3)	11 (6.6)	1 (0.6)	17 (10.4)	12 (7.5)	8 (4.9)	8 (5.0)	5 (3.3)	10 (6.5)	9 (6.1)	25 (15.2)
Positive, NTR, n (%)	8 (4.8)	7 (4.3)	8 (4.9)	8 (4.9)	8 (5.0)	7 (4.5)	7 (4.5)	7 (4.6)	8 (4.8)	11 (6.7)	7 (4.3)	7 (4.3)	6 (3.7)	7 (4.4)	7 (4.6)	7 (4.6)	6 (4.1)	11 (6.7)
Negative, n (%)	155 (93.4)	147 (90.2)	150 (92.0)	149 (90.9)	148 (92.5)	147 (93.6)	143 (92.3)	140 (92.1)	147 (88.6)	153 (92.7)	140 (85.4)	142 (88.2)	148 (91.4)	145 (90.6)	140 (92.1)	136 (88.9)	132 (89.8)	129 (78.2)
ADA Titer (log base 10) among positive																		
n	3	9	5	7	4	3	5	5		1	17	12	8	8	5	10	9	
Mean (SD)	NA	2.16 (0.453)	NA	2.26 (0.424)	NA	NA	NA	NA		NA	2.27 (0.634)	2.05 (0.688)	2.29 (0.636)	1.97 (0.396)	NA	1.93 (0.349)	1.80 (0.341)	
Median	1.69	2.01	2.01	2.10	1.88	2.03	1.98	2.16		2.60	2.40	1.69	2.35	2.04	2.06	1.94	1.75	
Min, Max	1.6, 2.0	1.6, 2.9	1.9, 2.5	1.8, 3.0	1.7, 2.1	2.0, 2.1	1.7, 2.6	1.7, 2.6		2.6, 2.6	1.3, 3.4	1.3, 3.4	1.4, 3.4	1.3, 2.5	1.6, 2.5	1.3, 2.4	1.3, 2.2	
Neutralizing ADA status (%) among positive																		
N1	3	9	5	7	4	3	5	5	11	1	17	12	8	8	5	10	9	25
Positive, n (%)	0	0	0	0	0	0	1 (20.0)	1 (20.0)	1 (9.1)	0	1 (5.9)	0	0	0	0	1 (10.0)	0	2 (8.0)
Negative, n (%)	3 (100.0)	9 (100.0)	5 (100.0)	7 (100.0)	4 (100.0)	3 (100.0)	4 (80.0)	4 (80.0)	10 (90.9)	1 (100.0)	16 (94.1)	12 (100.0)	8 (100.0)	8 (100.0)	5 (100.0)	9 (90.0)	9 (100.0)	23 (92.0)

Source: TVB009-IMB-30085 Clinical Study Report, Summary 14.2.6.1, Listing 16.2.6.5
ADA=anti-drug antibody; D =day; max=maximum; min=minimum; n=number of participants with the given status; N1=number of participants with any assessment at visit; NA=not applicable; NTR=not treatment related; Prolia US=United States licensed and sourced Prolia; SD=standard deviation; TVB-009P=drug product of TVB-009 as proposed biosimilar to Prolia; W=week

NOTE: Percentage (%) = n/N1*100%.

NOTE: "Any Time in Period" section included all visits, including unscheduled, in the main treatment period.

NOTE: Treatment-emergent ADA were ADA negative at baseline and positive some time after drug administration or ADA positive from baseline but showed increase in optic density signal or percent inhibition signal in the confirmatory tier at time points after drug administration.

NOTE: The ADA samples that were "Positive, NTR" were not investigated for titer and neutralizing potential.

Table 47: Trial TVB009-IMB-30085: Summary of Immunogenicity in the Transition Period (Transition Safety Analysis Set)

Assessment Statistic	TVB-009P/TVB-009P (N=148)				PROLIA US/PROLIA US (N=72)				PROLIA US/TVB-009P (N=71)			
	W54	W65	W78	Any Time in Period	W54	W65	W78	Any Time in Period	W54	W65	W78	Any Time in Period
ADA status												
N1	146	143	140	147	67	69	67	70	70	69	69	70
Positive, n (%)	6 (4.1)	3 (2.1)	6 (4.3)	7 (4.8)	5 (7.5)	3 (4.3)	3 (4.5)	5 (7.1)	2 (2.9)	3 (4.3)	3 (4.3)	4 (5.7)
Positive, NTR, n (%)	6 (4.1)	4 (2.8)	3 (2.1)	7 (4.8)	4 (6.0)	4 (5.8)	4 (6.0)	4 (5.7)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Negative, n (%)	134 (91.8)	136 (95.1)	131 (93.6)	133 (90.5)	58 (86.6)	62 (89.9)	60 (89.6)	61 (87.1)	67 (95.7)	65 (94.2)	65 (94.2)	65 (92.9)
ADA Titer (Log base 10) Among Positive												
n	6	3	6		5	3	3		2	3	3	
Mean (SD)	2.38 (0.693)	NA	2.18 (0.619)		NA	NA	NA		NA	NA	NA	
Median	2.11	2.96	2.25		2.21	2.36	2.43		1.72	1.72	1.92	
Min, Max	1.7, 3.6	2.4, 3.2	1.3, 2.8		1.6, 2.4	2.0, 2.5	2.3, 2.5		1.6, 1.8	1.5, 2.1	1.4, 2.4	
Neutralizing ADA status (%) among positive												
N1	6	3	6	7	5	3	3	5	2	3	3	4
Positive, n (%)	1 (16.7)	1 (33.3)	1 (16.7)	1 (14.3)	0	0	0	0	0	0	0	0
Negative, n (%)	5 (83.3)	2 (66.7)	5 (83.3)	6 (85.7)	5 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	2 (100.0)	3 (100.0)	3 (100.0)	4 (100.0)

