14 November 2024
EMA/560527/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report
Xbryk

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006468/0000

Note

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

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List of abbreviations

%AUCextrap - Percentage of AUCinf due to extrapolation from time of last measurable concentration (Tlast) to infinity

2-AB - 2-aminobenzamide

2H1L - 2 heavy chain 1 light chain

A280 - Absorbance at 280 nm

AAF - Accelerated aging factor

AAT - Accelerated aging time

ADA - Anti-drug antibody

ADI - Acceptable daily intake

AE - Adverse Event

AESI - Adverse Events of Special Interest

AET - Analytical evaluation threshold

AHU - Air handling unit

ANCOVA - Analysis of covariance

ANS - 1-Anilinonaphthalene-8-sulfonate

APCI - Atmospheric-pressure chemical ionisation

API - Active pharmaceutical ingredient = active substance

API - Analytical profile index

AS – active substance = API

ATC - Anatomical Therapeutic Chemical

AUCinf - Area under the concentration-time curve from time zero to infinity

AUClast - Area under the concentration-time curve from time zero to the last quantifiable concentration

AUEC0-D197 - Area under the effect curve from time zero to Day 197

$AUEC_{0\text{-}M6}$ - Area under the effect curve from time zero to Month 6

AU - Absorbance unit

Avg - Average

BDP - Bulk drug product

BDS - Bulk drug substance

BGH - Bovine growth hormone

BI - Biological indicators

BMI - Body mass index

BLA - Biologics license application

BMD - Bone mineral density

BP - Bisphosphonate

BPCI - Biologics price competition and innovation

BPD - Biological product development

BSE - Bovine spongiform encephalopathy

Ca - Calcium

CAPA - Corrective action and preventive action

CAS - Chemical abstracts service

CCE - Human-chromatin opening element

CCF - Cell culture fluid

CCI - Container closure integrity

CCIT - Container closure integrity test

CD - Circular dichroism

CD - Circular dichroism

CDR - Complementarity determining region

CE-SDS (NR) - Capillary electrophoresis-sodium dodecyl sulfate (non-reduced)

CE-SDS (R) - Capillary electrophoresis-sodium dodecyl sulfate (reduced)

CE-SDS - Capillary electrophoresis-sodium dodecyl sulfate

CEX-HPLC (CEX) - Cation exchange-high performance liquid chromatography

CHO - Chinese hamster ovary

CI - Confidence interval

CL/F - Apparent clearance

CIP - Clean in place

CIPG - Critical in-process gateway

CIPT - Critical in-process test

CMO - Contract manufacturing organisation

CMR - Carcinogenic, mutagenic, or toxic for reproduction

CoA - Certificate of analysis

CoC - Certificate of conformity

CPB - Carboxypeptidase B

Cpk - Process capability index

CPP - Critical process parameter

CQA - Critical quality attribute

CSR - Clinical study report

CTX - C-telopeptide of type I collagen

cGMP - Current good manufacturing practice

DNA - Deoxyribonucleic acid

DP - Drug Product

DS - Drug Substance

EPC - End product cell

EMA - European Medicines Agency

EPAR - European public assessment reports

ER - Engineering run

ET - Early Termination

ET - Exposure temperature

ETO – ethylene oxide

EU - European Union

Fab - Fragment antigen binding region

FAS - Full Analysis Set

Fc - Fragment crystallisation

FDA - Food and Drug Administration

FDA - Food and Drugs Administration

FDP - Finished drug product

FIP - Finger impression plate

FP - finished product

FSC - Forward scatter

FST - Functional stability testing

FTIR - Fourier transform infrared spectroscopy

FTM - Fluid thioglycollate medium

GC-MS - Gas chromatography-mass spectrometry

Geometric LSMean - Geometric Least Squares Mean

GlcNAc - N-Acetylglucosamine

GK - Glutamine synthase-deficient

GMP - Good Manufacturing Practice

GMP - Good manufacturing practice

GSPR - General safety and performance requirements

Hb - Hemoglobin

HC - Heavy chain

HCCF - Harvested cell culture fluid

HCD - Host cell DNA

HCP - Healthcare professional

HCP - Host cell protein

H/DX-MS - Hydrogen/deuterium exchange with mass spectrometry

HEPA - High efficiency particulate air

HETP - Height equivalent to a theoretical plate

HIAC - High accuracy liquid particle counter

HILIC-UPLC - Hydrophilic interaction-ultra performance liquid chromatography

HM - High mannose

HMW - High molecular weight species

HPLC - High performance liquid chromatography

HPLC-CAD - High performance liquid chromatography-charged aerosol detector

HPW - Highly purified water

HVAC - Heating, ventilation and air conditioning

IAA (IAM) - Iodoacetamide

ICH - International Conference on Harmonization

ICH - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

icIEF - Imaged capillary isoelectric focusing

ICP-MS - Inductively coupled plasma mass spectrometry

IEC - International electrotechnical commission

IgG - Immunoglobulin G

IgG2 - Immunoglobulin G2

INN - International Non-proprietary Name

INN - International non-proprietary name

IPA - Isopropyl alcohol

IPC - In-process control

IPG - In-process gateway

IPS - In-process specification

IPT - In-process test

IR - Infrared

IRS - Interim reference standard

ISO - International organization for standardization

ITF - Intrinsic Tryptophan Fluorescence

IU - International unit

JPC - Japanese Pharmaceutical Codex

JPE - Japanese Pharmaceutical Excipients

KDR - Kinase insert domain receptor

KPP - Key process parameter

LC - Light chain

LC-ESI-MS - Liquid chromatography-electrospray ionisation and mass spectrometry

LCMV - Lymphocytic choriomeningitis virus

LET - Light exposure time

LF - Laminar flow

LMW - Low molecular weight species

LN2 - Liquid nitrogen

LoA - Letter of authorisation

LOD - Limit of detection

LOQ - Limit of quantification

LPM - Liter per minute

LRF - Log reduction factor

LRV - Log10 reduction value

m/z - Mass to charge

mAb - Monoclonal antibody

MAC - Membrane attack complex

MAP - Mouse antibody production

MBR - Master batch record

MCB - Master cell bank

MDR - Medical device regulation

MedDRA - Medical Dictionary for Regulatory Activities

Met - Methionine

MFI - Micro-flow imaging

MMV - Mouse minute virus

MoA - Mechanism of Action

MoA - Mechanism of action

MS - Mass spectrometry

MSD - Meso Scale Discovery

MVA - Multivariate analysis

MW - Molecular weight

NAbs - Neutralizing Antibodies

N/A - Not available

N/A - Not applicable

N/D - Not detected

NANA - N-Acetylneuraminic acid

NF - National Formulary

NGHC - Non-glycosylated heavy chain

NGNA - N-Glycolylneuraminic acid

NHS/EDC - N-hydroxysuccinimide/N-ethyl-N'-(-3-dimethylamino-propyl) carbodiimide

NKPP - Non-key process parameter

NLP - Neuro-linguistic programming

NMT - Not more than

Non-CQA - Non-critical quality attribute

N/P - Not performed

N/T - Not tested

NTU - Nephelometric turbidity unit

NVOC - Non-volatile organic compound

OD - Optical density

ODP - Ophthalmic drug product

OFAT - One factor at a time

OOT - Out of trend

OOS - Out of specification

OQ - Operational qualification

OTR - Oxygen transfer rate

PC - Polycarbonate

PC - Process characterisation

PCR - Polymerase chain reaction

PD - Pharmacodynamics

PDE - Permissible daily exposure

PDP - Parenteral drug products

PFS - Pre-filled Syringe

Ph. Eur. - European Pharmacopoeia

PI - Prescribing Information

PI - Promoter/operator

pI - Isoelectric point

PK - Pharmacokinetics

P/O - Promoter/operator

P1NP - Procollagen type I N-terminal propeptide

PPQ - Process performance qualification

PQ - Performance qualification

PPS - Per-protocol Set

PRS - Primary reference standard

PSB - Primary seed bank

PT - Preferred Term

PTM - Post-translational modifications

PUPSIT - Pre-use post sterilisation integrity testing

P/V - Power per volume

PV - Process validation

PVDF - Polyvinylidene fluoride

QA - Quality Assurance

QC - Quality Control

QMS - Quality management system

QPS - Qualified presumption of safety

QSAR - Quantitative structure-activity relationship

QTPP - Quality target product profile

Q/V - Quantity per volume

RABS - Restricted access barrier system

RANK - receptor activator of nuclear factor-κB

RANKL - receptor activator of nuclear factor-κB ligand

RB - Reference Bacteria

RE - Residual error

RH – relative humidity

RNA - Ribonucleic acid

RP - Reverse phase

rProtein A - Recombinant Protein A

RV - Retrovirus

SAS - Sterile aqueous suspension

SCC - Sodium Chloride

SCT - Sterility test

SDS - Sodium dodecyl sulfate

SE - Standard Error

SEC-HPLC - Size exclusion-high performance liquid chromatography

SEC - Size exclusion chromatography

SF - Specific Function

SIP - Sterilise in place

SLS - Sodium lauryl sulfate

SLV - Systematic literature review

SM - Starting material

SN - Sialic acid

SOP - Standard operating procedure

SOT - Storage on test

SPP - Standard potency pool

SRC - Sequential release control

SSR - Steady state response

ST - Single test

STED - Summary technical documentation

SVT - Source verification testing

SW - Superficial velocity

T0 - Initial time

T1 - Time at endpoint

TAP - Tritiated adenosine triphosphate

TBW - Theoretical body weight

TC - T-cell

TCR - T-cell receptor

Tg - Tg

WCB - working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis NL B.V. submitted on 7 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Xbryk, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 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 number: 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 number: EU/1/11/703

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- 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 number: 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**
31 January 2019	EMEA/H/SA/4025/1/2018/III	*Juha Kolehmainen, Kirstine Moll Harboe*
14 October 2021	EMA/SA/0000066590	*Elena Wolff-Holz, Kerstin Wickström*

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

The strategy with regards to the comparability assessment, the approach to demonstrate non-clinical biosimilarity and the need for non-clinical studies, the design of the supporting clinical studies, and the extrapolation of the study results to all authorised indications of the reference product.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Hjalti Kristinsson

The application was received by the EMA on	7 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all	14 June 2024

CHMP and PRAC members on	
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	27 June 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	03 October 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	22 October 2024
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	30 October 2024
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 Xbryk on	14 November 2024

2. Scientific discussion

2.1. About the product

Xbryk was developed as a biosimilar product to Xgeva (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation:

• Xgeva: 120 mg/1.7mL single use vial

Denosumab is a human monoclonal antibody IgG2 that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Increased osteoclast activity, stimulated by RANKL, is also a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab prevents the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction. Giant cell tumours of bone are characterised by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

2.2. Type of application and aspects on development

During the development of denosumab SB16, the applicant sought scientific advice from the EMA Scientific Advice Working Party (SAWP) two times. All aspects that were discussed critically during these advice procedures and are deviating from the final study designs are discussed in the respective methods or result sections.

2.3. Quality aspects

2.3.1. Introduction

Xbryk is a proposed biosimilar to the reference medicinal product Xgeva. Of note, the active substance of Xbryk and Obodence, which is submitted simultaneously as proposed biosimilar to Prolia, is identical.

The finished product is presented as solution for injection in a single dose vial, containing 120 mg (70 mg /1.0 mL) of denosumab as active substance.

Other ingredients are: histidine, histidine hydrochloride monohydrate, sorbitol (E420), polysorbate 20, water for injections.

The product is available in a single-dose vial made from type I glass with stopper (chlorobutylrubber) and seal (aluminium) with flip-off cap, as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

Denosumab (SB16) is a human monoclonal immunoglobulin G2 (IgG2) antibody composed of two identical heavy chains (448 amino acid residues each) and two identical light chains (215 amino acid residues each) with a total molecular weight of approximately 147 kDa. Its molecular formula without the N-glycan moiety is $C_{6404}H_{9908}N_{1724}O_{2004}S_{50}$.

The heavy chain (HC) of SB16 contains 13 cysteine (Cys) residues at positions 22, 96, 136, 149, 205, 224, 225, 228, 231, 262, 322, 368, and 426, whereas the light chain (LC) contains 5 Cys residues at positions 23, 89, 135, 195, and 215. These Cys residues are linked via intra-chain and inter-chain disulfide bonds. SB16 contains one glycosylation site at asparagine 298 of the molecule.

Denosumab binds with high affinity and specificity to receptor activator of nuclear factor-κB ligand (RANKL), preventing activation of its receptor, receptor activator of nuclear factor-κB (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. Denosumab does not display Fc effector functions.

2.3.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls
The active substance (AS) is manufactured by Samsung Biologics Co. Ltd (300, Songdo bio-daero, Yeonsu-gu, Incheon, 21987, Republic of Korea). Manufacturing authorisations and/or valid GMP certificates have been provided. A satisfactory QP declaration concerning GMP compliance of sites involved in AS manufacture is provided.

The active substance, i.e., denosumab, is expressed in a transfected CHO cell line. After thawing of one working cell bank (WCB) vial, cells are serially expanded. Upon transfer into the production bioreactor, cells are finally expanded and maintained under controlled conditions. The bulk harvest is clarified.

Denosumab is captured and purified from the clarified, cell-free harvest using column chromatography steps. Depth filtration is performed after virus inactivation. Prior to filling, the AS is

ultrafiltered/diafiltered (UF/DF) into AS formulation solution (without polysorbate 20). Following the UF/DF step, formulation solution is added to achieve the final SB16 formulation (histidine, sorbitol, and polysorbate 20). AS bags are filled after a 0.2 µm filtration step.

Batch and scale definitions were provided. The traceability of AS batches is ensured by a unique batch numbering system, which is maintained throughout AS production.

The manufacturing process includes two dedicated, orthogonal virus clearance steps, i.e., low pH treatment and virus filtration using a virus reduction filter.

Definitions of batch and scale are provided. Starting from one WCB vial, one discrete DS batch is purified from production bioreactor run.

In general, the manufacturing process steps have been well described. Each process step is accompanied by flow charts, tables listing the process parameters and their classification. The process controls are divided into process (input) and performance parameters (output). Based on development and risk assessments process parameters are classified into key (KPP) and critical (CPP) process parameters. Performance parameters are designated as in-process gateways (IPGs), critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs). Acceptable ranges in-process specifications are included in the narrative description in dossier section S.2.2. IPC acceptance limits have been included in the narrative manufacturing process description in this section.

Results are evaluated against IPS or defined acceptable ranges. Failure to comply with in-process specification will results in batch rejection, excursions from acceptable ranges will trigger an investigation including an assessment on impact on product quality.

A detailed process risk assessment is provided in dossier section S.2.6. The analytical methods used for testing of performance parameters together with defined measurement limits are described in the dossier and respective analytical method validation data were provided demonstrating suitability of the methods for their intended purpose.

The composition of solutions and buffers for downstream purification has been described. The composition of media and solution used in the cell culture process is provided under dossier section S.2.3. No human- or animal-derived components are used in the manufacturing process of SB16 AS. Information on the reuse of chromatography resins and filter membranes is provided within dossier section S.2.5.

Hold times have been established for the process intermediates based on physio-chemical and microbial hold time studies. The defined hold times are adequately justified by the hold time studies.

Reprocessing is described in case of predefined failures failed post-use filter integrity test); this is acceptable.

The AS is packaged in bags and acceptable specifications for the container closure components were presented. The bags are sterilised by gamma irradiation and are certified BSE/TSE free.

An extractables study for the container closure system has been conducted in order to determine the extractable amount of chemical compounds. The results of this study indicate that the amount of extractables was low enough to conclude that the extractables pose a very low toxicological risk to the FP. Thus, the applicant`s conclusion that a leachable study can be omitted is agreed.

In conclusion, the description of the manufacturing process and controls is in line with regulatory expectations.

Control of materials

No animal- or human-derived materials are used from the cell line development to manufacturing process of SB16 active substance (AS) and finished product (FP). Qualitative composition of the cell culture media was presented. The components of the buffers and solutions used during the up- and down-stream processes; chromatographic resins, and filters are listed together with qualitative composition of each buffer, specifications of the chromatographic resins, and the filter types are stated. It was stated that the human insulin is used in the cell culture media. It is stated that protein A ligand of the affinity chromatography is of recombinant origin. The applicant provides a risk assessment on the compatibility of FP with process materials and presents an extractable/leachable study for concerned materials.

The construction of the expression vector and its genetic elements has been described in sufficient detail. The information provided on the origin and history of the parental CHO cell line is satisfactory. The CHO cells were transfected with the final expression vector which was constructed using separate intermediate vectors for the heavy and light chains of SB16. The production cell line was generated by stable pool selection and single clone selection in chemically defined media. The nucleotide sequence of the heavy chain and light chain inserts and flanking regions was confirmed by sequencing. The lead clone selection and the applicant's approach to prove monoclonality are sufficiently described.

A two-tiered cell bank system with MCB (master cell bank) and WCB has been established starting from the research cell bank (RCB). The description of the cell bank generation (both for the MCB and WCB) includes satisfactory details. All materials used in the manufacture of the MCB and WCB are of non-animal origin. Information on potential animal-derived materials used in cell-line development together with applied safety tests has been provided. An end product cell (EPC) was generated from the MCB, the cumulative PDL from MCB thaw to EPC is was stated and is acceptable. The cell banking system is adequately described with details on manufacture and storage of the MCB and WCB. Cell bank stability is monitored and satisfactory acceptance criteria were provided for storage stability tests of MCB and WCB.

Characterisation of the MCB, WCB and EPC was performed largely in line with ICH Q5A and ICH Q5D requirements. Brief descriptions of the state-of-the-art analytical procedures are provided; sterility and mycoplasma were tested according to the respective Ph. Eur. monographs. The genetic stability of the SB16 sequence of the MCB up to the EPC was sufficiently confirmed. Phenotypic stability (i.e. specific growth rate and specific productivity) was also confirmed . The limit of in vitro cell age from MCB thaw to EPC of was sufficiently justified based on the results from genetic and phenotypic testing.

Process validation

A traditional approach was chosen to verify process performance at commercial scale. Four process validation batches of the intended commercial scale at the proposed commercial AS manufacturing site Samsung Biologics were included.

A summary on the performed PPQ including the process and performance parameters per manufacturing step for each of the four PPQ batches, has been provided. For both, the cell culture and the purification process, all in process specifications were met, critical process parameters (CPP), key process parameter (KPP), in-process tests (IPTs) and in-process gateways (IPGs) were within their defined acceptable ranges, except for minor deviations. However, satisfying justification were provided and it is agreed that these deviations do not negatively impact product validation. Of note, several modifications of process control parameters have been introduced after process validation. For these changes, satisfactory justifications have been provided. In conclusion, the PPQ results demonstrate that the AS manufacturing process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions. Adequate and consistent performance of the cell culture and purification processes has been confirmed.

The clearance studies of process related impurities involved studies for cell derived impurities (HCD, HCP), cell-culture process derived impurities and impurities derived from the downstream purification process. The impurity clearance was validated by using analysis results of PPQ batches, or by using scale-down spiking models. The representativeness of the scale-down models is discussed in CTD section S.2.6. Consistent removal of process- and product-related to acceptable low levels/below LOD has been demonstrated across the PPQ batches.

Physicochemical hold time studies on the different AS manufacturing steps have been performed in order to establish the intermediate hold times for commercial manufacturing.

Microbial studies have been conducted using growth-promoting surrogate solutions for challenging the integrity of the hold vessels. A matrixing approach was chosen to include production bioreactors, harvest pool and product hold vessels. The results from these studies demonstrate appropriate microbial control over time. From a current perspective most of the proposed hold times are sufficiently justified.

Resin/membrane lifetime studies were performed at laboratory scale based on scale-down models. In terms of product quality and performance attributes the presented data show consistent performance of the resins and would support the proposed target resin lifetimes. In order to evaluate the lifetime of the resins at manufacturing scale, data for output parameters will be collected and monitored according to an presented acceptable protocol.

Sufficient data supporting the re-usability of the UF/DF membrane was provided upon request. The applicant describes that shipping qualification studies in order to validate the shipping system has been performed to assure the quality of the product.

Manufacturing process development
The applicant followed an enhanced development approach using existing knowledge, development and manufacturing experience, risk ranking and filtering, and process characterisation (PC) studies to develop a control strategy as outlined in ICH Q11 and EMA/CHMP/BWP/187338/2014. The outcome of a quality attribute risk assessment in order to categorise individual product quality attributes either critical or non-critical was presented and the critical quality attributes (CQAs) were stated. The CQAs related to the mechanism of action (MoA) of SB16 were described.

The development history of the AS manufacturing process (cell culture; purification) was summarised including a description of the pilot-scale, clinical, PPQ and commercial scale process. Differences between pilot and clinical batch manufacturing have been adequately described. Following the clinical AS production, process characterisation (PC) studies, were carried out for each unit operation of the SB16 DS process. The design of the process characterisation studies is presented satisfactorily and, overall, appears acceptable.

Based on the outcome of the PC studies, the proven acceptable ranges as well as the classification of the process parameters (PPs) were defined. Another risk assessment was performed after PC studies to establish risk mitigation and the control strategy for the PPQ process. The risk assessment appears reasonable. Minor process changes were introduced into the SB16 process prior to PPQ manufacturing process, and these changes have been adequately described and addressed.

Finally, the applicant introduced some changes post-PPQ activities: several modifications were made to the process control strategy and process parameter classification. These changes were driven by additional manufacturing and process development. Description and justification for these changes and modifications after PPQ manufacturing is found to be adequate.

In order to ensure that the batches used at each stage of SB16 development are representative for subsequent development stages, and that changes in the manufacturing process at each stage of

development do not affect product quality, three comparability studies were conducted using orthogonal state-of-the-art analytical procedures. Comparability was investigated and shown between SB16 pilot scale and clinical phase batches, between SB16 clinical phase batches and PPQ batches and between SB16 PFS FP and SB16 vial FP.

Comparability assessment was performed based on the quality attributes for release test items and extended characterisation studies. The extended characterisation included physicochemical and biological assays. In addition, comparative stability studies were performed to evaluate the degradation patterns among SB16 batches (pilot, clinical, and PPQ drug substance batches).

Elucidation of structure and other characteristics and Impurities
Structural and functional characteristics of the denosumab AS have been elucidated by testing a comprehensive list of physicochemical and biological parameters using sensitive and orthogonal state-of-the art qualified analytical methods in accordance with ICH Q6B. The characterisation studies of the structures (primary, secondary, and higher order), purity/impurities, charge variants, cellular potency, and binding activity.

It is mentioned that these characterisation tests were performed in the frame of the analytical biosimilarity evaluation in section 3.2.R. This confirms batch to batch consistency of all investigated parameters. There was no significant difference regarding the experimental outcome between orthogonal methods.

2.3.2.3. Specification

The release specification for SB16 AS comprises tests for general attributes (colour, clarity, pH, osmolality), identity, quantity, biological activity, purity and impurities, charge heterogeneity, and microbiological safety (bacterial endotoxins and microbial enumeration).

In summary, the set of quality attributes tested at release and during shelf life, complies with relevant guidelines and compendial requirements and is acceptable.

The acceptance criteria were established based on batch data from pilot and commercial scale AS and FP and stability data (including clinical phase batch), manufacturing capability and variability, analytical procedure capability and variability, developmental studies, compendial requirements, regulatory guidelines and certificates of analysis (CoA) of the reference product.

The strategy for establishing specification limits has been elaborated and is overall agreed.

Analytical procedures and reference standards
An overview of the analytical methods was included. The suitability of the compendial methods has been verified for their intended use. The analytical methods appear adequate for their intended purpose and overall, the implemented system suitability tests and sample acceptance criteria appear suitable to provide adequate control over analytical method performance. In general, the validation results demonstrate suitability of the analytical procedures for their intended use. The relevant parameters have been assessed in accordance with ICH Q2(R1). The capability of the stability indicating methods to detect product degradation/modification has been demonstrated adequately by forced degraded sample during method validation. Where relevant, method transfer reports were included.

The applicant has described its reference standards used throughout the development of SB16. Different classes of reference standards including the research reference standards (RRS), the interim reference standard (IRS), the primary reference standard (PRS) and the working reference standard (WRS) were defined.

The history of the reference standards used throughout development of SB16 was described satisfactorily. SB16 IRS preparation and qualification has been described. As comparability of clinical and PPQ DS batches of SB16 was confirmed according to the applicant, PRS can be considered representative of production. The reference standards have been appropriately qualified.

The applied strategy to bridge RRS, IRS, and PRS via potency assays has been presented and is acceptable. The same strategy of potency assignment used for the primary reference standard is also proposed for qualification of future primary reference standards and the working reference standard to be implemented. The defined acceptance criteria are considered sufficient to avoid a potential drift in potency to future reference standards and hence is accepted. The protocol for qualification and annual re-qualification of future primary and working reference standards is acceptable.

Batch analyses
Batch analyses data were presented for pilot clinical and commercial scale batches. All results comply with the proposed commercial specifications. In summary, the presented results demonstrate that the manufacturing process reliably delivers drug substance with consistent quality.

2.3.2.4. Stability

The applicant provided the stability data of AS for supporting the proposed shelf-life.

Real time stability data at long-term storage condition was provided for a pilot, clinical, PPQ batches. Also, stability data under intermediate and accelerated storage conditions were provided. The applicant claims that the above batches can be used for establishing the shelf-life claim as representativeness for the commercial product is shown.

The batches were tested against the stability specifications and no noteworthy changes or trends over the storage period were observed. The container used for stability studies is composed of the same material as that used for the commercial product, but only smaller in size which is acceptable. Thus, the stability data indicate that the AS is stable and not susceptible to degradation.

The applicant commits to continue the formal stability testing of the primary stability batches and to place one batch per year (unless none is produced that year) on stability under approved storage conditions, following good manufacturing practice (GMP) requirements.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Xbryk is a clear, colourless to slightly yellow, sterile and preservative-free solution for injection, presented as a single-dose vial containing 120 mg (70 mg/1.7 mL) of denosumab for subcutaneous injection. All excipients used are of compendial quality.

SB16 has being developed as a biosimilar to Xgeva. The excipients of the SB16 are identical to the excipients of EU-approved Xgeva except for the buffer system. The applicant has investigated formulations with different protein concentration, buffer and stabiliser. Formulation studies were performed under thermal stress, Long-term, Freeze-thaw stress and Agitation stress.

The results pointed at adequate performance of all formulation variants tested.

Overall, the formulation for SB16 vial; 70 mg/ml denosumab with histidine and sorbitol, polysorbate 20 was confirmed with the present study. Of note that the formulation for SB16 PFS, 60 mg/ml

denosumab, comprises histidine and sorbitol, polysorbate 20 was also confirmed with the present study. However SB16 PFS formulation is part of a separate MAA (Obodence) submitted in parallel as biosimilar to Prolia. This is acceptable. There are no overages applied for SB16 FP.

The development history and improvement steps from clinical to commercial manufacturing phase of the SB16 PFS drug product were presented. In brief, only minor process optimisation steps and subsequent verification runs were executed to check process consistency. During bulk AS thawing, buffer preparation, bulk AS formulation, bioburden reduction; AS pooling/mixing, buffer transfer and compounding, Bulk intermediate storage and equilibration, sterile filtration, aseptic filling and stoppering and visual inspection all predefined acceptance criteria were met.

To verify the changes, an engineering run was conducted before initiating the PPQ Process. Engineering run studies were performed to confirm manufacturing process parameters and process consistency. A detailed description of the engineering run studies is provided. The results for tested process parameter and the analytical results for tested QA of the AS met the acceptance criteria. Because of that, the overall performance of the engineering runs is considered useful and confirmed appropriate processing conditions for commercial aseptic filling of SB16 vial as FP.

The applicant performed extractables and leachables studies to determine the appropriateness of the primary packaging material for the vial product, which consists of a glass vial and a stopper.

For the extractables study, a standard approach was applied which is acceptable. Values were measured below permissible daily exposure.

Leachables studies were done to determine the amount of leachable compounds present in the FP migrated from the container closure system. The applicant stated that the compounds will be continuously monitored and subjected to toxicological assessment if necessary, which is endorsed. It was confirmed that the analytical methods are sufficiently sensitive for the intended purposes.

Container Closure System
The primary packaging material consists of a 2 mL type I glass vial, a rubber stopper, and an aluminium seal with plastic flip-off cap. The glass vial and stopper are of Ph. Eur. quality. Drawings including dimensions are provided for the vial, stopper and cap.

Certification from the manufacturers of the vials and stoppers is provided containing that the sterilisation of the vials has been conducted with ETO and validated in accordance with ISO 11135 and ISO 11137.

Depyrogenation of vials and sterilisation of stoppers are performed at Samsung Biologics Co. Ltd. in accordance with Ph. Eur. 5.1.1. This confirmation is acceptable and no validation data for the sterilisation cycle is requested in the dossier. Regarding the depyrogenation of the glass vials by Samsung Biologics a 3 log10 reduction in heat-resistant endotoxin is demonstrated in accordance with Ph. Eur.

2.3.3.1. Manufacture of the product and process controls

Manufacture
The FP manufacturing sites and their respective responsibilities are appropriately listed in the dossier. All sites are covered by valid GMP certificates.

Description of manufacturing process and process controls
The FP is manufactured according to a standard process including the following steps: AS thawing and formulation, filtration, filling and stoppering. The manufacturing process is sufficiently described and process parameters are sufficiently justified based on process characterisation and validation data.

Process controls
The control strategy in place for the FP manufacturing process is adequate.

Process parameters (input variables or conditions used to control the process) and performance parameters (outputs from the process indicating whether the process is performing accordingly) are part of the overall control strategy. Definitions of critical and key process parameters (CPP/KPP) and performance parameters such as in-process gateways (CIPG/IPG) and in-process tests (CIPT/IPT) are provided. For each step of the manufacturing process, process parameter and performance parameters are adequately defined including acceptance ranges. Critical process gateways clearly identify Step 4: Sterile filtration and Step 5: Aseptic filling as the critical steps of the manufacturing process. Results from the manufacturing process development studies are reflected in the selected acceptable ranges and the designation of the process/performance parameters.

Hold-times are clearly identified and controlled and they are acceptable.

Process validation
The process performance qualification was performed following a classical approach. For that purpose, three consecutive lots of FP were manufactured according to the commercial process in the commercial facility at Samsung Biologics Co. Ltd., Korea, are covered in PPQ, as well as all manufacturing process steps. Three complete validation batches were planned according to the initial protocol. The PPQ batches can be regarded as entirely independent FP batches. Each PPQ batch is manufactured from a different AS batch, thereby suitably considering the variability of the AS.

Two PPQ batches met the prospective acceptance criteria and in-process controls, and pre-defined specifications. Hold times are sufficiently justified based on PPQ data. For one PPQ batch the applicant described that minor cosmetic defects were found and exceeded the range of total defect rate during 100% visual inspection. Above deviations were concluded by the company to not have an impact on the product quality attributes and, through re-inspection, all AQL inspections were concluded to be passed. This conclusion by the applicant is endorsed.

In summary, PPQ demonstrated that the manufacturing process when operated within the established parameters performs effectively and reproducibly to produce medicinal product meeting predetermined specifications and quality attributes. The validation of the SB16 vial FP manufacturing process is considered acceptable.

Sterile filter validation was conducted confirming pre- and post-use sterilising filters conformed to specifications.

In summary, the sterile filter validation for Xbryk FP manufacturing was successfully validated by the manufacturer of the filter. The filter is appropriate for the sterile filtration of SB16 under the selected process parameters.

Media fill qualification was conducted at the proposed manufacturing site. Procedures and specifications for media fills to evaluate the reliability and reproducibility of the aseptic process are sufficiently described. Results from three media fill qualification runs were provided covering the manufacturing process and including the primary CCS, whereby one run was performed under worst conditions. All results met the pre-defined acceptance criteria, and no contaminated vials were detected after

incubation demonstrating that aseptic conditions are maintained during the filling process. The filling hold time has been defined and it is justified by the overall duration of the media fill runs.

Furthermore, a shipping qualification considering worst-case shipping conditions was performed. Based on the results of the shipping qualification, including Container Closure Integrity Testing (CCIT) testing, it is agreed that the shipping container/system can maintain product temperature as well as product integrity during the transportation.

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

2.3.3.2. Product specification

The finished product release and shelf life specifications, include tests for appearance (clarity, colour, visible particles), general attributes (osmolality, pH, extractable volume, protein concentration), identity, biological activity, purity and impurity, charge heterogeneity and safety.

Specifications were defined considering ICH Q6B guidance, Ph. Eur. monograph "Monoclonal Antibodies for Human Use" #2031, but also product risk assessment, manufacturing experience, batch history, stability studies, regulatory guidelines, and the specifications of refence product. Overall, the list of quality attributes proposed for SB16 DP release and stability testing is acceptable.

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 in the finished product specification. Based on the information provided, it can be concluded that the overall risk as regards elemental impurities is negligible. The information on the control of elemental impurities is satisfactory.

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

Analytical methods and Method validation
Several methods are performed in compliance with Ph. Eur. In-house methods are used for others. To follow ICH Q10 (4.2(b), the applicant is encouraged to consider the feasibility of transitioning to Ph. Eur. 2.6.32 Test for bacterial endotoxins using recombinant factor C, eliminating the need for horseshoe crab derived material.

Methods and method validations common to AS and FP are described and discussed in 3.2.S.4.2 and 3.2.S.4.3, respectively. Compendial methods were verified, however, no data have been provided.

The CCIT method was described, and the validation data are provided in dossier section 3.2.P.8.3.

For a discussion on the reference standards, refer to the respective AS section.

Batch Analyses
Batch analyses data have been provided for 3 clinical phase batches and 3 commercial scale PPQ batches. Results of all batches complied with pre-defined acceptance criteria at release valid at the time of testing. Furthermore, the provided batch data confirm that the manufacturing process of SB16 vial FP is robust demonstrating batch-to-batch consistency.

2.3.3.3. Stability of the product

The proposed shelf-life is 3 years when stored at 5°C ± 3°C.

Stability data has been provided for multiple batches for up to 36 months stored at the long-term condition (5°C ± 3°C.). The study at accelerated condition (25 ± 2°C/ 60% ± 5% RH) is completed for all batches. The same batches were also stored under stress conditions (40 ± 2°C) for 3 months.

The stability batches are either representative of the commercial material or of commercial scale and manufactured according to the final commercial process. Differences in the manufacturing process of the stability batches were evaluated and cause no product impact. Comparability between batches tested for stability has been sufficiently demonstrated.

At long-term conditions all batches met the acceptance criteria at long-term conditions over the storage period for all quality attributes. At accelerated conditions, overall, the observed changes in the different tested parameters were within the defined acceptance limits.

Photostability testing was performed in line with ICH Q1B guideline (option 2). The study results demonstrated that SB16 DP is sensitive to light and protected from light when stored in the secondary packaging material.

Two temperature cycling studies (i.e. a short-term temperature cycling study and a supply chain cycling study) were performed. Regarding available stability data, no out-of-specification results and no significant trends have been observed when stored at temperature cycling storage condition.

A room temperature stability study (label claim) was conducted with aged FP (= FP, stored under long-term condition for the shelf-life, was stored for 60d at 25± 2°C/60 ± 5% RH and an additional 28 days at 5 ± 3°C) to support the storage condition/duration as described in the PI. The results met the acceptance criteria, whereby the same trends were observed as during long-term and accelerated conditions. The results support the storage condition of up to 60 days at RT (25 ± 2ºC/60 ± 5% RH) and an additional 3 days at 5 ± 3°C after storage at the long-term conditions for the shelf life.

The provided post-approval stability protocol and commitment is acceptable.

The provided stability data support the proposed shelf-life of 36 months and storage conditions "Store in a refrigerator (2 °C – 8 °C)", "Do not freeze", "Keep the container in the outer carton in order to protect from light", as stated in the SmPC sections 6.3 and 6.4. Also according to the SmPC section 6.3, Xbryk may be stored at temperature up to a maximum of 25°C for a single period of up to 60 days, but not exceeding the original expiry date. If not used within this period of up to 60 days, Xbryk may be returned to the refrigerator for 28 days for future use.

2.3.3.4. Biosimilarity

The applicant has performed multiple bridging studies comparing SB16 in different strengths and presentations and with the reference medicinal product Xgeva. Briefly, four bridges have been made; bridge one describes similarity studies with SB16 PFS and EU Prolia, bridge two were similarity studies

with SB16 vial and EU Xgeva, bridge three were comparability studies with SB16 PFS and SB16 vial and bridge four comparability studies with EU Prolia and EU Xgeva.

Criticality and risk priority numbers have been calculated for the quality attributes. Quality ranges were used for high and moderate risk attributes, qualitative comparisons for low risk and attributes that could not be measured quantitatively. Similarity was concluded, given that 90% of data are within the similarity range. This is considered a common and practicable approach and thus appropriate and acceptable. Further, the described and applied methodology is considered state-of-the-art.

Several batches of SB16 and EU-sourced Xgeva have been used. The sourcing of in-house batches and reference batches is regarded meaningful and sufficient.

Table 1. Summary of the of analytical similarity between Xbryk and Xgeva

Category	Test Item		Similarity Assessment Result
Physicochemical Properties: Primary structure and post translational modification	Molecular weight		Minor differences
	Amino acid sequence		Similar
	Peptide mapping		Similar
	N-terminal sequence		Similar
	C-terminal sequence		Minor differences
	Extinction coefficient		Similar
	Oxidation		Minor differences
	Deamidation		Similar
Physicochemical Properties: Glycan profiles	N-linked glycosylation site		Similar
	N-glycan identification		Minor differences
	N-glycan profile	%High mannose	Similar
		%Charged glycan	Similar
		%Galactosylation	Minor differences (Justified in Section 2.3.2.2)
Physicochemical Properties: Size variants	SE-HPLC	%HMW	Similar
		%Monomer	Similar
	CE-SDS (non-reduced)	%2H1L	Similar
		%IgG	Similar
	CE-SDS (reduced)	%LC+%HC	Similar
		%NGHC	Similar
Physicochemical Properties: Charge heterogeneity	CEX-HPLC	%Acidic	Similar
		%Main	Similar
		%Basic	Similar
	icIEF	%Acidic	Similar
		%Main	Similar
		%Basic	Similar
Physicochemical Properties: Hydrophobicity	RP-UPLC	%Main	Similar
		%Post-main	Similar
	Disulfide bond		Similar
	Free sulfhydryl group quantification		Similar

Category	Test Item		Similarity Assessment Result
Physicochemical Properties: Higher order structure	CD		Similar
	ITF		Similar
	FTIR		Similar
	DSC		Similar
	H/DX-MS		Similar
	SEC-MALS		Similar
	SV-AUC		Similar
	DLS		Similar
	MFI		Similar
Physicochemical Properties: Quantity	Protein concentration (mg/mL)		Similar
Biological properties	RANKL binding assay	%Relative binding activity	Similar
	Anti-differentiation assay	%Relative potency	Similar
	RANKL neutralisation assay	%Relative potency	Similar
	FcRn binding assay	%Relative binding activity	Similar
Additional biological properties	FcγRIa binding assay	Binding response (RU)	Similar
	FcγRIIa binding assay	%Relative binding activity	Similar
	FcγRIIb binding assay	%Relative binding activity	Similar
	FcγRIIIa binding assay	%Relative binding activity	Similar
	C1q binding assay	%Relative binding activity	Similar
	mRANKL binding assay	Binding response (APC-A)	Similar
	ADCC assay		Similar
	CDC assay		Similar

Similarity between SB16 vial and EU Xgeva

Demonstration of biosimilarity between the proposed biosimilar SB16 and EU-Xgeva started with an extensive characterisation of EU-sourced reference product lots. From the data collected thereof similarity ranges, where possible, have been established for the CQAs.