Source: TVB009-IMB-30085 Clinical Study Report, Summary 14.2.6.2, Listing 16.2.6.5
ADA=anti-drug antibody; D=day; max=maximum; min=minimum; n=number of participants with the given status; N1=number of participants with any assessment at visit; NA=not applicable; NTR=not treatment related; Prolia US=United States licensed and sourced Prolia; SD=standard deviation; TVB-009P=drug product of TVB-009 as proposed biosimilar to Prolia; W=week
NOTE: Percentage (%) = n/N1*100%.
NOTE: "Any Time in Period" section included all visits, including unscheduled, in the transition period.
NOTE: The ADA samples that were "Positive, NTR" were not investigated for titer and neutralizing potential.

Of the 13 participants in the TVB-009P treatment group with treatment-emergent ADA, 6 participants had transient ADA positive values throughout the complete trial period. Of the 25 participants in the Prolia US treatment group with treatment-emergent ADA, transient positive ADA response was detected throughout the complete trial period for 18. The onset of ADA was early for most of the participants. Only 1 participant in each treatment group had initial positive ADA sample after the second dose.

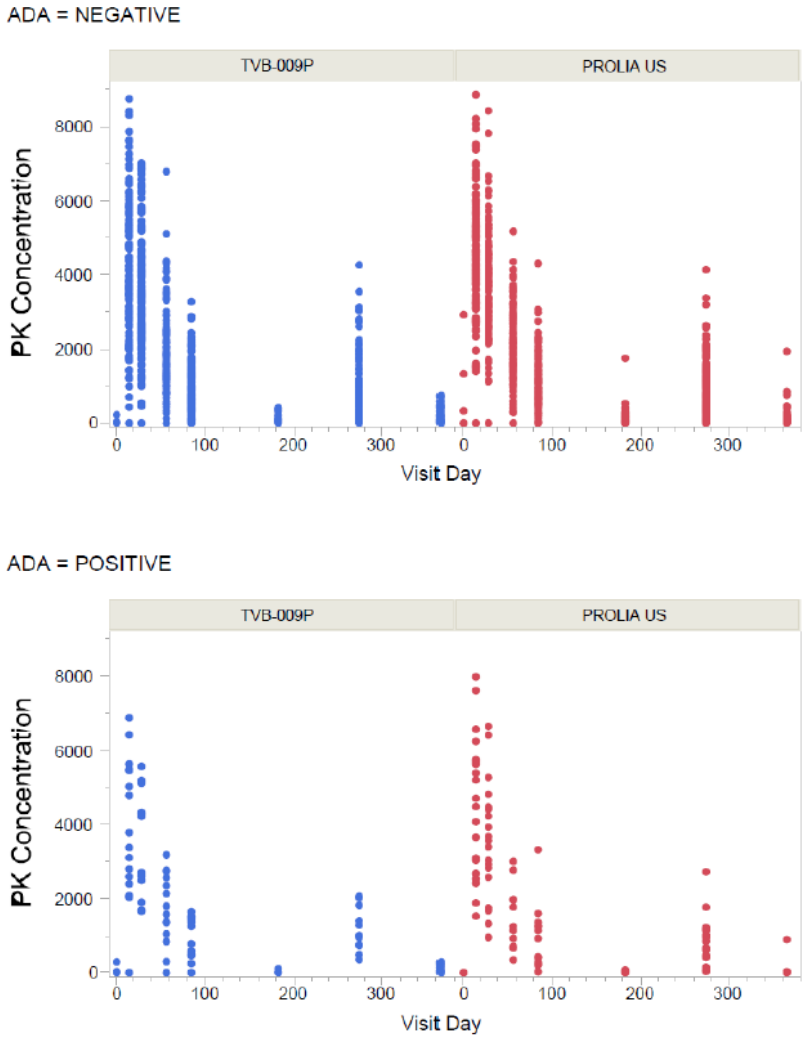
Only 1 participant in the transition group developed ADA after the transition from Prolia US to TVB-009P and had a single positive sample at Week 54 without neutralizing potential. There was no significant difference in frequency of ADA following transition compared to participants who remained on Prolia US or TVB-009P.

Impact on pharmacokinetics

Due to the small number of ADA positive participants in each treatment group, no statistical comparison of PK among ADA positive participants was conducted. Instead, individual drug concentration-time curves for the ADA positive participants were reviewed and compared between treatment groups as well as to the ADA negative population.

The denosumab serum concentrations after TVB-009P and Prolia US administration show a high inter-subject variability in both ADA positive and ADA negative participants. The range of concentrations overlaps between ADA positive and ADA negative participants for both treatment arms. There is no indication of differences between treatment groups or changed PK caused by the presence of ADA.

Figure 9: Trial TVB009-IMB-30085: Pharmacokinetic Concentration by Visit Day and Anti-Drug Antibody Status (Positive/Negative) for Main Treatment Period



Note: ADA = POSITIVE includes ADA status = positive and ADA status = positive, not treatment related

Source: Trial TVB009-IMB-30085 Post-Hoc Figure 1
ADA=anti-drug antibodies; PK=pharmacokinetics; Prolia US= United States licensed and sourced Prolia; TVB-009P=drug product of TVB-009 as proposed biosimilar to Prolia

Impact on pharmacodynamics and efficacy

Due to the small number of ADA positive participants in each treatment group, no statistical comparison of PD and efficacy was conducted. Instead, individual PD marker concentration-time curves

and responses of the ADA positive participants were reviewed and compared between treatment groups and to the ADA negative population.