The results of the analytical similarity study and their evaluation are well presented in the dossier. Individual results and data distribution for each parameter is clearly presented in tables and figures. Spectra, chromatograms, etc. are also included in the analytical similarity report. Furthermore, individual analytical results for each batch are listed in an appendix.

Similarity assessment has been performed on several batches of SB16 and EU-Xgeva. Comparability between clinical and PPQ batches has been demonstrated.

Free Sulfhydryl groups were quantified by a 'Measure-iT Thiol' assay. Free thiols were slightly different between SB16 and Xgeva, the applicant stated that this is negligible. Upon request, the applicant provided a comprehensive and acceptable explanation on the observed difference in free thiol groups.

Subvisible particles in the µm range were analysed by micro-flow imaging. For not-round particles the counts of sizes ≥10 µm, and ≥25 µm of SB16 were similar to those of EU Xgeva. However, differences were observed between SB16 and EU Xgeva in the counts for particles of sizes ≥1 µm, ≥2 µm, and ≥5 µm. As a question on these differences was posed, the applicant performed the orthogonal method HIAC to investigate subvisible particles. This is endorsed and further, the explanation on the slightly differing results of the two methods is acceptable and these differences are negligible, not posing a risk on the quality performance of the product.

Upon request, the applicant discussed on differences in hydrophobicity of SB16 and Xgeva. The extensive discussion could convincingly show that the observed different isoforms have no overall influence on the performance of the molecule and are an intrinsic feature of the IgG2 molecule leading to hydrophobic heterogeneity. The applicant stated that results showed similar membrane-bound RANKL binding activities. This could not be followed as the binding responses differed between analysed samples. Upon request, Samsung Bioepis extensively discussed and re-evaluated the differences in mRANKL binding with acceptable outcome, posing no risk to the similarity statement. This is of acceptable quality and endorsed.

Sialylation is not part of the biosimilarity exercise. A justification supported by data is provided demonstrating that the observed difference can be regarded as negligible to have clinical impact in terms of efficacy, PK and immunogenicity/safety. Overall, there is no significant difference between SB16 and Xgeva in terms of sialylation. As requested, the applicant considered the demand for documentation of sialylation and carried out appropriate analysis of these glycan compounds in SB16 clinical, PPQ, EU-Prolia and EU-Xgeva samples. The differences were found negligible and thus are not considered to have a different impact on efficacy, PK and immunogenicity/safety.

In summary, the majority of physico-chemical attributes and biological activity is regarded as highly similar between the proposed biosimilars SB16 vial and the reference medicinal product Xgeva provided the minor concerns are appropriately discussed.

Comparative stability between SB16 vial and EU Xgeva

Comparative stability studies under stress conditions such as heat, basic, acidic, oxidative and photostress conditions were conducted in accordance with ICH Guidelines Q5C and Q1A (R2).

Samples were analysed for several quality attributes including QC release test items.

The forced degradation results under each storage condition are provided for all parameters tested and are sufficiently discussed. Supportive graphs of the degradation trend for each parameter are included.

Overall, the degradation pathways between SB16 and EU Xgeva are similar heat, acidic, oxidative and photo stress conditions.

Comparability assessment between EU Prolia and EU Xgeva

To establish bridging similarity at quality level between EU-Xgeva and EU-Prolia a comparability assessment was conducted. A tiered approach was applied in the same way as for the analytical similarity assessment between SB16 vial and EU Xgeva. For high and moderate risk quality attributes, the similarity ranges established by EU Prolia were employed as comparability range to evaluate the comparability between EU Prolia and EU Xgeva. EU Xgeva lots were evaluated against the

comparability range. For low-risk quality attributes or the quality attributes that cannot be quantitatively measured, raw data/graphical comparison was employed. The analytical and statistical approach is considered acceptable.

Where applicable, figures are presented showing the individual results and the corresponding quality range for EU-Prolia. Tables are also provided listing the individual analytical results for each lot tested for a specific QA.

Most of the QAs are comparable between EU Prolia and EU Xgeva. Small differences have been observed between EU Prolia and EU Xgeva. In all cases over 90% of EU Xgeva batches were found to be in the similarity range of EU Prolia indicating comparability between EU Xgeva and EU Prolia. Further, the differences between EU Prolia and EU Xgeva are observed for products already proven in efficacy and safety.

Overall, analytical similarity and similar degradation profiles of SB16 vial to reference product Xgeva could be shown with the presented data.

2.3.3.5. Adventitious agents

Multiple complementing measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and process intermediates for microbial and viral contaminants, testing of microbial attributes as in-process controls and at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (microbial reduction filtrations, sterile filtration, aseptic processing) and sanitisation procedures.

TSE

No raw materials of animal origin were used during preparation of cell banks and during the DS and DP manufacturing. Based on the information provided, it is agreed that the overall risk with regard to TSE is minimal.

Microbial agents

The cell banks were tested for the absence of bacterial/fungal contamination and mycoplasma according to Ph. Eur. Absence of mycoplasma is routinely confirmed for the unprocessed bulk material. Bioburden and endotoxin tests are performed at multiple stages of the drug substance and drug product manufacturing processes. At the release stage, drug substance and drug product are tested for bioburden or sterility, respectively, as well as for endotoxin content. In conclusion, the risk for microbial contamination is adequately controlled.

Adventitious viruses

No substances of human or animal origin are used during manufacture, and the safety of the cell substrate has been suitably demonstrated. No virus like particles were detected other than retrovirus-like particles which were identified as intracytoplasmic A and C-type particles, which are known to be present in CHO cells.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models. The design of the studies appears to be largely in line with the guidance documents ICH Q5A and CPMP/BWP/268/95. Thus, orthogonal manufacturing steps were evaluated in virus clearance studies using relevant model viruses. Tabular comparisons of the process parameters for the manufacturing scale and small-scale process steps have been provided.

A summary of virus clearance study results is presented in the dossier.

Generally, the information on the virus clearance studies is sufficient.

2.3.3.6. GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Xbryk has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Xgeva. Its active substance denosumab is manufactured using a typical manufacturing process for monoclonal antibodies.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. Comparability among the batches of AS produced during the different phased of development has been demonstrated by comparability studies using orthogonal state-of-the-art analytical procedures. The overall control strategy was established in accordance with ICH Q11 using an enhanced development approach and is acceptable. Process characterisation and process verification (PPQ) data support the conclusion that the AS manufacturing process reliably generates active substance (and subsequently drug product) meeting its predetermined specifications and quality attributes.

Th finished product (FP) is manufactured according to a standard process. Comparability of the clinical phase SB16 batches and the PPQ batches has been demonstrated. The manufacturing process is appropriately described, and process parameters are sufficiently justified based on process characterisation and validation data. The validation of the manufacturing process has been satisfactorily demonstrated ensuring the manufacturing process for SB16 is capable of consistent and robust performance.

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

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

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

No studies were submitted in *Module 4 – Non-clinical data*. This is acceptable according to regulatory guidance on the non-clinical development of biosimilars (EMA/CHMP/BMWP/42832/2005 Rev 01). Note that the conducted in vitro biocomparability assays were submitted in *Module 3 – Quality data* and were therefore evaluated in the frame of the quality assessment.

2.4.2. Ecotoxicity/environmental risk assessment

Due to the proteinaceous nature of Xbryk, it is unlikely to result in a risk to the environment, as it will be degraded by naturally occurring proteolytic enzymes into innocuous smaller peptides and amino acids once it ends up in the environment. Considering this aspect, no detailed ERA is necessary.

2.4.3. Discussion on non-clinical aspects

No studies were submitted in *Module 4 – Non-clinical data*. This is acceptable according to regulatory guidance on the non-clinical development of biosimilars (EMA/CHMP/BMWP/42832/2005 Rev 01). The data submitted in relation to the conducted in vitro biocomparability assays were assessed and discussed in the frame of the quality assessment.

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, denosumab is not expected to pose a risk to the environment.

2.4.4. Conclusion on the non-clinical aspects

From a non-clinical perspective, the non-clinical data provided by the applicant is considered adequate to support the approval of Xbryk as a biosimilar to Xgeva.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 2. Listing of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Dosage Regimen	Number of Subjects	Test Subjects	Duration of Study	Study Status; Type of Report
Phase I	SB16-1001 (EudraCT No. 2020-002592-35)	CTD Section 5.3.3.1	Primary objective: To demonstrate the pharmacokinetic (PK) similarity between SB16 and EU Prolia in healthy male subjects. Secondary objective: To investigate and compare the pharmacodynamics (PD), safety, tolerability, and immunogenicity between SB16 and EU Prolia in healthy male subjects.	Randomized, double-blind, three-arm, parallel group, single-dose study Active Control/ Comparator	A single-dose 60 mg of either SB16 or US Prolia or EU Prolia by subcutaneous (SC) injection	Randomized Set (RAN): N =168 SB16: 56 US Prolia: 56 EU Prolia: 56 Safety Set (SAF): N =168 SB16: 56 US Prolia: 56 EU Prolia: 56 Pharmacokinetic Analysis Set (PKS): N =166 SB16: 55 US Prolia: 56 EU Prolia: 55 Pharmacodynamic Analysis Set (PDS): N =166 SB16: 55 US Prolia: 56 EU Prolia: 55	Healthy male subjects	Approximately 32 weeks including 28 days screening period	Complete ; Clinical Study Report (CSR)
Phase III	SB16-3001 (EudraCT No. 2020-001479-34)	CTD Section 5.3.5.1	Primary objective: To demonstrate the equivalence of SB16 to Prolia, in terms of percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12 in subjects with postmenopausal osteoporosis (PMO). Secondary objective: To evaluate the efficacy of SB16 compared to Prolia by percentage change from baseline in lumbar spine BMD, percentage change from baseline in total hip BMD, percentage change from baseline in femoral neck BMD. To evaluate the PK profile, PD profile,	Randomized, double-blind, multicenter study Active Control/ Comparator	Patiens were administered subcutaneous (SC) 60 mg SB16 or Prolia once every 6 months for up to 18 months (total of 3 doses).	Randomized Set (RAN): N = 457 SB16: 225 Prolia Overall: 232 Prolia+SB16: 100 Prolia+Prolia: 101 Safety Set 1 (SAF1): N = 456 SB16: 225 Prolia Overall: 231 Prolia+SB16: 100 Prolia+Prolia: 101 Safety Set 2 (SAF2): N = 407 SB16: 206 Prolia Overall: 201 Prolia+SB16: 100 Prolia+Prolia: 101 Pharmacokinetic Analysis Set (PKS): N = 456 SB16: 225 Prolia Overall: 231 Prolia+SB16: 100 Prolia+Prolia: 101	Patients postmenopausal osteoporosis (PMO)	Total duration of treatment of approximately 18 months	Complete ; Final CSR

			immunogenicity, and safety and tolerability of SB16 compared to Prolia. To evaluate the safety, tolerability, immunogenicity, PK, PD, and efficacy in patients with PMO who transitioned to SB16 from Prolia compared to patients who maintained Prolia from the Main period.			Pharmacodynamic Analysis Set (PDS): N = 443 SB16: 218 Prolia Overall: 225 Prolia+SB16: 100 Prolia+Prolia: 97			

2.5.2. Clinical pharmacology

The clinical pharmacology of SB16 and the reference products have been investigated in two studies:

• Clinical Phase I study (SB16-1001): A randomised, double-blind, three-arm, parallel group, single-dose study to compare the PK, PD, safety, tolerability, and immunogenicity of denosumab (SB16, European Union [EU]-sourced Prolia [hereafter referred to as, 'EU Prolia'], and US-sourced Prolia [hereafter referred to as, 'US Prolia']) in healthy male subjects.

• Clinical Phase III study (SB16-3001): A randomised, double-blind, multicentre clinical study to compare the efficacy, safety, PK, PD, and immunogenicity between SB16 and EU Prolia in postmenopausal women with osteoporosis.

Apart from the above-mentioned studies, no other clinical pharmacology studies (i.e., drug interaction studies, or studies in special populations such as hepatic or renal impairment) were performed.

2.5.2.1. Pharmacokinetics

Analytical Methods

PK immunoassay

The electrochemiluminescence bridging immunoassay used for quantification of denosumab in human serum of healthy volunteers and patients with postmenopausal osteoporosis has been validated according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). All measured parameters were acceptable. The assay can be used as a method for quantification of SB16 as well as EU/US Prolia.

Overall, the PK ECL assay used for quantification of denosumab is found to be suitable for its intended purpose. Performance of the assay during clinical studies SB16-1001 and SB16-3001 is considered acceptable.

Study SB16-1001

Study Design

This study was a randomised, double-blind, three-arm, parallel group, and single-dose study. A total of 168 healthy male subjects aged 28-55 years were randomised 1:1:1 to receive a single dose of either

SB16, EU sourced Prolia, or US sourced Prolia. All investigational products (IPs) were administered subcutaneously in the abdomen.

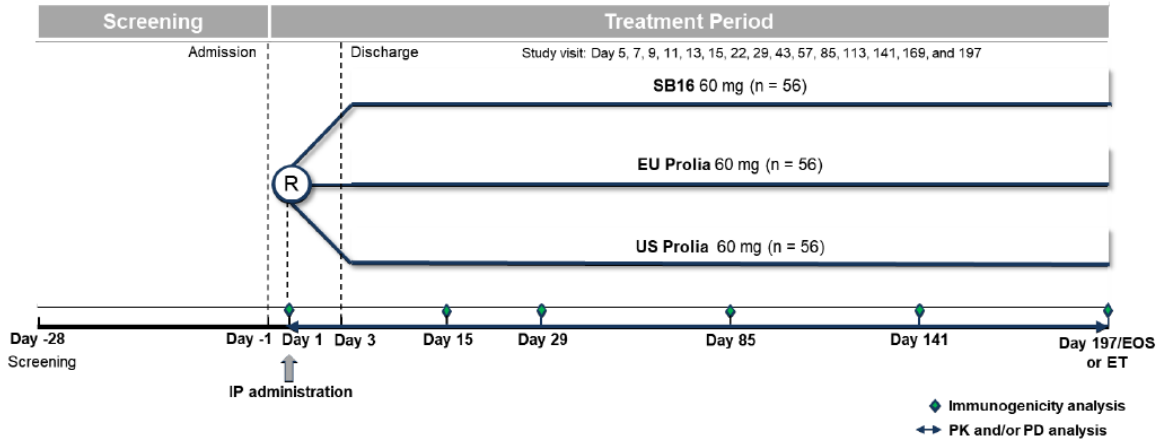
Blood samples for PK analysis were collected at 0 (pre-dose), 12, 24, 48, 96, 144, 192, 240, 288, 336, 504, 672, 1008, 1344, 2016, 2688, 3360, 4032, and 4704 h post-dose.

All subjects were provided with calcium (at least 1000 mg) and vitamin D (at least 400 IU) daily during the treatment period. Administration of calcium and vitamin D was recommended from Screening.

An interim safety analysis was conducted during the course of the study. The analysis occurred approximately 3 days after IP administration in 17 subjects. The main analysis was performed after study completion of the last subject.

A subject was considered to have completed the study if he had completed the whole period of the study, including the last scheduled visit. The end of study (EOS) was defined as completion of the last scheduled visit (Day 197).

Figure 1. Graphical study design for study SB16-1001



EOS = End of Study; ET = Early Termination; EU = European Union; IP = Investigational Product; PD = Pharmacodynamic; PK = Pharmacokinetic; US = United States of America; ® = Randomisation

PK Data Analysis

The PK parameters listed in

Table **3** and Table 4 were calculated based on actual elapsed time in hours (6 decimal places) and non-compartmental analysis methods using Phoenix WinNonlin® version 8.1. If the actual time was missing, the nominal time could be substituted in order to calculate the PK parameters.

Missing concentrations were not imputed for calculating the PK parameters. The following rules on how to deal with BLQ values were applied when calculating the PK parameters:

- All BLQ values at pre-dose were treated as zero.
- Terminal BLQ values were disregarded.
- All other BLQ values were handled on a case-by-case manner and were documented in this report.

Table 3. Primary pharmacokinetic parameters

Parameter	Description
AUC_{inf}	AUC_{inf} was calculated as area under the concentration-time curve from time zero (pre-dose measurement) to the last quantifiable concentration (AUC_{last}) + last observed concentration (C_t)/terminal rate constant (λ_z) - AUC was determined by linear-up/log-down trapezoidal rule.
C_{max}	C_{max} was obtained directly from the concentration-time data.
AUC_{last} (only for FDA review)	AUC_{last} was determined by $\int_0^t C(t)dt$.

Table 4. Secondary pharmacokinetic parameters

Parameter	Description
AUC_{last} (only for EMA review)	AUC_{last} was determined by $\int_0^t C(t)dt$.
T_{max}	T_{max} was the time at which C_{max} was observed.
V_z/F	V_z/F was calculated as $(CL/F)/\lambda_z$.
λ_z	λ_z was estimated at terminal phase by linear regression after $\log_e$-transformation of the concentrations (Phoenix WinNonlin® best fit method): - Regression was repeated using the last three data points with non-zero concentrations, then the last four data points, last five data points, etc. - Data points prior to or at C_{max} were not to be included in the regression slope. - For each regression, an adjusted R^2 was computed: Adjusted $R^2 = 1 - \frac{(1-R^2)\times(n-1)}{(n-2)}$, when n was the number of data points in the regression and R^2 was the square of the correlation coefficient. - If the adjusted R^2 did not improve, but was within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of data points was used. - λ_z had to be positive. A visual check for each subject was performed to ensure adequacy of points selection. The adjusted R^2 had to be greater than 0.90. Any value less than 0.90 could be used at the PK Scientist's best knowledge and judgment and these values were reported in PK data review document.
$t_{1/2}$	$t_{1/2}$ was calculated by $\ln(2)/\lambda_z$.
CL/F	CL/F was calculated as dose/AUC_{inf}.
$\%AUC_{extrap}$	Percentage of AUC_{inf} due to extrapolation from T_{last} (time of last measurable concentration) to infinity: $\%AUC_{extrap}$ was calculated as $(1 - [AUC_{last}/AUC_{inf}]) \times 100$

When for a subject the $\%AUC_{extrap}$ was > 20% or there was no adequacy of points selection for λ_z, it was decided based on the PK data review document whether the AUC_{inf} and related PK parameters (CL/F and Vz/F) had to be excluded or not from all statistical analyses; if applicable, decision of exclusion was made in agreement with the Sponsor. But these PK parameters were included in the listing.

Descriptive statistics for calculated PK parameters included: n, mean, SD, CV%, SEM, geometric mean, geometric SD, geometric CV%, 90% CI of geometric mean, median, Min and Max values. T_{max} summary statistics included only the n, Min, median and Max.

PK parameters were listed by subject and summarised by treatment group.

The statistical analysis of the loge-transformed primary endpoint(s) was performed by the Analysis of Variance (ANOVA) model with treatment group as a fixed effect. The difference in least squares means (LSMeans) between SB16 and EU sourced Prolia, between SB16 and US sourced Prolia, or between EU sourced Prolia and US sourced Prolia and the corresponding 90% CIs were determined. Back transformation provided the ratio of geometric LSMeans and 90% CIs for these ratios.

Equivalence for the primary endpoint(s) was to be determined as follow:

- For the EMA review, equivalence for the primary endpoints (AUC_{inf} and C_{max}) are determined if 90% CI for the ratio of geometric LSMeans of SB16 to EU sourced Prolia is within the equivalence margin of 0.80 to 1.25.

ANOVA for the primary endpoint was repeated:

- By post-dose ADA status of subject
- With centre as a covariate

Study Participants

Inclusion Criteria

1. Healthy male, aged 28-55 years (inclusive) on the day of signing the informed consent.
2. Had a body weight between 60.0-95.0 kg (inclusive) and a body mass index (BMI) between 20.0-29.9 kg/m2 (inclusive) at Screening and Day -1.
3. Had 12-lead electrocardiogram (ECG) results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day -1.
4. Had vital sign results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day -1.
5. Had physical examination results without clinically significant abnormal findings confirmed by the Investigator at Screening and Day -1.
6. Male subjects who did not have surgical sterilisation had to be willing to abstain from sexual intercourse or willing to use a condom in addition to having their female partner use another form of contraception, such as an intra-uterine device, oral contraceptive, injectable progesterone, sub-dermal implant, or tubal ligation unless their partners were infertile (confirmed with written verifications) during the treatment period.
7. Had to be willing and able to comply with scheduled visits, treatment plan, clinical laboratory tests, and other study procedures including lifestyle considerations.
8. Had to be able to provide written informed consent, which was to be obtained prior to any study-related procedures being performed.
9. Had competence in speaking, writing, and comprehending the local language(s) where the study was conducted.

Exclusion Criteria

1. Had a history and/or current presence of clinically significant atopic allergy, hypersensitivity, or allergic reactions (either spontaneous or following drug administration), also including known or suspected clinically relevant drug hypersensitivity to denosumab or to any of the excipients.

2. Had a history of and/or current clinically significant gastrointestinal, renal, hepatic, cardiovascular, haematological, pulmonary, neurologic, metabolic, psychiatric disorder, drug or alcohol abuse, or allergic disease excluding mild asymptomatic seasonal allergies.
3. Had a history of bone disease or any medical condition that could have affected bone metabolism (including osteoporosis, osteogenesis imperfecta, osteomalacia, hyperparathyroidism, hyperthyroidism, hypothyroidism, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Paget's disease of the bone, and malabsorption syndrome).
4. Had a history of malignancy (including lymphoma, leukaemia, and skin cancer).
5. Had osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) or active periodontal disease within 180 days prior to Randomisation.
6. Had bone fractures within 180 days prior to Randomisation.
7. Had a history of serious infection (associated with hospitalisation and/or which required intravenous antibiotics) within 180 days prior to Randomisation.
8. Had a clinically significant active infection (bacterial, viral, or fungal) including skin infections within 28 days prior to Randomisation.
9. Had any systemic or local infection, a known risk for developing sepsis at Screening or Day -1.
10. Had known intolerance to calcium or vitamin D supplements.
11. Had previously been exposed to denosumab (Prolia/Xgeva) and its biosimilar.
12. Had previously been exposed to a monoclonal antibody or fusion protein within 270 days (other than denosumab) prior to Randomisation and/or there was confirmed evidence or clinical suspicion of immunogenicity from previous exposure to a monoclonal antibody or fusion protein.
13. Had previously been exposed to an immunosuppressive agent or biological agent (any other than a monoclonal antibody or fusion protein) within 120 days prior to Randomisation.
14. Had received live vaccine(s) within 30 days prior to Randomisation or who required live vaccine(s) during the study period.
15. Had a personal or family history of prolonged QT interval syndrome or Torsade de Pointes, or family history of sudden death.
16. Had any of the following abnormal laboratory test results at Screening or Day -1:
    a. Albumin-adjusted serum calcium levels below the lower limit of normal (LLN) or above the upper limit of normal (ULN).
    b. Serum creatinine levels above 1.5 × ULN.
17. Had a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) 1 or 2 at Screening.
18. Had a history of immunodeficiency.
19. Had surgery within 90 days prior to Randomisation, and/or planned to have an operation (including invasive dental procedure) during the study period.

20. Had a history and/or current presence of an illness (including, but not limited to respiratory symptoms [e.g., difficulty breathing or persistent cough] or low-grade fever) within 14 days prior to Randomisation that was classified as clinically significant by the Investigator.
21. Had smoked more than 10 cigarettes, 2 cigars, or 2 pipes per day within 90 days prior to Screening.
22. Had regular consumption of alcoholic beverages that exceeded 14 units per week (1 unit = 12 g of pure alcohol).
23. Had a positive urinary drug screening result or alcohol breath test result at Screening or Day -1.
24. Had taken any prescription medicines or over-the-counter medicines (except paracetamol) that might have had an effect on the objectives of the study in the opinion of the Investigator, within 30 days or 10 half-lives of the medication (whichever period was the longest) prior to Randomisation. This included medications such as, but not limited to: Bisphosphonates, parathyroid hormone, hormone replacement therapy, selective oestrogen receptor modulators, calcitonin, calcitriol, glucocorticoids, fluoride, strontium, or anabolic steroids.
25. Had donated > 100 mL blood or plasma within 28 days prior to Randomisation.
26. Had participated in another study with an investigational drug within 60 days prior to Randomisation or were currently participating in or intending to participate in another clinical study of an investigational drug before completion of all scheduled evaluation in this clinical study.
27. Subjects who, in the opinion of the Investigator, were not likely to complete the study for whatever reason (e.g., clinically significant medical condition).
28. Subject who was the Investigator or any sub-Investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the clinical study.
29. Vulnerable subjects (e.g., persons kept in detention).

Treatments

SB16, EU sourced Prolia, or US sourced Prolia was administered subcutaneously at a single dose of 60 mg as a pre-filled syringe (PFS) in the morning of Day 1.

IP was administered in the periumbilical area, except for the 5 cm area around the navel, while subjects were supine. The location of the injection had to be the left or right lower quadrant of the abdomen. The skin area were not to be tender, bruised, red, or hard. Area with scars or stretch marks had to be avoided. The actual area for injection was recorded in the source document and electronic case report form (eCRF). Subjects had to remain in a semi-supine or semi-recumbent position for at least 2 h post-dose.

Table 5. Investigational product description

Active Ingredient: Denosumab			
	Test	Reference	
	SB16	EU Sourced Prolia	US Sourced Prolia

Formulation	Solution for subcutaneous injection in PFS	Solution for subcutaneous injection in PFS	Solution for subcutaneous injection in PFS
Fill volume	1 mL/PFS	1 mL/PFS	1 mL/PFS
Active compound	60 mg of denosumab/PFS	60 mg of denosumab/PFS	60 mg of denosumab/PFS

Non-Investigational Products Administered

All subjects were provided calcium (at least 1000 mg) and vitamin D (at least 400 IU) daily during the treatment period. Administration of calcium and vitamin D was recommended from Screening.

Treatment Compliance

All IP administrations were completed by the Investigator or designee to ensure compliance.

Non-IP (calcium and vitamin D) compliance was checked and recorded in the source documents and eCRF during the treatment period.

If hypocalcaemia or hypercalcemia occurred, the Investigator could adjust the calcium and/or vitamin D dosage if needed. Also, the dose regimen for these non-IPs could be modified per the Investigator's discretion when intolerance to calcium and/or vitamin D was reported. In such cases, the change had to be recorded in the source document and eCRF.

Objectives and endpoints

Primary Objectives

The primary objective of this study was to demonstrate the pharmacokinetics (PK) similarity between SB16 and European Union (EU) sourced Prolia in healthy male subjects.

Secondary Objectives

The secondary objectives were to investigate and compare the pharmacodynamics (PD), safety, tolerability, and immunogenicity between SB16 and EU sourced Prolia in healthy male subjects.

Primary Pharmacokinetic Endpoints

- Area under the concentration-time curve from time zero to infinity (AUC_{inf})
- Maximum serum concentration (C_{max})

Secondary Endpoints

PK Endpoints

- AUC_{last} (for EMA review only)
- Time to reach C_{max} (T_{max})
- Apparent volume of distribution during the terminal phase (V_z/F)
- Terminal rate constant (λ_z)
- Terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F)

- Percentage of AUC_{inf} due to extrapolation from time of last measurable concentration (T_{last}) to infinity ($\%AUC_{extrap}$)

PD Endpoint

- Area under the effective curve from time zero to Day 197 ($AUEC_{0\text{-}D197}$) for C-telopeptide of type I collagen (CTX) percent inhibition

Safety Endpoints

- AEs and SAEs
- Clinical laboratory tests including haematology, chemistry, and urinalysis
- 12-lead ECG
- Vital signs
- Physical examination
- Injection site assessment

Immunogenicity Endpoints

- Incidence of anti-drug antibodies (ADAs) to denosumab
- Incidence of neutralising antibodies (NAbs) to denosumab

Blood samples for PK analysis were collected at 0 h (pre-dose), 12, 24, 48, 96, 144, 192, 240, 288, 336, 504, 672, 1008, 1344, 2016, 2688, 3360, 4032, and 4704 h post-dose.

Blood samples for PD analysis were collected in the morning hours after fasting for at least 8 h on Day -1, at 0 h (pre-dose), 24, 48, 96, 144, 192, 336, 672, 1344, 2016, 3360, 4032, and 4704 h post-dose.

Blood samples for immunogenicity analysis were collected at 0 h (pre-dose), 336, 672, 2016, 3360, and 4704 h post-dose.

Pre-dose blood samples for PK, PD, and immunogenicity analyses were collected within 60 min prior to IP administration.

Sample size

Sample size was based on an inter-subject CV% of 35.14%, which was reported in the previously published data. With the sample size of 50 in each of the 3 treatment arms (and the total sample size of 150), a parallel study design would have had 80% power, assuming a true geometric mean ratio of 1.05, to be able to reject both the null hypotheses that 1) the true geometric mean ratio of the test to the reference was less than 0.80 and 2) the true geometric mean ratio of test to the reference was greater than 1.25, where both of these null hypotheses could be rejected simultaneously if the 90% CIs for the true geometric mean ratio lay completely between 0.80 and 1.25. Assuming a 10% drop-out rate, a total of about 168 subjects (56 in each arm) were randomised.

Randomisation

A screening number was assigned to the subjects sequentially after signing the informed consent form (ICF) and prior to any screening procedure. Each screening number was assigned to only one subject and was not re-used.

On Day 1, subjects who fulfilled all the inclusion criteria and met none of the exclusion criteria were randomised by the Investigator and assigned to one of the 3 treatment groups according to the randomisation lists generated by an independent statistician using SAS® software. All randomised subjects had a unique 4-digit randomisation number to keep the assigned treatment group blinded. Randomisation numbers were not re-used once assigned. In order to have treatment balance within each centre, the randomisation number was assigned as following rule for each centre: For subjects at French site, randomisation numbers were assigned from the beginning of the randomisation list starting from 1001 then 1002, etc., and for subjects at US 1st site, the numbers were assigned from the end of the randomisation list starting from 1168 then 1167, etc. Moreover, subjects randomised at US 2nd site were assigned randomisation numbers starting from 3001, then 3002, etc.

Blinding

A double-blind technique was used. The subject, the Investigator, the site staff, the Sponsor, and other study personnel who were involved in the treatment or clinical evaluation of subjects were unaware of the treatment group assignments.

The IP (SB16 and Prolia) PFS were packaged and labelled identically to ensure the blinding of the treatment group assignment.

Randomisation code/disclosure envelopes had to be received by the designated staff at the clinical study site and kept in a secured location where only the Investigator and delegate(s) had access. The randomisation code/disclosure envelopes were to be opened only in the event of emergency when the information could have influenced medical care.

Statistical methods

An interim safety analysis was performed to show the preliminary safety profiles of healthy subjects by an unblinded statistical reporting team at French site, as described in the interim safety analysis SAP. The safety analysis was based on the cut-off data on Nov 15, 2020 which included 17 subjects that received single dose of SB16, EU sourced Prolia, or US sourced Prolia during the study period. The data included AE and clinical laboratory results for all subjects who completed IP administration at that time. The results did not show any early safety signal in subjects exposed to any of the IPs.

The statistical analysis of the $\log_e$-transformed primary endpoint(s) was performed by the Analysis of Variance (ANOVA) model with treatment group as a fixed effect. The difference in least squares means (LSMeans) between SB16 and EU sourced Prolia, between SB16 and US sourced Prolia, or between EU sourced Prolia and US sourced Prolia and the corresponding 90% CIs was determined. Back transformation provided the ratio of geometric LSMeans and 90% CIs for these ratios.

Randomisation was stratified by centre or region, but centre or region was not included in the analysis as covariate or stratification variable as recommended in the Guideline on adjustment for baseline covariates in clinical trials.

Equivalence for the primary endpoint(s) for the EMA review were determined as follows: equivalence for the primary endpoints (AUC_{inf} and C_{max}) was to be determined if 90% CI for the ratio of geometric LSMeans of SB16 to EU sourced Prolia is within the equivalence margin of 0.80 to 1.25.

Conduct of study

Recruitment

Study initiation date: Oct 21, 2020 (first subject signed informed consent)

Study completion date: Nov 09, 2022 (last subject last visit)

Database lock: Dec 21, 2022

This study was conducted by multiple Investigators at multiple centres internationally (i.e., 1 centre in France and 2 centres in the US).

Amendments

Four global amendments and one country-specific amendment were made to the original protocol (version 1.0, dated Jun 10, 2020).

The key features of each amendment are as follows:

Global protocol amendment 1 (version 2.0): Aug 19, 2020

Clarification was made to address the prohibited period for invasive dental procedure in Section 4.4.5 of the protocol according to ANSM's feedback.

Global protocol amendment 2 (version 3.0): Dec 17, 2020

Removal of 4 ambulatory visits was implemented to minimise the risk of subject exposure to COVID-19 during ambulatory visit in pandemic and recommendation was added to intake non-IP from screening to prevent hypocalcaemia (contraindication of Prolia). Accordingly, changes were to synopsis, Table 1, Section 3.1, Section 5.1.1, Section 5.3, Section 7.1 of the protocol.

Global protocol amendment 3 (version 4.0): Feb 10, 2021

US site information was added to reflect new clinical study site in synopsis and list of study staff of the protocol.

Global protocol amendment 3.1 (version 4.1): Jun 07, 2021

This amendment was released to the US only to update blood volume required for new US safety lab in Appendix II of the protocol.

Global protocol amendment 4 (version 5.0): Oct 19, 2021

Modifications were made to include 90.0-95.0 kg subjects (inclusion criterion 2) and to exclude subjects who had not only CS lab abnormality but also CS medical condition assessed by the Investigator (exclusion criterion 27).

Participant flow and numbers analysed

A total of 438 subjects were screened of whom 168 subjects were randomised. The most common reason for screening failure was failure to meet eligibility criteria. Of the subjects who were randomised, 160 completed the study and 8 subjects discontinued the study (i.e., 3 subjects withdrew consent for further participation, 2 subjects discontinued due to protocol deviation, 2 subjects were lost to follow-up, 1 subject died). None of the subjects, other than the subject who committed suicide, discontinued the study due to TEAEs.

Table 6. Disposition of subjects (enrolled set)

Treatment	SB16	EU sourced Prolia	US sourced Prolia	Total
Number (%) of subjects	n (%)	n (%)	n (%)	n (%)

Screened				438
Screening failures				270
Reasons for screening failure				
Failure to meet eligibility criteria				235 (87.0)
Consent withdrawal				27 (10.0)
Other				8 (3.0)
Randomised	56 (100.0)	56 (100.0)	56 (100.0)	168 (100.0)
Completed	53 (94.6)	52 (92.9)	55 (98.2)	160 (95.2)
Withdrew before completion	3 (5.4)	4 (7.1)	1 (1.8)	8 (4.8)
Primary reasons for withdrawal				
Withdrawal by subject	0 (0.0)	2 (3.6)	1 (1.8)	3 (1.8)
Protocol deviation	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.2)
Lost to follow-up	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.2)
Death	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)
Related to COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n = number of subjects within assessment category Percentages were based on the number of randomised subjects. Percentages of screening failure reasons were based on number of screening failures.

The number of subjects in each of the analysis sets are summarised by treatment group in Table 7. A total of 168 subjects were randomised in this study all of whom were included in the SAF. Two subjects with a major protocol deviation were not included in the PKS (1 subject in the SB16 treatment group and 1 subject in the EU sourced Prolia treatment group).

Table 7. Datasets analysed (randomised set)

Treatment	SB16	EU sourced Prolia	US sourced Prolia	Total
Number (%) of subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Randomised Set	56 (100.0)	56 (100.0)	56 (100.0)	168 (100.0)
Safety Set	56 (100.0)	56 (100.0)	56 (100.0)	168 (100.0)
PK Analysis Set	55 (98.2)	55 (98.2)	56 (100.0)	166 (98.8)
PD Analysis Set	55 (98.2)	55 (98.2)	56 (100.0)	166 (98.8)

n = number of subjects within assessment category; PK = Pharmacokinetic; PD = Pharmacodynamic Percentages were based on the number of subjects in the Randomised Set.

Protocol deviations

Table 8. Summary of protocol deviations by treatment group (randomised set)

Treatment	SB16 N=56	EU sourced Prolia N=56	US sourced Prolia N=56	Total N=168
Number (%) of subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any protocol deviations	40 (71.4)	43 (76.8)	32 (57.1)	115 (68.5)
Related to COVID-19	5 (8.9)	1 (1.8)	2 (3.6)	8 (4.8)
With at least one major protocol deviation	5 (8.9)	8 (14.3)	5 (8.9)	18 (10.7)
Excluded from PK Analysis Set	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.2)
Exclusion criteria	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.2)

- Subject has any of the following abnormal laboratory test results at screening or day -1: albumin-adjusted serum calcium levels below the LLN or above the ULN, serum creatinine levels above 1.5 x ULN, any other laboratory abnormalities assessed as clinically significant by the investigator	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)
- Subject has any of the following abnormal laboratory test results at screening or day -1: albumin-adjusted serum calcium levels below the LLN or above the ULN, serum creatinine levels above 1.5 x ULN	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.6)
Not excluded from PK Analysis Set	4 (7.1)	7 (12.5)	5 (8.9)	16 (9.5)
Other	4 (7.1)	7 (12.5)	5 (8.9)	16 (9.5)
- Other major GCP non-compliances which might impact on data integrity or subject safety	4 (7.1)	7 (12.5)	5 (8.9)	16 (9.5)
With at least one minor protocol deviation	37 (66.1)	39 (69.6)	31 (55.4)	107 (63.7)
Study procedures criteria	37 (66.1)	39 (69.6)	31 (55.4)	107 (63.7)
- Blood sample for PK analysis is not taken, or taken outside the allowed time window	20 (35.7)	18 (32.1)	15 (26.8)	53 (31.5)
- Physical examination assessment is not done, or assessed outside the allowed time window	18 (32.1)	19 (33.9)	20 (35.7)	57 (33.9)
- Blood sample for pharmacodynamic analysis is not taken, or taken outside the allowed time window	16 (28.6)	15 (26.8)	12 (21.4)	43 (25.6)
- Vital signs assessment is not done, or assessed outside the allowed time window	15 (26.8)	16 (28.6)	13 (23.2)	44 (26.2)
- Blood/urine sample for safety laboratory assessment is not taken, or taken outside the allowed time window	13 (23.2)	14 (25.0)	12 (21.4)	39 (23.2)
- Blood sample for immunogenicity analysis is not taken, or taken outside the allowed time window	11 (19.6)	10 (17.9)	10 (17.9)	31 (18.5)
- Blood sample for pharmacodynamic analysis is not collected in the morning	9 (16.1)	9 (16.1)	8 (14.3)	26 (15.5)
- 12-lead ECG is not done, or assessed outside the allowed time window	8 (14.3)	4 (7.1)	7 (12.5)	19 (11.3)
- Fasting conditions not respected for laboratory and/or pharmacodynamic sampling.	8 (14.3)	9 (16.1)	8 (14.3)	25 (14.9)
- Subject who did not comply to activity restrictions	6 (10.7)	3 (5.4)	6 (10.7)	15 (8.9)
- Visit not done	5 (8.9)	5 (8.9)	6 (10.7)	16 (9.5)
- Injection site assessment is not done, or assessed outside the allowed time window	2 (3.6)	7 (12.5)	3 (5.4)	12 (7.1)
- Invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.6)
- Subject who did not comply to alcohol consumption restrictions	1 (1.8)	3 (5.4)	1 (1.8)	5 (3.0)
- Non-IP compliance check not done by medical staff during visit	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.6)

- Subject who did not comply to smoking restrictions	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.6)

N = number of subjects in the Randomised Set; n = number of subjects within assessment category; PK = pharmacokinetic; LLN = lower limit of normal; ULN = upper limit of normal. Percentages were based on the number of subjects in the Randomised Set.