ADA positive participants showed a similar PD response as negative participants for both PD marker serum cross-linked C-telopeptide of type I collagen (sCTX) and procollagen type 1 N-terminal propeptide (P1NP). There was 1 participant in the TVB-009 treatment group with an early increase of sCTX following the expected initial decrease. However, this participant was ADA positive throughout the trial including baseline and neutralizing potential could not be detected. The participant withdrew from the trial before the second dose.

One (0.6%) participant in the TVB-009P treatment group (n=166) and 2 (1.21%) participants in the Prolia US treatment group (n=165) had positive neutralizing ADA status.

The participant from the TVB-009P treatment group tested positive for neutralizing ADA at Weeks 8, 39, and 52 in the main treatment period (ADA Titre Log base 10 values 3.04, 2.61 and 2.49, respectively). The participant remained on TVB-009 treatment during the transition period and tested positive for neutralizing ADA at Weeks 54, 65, and 78 with titres (Log base 10) of 2.73, 2.44 and 2.08, respectively. The participant showed reduction of sCTX and P1NP comparable to ADA negative participants and an increase in BMD at Week 52 and 78 compared to baseline.

Samples from one participant in the Prolia US treatment group were ADA positive on Day 15, at Week 4 and at Week 52 (ADA Titre values (Log base 10) 2.75, 2.26 and 1.3, respectively) and negative thereafter. Neutralizing potential was only detected in the Day 15 sample. The participant remained on Prolia US during the whole trial and showed reduction of sCTX and P1NP comparable to ADA negative participants and an increase in BMD compared to baseline.

The other participant from the Prolia US treatment group was ADA positive at all time points including pre-dose with emergent treatment response, the titre values (Log based 10) were between 2.18 and 2.95 and a single neutralizing sample at Week 39. The participant remained on Prolia US during the whole trial and showed reduction of sCTX and P1NP comparable to ADA negative participants and an increase in BMD compared to baseline.

Impact on safety

In the TVB-009P/TVB-009P arm, a total of 13 participants tested positive for ADA (treatment-emergent ADA) at some point during the entire trial period. Additionally, 1 participant exhibited persistent NAb positivity on multiple nominal days. Adverse events were reported in 11 of the ADA-positive participants. Specifically, causality was assessed as possible for events of arthralgia and haematuria in 1 participant, and for increased body temperature in a second participant. These aforementioned events recovered in both participants. For the remaining 9 participants, causality was deemed not related.

Notably, 1 participant in the NAb-positive group reported arthralgia after 447 days from the first dose, which was assessed as not related to the trial drug and subsequently recovered.

Furthermore, a serious adverse event related to hepatitis was reported in 1 participant, but it was considered unrelated to the trial drug. The time to onset of this event from the first dose was 227 days, and the participant tested positive for ADA on Day 15.

Additionally, 6 participants had persistent ADA at the end of the trial. Among these participants, 2 individuals experienced events of hyperbilirubinemia and vitamin D deficiency, which were considered not related to the trial drug. The events did not recover and were recovering, respectively.

Among the adverse events reported in the TVB009P/TVB009P arm, only arthralgia and increased body temperature could potentially be attributed to ADA positivity. However, these events were assessed as

non-serious. Notably, a serious event of Hepatitis C was reported, but it is unlikely to be related to ADA positivity.

Furthermore, the ADA-positive titre in the TVB009P/TVB009P arm and the overall adverse event pattern did not significantly alter the incidence, frequency, or nature of adverse events when compared to ADA-negative participants. Therefore, the ADA positivity observed in the TVB009P/TVB009P arm is unlikely to have any safety impact in the PMO patient population.

In the Prolia/Prolia arm, a total of 16 participants tested positive for ADA positive (treatment-emergent ADA) at some point during the entire trial period. Out of 16, 2 participants exhibited NAb positivity which was not observed during subsequent visits. Adverse events were reported in 9 of the ADA-positive participants. None of the adverse events were considered serious. Specifically, causality was assessed as "possible" for symptoms such as constipation, arthralgia, pyrexia, alopecia, weight decrease, and fatigue in 3 participants. Subsequently, these events recovered, except in 1 participant with arthralgia, which was not recovered. For the remaining 6 participants, causality was assessed as "not-related." Additionally, at the end of the trial, 3 participants had persistent ADA, and no unresolved adverse events were reported.

In the Prolia/TVB-009P arm, a total of 9 participants tested positive for ADA (treatment-emergent ADA) at some point during the entire trial period. Notably, 1 participant had new ADA positivity on nominal Day 379 after transition, which resolved and was not observed during the subsequent visit. This ADA-positive patient did not report any adverse events. However, adverse events were reported in 7 other participants. A serious adverse event related to Coronavirus disease 2019 pneumonia was reported, but it was considered unrelated to the trial drug. Additionally, 3 participants had persistent antibodies at the end of the trial. Of these 3 participants, 1 participant did not experience any adverse events. The second participant reported a non-serious adverse event of vitamin D deficiency which was deemed not related to the trial drug and this adverse event recovered. The third participant reported a mild treatment-emergent adverse event of hypersensitivity along with other events of headache, nausea, eye pain and hypertension at Day 14, osteoarthritis at Day 190, arthralgia (2 events on Day 190 and Day 314, respectively), viral upper respiratory tract infection at Day 372. The adverse events of hypersensitivity, osteoarthritis, and arthralgia were ongoing and not recovered/resolved, while all the remaining events were recovered.