A total of 18 (10.7%) subjects had major protocol deviations reported. Among them, 2 (1.2%) subjects failed to meet the exclusion criterion 16, leading to subject discontinuation, and they were excluded from the PKS. The most frequently reported major protocol deviation was other major GCP non-compliance which might impact on data integrity or subject safety (i.e., ICF re-consent was not obtained at the earliest next visit after effective date of the revised informed consent obtained, if any). However, those subjects were not excluded from the PKS as per protocol deviation definition list, as this deviation was likely not to have an impact on PK analysis. Therefore, this does not raise further concerns.

Demographic and other baseline characteristics

The demographic characteristics for the RAN are summarised in Table 9. Demographic and other baseline characteristics were generally comparable among the treatment groups.

Table 9. Demographic characteristics (Randomised set)

Characteristics	SB16 N=56	EU sourced Prolia N=56	US sourced Prolia N=56	Total N=168
Age (years)				
Mean	39.1	40.2	40.8	40.0
SD	7.71	8.13	7.88	7.89
Median	39.5	40.5	41.0	41.0
Min	28	28	28	28
Max	55	55	55	55
Gender, n (%)				
Male	56 (100.0)	56 (100.0)	56 (100.0)	168 (100.0)
Race, n (%)				
White	38 (67.9)	36 (64.3)	41 (73.2)	115 (68.5)
Black or African American	17 (30.4)	17 (30.4)	12 (21.4)	46 (27.4)
Asian	1 (1.8)	3 (5.4)	3 (5.4)	7 (4.2)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic or Latino	10 (17.9)	9 (16.1)	4 (7.1)	23 (13.7)
Not Hispanic or Latino	46 (82.1)	47 (83.9)	52 (92.9)	145 (86.3)
Country, n (%)				
France	30 (53.6)	30 (53.6)	30 (53.6)	90 (53.6)
United States of America	26 (46.4)	26 (46.4)	26 (46.4)	78 (46.4)
Height (cm)				

Mean	176.3	175.6	176.8	176.3
SD	6.63	6.07	7.01	6.56
Median	175.0	175.0	176.5	176.0
Min	165	163	163	163
Max	197	193	193	197
Weight (kg)				
Mean	80.84	77.56	79.54	79.31
SD	7.614	8.502	7.524	7.961
Median	83.05	76.05	81.10	79.65
Min	63.7	60.5	62.2	60.5
Max	94.7	92.8	94.6	94.7
BMI (kg/m²)				
Mean	26.04	25.14	25.48	25.55
SD	2.471	2.315	2.443	2.425
Median	26.55	24.85	25.50	25.75
Min	21.2	21.0	20.5	20.5
Max	29.9	29.5	29.8	29.9

N = number of subjects in the Randomised Set; n = number of subjects within assessment category; SD = standard deviation; Min = minimum; Max = maximum; BMI = body mass index. Percentages were based on the number of subjects in the Randomised Set. Height (cm) at Screening, Weight (kg) on Day -1, and BMI (kg/m^2) on Day -1 were summarised.

The subjects' medical and surgical history are available. There was no medical history that might have interfered with the objectives of the study. Baseline characteristics (i.e., smoking habits and alcohol consumption) are balanced between treatment arms. All of the subjects tested negative for HBsAg, anti-HCV antibody, anti-HIV 1 and 2 antibody, urine drug screening, and alcohol breath test. Statistics of demographic characteristics by centre and treatment group is similar.

Outcomes

Primary PK endpoints

The geometric LSMean ratio (90% CI) for SB16 and EU sourced Prolia in AUC_{inf}, C_{max}, and AUC_{last} were 1.01 (0.93 to 1.10), 1.02 (0.95 to 1.10), and 1.02 (0.94 to 1.12), respectively, which were within the pre-defined equivalence margin of 0.80 to 1.25 (Table 10).

Table 10. Statistical comparison of primary pharmacokinetic parameters between SB16 and EU-sourced Prolia (pharmacokinetic analysis set)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (h·µg/mL)	SB16	55	55	6403.1	1.01	[0.93, 1.10]
	EU sourced Prolia	55	52	6340.5		
C_{max} (µg/mL)	SB16	55	55	5.651	1.02	[0.95, 1.10]
	EU sourced Prolia	55	54	5.541		
AUC_{last} (h·µg/mL)	SB16	55	55	6292.4	1.02	[0.94, 1.12]
	EU sourced Prolia	55	54	6156.2		

N = number of subjects in PK Analysis Set; n = number of subjects in the analysis; A = SB16; B = EU sourced Prolia; PK = pharmacokinetic; Geo-LSMean = geometric least squares mean; CI = confidence interval

One subject in the EU sourced Prolia was excluded from ANOVA on primary PK parameters due to incomplete PK profile. Two subjects in the EU sourced Prolia were excluded from ANOVA on AUC_{inf} due to incomplete PK profiles.

Comparison between SB16 and US sourced Prolia

The geometric LSMean ratio (90% CI) for SB16 and US sourced Prolia in AUC_{inf}, C_{max}, and AUC_{last} were 0.99 (0.91 to 1.08), 1.07 (0.99 to 1.15), and 1.01 (0.92 to 1.10), respectively, which were within the pre-defined equivalence margin of 0.80 to 1.25 (Table 11).

Table 11. Statistical comparison of primary pharmacokinetic parameters between SB16 and U- sourced Prolia (pharmacokinetic Analysis set)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (h·µg/mL)	SB16	55	55	6403.1	0.99	[0.91, 1.08]
	US sourced Prolia	56	55	6484.8		
C_{max} (µg/mL)	SB16	55	55	5.651	1.07	[0.99, 1.15]
	US sourced Prolia	56	56	5.305		
AUC_{last} (h·µg/mL)	SB16	55	55	6292.4	1.01	[0.92, 1.10]
	US sourced Prolia	56	56	6259.1		

N = number of subjects in PK Analysis Set; n = number of subjects in the analysis; A = SB16; B = US sourced Prolia; PK = pharmacokinetic; Geo-LSMean = geometric least squares mean; CI = confidence interval

One subject in the US sourced Prolia was excluded from ANOVA on AUC_{inf} due to incomplete PK profile.

Comparison between EU sourced Prolia and US sourced Prolia

The geometric LSMean ratio (90% CI) for EU sourced Prolia and US sourced Prolia in AUC_{inf}, C_{max}, and AUC_{last} were 0.98 (0.89 to 1.07), 1.04 (0.97 to 1.13), and 0.98 (0.89 to 1.08), respectively, which were within the pre-defined equivalence margin of 0.80 to 1.25 (Table 12).

Table 12. Statistical comparison of primary pharmacokinetic parameters between EU sourced Prolia and US-sourced Prolia (pharmacokinetic analysis set)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (h·µg/mL)	EU sourced Prolia	55	52	6340.5	0.98	[0.89. 1.07]
	US sourced Prolia	56	55	6484.8		
C_{max} (µg/mL)	EU sourced Prolia	55	54	5.541	1.04	[0.97, 1.13]
	US sourced Prolia	56	56	5.305		
AUC_{last} (h·µg/mL)	EU sourced Prolia	55	54	6156.2	0.98	[0.89, 1.08]
	US sourced Prolia	56	56	6259.1		

N = number of subjects in PK Analysis Set; n = number of subjects in the analysis; A = EU sourced Prolia; B = US sourced Prolia; PK = pharmacokinetic; Geo-LSMean = geometric least squares mean; CI = confidence interval

One subject in the EU sourced Prolia was excluded from ANOVA on primary PK parameters due to incomplete PK profile. Three subjects (2 subjects in the EU sourced Prolia and 1 subject in the US sourced Prolia) were excluded from ANOVA on AUC_{inf} due to incomplete PK profiles.

Serum Denosumab Concentrations

Three subjects (2 subjects in the SB16 and 1 subject in the US sourced Prolia) had unexpected embedded BLQ values (BLQ value between 2 quantifiable concentrations) and these BLQ values were considered as missing as they occurred after the expected individual C_{max}.

The mean serum concentration vs nominal time curves on linear and semi-logarithmic scale for the PKS are presented in Figure 3, Figure **4** and Figure 5 for pairwise comparisons of SB16 and EU sourced Prolia, SB16 and US sourced Prolia, and EU sourced Prolia and US sourced Prolia, respectively.

Figure 2. Mean (± SD) serum Concentrations versus nominal times on linear (top) and semilogarithmic scale (bottom) of SB16 and EU-sourced Prolia

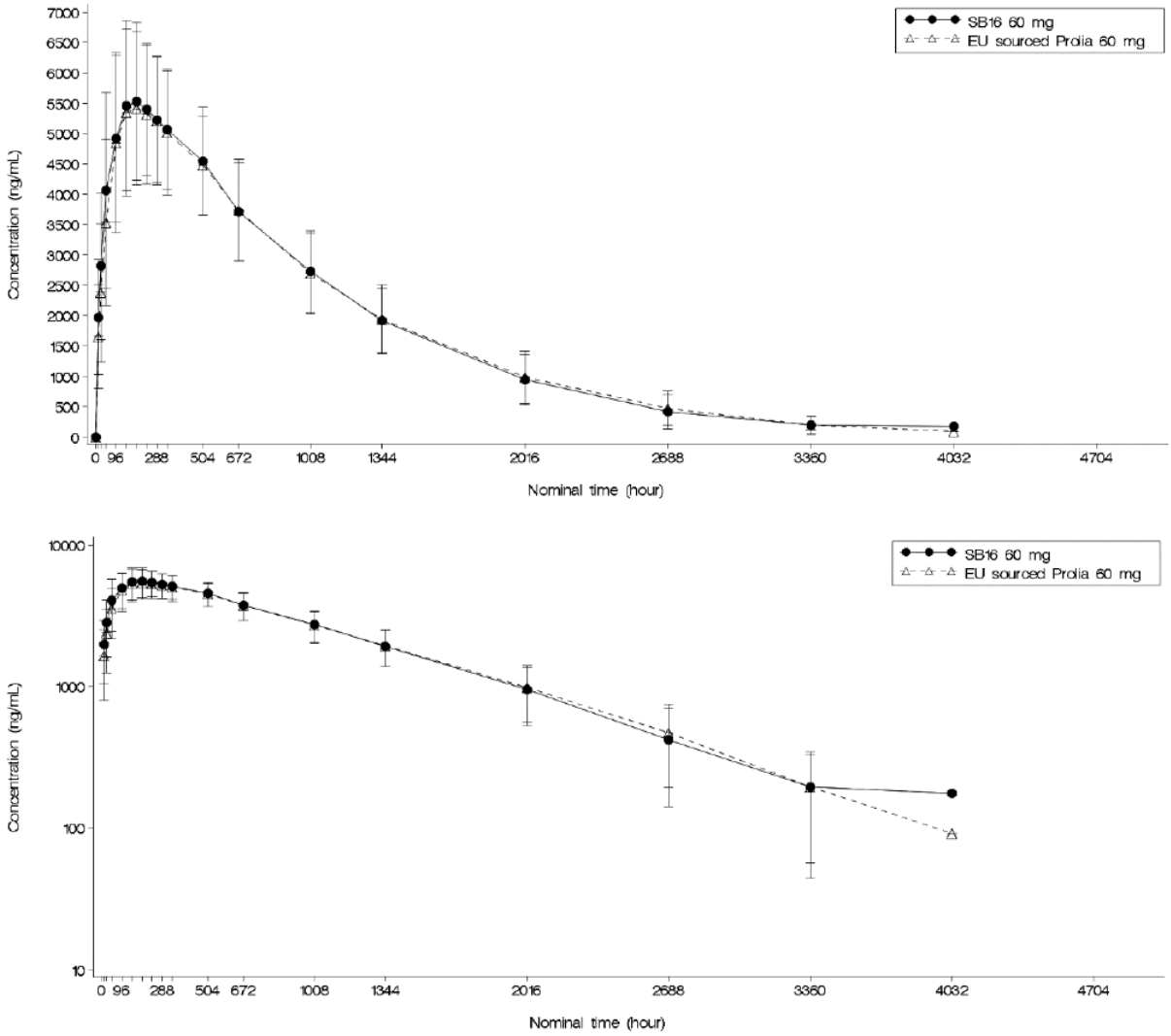


Figure 3. Mean (± SD) Serum concentrations versus nominal times on linear (top) and semilogarithmic scale (bottom) of SB16 and US-sourced Prolia

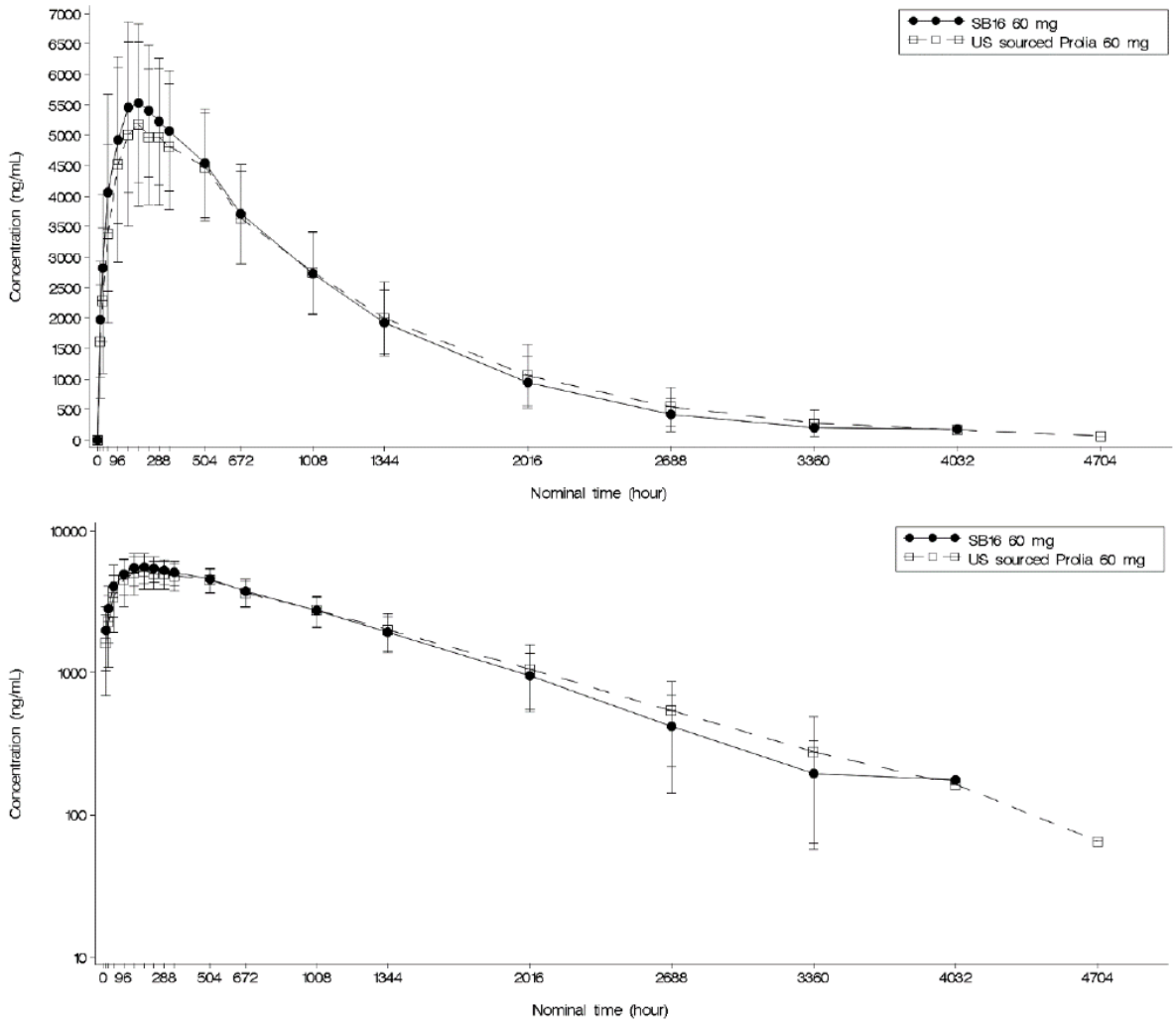
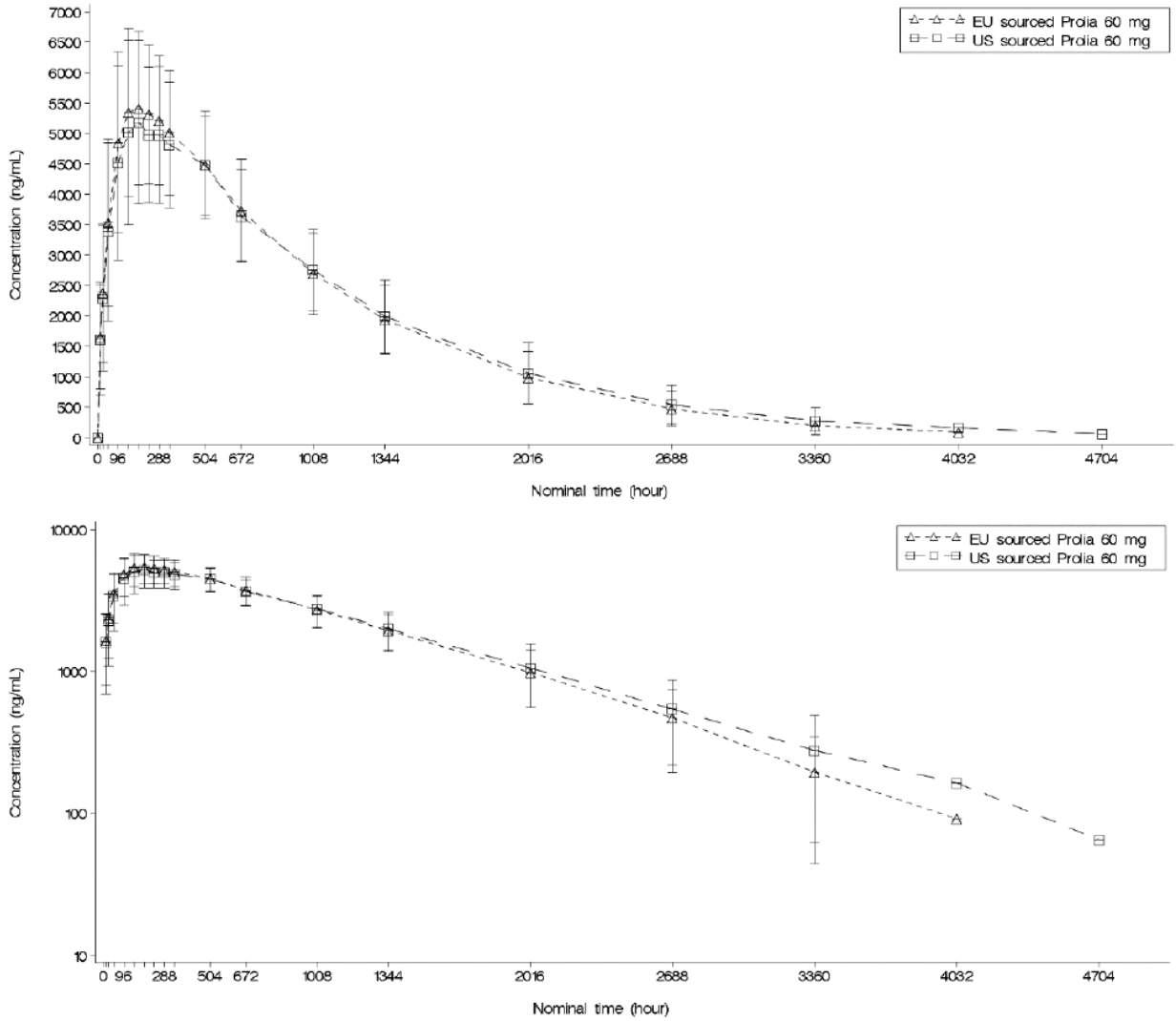


Figure 4. Mean (± SD) serum concentrations versus nominal times on linear (top) and semilogarithmic scale (bottom) of EU-sourced Prolia and US-sourced Prolia



Study SB16-3001

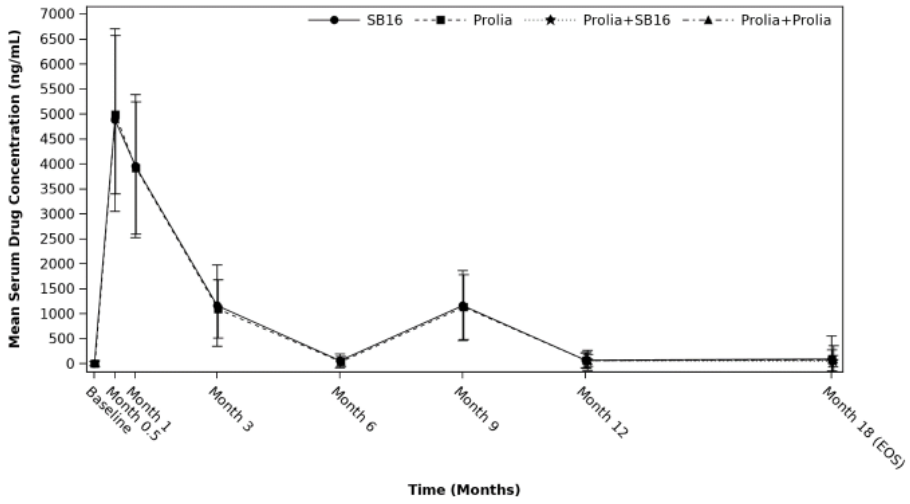
SB16-3001 was a randomised, double-blind, multicentre phase III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of SB16 and EU-authorised Prolia.