One trial participant had a hypersensitivity reaction (sores on legs) with no ADA present.

None of the trial participants developed hypersensitivity reactions during the transition period.

The transition of Prolia to TVB-009P did not have any significant impact either on ADA positivity or adverse event profile.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Not applicable.

2.5.8.8. Discontinuation due to adverse events

No discontinuations due to adverse events were reported for the phase 1 trial.

Numerically more TEAE leading to discontinuation of denosumab occurred in the reference group during the main treatment period of the comparative phase 3 trial. However, the numbers were overall low (3.0%) and differences between the groups are not considered significant.

2.5.8.9. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

The safety of TVB-009P has been evaluated in two clinical trials.

Trial TVB009-BE-10157 was a Phase 1, randomized, double-blind, single-dose, 3-arm parallel-group trial that evaluated the PK and PD similarity of TVB-009P versus Prolia US, and Prolia EU in healthy participants.

Trial TVB009-IMB-30085 was a randomized, double-blind, multinational, multicentre trial with an objective to demonstrate similar efficacy and safety of TVB-009P compared to Prolia US administered sc in patients with postmenopausal osteoporosis.

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 Prolia label and are considered appropriate.

The studies included postmenopausal women aged 55 to 80 years with osteoporosis (T-scores between -2.5 and -4.0) and varying fracture risks, representing a globally diverse patient population. The safety database covered both short-term exposure during the 26-week main treatment period and long-term exposure from transition and extended monitoring periods beyond 52 weeks. Overall, 352 participants received at least 1 dose of TVB-009P in the two clinical trials; 115 healthy volunteers in Study TVB009-BE-10157 and 237 osteoporosis patients in Study TVB009-IMB-30085. Of the latter, 148 patients were treated >12 months receiving 3 doses of TVB-009P.

The overall design of the clinical studies is considered adequate for a comparative safety assessment of TVB-009 to the reference product.

In the comparative phase 1 PK study TVB009-BE-10157 in healthy volunteers, adverse events were reported in 106 (31%) participants overall with no relevant differences between treatment groups. Adverse events considered by the investigator to be related to trial drug were reported for 6 (5%) participants in the TVB-009P treatment group, 11 (10%) participants in the Prolia US treatment group, and 14 (12%) participants in the Prolia EU treatment group. Overall, 3 (<1%) participants experienced AEs considered to be severe. There were no SAEs, AEs leading to discontinuation or deaths in Trial TVB009-BE-10157. Local tolerability reactions at the injection site occurred in less than 5% of participants and were comparable between treatment groups.

There were no apparent trends in mean changes from baseline throughout the trial for any haematology parameters after administration of TVB-009P, Prolia US or Prolia EU. Overall, the incidence of potentially clinically significant (PCS) haematology abnormalities was low (3% overall) and similar across treatments. No participant reported changes in haematology values that were reported as an AE.

The most frequently occurring adverse events were increased blood creatine phosphokinase (CPK) and alanine aminotransferase (ALT), which were reported more commonly in the Prolia (US) and Prolia (EU) treatment groups than in the TVB-009P treatment group. The elevations were asymptomatic, mostly transient, and observed throughout the study (including at pre-dose in some instances). Although no unfavourable differences are noted between the test and the reference product, it is noted that CPK and liver enzymes elevations are not reported in the originator´s SmPC, despite the fact that in this study, they were considered as treatment related. The ALT and AST elevations were further analysed post-hoc based on FDA toxicity grades. When pooled, ALT or AST ≥1 Grade were comparable

between groups (45 (39%), 42 (37%) and 52 (45%) participants in the TVB-009, Prolia US and Prolia EU group, respectively), but ALT or AST ≥2 Grade were lower in the TVB-009 group compared to the reference groups (4 (3%), 11 (10%) and 14 (12%) participants in the TVB-009, Prolia US and Prolia EU group, respectively). ALT or AST ≥3 Grade were not observed in the TVB-009 group compared to 2 (2%) and 6 (5%) participants in the Prolia US and Prolia EU group, respectively.

There were no apparent trends in mean changes from baseline throughout the trial for urinalysis parameters after administration of TVB-009P, Prolia US and Prolia EU. No relevant differences were observed between the 3 treatment groups. One participant in the TVB-009P group reported an AE of haematuria, which was mild in severity, considered by the investigator as unrelated to trial treatment, and resolved.

One participant had an ECG finding reported as an AE, which was mild in severity, asymptomatic, considered by the investigator as not related to trial drug and resolved. Overall, no clinically meaningful trends were observed in mean changes from baseline throughout the trial for ECG parameters after administration of TVB-009P, Prolia US and Prolia EU.

Study TVB009-IMB-30085

In the comparative phase 3 efficacy and safety study in patients with postmenopausal osteoporosis, safety data collection was conducted through patient diaries, site visits, and periodic phone calls, covering both the main treatment and transition periods. Compliance with ICH GCP guidelines ensured reliable data collection and reporting, with key AE patterns, including hypocalcaemia and injection site reactions, reflected in the SmPC, reinforcing the importance of calcium and vitamin D supplementation. Patient diaries and phone follow-ups were utilized to capture safety data during the main and transition periods of the study.

The percentage of patients experiencing AEs was higher after treatment with TVB009 compared to the reference product in both, the main treatment period and the transition period. This also holds true for serious AEs and for AEs related to trial drug.

After adjusting for the event rate, the overall incidence of TEAEs was slightly (approx. 5%) higher in the test group (N=166, 489 events, 2.09 events per participants) compared to the reference group (N=94, 247 events, 1.99 events per participant). Differences are noted in the following SOCs (test versus reference group):

- Musculoskeletal and connective tissue disorders: 0.38 versus 0.49 (lower in test group)
- Investigations: 0.26 versus 0.07 (higher in test group)
- Renal and urinary disorders: 0.05 versus 0.02 (higher in test group)
- Vascular disorders: 0.08 versus 0.03 (higher in test group)

Overall, most TEAEs were assessed as not related to the trial drug by both the investigator and the applicant and no new safety concerns emerged from the trial.

The higher incidence of serious TEAEs in the TVB-009P group, in both the main period and the transition period, was attributed to several factors, including underlying health conditions and pre-existing medical histories.

Vitamin D levels were investigated at screening, week 12, week 26, week 52, and week 78. A participant with a serum 25 (OH) Vitamin D level ≤20 ng/mL at baseline was rescreened again at baseline to re-evaluate Vitamin D levels post repletion. The normal range of Vitamin D was 75–250 nmol/L or 30-100 ng/mL. Higher or lower values of vitamin D, which were judged by the investigator as clinically significant, were recorded as adverse events. The investigators assessed measurements as

TEAEs for Vitamin D deficiency/decreased in 72 participants. According to the applicant, however, there were another 134 participants whose Vitamin D levels were in the range of Vitamin D deficiency/decreased that were not deemed clinically significant and thus not assessed as adverse events. Specific numbers for Vitamin D levels assessed as low but not adverse were not presented.

In total, 206 participants had low Vitamin D levels. Out of 108 participants with low Vitamin D in the TVB009P group, the investigators assessed measurements as TEAEs for Vitamin D deficiency/decreased in 46 participants. Similarly, out of 98 participants with low Vitamin D in the Prolia US group, 26 participants were assessed with TEAEs for Vitamin D deficiency/decreased. Therefore, 62 participants in the TVB009P group and 72 in the Prolia US group had low Vitamin D levels that were not assessed as adverse by the investigators. Of those participants with events assessed as adverse, a slightly higher percentage had low Vitamin D levels already at baseline in the TVB009P group compared to the reference group (56.5% versus 46.2%). Conversely, fewer had a Vitamin D decline post baseline in the TVB009P group compared to the reference group (43.5% versus 53.8%). The respective percentages were more similar between groups in those participants who had low Vitamin D levels that were not assessed as adverse. Thus, the applicant is of the opinion that the low Vitamin D levels considered as adverse in the TVB009P group were driven by the higher percentage of participants who already had low levels at baseline. This, however, does not explain the overall higher incidence of Vitamin D deficiency in the TVB009P group compared to the reference. Also, data for Vitamin D supplementation do not provide an explanation. However, no correlation to ECG findings was substantiated.

Calcium levels were investigated at screening, day 1, week 4, week 12, week 26, week 39, week 52, week 65, and week 78. The normal range of calcium was 8.5–10.2 mg/dl. Higher or lower values of calcium, which were judged by the investigator as clinically significant, were recorded as adverse events. Calcium and vitamin D were supplemented as per protocol (1000 mg calcium daily and at least 400 IU vitamin D daily from screening to EOS).

A total of 27 participants experienced low calcium levels during the trial, 16 participants were in the TVB-009P group, and 11 participants were in the Prolia group. The lowest recorded calcium level was 7.74 mg/dL, though most declines were mild to moderate and improved by the next visit. A notable drop in calcium levels was observed at Week 4, with five participants having levels below 8.5 mg/dL. However, levels generally stabilized in subsequent visits. By Week 26, only two participants had calcium levels below 8.5 mg/dL, indicating no widespread, persistent hypocalcaemia. By Week 78, calcium levels remained within normal limits for all participants. Hypocalcaemia was considered an adverse event (5 events) in 4 participants. Four events of hypocalcaemia were reported in the TVB-009P group. All events were considered non-serious, mild in severity, and recovered. Three events in 3 participants in TVB-009P group were assessed as related to the trial drug by the investigator.

The highest recorded calcium level was 12.06 mg/dl for TVB-009P. Elevated calcium levels were most frequently noted at Week 26, followed by Weeks 12, 52, and 78. According to the Prolia SmPC section 5.1, treatment with 60 mg of Prolia leads to a rapid reduction in bone turnover, with CTX levels decreasing by up to 87% and then partially recovering at the end of each dosing interval. This reversibility in bone remodelling effects may influence calcium and Vitamin D homeostasis, potentially contributing to the observed fluctuations. Hypercalcemia was reported as an adverse event in 33 participants, in addition, one participant had an event recorded as 'blood calcium increased’. None of these events were considered serious or treatment related. The observed increase in recorded hypercalcemia events is due to uncorrected calcium levels. Higher calcium supplements were noted in 18 participants.

Overall, there was no correlation between changes in calcium or vitamin D levels and clinically relevant ECG abnormalities, and no cardiac safety concerns were identified.

It can be concluded that – despite minor differences between treatments – the observed shifts in vitamin D and calcium levels in this trial align with known effects of denosumab and do not suggest any new safety risks. It is, however, noted that events of low Vitamin D level and hypocalcaemia were overall more frequent after TVB009P treatment compared to the reference product.

There were no deaths in Study TVB009-IMB-30085. In the main treatment period, 8 (4.8%) participants experienced serious TEAEs in the TVB-009P treatment group and 6 (3.6%) participants in the Prolia US treatment group. Most of these events were considered unrelated to study drug and no major imbalances were observed between groups, except for 2 events of osteonecrosis, which occurred in 2 patients in the reference group and were considered drug related. As osteonecrosis is a known adverse reaction to denosumab and as these events only occurred in the reference group, no concern is raised.