The design, methods and efficacy results of study SB16-3001 are presented in the Clinical Efficacy section. The PK results of this study are presented below.

Pharmacokinetics Results

The mean (± SD) serum concentration-time profiles by treatment group for the PKS are presented in the figure below.

Figure 5. Arithmetic mean (± SD) serum drug concentration profiles in overall study period (pharmacokinetic analysis set)



2.5.2.2. Pharmacodynamics

Analytical Methods

PD assays CTX-1

The assay to quantify C-telopeptide of Type 1 Collagen in human serum from HV and patients with PMO was validated in line with guideline EMEA/CHMP/EWP/192217/2009 on bioanalytical method validation. All validation parameters passed the acceptance criteria. However, PMO serum has not been used for validation of parameters accuracy/precision and effect of haemolytic/lipemic serum.

Taken together, the assay for quantification of CTX-I is considered suitable for its intended use. Performance of the assay during clinical studies SB16-1001 and SB16-3001 is considered acceptable.

PD assays P1NP

The assay to quantify Procollagen Type 1 N-terminal Propeptide in human serum from HV and patients with PMO was validated in line with guideline EMEA/CHMP/EWP/192217/2009 on bioanalytical method validation. All validation parameters passed the acceptance criteria. However, PMO serum has not been used for validation of parameters accuracy/precision and effect of haemolytic/lipemic serum.

Taken together, the assay for quantification of P1NP is considered suitable for its intended use. Performance of the assay during clinical study SB16-3001 is considered acceptable.

Mechanism of action

Denosumab is a human Immunoglobulin G2 (IgG2) monoclonal antibody with affinity and specificity for RANKL. By preventing RANKL from activating RANK, its receptor on the osteoclast precursors and osteoclasts, denosumab inhibits osteoclast formation, function and survival. With respect to the MoA in each condition of use, all indications approved for Prolia are based on the same MoA as related to the common pathogenesis of all indications. Blocking RANKL-RANK activity on osteoclasts is also effective against bone loss associated with bone metastases and skeletal-related events (SREs) in solid tumour, prostate cancer or breast cancer. In addition, the inhibition of RANKL-RANK has shown clinical efficacy in giant cell tumours. Giant cell tumours express RANK where neoplastic stromal cells express RANKL. By binding to RANKL and inhibiting the activation of RANK expressed on osteoclast-like giant cells,

denosumab significantly reduces stimulation of osteoclast-like giant cells, and thus, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

All indications approved for Xgeva/Prolia (denosumab) are based on the same MoA as related to the common pathogenesis of all indications approved for Xgeva/Prolia (denosumab).

Primary and Secondary pharmacology

Study SB16-1001

For a detailed description of the design of study SB16-1001, please refer to Section 2.5.2.1. Pharmacokinetics. Only PD specific aspects are provided below.

PD Endpoint

• Area under the effective curve from time zero to Day 197 ($AUEC_{0\text{-}D197}$) for C-telopeptide of type I collagen (CTX) percent inhibition

PD Analysis

Table 13. Pharmacodynamic parameters

Parameter	Description
I_{max} (%inhibition)	Maximum percent inhibition (I_{max}) was the maximum CTX percent inhibition (PI), calculated as (CTX at baseline – CTX at each timepoint)/CTX at baseline × 100, from time zero (pre-dose measurement) to Day 197/ET. In case of fasting/morning hour restriction not respected, PI was excluded from the I_{max} calculation.
$AUEC_{0\text{-}D197}$ (%inhibition·h)	AUEC was calculated as area under the curve CTX PI from time zero (pre-dose measurement) to Day 197 and calculated using the linear trapezoidal summation based on actual elapsed time in hours (6 decimal places): $AUEC_{0\text{-}D197} = \sum_{ii=aa}^{bb-1}\{0.5 \times (tt_{ii+1} - tt_{ii}) \times (YY_{ii} + YY_{ii+1})\}$, where YY_{ii} was the CTX PI at Day i, tt_{ii} was the actual elapsed time Day i, aa was the baseline timepoint, and bb was the last available timepoint up to Day 197 or ET. If the actual time was missing, the nominal time could be substituted in order to calculate the AUEC. In case of the rebound effect, the area where PI was negative was substituted while AUEC calculation. In case of missing value or fasting/morning hour restriction not respected, it was excluded and the AUEC calculation was done with the timepoint before and the timepoint after.

The following descriptive statistics were presented at each nominal time point: n, mean, SD, SEM, median, Min, first quartile (Q1), third quartile (Q3), and Max values. No descriptive statistics were calculated in case of very few observations (n < 3).

CTX data were listed with original number of digits in the original unit (ng/mL) by subject including percent change from baseline.

The median CTX (Interquartile Range [IQR]) over nominal time was plotted by treatment group on a linear scale [4]. The arithmetic median (IQR) CTX percent change from baseline over nominal time was also plotted by treatment group on a linear scale.

In case of fasting/morning hour restriction not respected, value was excluded from all tables and figures but included in the listing.

The rules for handling BLQ and missing values

The BLQ terminal complement activities were imputed as follows for the descriptive statistics and plots: Values BLQ '< xxx' were set to 'xxx'. However, the original values of '< xxx' were presented as they were recorded for the listings.

Missing values were ignored when calculating descriptive statistics. All BLQ values or missing data were labelled as such in the CTX data listings.

PD Results

The serum CTX concentrations and change from baseline are summarised by nominal timepoint and treatment group.

The arithmetic median serum CTX percent change from baseline versus nominal time curves on linear scale for the PDS are presented for pairwise comparisons of all study treatment groups in Figure 6 (for comparison of SB16 and EU sourced Prolia), Figure 7 (for comparison of SB16 and US sourced Prolia), and Figure 8(for comparison of EU sourced Prolia and US sourced Prolia).

Figure 6. Percent change from baseline in median (IQR) serum CTX versus nominal times on linear scale of SB16 and EU-sourced Prolia

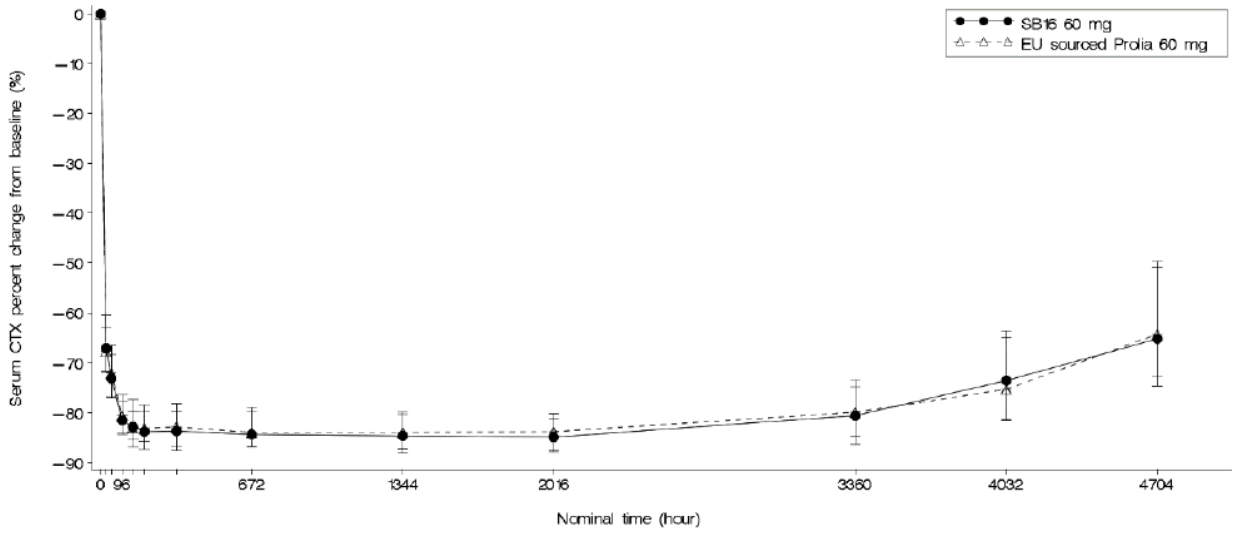


Figure 7. Percent change from baseline in median (IQR) serum CTX versus nominal times on linear scale of SB16 and US-sourced Prolia

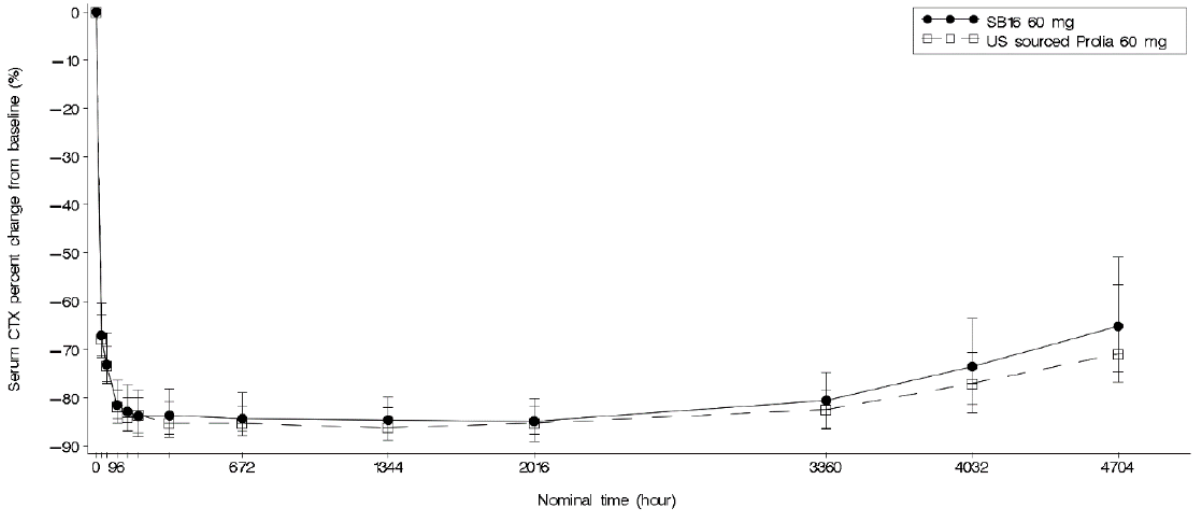
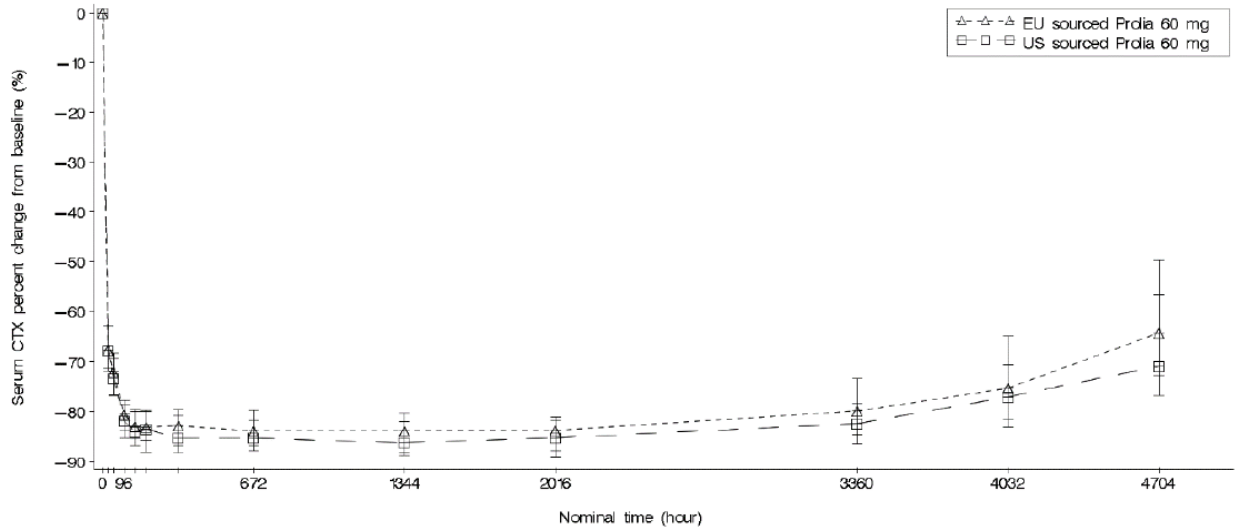


Figure 8. Percent change from baseline in median (IQR) serum CTX versus nominal times on linear scale of EU-sourced Prolia and US-sourced Prolia



The PD parameters for all treatment groups are presented for the PDS in the table below.

Table 14. Summary of pharmacodynamic parameters by treatment group (pharmacodynamic analysis set)

PD Parameter	Statistics	SB16 N=55	EU sourced Prolia N=55	US sourced Prolia N=56
I_{max}	n	55	55	56
(% inhibition)	Mean	84.48	84.91	86.24
	SD	5.890	4.917	4.320
	Median	86.49	85.02	86.41
	Q1, Q3	80.63, 89.09	82.54, 88.26	82.90, 89.25
	Min, Max	66.9, 94.2	70.9, 95.0	73.1, 93.8
$AUEC_{0\text{-}D197}$	N	55	55	56
(% inhibition·h)	Mean	352205.95	348254.45	374823.13
	SD	64662.676	79232.448	50370.744

Median	366317.92	368177.63	379301.88
Q1, Q3	327500.02, 389944.66	335421.26, 389920.30	361747.36, 405978.04
Min, Max	27810.5, 419497.6	5822.4, 418052.8	85959.8, 430719.9

N = number of subjects in the PD Analysis Set; n = number of subjects for the assessment parameter; PD = pharmacodynamic; I_{max} = maximum percent inhibition; $AUEC_{0\text{-}D197}$ = area under the effect curve from time zero to Day 197; SD = standard deviation; Q1 = first quartile; Q3 = third quartile; Min = minimum; Max = maximum

Study SB16-3001

Pharmacodynamic data analysis

The PD analysis was performed for the PDS. All PD assessment data were reported and analysed with the same precision as the source regardless of how many significant figures or decimals the data carried. Values of serum CTX and P1NP concentration outside the quantification range were imputed as for the descriptive statistics: values with '< xxx' were set to 'xxx', where xxx was lower limit of quantification (LLOQ). However, for the listing, the original values of '< xxx' were presented as recorded.

Blood sample collection compliance was confirmed during protocol deviation review. In the case of a major protocol deviation, PD assessment data collected during the affected treatment period was excluded from summary statistics but was included in listing and individual serum CTX and P1NP concentrations figure. If the serum CTX and/or P1NP concentration results at ET visit were not mapped to the analysis visit, they were listed only.

Pharmacodynamic Parameters

The geometric mean of area under the effect curve (AUEC) from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX concentration will be analysed by main treatment group using ANOVA on the log-transformed $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX concentration with the main treatment group as a fixed effect. The ratio of least-squares geometric mean (SB16 vs. Prolia) will also be presented with corresponding 90% CI.

The $AUEC_{0\text{-}M6}$ will be calculated using the trapezoidal rule, including serum CTX concentration at Month 0, 0.5, 1, 3, and 6. Actual study day of serum CTX sample collection should be used. Subjects who have serum CTX concentration available for analysis at Month 0, 0.5, 1, 3, and 6 will be included in the calculation of AUEC.

AUEC will be calculated as:

$$\Sigma\{0.5\times(Yib-1i=a+Yi+1)\times(ti+1-ti)\}$$

where Yi is the percent change from baseline in serum CTX concentration at visit i, t is the time at the specified visit i (the actual date and time of serum CTX sample collection for post-baseline visit; the actual date and time of first IP administration at Month 0 for baseline visit), a is the baseline assessment, and b is the last assessment up to Month 6. If AUEC yield a negative value, the absolute value of AUEC will be used in summary and further analysis.

Serum CTX concentration is expected to decrease after IP administration. After reaching maximum reduction, the reduction effect of serum CTX will gradually diminish, may become zero, or even increase from baseline. If change from baseline in serum CTX concentration at Month 6 is positive value, the $AUEC_{0\text{-}M6}$ will be calculated from baseline up to the time where percent change from baseline equals zero. Upon the first measurement of CTX value increase from baseline, Yi' and ti' at the time when percent change equals zero can be calculated based on

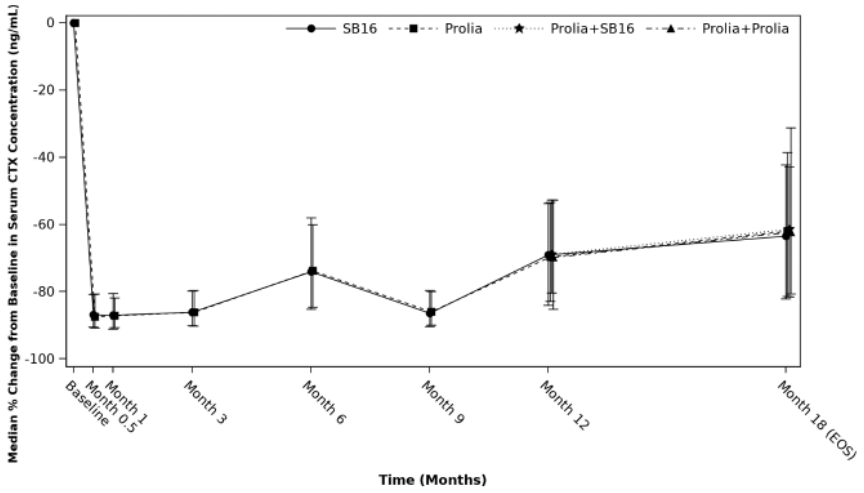
linear equation, $ti' = Yiti-1-Yi-1tiYi-Yi-1$, $Yi' = 0$. $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}ti'}$. Considering this rebound effect, the net $AUEC_{0\text{-}M6}$ will be provided for listing. If the rebound is seen, the net $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}ti'}$ minus $AUEC_{ti'\text{-}M6}$. Otherwise, net $AUEC_{0\text{-}M6}$ equals $AUEC_{0\text{-}M6}$.