Adverse drug reactions (ADRs) for TVB-009 were notably observed in special populations, such as elderly patients and those with renal impairment. Elderly patients experienced a higher prevalence of hypocalcaemia, particularly those with impaired renal function, which was effectively managed with calcium and vitamin D supplementation. Musculoskeletal pain, including back pain and joint stiffness, was also more frequent in older adults, aligning with age-related comorbidities. Patients with renal impairment, especially those with an eGFR <30 mL/min, were at a greater risk of severe hypocalcaemia due to reduced calcium regulation capacity.

Serious systemic infections, though infrequent, were reported more often in patients with compromised immunity or renal dysfunction, highlighting the importance of close monitoring in these populations. Hypocalcaemia was classified as an ADR due to its predictable occurrence based on the pharmacodynamic effects of denosumab, which was consistently observed across populations. Infections were also deemed ADRs, as their incidence increased relative to baseline in immunocompromised individuals and those with renal impairments. These findings emphasize the need for proactive management and monitoring in vulnerable patient groups receiving TVB-009.

Treatment discontinuations due to adverse events for TVB-009 primarily occurred during the main treatment period, with severe hypocalcaemia and gastrointestinal disturbances being the leading causes. Hypocalcaemia was most common among patients with pre-existing renal impairment or inadequate calcium and vitamin D supplementation. Systemic infections, though infrequent, also contributed to discontinuations, particularly in patients with compromised immunity. The overall proportions of TEAEs leading to trial discontinuation and/or discontinuation of IMP were low and comparable between treatments. One of these TEAEs (fibula fracture, moderate in intensity) had a possible relationship to the IMP in the TVB-009P treatment group. In the Prolia US treatment group, three TEAEs leading to discontinuation of the IMP had a possible relationship to the IMP (pain in extremity, osteonecrosis, and osteonecrosis of jaw). In the transition period, more patients experienced serious TEAEs in the TVB-009P/TVB-009P group compared to the Prolia US/TVB-009P group and the Prolia US/Prolia US group (3.4%, 1.4% and 0%, respectively). However, none of the serious TEAEs present in the transition period had a reasonable possible relationship to the trial drug.

The incidence of injection site reactions (ISR) was comparable between both treatment groups (TVB-009P, 8.4% vs. Prolia US, 9.1%) in the main treatment period. All ISR were mild except for 2 events in the Prolia US group which were moderate in severity. No severe injection site tolerability signs were reported and the mean pain numerical response scale for local tolerability and pain was comparable in both treatment groups on day 1 (0.5 vs. 0.4) and at week 26 (0.3 vs. 0.4).

In the transition period, the incidence of ISR was higher in the Prolia US/Prolia US group (9.7%) compared to the TVB-009P/TVB-009P group (4.7%) and the Prolia US/TVB-009P group (5.6%). No moderate or severe injection site tolerability signs were reported in the transition period and the mean

pain numerical response scale for local tolerability and pain was also comparable between the treatment groups in the transition period.

The majority of participants had normal results for all haematology parameters. However, decreased leukocytes were observed more frequently after treatment with TVB-009 as compared to Prolia US (in 6.7% versus 2.2% of patients). The applicant provided the following justifications for the safety of TVB-009P in relation to reduced WBC count:

Several participants had low WBC counts at baseline, indicating pre-existing conditions rather than treatment effects. The number of participants with clinically significant low WBC values was relatively small and spread across different weeks, suggesting isolated incidents rather than a consistent pattern. Most participants (20/22) in TVB-009P group had WBC values > 2.0 $x10^9$/L, which generally do not have major impact on participants. The data showed no correlation between low WBC counts and immunogenicity, indicating that the decreases were not related to the immune response to the treatment. Overall, it is concurred that the observed decreases in WBC counts are isolated, non-significant, and can be explained by alternative factors such as baseline values, pre-existing conditions, and the spread of incidents across different weeks.

Two patients in the TVB-009P/TVB-009P treatment group had abnormal clinically significant ECG results (atrial fibrillation and left bundle branch block, respectively). Both patients had previous cardiovascular histories, thus the abnormal ECG results are likely attributable to pre-existing condition. It is therefore concluded that the observations are not relevant for the comparative safety assessment.

Immunogenicity

The methods to determine immunogenicity (ADA, nAB assay) were well described and developed. The assays were validated and established according to the guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). All critical reagents, drugs, matrices and antibodies and used lot numbers were provided. The assays were validated with respect to cut-points (screening, confirmatory), sensitivity, drug tolerance, target interference, assay precision, selectivity, haemolytic/lipemic interference, robustness, and the analyte was tested for stability (short-term, freeze/thaw).

None of the healthy volunteers who received TVB-009 had detectable ADAs against denosumab following single dose sc administration of 60 mg study drug. In contrast, two participants who received Prolia were ADA positive at baseline and after denosumab administration, and one additional participant had treatment-emergent ADA in the Prolia US group. However, all three subjects had very low ADA titres and were therefore not screened for nAb.

Eleven (6.6%) participants in the TVB-009P treatment group and 25 (15.2%) participants in the Prolia US treatment group were ADA positive in the main treatment period. Neutralizing Abs were detected in one and two patients per group, respectively. Only 1 participant in the transition group developed ADA after the transition from Prolia US to TVB-009P and had a single positive sample without neutralizing potential. Overall, the numbers of subjects with ADA were comparable between groups in the comparative phase 3 study, with a tendency towards less immunogenicity after treatment with TVB-009 as compared to the 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 reference product.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 48: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcaemia 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 • Hypercalcaemia 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 49: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Osteonecrosis of the jaw	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** Patient card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Osteonecrosis of the jaw questionnaire v1.0 **Additional pharmacovigilance activities:** None.
Atypical femoral fracture	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire: Denosumab – Atypical fractures questionnaire v1.0 **Additional pharmacovigilance activities:** 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 4.2, 4.4 and 4.8. PL sections 2 and 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
IMPORTANT POTENTIAL RISKS		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiovascular events	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Malignancy	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 4. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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 tumor of bone	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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 tumor of bone or growing skeletons	**Routine risk minimisation measures:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
MISSING INFORMATION		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with prior intravenous bisphosphonate treatment	**Routine risk minimisation measures:** SmPC sections 4.5 and 5.1 PL section 2. Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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:** Medicinal product subject to restricted medical prescription. The administration of the denosumab 120 mg/1.7 mL vial should only be performed by a healthcare professional. **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 1.1 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Degevma (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

Quality aspects

In general, a very comprehensive and sound biosimilarity assessment has been conducted. Since both EU-sourced reference product and US-sourced comparator product have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product has been established. TVB-009 has been developed as pre-filled syringe presentation similar to the reference product presentation.

The analytical similarity assessment was performed with orthogonal state-of-the-art methods including analysis of primary and higher order structure, purity/impurity, post-translational modifications, charge variants, glycan profile, and biological activity. The observed differences have been adequately discussed and justified and shown not to impact biological function related to mechanism of action.

Degradation profiles have been analysed in comparative stability studies. Additional extended stability and characterization studies were performed to support the biosimilarity evaluation.

Clinical aspects

All clinical studies were conducted with the Prolia configuration (TVB-009P) and using Prolia as a reference product. No clinical studies were conducted with the Xgeva configuration (TVB-009X) using Xgeva as a reference product. This approach was considered acceptable by the CHMP (see section 2).

The clinical development program for TVB-009P comprised one Phase I in healthy subjects (TVB009-BE-10157) and one Phase III study in female patients with postmenopausal osteoporosis (TVB009-IMB-

30085). This approach has been agreed on during scientific advice procedures. These two studies were considered sufficient for a biosimilarity exercise and extrapolation to other indications approved for Prolia.

Study TVB009-BE-10157 was a randomized, double-blind, single-dose, 3-arm parallel-group study, with an aim to demonstrate the PK and PD similarity of TVB-009P versus US-Prolia, and EU-Prolia in healthy subjects. A total of 345 healthy subjects (115 subjects per arm) were randomised in a 1:1:1 ratio to receive a single injection of 60 mg of either TVB-009, EU-Prolia or US-Prolia via s.c. injection. Subjects were treated on Day 1 and followed up for 253 days for PK, PD, safety and immunogenicity assessments. The primary objective was to demonstrate PK similarity between TVB-009 and EU-Prolia using the co-primary endpoints of C_{max}, $AUC_{0-\infty}$and AUC_{0-t}. Bioequivalence was to be concluded if the 90% CIs of the LS GMRs for all co-primary PK endpoints fell entirely within the pre-defined bounds of the standard bioequivalence margin [0.80 to 1.25]. Secondary objectives included additional PK parameters, PD assessments, safety and immunogenicity.

Study TVB009-IMB-30085 was a randomized, double-blind, multinational, multicentre trial with an objective to demonstrate similar efficacy and safety of TVB-009 compared to US-Prolia administered subcutaneously (sc) in women with postmenopausal osteoporosis (PMO). Participants were randomized in a 1:1 ratio to receive the first 2 doses of TVB-009P or US-Prolia ("main treatment period") administered in a 26-week interval. At week 52 participants in the Prolia US arm were re-randomized in a 1:1 ratio to either continue with a third dose of US-Prolia or transition to TVB-009 and receive a single dose of TVB-009 ("transition period"). A total of 332 patients were randomized in a 1:1 ratio to receive either TVB-009 or US-Prolia in the Main Period. The co-primary endpoints in this study were percent change from baseline in lumbar spine BMD at Week 52 and percent change from baseline in sCTX at week 26. Both endpoints are of importance, s-CTX for having a better dynamic response and therefore being more sensitive, and BMD for being of greater clinical relevance. Evaluation of both endpoints as co-primary increases the totality of evidence in the process of demonstrating similarity. For the co-primary endpoint LS-BMD, similarity was demonstrated if the 95% confidence interval (CI) for the least squares (LS) mean difference between TVB-009P and US-Prolia fell entirely within the similarity margin of ±1.45%. For the co-primary endpoint sCTX-1, similarity was demonstrated if the 95% CI for the LS mean difference between TVB-009P and Prolia US fell entirely within the similarity margin of ±20%.

The safety and immunogenicity profiles of TVB-009 and reference products (EU- and US-Prolia) were assessed in the Phase I study as well as in the Phase III study.

3.2. Results supporting biosimilarity

Quality

The provided results support the biosimilarity claim. For most of the quality attributes similarity was demonstrated, observed differences in certain quality attributes are minor and are sufficiently justified to have no impact on the clinical performance of the product. In addition, comparability of US sourced comparator with EU sourced reference product could be demonstrated. Additional stability and characterization studies with orthogonal methods support the biosimilarity evaluation.