Pharmacodynamic results

Serum CTX Concentrations

The median percent change from baseline in serum CTX concentrations for the PDS are presented in the figure below.

Figure 9. Median percent change from baseline in serum CTX concentration profiles in overall study period (pharmacodynamic analysis set)



% Change = [(value – baseline) ÷ baseline] × 100; CTX = c-telopeptide of type I collagen; EOS = end of study

The symbol and error bar represented median percent change and interquartile range at each timepoint.

Below the limit of quantitation concentrations were set to lower limit of quantitation. The lower limit of quantitation is 0.043 ng/mL.

$AUEC_{0\text{-}M6}$ of Percent Change from Baseline in Serum CTX Concentration

The analysis of the $AUEC_{0\text{-}M6}$ in percent change from baseline in serum CTX concentration is provided in the table below.

Table 15. Analysis of $AUEC_{0\text{-}M6}$ (day × % inhibition) in percent change from baseline in serum CTX concentration by main treatment group (pharmacodynamic analysis set)

			Geo. LSmean Ratio (SB16 vs Prolia)	
Treatment	n	Geo. LSmean	Ratio (%)	90% CI
SB16 (N = 218)	188	13261.9	0.98	[0.94, 1.03]
Prolia (N = 225)	187	13482.1		

N = total number of subjects in the Pharmacodynamic Analysis Set in each treatment group; $AUEC_{0\text{-}M6}$ = area under the effect curve from time zero to Month 6; CI = confidence interval; Geo. = geometric; LSmean = least squares mean; n = number of subjects with available data

Inferential statistics were based on analysis of variance model with treatment group as a fixed factor.

Geometric LSmean ratio and corresponding 90% CI were back-transformed and presented as percentages. Geometric LSmean was also back transformed.

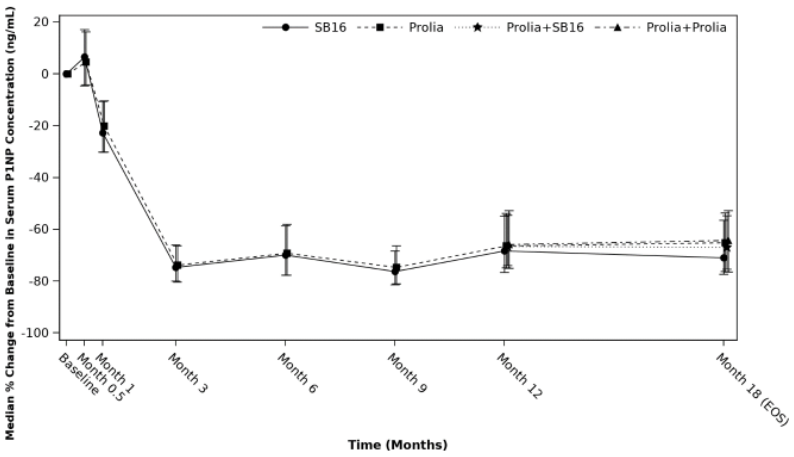
The area during the rebound where serum CTX concentration was above the baseline was excluded from the $AUEC_{0\text{-}M6}$ calculation.

If a blood sample at a certain visit was not collected until Month 6, or was not collected prior to dosing at Month 0 and 6, or was not collected after fasting for at least 8 hours, or was not collected in the morning (prior to 12:00 PM), or a blood sample for CTX at Month 0 was collected after taking calcium, or IP administration was not performed at Month 0, or treatment group was switched at Month 0, or IP which underwent a temperature excursion was administered and it was deemed unacceptable use at Month 0, or prohibited medication was used or fracture occurred until Month 6, the subject was excluded from the analysis.

Serum P1NP Concentrations

The median percent change from baseline in serum P1NP concentrations for the PDS are presented in the figure below.

Figure 10. Median percent change from baseline in serum P1NP concentration profiles in overall study period (pharmacodynamic analysis set)



% Change = [(value – baseline) ÷ baseline] × 100; EOS = end of study; P1NP = procollagen type I N-terminal propeptide

The symbol and error bar represented median percent change and interquartile range at each timepoint.

Below the limit of quantitation concentrations were set to lower limit of quantitation. The lower limit of quantitation is 9.92 ng/mL.

2.5.3. Discussion on clinical pharmacology

The clinical development program of denosumab SB16 comprised two studies to demonstrate PK and PD similarity between SB16 and the reference product in the studies (Prolia): Phase I Study SB16-1001 and Phase III Study SB16-3001. No drug interaction studies, or studies in special populations, such as hepatic or renal impairment, were performed. This is acceptable for biosimilars.

PK Assays

In general, the bioanalytical methods described meet the requirement for their intended use for PK and PD markers as set out regarding validation for such assays. There was varying detection of values within the limit of detection at day zero in the Phase III study for five patients including values up to 800 ng/mL. The applicant was asked to perform a root cause analysis and discuss especially with regard to the method validation what is the most plausible explanation for those results. Furthermore, the applicant was asked to justify retaining those values and/or individuals in the study. In addition, there were outliers in the same study, which had highest values of denosumab at month 9 and 18. The applicant was asked to evaluate if the results at day zero and high values at month 9 and 18 are considered reliable and if it is related to assay performance. The applicant provided a root cause analysis and ad-hoc analysis. The applicant has further provided compelling argumentation and reasoning behind the claim that, despite the unknown reason for the measurable denosumab levels at baseline, it should not affect the PK similarity outcome. This also applies to trustworthiness of the assay and data analysis. Taken together, the impact is negligible and, because of the thorough answer, it is deemed that these abnormal baseline values are not indicative of a general fault with sample measurements or analysis.

Phase I PK/PD Study SB16-1001

Design and Conduct of PK/PD Study

Phase I study SB16-1001 was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the PK, PD, safety, tolerability, and immunogenicity of SB16, EU-sourced Prolia, and US-sourced Prolia in healthy male subjects. Overall, the design of study SB16-1001 is acceptable and was discussed in EMA Scientific Advice procedure EMEA/H/SA/4025/1/2018/III.

Subjects were randomised in a 1:1:1 ratio to receive SB16, EU Prolia or US Prolia. Thus, the advice to conduct a 3-arm study has been followed. Due to the long half-life of denosumab (mean half-life 28 days), a parallel design rather than a cross-over design is considered appropriate. After a screening period of 28 days, subjects received a single 60 mg dose of IP subcutaneously in the abdomen. The PK sampling schedule is considered the minimum requirement to capture C_{max}, as one additional time point (288 h post-dose, i.e. 12 d) has been added around the expected t_{max}, as recommended. However, extending the study duration to 9 months to appropriately characterise PD and target-mediated clearance has not been followed. Instead, the last sampling time point was at 4704 h (6.6 months).

The PK parameters were calculated based on non-compartmental analysis methods using Phoenix WinNonlin® version 8.1, which is appropriate. Terminal BLQ values were disregarded and considered missing. This may lead to an overestimation of mean concentrations when the majority of subjects will have denosumab levels BLQ, in particular during the terminal target-mediated elimination phase of denosumab. A sensitivity analysis with terminal BLQ values set to ‘was provided upon request. BLQ values other than pre-dose and terminal were handled on a case-by-case manner. If $\%AUC_{extrap}$ was > 20% or there was no adequacy of points selection for λ_z, AUC_{inf} and related PK parameters may have been excluded from all statistical analyses. This is acceptable and summaries of these exclusions were provided in the submitted dossier.

Healthy male subjects aged 28-55 years were included to assess the comparative pharmacology of SB16 and Prolia in study SB16-1001. Overall, the inclusion and exclusion criteria are considered appropriate for the recruitment of a healthy male subject population. This population represents a homogeneous and sensitive model to demonstrate or exclude differences between treatment arms, should they exist. The lower age limit was 28 years, which was recommended during Scientific Advice to ensure skeletal maturity.

The selected dose was 60 mg, which is the therapeutic dose of Prolia. However, in dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, but approximately dose-proportional increases in exposures for doses of 60 mg and greater (SmPC Prolia). Thus, the 60 mg therapeutic dose for denosumab falls close to the plateau of the dose-response relationship and is less sensitive as compared to lower doses. As denosumab is eliminated through a non-target-mediated, linear pathway at higher concentrations and a target-mediated non-linear pathway at lower concentrations, a sub-therapeutic dose would have allowed the target-mediated part of denosumab elimination to manifest earlier. Furthermore, a sub-therapeutic dose is likely to be more sensitive to differences in PD parameters. Therefore, the selected 60 mg dose in combination with a short study duration (6.6 months instead of 9 recommended), are considered limitations of study SB16-1001, and demonstration of biosimilarity should also be supported from Phase III study results, which the applicant has provided. To investigate whether target-mediated non-linear clearance is comparable between SB16 and Prolia, pAUCs were provided upon request, dividing the time-concentration curve when the target-mediated clearance starts to predominate (at 16 weeks). Calcium and vitamin D supplements were provided for all participants. This is endorsed, as this measure reduces heterogeneity in bone metabolism.

For the purpose of this application, the primary objective of study SB16-1001 was to demonstrate the pharmacokinetics (PK) similarity between SB16 and European Union (EU) sourced Prolia. The secondary objectives were to investigate and compare the pharmacodynamics (PD), safety, tolerability, and immunogenicity between SB16 and EU sourced Prolia in healthy male subjects. The primary PK endpoints in study SB16-1001 were AUC_{inf} and C_{max} after a single subcutaneous dose of 60 mg denosumab. This is in accordance with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)". AUC_{last} was added as secondary endpoint for EMA review. This is acceptable. Other secondary PK endpoints (T_{max}, Vz/F, λ_z, $t_{1/2}$, CL/F, $\%AUC_{extrap}$) are considered adequate. The PD endpoint AUEC0-D197 for CTX percent inhibition was added following Scientific Advice and is endorsed. Safety and immunogenicity endpoints are considered appropriate.

A total of 168 subjects (56 in each arm) were planned to be randomised. The sample size was increased after advice given by CHMP. The assumptions for the sample size planning are supported by literature and the assumed dropout rate of 10% is supported. An unblinded interim safety analysis was conducted based on the data of 17 subjects. No early stopping for success was planned, so the interim safety analysis is of no concern with respect to the type I error rate of the primary analysis. Since the analysis was done unblinded, details on the conduct of the interim analysis were provided upon request to rule out leaking of unblinded information to study personnel.

The study was conducted at one centre in France and two centres in the US from Oct 21, 2020 (first subject signed informed consent) – Nov 09, 2022 (last subject last visit). Database lock was Dec 21, 2022. The interim safety analysis (Nov 15, 2020) was adequately described in the SAP and is therefore acceptable. Four global amendments and one country-specific amendment were made to the original protocol. The applicant appropriately provided a detailed overview of the protocol amendments and all relevant protocol versions.

Of 438 screened subjects, 168 subjects were randomised (56 in each group), all of whom were included in the SAF. Of those, 8 subjects discontinued study. None of the subjects, other than the subject who committed suicide, discontinued the study due to TEAEs (SB16 group). Two subjects discontinued due to a protocol deviation (1 subject in the SB16 treatment group and 1 subject in the EU sourced Prolia treatment group) and were not included in the PKS/PDS. The most frequently reported major protocol deviation was other major GCP non-compliance which might impact on data integrity or subject safety (i.e., ICF re-consent was not obtained at the earliest next visit after effective date of the revised informed consent obtained, if any.). However, those subjects (a total of 16 [9.5%] subjects) were not excluded from the PKS as per protocol deviation definition list, as this deviation was likely not to have an impact on PK analysis. No subject was excluded due to non-zero pre-dose concentrations greater than 5% of the C_{max} value, unreliable PK parameter for analysis, or concomitant medication, which could have rendered the serum concentration-time profile unreliable.

Outcomes of PK/PD Study

Overall, the baseline characteristics were well balanced among the SB16, EU-Prolia, and US-Prolia groups. All subjects were male, with a mean age of 39.1, 40.2 and 40.8 years, respectively. In the US-Prolia group, more subjects were White (73.2% vs 67.9% and 64.3% in the SB16 and EU-Prolia group, respectively) and fewer were Black or African American (21.4% vs 30.4% in both the SB16 and EU-Prolia groups). However, these differences are not expected to influence the outcome. While height was very similar across groups (mean 176.3, 175.6 and 176.8 cm in the SB16, EU-Prolia and US-Prolia group, respectively), body weight (and BMI) was lowest in the EU-Prolia group: mean body weight 77.56 kg vs 80.84 kg and 79.54 kg in the SB16 and US-Prolia group, respectively. These differences may have a minor impact on PK/PD results. The subjects' medical and surgical history, smoking habits

and alcohol consumption are also available. Overall, these aspects showed a similar pattern across treatment groups and no concerns arise from these data.

The geometric LSMean ratios (90% CI) for SB16 and EU-Prolia for AUC_{inf}, C_{max}, and AUC_{last} were 1.01 (0.93 to 1.10), 1.02 (0.95 to 1.10), and 1.02 (0.94 to 1.12), respectively. Thus, all primary PK parameters were within the pre-defined equivalence range of 0.80 to 1.25. Furthermore, the primary PK analyses of the SB16/US-Prolia and the EU-Prolia/US-Prolia comparisons were provided. Similar to the SB16/EU-Prolia comparison, all 90% CIs for the ratios (SB16/US-Prolia and EU-Prolia/US-Prolia) of the geometric means for AUC_{inf}, C_{max} and AUC_{last} were within the prespecified equivalence criteria.

Thus, the primary PK endpoints of Study SB16-1001 were met, supporting biosimilarity.

The mean serum concentration vs nominal time curves were provided for pairwise comparisons of SB16 vs EU-Prolia, SB16 vs US-Prolia and EU-Prolia vs US-Prolia. Individual serum concentration profiles were also provided for all subjects. Overall, profiles were comparable between all groups. However, from 3360 h (Day 141) to 4032 h (Day 169), mean concentrations of SB16 only marginally decreased from 194.10 ng/ml to 175.92 ng/ml, while EU-Prolia and US-Prolia concentrations decreased from 194.94 ng/ml to 91.90 ng/ml, and from 277.07 ng/ml to 163.86 ng/ml, respectively, between the same time points. As the PK profile of denosumab is known to show a more rapid terminal elimination due to target-mediated drug disposition (TMDD) at lower concentrations, the observed difference may suggest differences during the target-mediated part of denosumab elimination. On the other hand, most subjects had denosumab levels BLQ during the terminal elimination phase, which were not included in the statistical analyses. Upon request, sensitivity analyses setting terminal BLQ concentrations to 'zero' were provided and showed comparable results with the main analyses. In addition, to assess target-mediated non-linear elimination, the applicant presented pAUCs, dividing the time-concentration curve when the target-mediated clearance at the given dose starts to predominate (at week 16). The LSM ratio (90% CI) of SB16 and EU Prolia for $pAUC_{Weeks\ 16\text{-}28}$ was 0.82 (0.58 to 1.15). As expected, results indicate high variability of $pAUC_{Weeks\ 16\text{-}28}$, therefore it cannot be expected that the results lie fully within the standard criterion for PK equivalence and this is not a requirement. Descriptive assessment is sufficient, and the results are considered to be in line with the conclusion of biosimilarity between SB16 and EU Prolia.

The summary statistics of the PK parameters revealed that the PK parameters AUCinf, AUC_{last}, C_{max}, $T_{1/2}$, λ_z and T_{max} were similar among the three treatment groups SB16, EU-Prolia and US-Prolia. Overall, these data support the PK similarity of the test and reference products. An observed difference in $\%AUC_{extrap}$ between SB16 and EU Prolia (mean 1.70 vs. 1.23 - median 1.30 vs. 0.87) was discussed by the applicant in conjunction with pAUC data. It was concluded that the difference does not impact the conclusion of biosimilarity between SB16 and EU Prolia.

PK in Phase III Study SB16-3001

For study SB16-3001, the pharmacokinetic concentrations were summarised descriptively by overall treatment group and scheduled visit. For the computation of descriptive statistics, values below the limit of quantitation were treated as zero, which is regarded acceptable.

The PK profiles were similar for the SB16 and EU-Prolia group for the main period, which is acknowledged. Additionally, the profiles were comparable among the groups in the transition period. Furthermore, the applicant also provided the individual serum concentration-time profiles for each subject up to month 18. This is acknowledged.

According to the explanations provided by the applicant, there was one subject who received commercial Prolia prior to month 18 visit, which explains the high serum drug concentration of this subject at Month 18. However, there were further two subjects with conspicuous serum concentration-time profiles. One subject had the highest serum concentration at month 9 and the other subject had

the highest serum concentration at month 18. According to the concomitant medication listings, these subjects did not receive commercial Prolia/Xgeva.

Beside mean serum concentrations, no further analyses on PK parameters were foreseen in this study. It would have been interesting to also analyse geometric mean ratios of AUC_{inf} and C_{max} after the first dose and also provide summary statistics of other PK parameters. However, with the sparse sampling in the Phase 3 study, any further question on PK parameters is not regarded fruitful. Therefore, the PK characterisation in the Phase 3 study is regarded acceptable. The PK profiles from the osteoporosis patients support PK similarity of the test and reference product.

Pharmacodynamics

SB16 was developed as a biosimilar product to Prolia and Xgeva. The mechanism of action is identical to the reference products. The monoclonal antibody denosumab targets and binds to human receptor activator of nuclear factor kappa-B ligand (RANKL), thus preventing interaction of RANKL with receptor activator of nuclear factor kappa-B (RANK). Block of this interaction leads to reduced osteoclast number and function. Thus, bone resorption and cancer-induced bone destruction is decreased. In patients with giant cell tumour of bone, denosumab binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. The applicant describes that the mechanism of action is identical across all indications for Prolia and Xgeva. Thus, based on the same mechanism of action, extrapolation to all indications is justified, considering that similarity was shown regarding quality and extended functional characterisation and that clinical data showed comparability in terms of PK, PD, efficacy and safety.

PD in Phase I Study SB16-1001

The only PD marker assessed in PK/PD study SB16-1001 was C-telopeptide of type I collagen (CTX), and the corresponding PD endpoint was $AUEC_{0\text{-}D197}$ for CTX percent inhibition. The PD endpoint was included following Scientific Advice. Descriptive statistics were presented for PD parameters Imax (%inhibition) and $AUEC_{0\text{-}D197}$ (%inhibition*h). This is considered acceptable. However, it is critically noted that the study duration was too short to appropriately characterise the PD profile, as CTX values have not yet returned to baseline at the last sampling time point at 4704 h (6.6 months).

At the last sampling timepoint (4704 h or Day 197), serum CTX levels have not yet returned to baseline, but were similar between treatment groups (mean -58.73%, -58.95%, and -65.47% change from baseline for SB16, EU-Prolia and US-Prolia, respectively). Descriptive statistics of pharmacodynamic parameters show similar PD profiles between the treatment groups. No formal comparison was provided, but results are supporting the conclusion on biosimilarity.