Clinical

Pharmacokinetics

In the pivotal Phase 1 PK similarity study TVB009-BE-10157, the 90% CIs around the geometric LS mean ratio (TVB-009P/EU-Prolia) for all three co-primary endpoints were entirely contained within the [80.00%, 125.00%] equivalence range. Based on these results, the equivalence was demonstrated.

The sensitivity analyses supported the primary analysis. Secondary PK endpoints were also similar between treatments.

In post-menopausal women with osteoporosis (TVB009-IMB-30085) C_{trough} levels before second and third dose were low in both groups, and the majority of participants had denosumab concentrations below LLOQ.

Pharmacodynamics

In Study TVB009-BE-10157, the concentration-time profiles for each biomarker of bone turnover (sCTX-1, uNTX/Cr and P1NP) were similar in all 3 treatment groups over the course of the study. The percent change from baseline to Day 169 (Week 25) was very similar between TVB-009P, US-Prolia and EU-Prolia groups. Median time to reach maximal reduction, of sCTX-a, uNTX/Cr and P1NP was similar in all 3 treatment groups for each biomarker. The proportion of subjects with sCTX-1 suppression was similar between 3 treatment arms up to day 141.

In study TVB009-IMB-30085 the PD marker sCTX-1 was one of two co-primary endpoints. The 95% CI around the LS mean difference (TVB009 – Prolia) for the percent change from baseline in sCTX-a at Week 26 (mITT) fell within the pre-specified equivalence margin of ±20%. Based on these results, the equivalence was demonstrated. Following the first administration of denosumab, the levels of P1NP decreased in both treatment arm similarly and started increasing at Week 26 prior to the administration of the second dose.

Efficacy

Similarity in efficacy was demonstrated in Study TVB009-IMB-30085, as the 95% CI around the LS mean difference (TVB009 – Prolia) for the percent change from baseline at week 52 in LS-BMD (mITT) fell entirely within the equivalence margin of ±1.45%. Sensitivity and supplementary analyses for %cfb to Week 52 in LS-BMD supported the primary analysis.

Treatments were also similar as regards to changes from baseline in femoral neck BMD, total hip BMD as well as vertebral and non-vertebral fractures.

Safety

In the pivotal Phase 1 PK and PD similarity study TVB009-BE-10157, comparable safety and immunogenicity was demonstrated between TVB-009 and the reference product Prolia. No SAEs, deaths, AEs of special interest (e.g., anaphylaxis), and no AEs leading to trial discontinuation were reported in that trial. ADA formation was reported in <1% of subjects.

In the comparative efficacy and safety study TVB009-IMB-30085 conducted in female patients with postmenopausal osteoporosis, the number of TEAEs leading to trial discontinuation and/or discontinuation of IMP were overall low and comparable between treatments. No deaths occurred in that trial. ADA formation was observed in 6 to 15% of subjects, with a tendency towards less immunogenicity after treatment with TVB-009 as compared to the reference product.

Overall, the safety findings observed in the clinical studies were in line with the Prolia label. The incidence of severe (grade 3 or 4) AEs as well as of SAEs was generally low. No new or unexpected safety issues arose during the course of the studies.

3.3. Uncertainties and limitations about biosimilarity

Quality

No uncertainties about biosimilarity remain.

Clinical

Pharmacokinetics

In the pivotal PK study, large fluctuations in denosumab concentrations were observed in several subjects' individual serum concentration profiles with potential implications for estimation of both AUC as well as on C_{max}, since many of these questionable concentration values were observed close to t_{max}. Despite a thorough investigation, neither the applicant nor the MWP were able to identify a (single) definitive reason for denosumab fluctuations in PK concentration data. A similar phenomenon was also observed in the phase 3 study in patients.

Safety

In the comparative efficacy and safety study TVB009-IMB-30085 conducted in female patients with postmenopausal osteoporosis, the percentage of patients experiencing TEAEs, serious TEAEs and drug related TEAEs was numerically higher after treatment with TVB-009 compared to the reference product in both, the main treatment period and the transition period. Additionally, events of low Vitamin D level and hypocalcaemia were overall more frequent after TVB009P treatment compared to the reference product.

3.4. Discussion on biosimilarity

Quality

From a qualitative perspective, the results derived from a robust and well-designed biosimilarity exercise supporting the similarity claim. In addition, comparability of US sourced comparator with EU sourced reference product could be demonstrated.

Clinical

The exact reason for large fluctuations in denosumab concentrations, observed with both the biosimilar candidate and the reference product, remains elusive. Despite a thorough investigation, neither the applicant nor the MWP could identify a (single) definitive reason for denosumab fluctuations in PK concentration data. Further pursuit of the issue was considered unlikely to solve the issue.

While PK equivalence was demonstrated based on the available evidence, some uncertainty regarding the validity of data persists. From a methodological perspective, it cannot be entirely ruled out that the observed phenomenon could bias the equivalence testing towards too liberal similarity conclusion (making the compared groups more similar that they actually are).

Despite the largely unexplained nature of the observed phenomenon, on the evaluable PK data, PK equivalence was demonstrated.

Based on the provided safety and immunogenicity data, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the reference product.

3.5. Extrapolation of safety and efficacy

TVB009 was developed as a biosimilar product to Prolia/Xgeva. The mechanism of action is identical to 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 is acceptable.

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.

The clinical data were derived from healthy subjects and postmenopausal women with osteoporosis (PMO). These are regarded sensitive populations in terms of evaluating biosimilarity of TVB-009 and the reference products.

Based on the above, the safety and efficacy profile of TVB-009 can be extrapolated to all indications applied for Degevma.

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Degevma 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 Degevma 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.

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 subject 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

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.