PD in Phase III Study SB16-3001

In Study SB16-3001, the "$AUEC_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" was evaluated as a secondary endpoint. The point estimate of the geometric mean ratio (SB16/EU-Prolia) for AUEC was 0.98 with the corresponding 90% CI being (0.94; 1.03). The results observed for the serum CTX concentrations principally support the PD similarity of the test and reference product. However, the "$AUEC_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration", would have been expected to be a co-primary endpoint in the Phase 3 study. This issue is further discussed below on the design of the Phase 3 study. After request, the applicant also provided an analysis of "$AUEC_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" with the corresponding 95% CIs, which supported the results of the main analysis.

The profiles of the median percent change from baseline in CTX concentration for the PDS were comparable between the SB16 and the EU-Prolia group. The applicant also provided the summary statistics of CTX serum concentration for each timepoint. The mean baseline CTX levels were 0.442

ng/ml and 0.441 ng/ml for the SB16 and EU-Prolia group, respectively. Thus, the baseline levels were similar between the treatment groups. The results for each of the other timepoints (month 0.5, 1, 3, 6, 9, 12) were also similar for each treatment group. Similarly, in the transition period (month 18), results were comparable among the treatment groups, indicating that the switch from Prolia to SB16 does not cause any difference in terms of CTX serum levels compared to staying on the same product. This is endorsed.

The profiles of the median percent change from baseline in P1NP concentration for the PDS were also comparable between the SB16 and the EU-Prolia group. The applicant also provided the summary statistics of P1NP serum concentration for each timepoint. The mean baseline P1NP levels were 60.2 ng/ml and 59.9 ng/ml for the SB16 and EU-Prolia group, respectively. Thus, the baseline levels were similar between the treatment groups. The results for each of the other timepoints (month 0.5, 1, 3, 6, 9, 12) were also similar for each treatment group. Similarly, in the transition period (month 18), results were comparable among the treatment groups, indicating that the switch from Prolia to SB16 does not cause any difference in terms of P1NP serum levels compared to staying on the same product. This is endorsed.

Overall, the levels of serum CTX/P1NP and corresponding percent change from baseline were comparable between the treatment groups at each timepoint. Thus, the results support the PD similarity of the test and reference product.

2.5.4. Conclusions on clinical pharmacology

In Phase I PK/PD study SB16-1001, the geometric LSMean ratio (90% CI) for SB16 and EU-Prolia for AUC_{inf} and C_{max} were 1.01 (0.93 to 1.10) and 1.02 (0.95 to 1.10), respectively. Thus, primary PK parameters were within the pre-defined equivalence range of 0.80 to 1.25, suggesting biosimilarity. Limitations of the study were the short study duration (6.6 months) and administration of a (single) 60 mg therapeutic dose, which was advised against in EMEA/H/SA/4025/1/2018/III. Therefore, to investigate the terminal target-mediated clearance of denosumab, pAUCs were provided upon request, and due to high variability descriptive assessment is sufficient, and the results are in line with the conclusion for biosimilarity.

In the Phase III study SB16-3001, PK sampling was only sparse. Nevertheless, the PK profiles from the osteoporosis patients were similar between the SB16 and EU-Prolia group and support PK similarity of the test and reference product. Regarding PD, the point estimate of the geometric mean ratio (SB16/EU-Prolia) for "$AUEC_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" was 0.98 with the corresponding 90% CI being (0.94; 1.03). The applicant also provided this analysis with the corresponding 95% CIs, which also supports the main analysis. In addition, the levels of serum CTX/P1NP and corresponding percent change from baseline were comparable between the treatment groups at each timepoint. Thus, the results support the PD similarity of the test and reference product.

2.5.5. Clinical efficacy

The clinical Phase III study (SB16-3001) is not aimed to demonstrate efficacy of denosumab SB16 per se, but to confirm clinical equivalence between SB16 and Prolia in a representative indication evaluating the efficacy, safety and immunogenicity. Therefore, comparative efficacy of SB16 and Prolia was assessed in patients with postmenopausal osteoporosis (PMO) by evaluating percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12. An overview of the study is provided in the table below.

Table 16: Clinical efficacy study

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
SB16-3001	Study status: Completed Study initiation date: Nov 26, 2020 (first subject signed informed consent) Study completion date: Jan 03, 2023 (last subject's last activity) Planned for Inclusion: 432 subjects were planned to be randomised. Enrolled and Randomised: A total of 998 subjects were screened in the study of which 457 subjects were randomised	Randomised, double-blind, multicentre	Test product: SB16 (proposed denosumab biosimilar) Reference Product: Prolia (EU sourced) Mode of Administration: Subcutaneous injection Dose: 60 mg every 6 months Duration of Treatment: Subjects were administered subcutaneous 60 mg SB16 or Prolia once every 6 months for up to 18 months (total of 3 doses).	Postmenopausal women with osteoporosis

2.5.5.1. Dose response study(ies)

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

2.5.5.2. Main study(ies)

SB16-3001: A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Compare the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity between SB16 (proposed denosumab biosimilar) and Prolia in Postmenopausal Women with Osteoporosis

Main Period

This was a Phase III, randomised, double-blind, parallel group, multicentre, equivalence study to evaluate the efficacy, safety, PK, PD, and immunogenicity of SB16 compared to Prolia in PMO. Subjects were randomised in a 1:1 ratio to receive either SB16 or Prolia subcutaneously at Months 0 and 6. Study visits occurred at Months 0, 0.5, 1, 3, 6, 9, and 12.

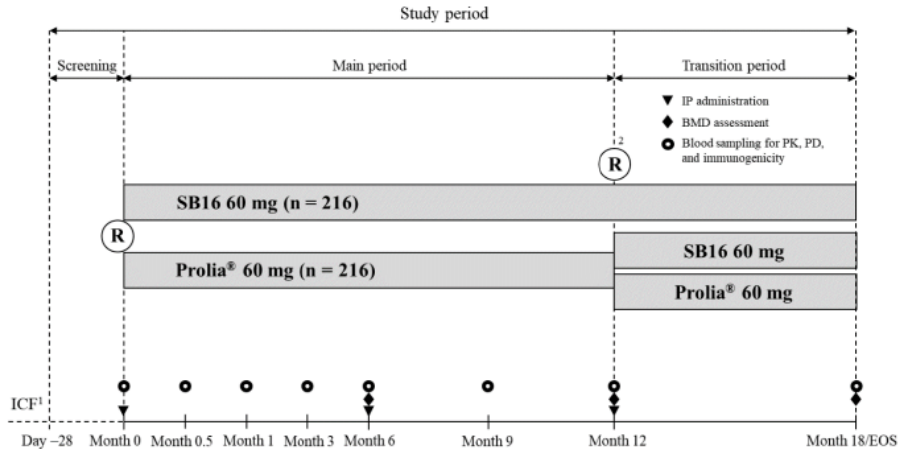
BMD assessments were done at Months 6 and 12. Blood sampling for safety, PK, PD, and immunogenicity were done at Months 0, 0.5, 1, 3, 6, 9, and 12.

Transition Period

At Month 12, subjects who had received Prolia in the main period were randomised again in a 1:1 ratio to either continue on Prolia (Prolia+Prolia) or transitioned to SB16 (Prolia+SB16). Subjects who received SB16 in the main period continued to receive SB16, but they also followed the randomisation procedure to maintain blinding. Subjects were followed up to Month 18. BMD assessment and blood sampling for safety, PK, PD, and immunogenicity was done at Month 18.

An overview of the study design is presented in the figure below.

Figure 11: Study schema



ICF = informed consent form; ® = Randomisation; n = number of subjects; IP = investigational product; BMD = bone mineral density; PK = pharmacokinetic; PD = pharmacodynamic; EOS = end of study

[1] Informed consent should be obtained prior to any study related procedures.

[2] At Month 12, subjects receiving Prolia will be randomised in a 1:1 ratio to either continue to receive Prolia or be transitioned to SB16. Subjects receiving SB16 will continue to receive SB16 up to Month 18 but they will also follow the randomisation procedure to maintain blinding.

Methods

- **Study Participants**

This study was conducted at a total of 40 study centres: 9 centres in Czech Republic, 4 centres in Denmark, 4 centres in Lithuania, 13 centres in Poland, and 10 centres in Republic of Korea.

Inclusion Criteria

Subjects had to meet all of the following criteria to be eligible for the study:

1. Postmenopausal women (defined as lack of menstrual period for at least 12 months prior to Screening, for which there was no other pathological or physiological cause) who were 55 to 80 years of age

    • Serum follicle stimulating hormone (FSH) test could have been done at Screening in case of uncertainty

2. Ambulatory and visually unimpaired to participate in the study at Screening, in the opinion of the Investigator

3. Absolute BMD consistent with T-score at the total hip or lumbar spine of ≥ –4 and ≤ –2.5, determined by central imaging centre at Screening

4. At least three evaluable vertebrae within L1 to L4, one evaluable femoral neck, and one evaluable hip joint for BMD measurement, determined by central imaging centre at Screening

5. Biologic (defined as any therapeutic monoclonal antibody or fusion receptor protein, including denosumab, denosumab biosimilars, or romosozumab) naïve at Screening

6. Body weight of ≥ 50 kg and ≤ 90 kg at Screening

7. Provided informed consent voluntarily and was able to, in the opinion of the Investigator, understand the implications of taking part in the study, and was willing to follow the study requirements and complete the study

Subjects had to meet the following criteria to be enrolled in the transition period:

1. Had been enrolled and completed the scheduled Month 12 of the main period of the SB16-3001 study

Exclusion Criteria

Subjects who met any of the following criteria were not eligible for the study:

1. One severe or more than two moderate vertebral fractures on spinal X-ray according to Genant classification, determined by central imaging centre at Screening

2. History of hip fracture or bilateral hip replacement at Screening

3. Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L]) at Screening

4. Hypercalcaemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcaemia > 2.62 mmol/L [10.5 mg/dL]) at Screening

5. Inadequate haematological function at Screening defined as the following:

a. White blood cell count < 3.5 × 10^3 cells/µL (< 3.5 × 10^9 cells/L)

b. Haemoglobin < 9 g/dL

c. Platelet count < 100,000/mm3 (< 100 × 10^9/L)

6. Inadequate renal or hepatic function at Screening defined as the following:

a. Estimated glomerular filtration rate (eGFR) < 45 mL/min by the Modification of Diet in Renal Disease (MDRD) formula or under dialysis

b. Serum alanine transaminase and aspartate transaminase ≥ 2 × upper limit of reference range

7. Known allergic reactions, hypersensitivity, or intolerance to denosumab or to any ingredients of the IP, including latex allergy or hereditary problems of fructose intolerance at Screening

8. Not able to tolerate long-term calcium or vitamin D supplementation or had malabsorption of calcium or vitamin D supplements, in the opinion of the Investigator, at Screening

9. Use of any of the below medications that could affect BMD:

a. Oral bisphosphonate at any dose for osteoporosis treatment:

- Used for > 3 years cumulatively at Screening
- Used for ≤ 3 years cumulatively and passed < 1 year since the last dose at Screening

b. Intravenous bisphosphonate at any dose within 5 years prior to Screening

c. Parathyroid hormone (PTH) or PTH analogues at any dose within 2 years prior to Screening

d. Systemic hormone replacement therapy (oral or transdermal oestrogen), SERMs, tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening

- Exceptionally, non-systemic vaginal oestrogen treatment was permitted.

e. Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide), or calcitriol at any dose within 3 months prior to Screening

f. Systemic glucocorticoids (≥ 5 mg prednisone equivalent per day or cumulative dose ≥ 50 mg) for more than 10 days within 3 months prior to Screening

g. Fluoride or strontium intended for osteoporosis treatment at any dose at any time at Screening

h. Any non-biologic IP for osteoporosis treatment that mechanism of action was not within excluded medications in exclusion criteria number 9-a to 9-g at any dose within 5 years prior to Screening

i. Other bone active drugs at any dose within 3 months prior to Screening

10. Use of any non-biologic IP that was not indicated for osteoporosis from another study at any dose within five half-lives of that product prior to Randomisation or use of an investigational device at Screening

11. Non-osteoporosis medical conditions that could affect BMD at Screening:

a. History of hyperparathyroidism or hypoparathyroidism, or current hyperparathyroidism or hypoparathyroidism

b. Current uncontrolled hyperthyroidism or hypothyroidism

c. History of bone disease such as osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, or Paget's disease of the bone

d. History of chronic inflammatory diseases, obvious sclerosis, osteophytosis, severe scoliosis, or other degenerative changes due to other co-morbidities that could interfere with the interpretation of dual-energy X-ray absorptiometry (DXA) imaging results

e. History of metabolic or other endocrinologic diseases such as malabsorption syndrome (including celiac disease), Cushing disease, acromegaly, or hyperprolactinemia

12. History of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fracture at Screening or related risk based on the physical examination including oral at Screening

13. History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or planned to have invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) during the study period

14. Fracture (except atypical femoral fracture and hip fracture) that had been actively healing within 12 months prior to Screening at the discretion of the Investigator

15. History of clinically significant active infection within 2 weeks prior to Randomisation, and for cellulitis, erysipelas, or infections that required hospitalisation or intravenous antibiotics, within 8 weeks prior to Randomisation

16. Known history of hepatitis B or hepatitis C or human immunodeficiency virus infection, or positive test for hepatitis B (hepatitis B virus surface antigen [HBsAg]) or hepatitis C (hepatitis C virus antibody [HCV Ab]) virology at Screening

17. History of acute or chronic pancreatitis at Screening

18. History of acute myocardial infarction or New York Heart Association III/IV congestive heart failure within 1 year prior to Randomisation

19. History of cardiac arrythmia or long QT syndrome or electrocardiogram (ECG) abnormalities (e.g., that required hospitalisation, emergency cardioversion, or defibrillation) indicating a safety risk at Screening

20. Malignancy not cured within 5 years prior to Randomisation, with the exception of completely excised and cured basal cell carcinoma or cervical carcinoma in situ which was permitted.

21. History of organ transplantation at Screening

22. History of alcohol or substance-abuse within 12 months prior to Screening

23. Any clinically significant disease or disorder or laboratory abnormality which, in the opinion of the Investigator, prevented the subject from completing the study or prevented accurate interpretation of the study results at Screening and Randomisation

Subjects who met the following criteria were not to be enrolled in the transition period:

1. Found to be of increased risk to continue enrolment, in the opinion of the Investigator

- **Treatments**

Treatments Administered

Subjects were administered SB16 or Prolia 60 mg pre-filled syringe (PFS) as a single subcutaneous injection at Months 0 and 6 in the main period and Month 12 in the transition period.

Dosing visits allowed a window of ± 7 days from the scheduled dosing date except Month 0. No visit windows were allowed for Month 0; the first IP administration was performed at the visit.

Dose modifications of IP were not allowed.

Non-investigational Products Administered

• Elemental calcium (at least 1 g per day)

• Vitamin D (at least 800 IU per day)

The above doses of daily calcium and vitamin D were given from Randomisation to end of study (EOS)/ET. During the screening period, subjects might have received the calcium and vitamin D at the discretion of the Investigator.

Concomitant and rescue therapies

The following medications were prohibited during the study period:

• Xgeva

• Drugs used for osteoporosis, including but not limited to romosozumab, bisphosphonates, SERM, hormone replacement therapy, tibolone, PTH and its analogues, calcitonin, fluoride, and strontium

- During the study period, non-systemic vaginal oestrogen treatment was permitted at the Investigator's discretion if clinically needed.

• Drugs that affect bone metabolism, including but not limited to androgens, aromatase inhibitors, calcitriol, adrenocorticotropic hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, corticosteroids, calcimimetics (cinacalcet and etelcalcetide), aluminium, lithium, heparin (including unfractionated heparin and low molecular weight heparins), warfarin, phenytoin, primidone, carbamazepine, phenobarbital, valproate, oxcarbazepine, topiramate, barbiturate, protease inhibitors, methotrexate, chemotherapeutic agents, cyclosporine, tacrolimus, and prescribed vitamin K

- During the study period, inhaled or topical glucocorticoid was permitted at the Investigator's discretion if clinically needed.

• Any kind of monoclonal antibodies or fusion receptor proteins

Planned invasive dental procedures (e.g., dental or oral surgery) and major surgeries or bone surgeries (unless required for AE/serious AE [SAE] management) were prohibited during the study period.

- **Objectives**

Primary objective

The primary objective of this study is to demonstrate the equivalence of denosumab SB16 to Prolia, in terms of percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12 in postmenopausal osteoporosis (PMO).

The equivalence margin for the mean difference of percent change from baseline in lumbar spine BMD at Month 12 was derived from three historical studies with Prolia. In a denosumab Phase II study, mean (standard error [SE]) percent change from baseline in lumbar spine BMD at Month 12 was 4.55% (0.47) and –0.81% (0.48) for the denosumab and placebo arms, respectively. The FREEDOM study reported the mean percent change from baseline as 5.5% and 0.0%, and in the Bone study, the mean percent change from baseline was 4.4% and –0.5% for the denosumab and placebo arms, respectively.

A meta-analysis estimated a 5.35% mean percent change from baseline in lumbar spine BMD at Month 12 (95% CI [4.83, 5.87]). For the EMA submission, to ensure that the treatment effect preserved an approximately 60% treatment effect over placebo, the lower limit of the equivalence margin was set to 2.0%, which is 40% of the lower limit of the 95% CI.

Secondary objectives

The secondary objectives are:

• To evaluate the efficacy of SB16 compared to Prolia by

- Percentage change from baseline in lumbar spine BMD
- Percentage change from baseline in total hip BMD
- Percentage change from baseline in femoral neck BMD

• To evaluate the safety and tolerability of SB16 compared to Prolia

• To evaluate the PK profile of SB16 compared to Prolia

• To evaluate the PD profile of SB16 compared to Prolia

• To evaluate the immunogenicity of SB16 compared to Prolia

• To evaluate the safety, tolerability, immunogenicity, PK, PD, and efficacy in subjects with PMO who transitioned to SB16 from Prolia compared to subjects who maintained Prolia from the main period

- **Outcomes/endpoints**

Primary endpoint

Percent change from baseline in lumbar spine BMD at Month 12

Secondary endpoints for the main period

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 6
- Percent change from baseline in total hip BMD at Months 6 and 12
- Percent change from baseline in femoral neck BMD at Months 6 and 12

Safety endpoints

- Incidence of adverse events (AEs)
- Incidence of serious AEs (SAEs)

PK endpoint

- Serum drug concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

PD endpoints

- Serum C-telopeptide of type I collagen (CTX) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12
- Area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX
- Serum procollagen type I N-terminal propeptide (P1NP) concentration at Months 0, 0.5, 1, 3, 6, 9, and 12

Immunogenicity endpoint

- Incidence of anti-drug antibodies (ADAs) at Months 0, 0.5, 1, 3, 6, 9, and 12
- Incidence of neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12

Secondary endpoints for the transition period

Safety endpoints

- Incidence of AEs

- Incidence of SAEs

Immunogenicity endpoint

- Incidence of ADAs at Month 18
- Incidence of NAbs at Month 18

Efficacy endpoints

- Percent change from baseline in lumbar spine BMD at Month 18
- Percent change from baseline in total hip BMD at Month 18
- Percent change from baseline in femoral neck BMD at Month 18

PK endpoint

- Serum drug concentration at Month 18

- **Sample size**

The assumptions underlying the sample size calculations were based on a meta-analysis of the Prolia arm of three historical studies.

With the given equivalence margin of [−2.0, 2.0] for the EMA submission, 140 subjects per treatment group was calculated with the assumptions of no mean difference, common standard deviation of 5.13 at the overall 5% significance level. Assuming a 15% loss from randomised subjects after 12 months, a sample size of 165 subjects per treatment group (overall sample size of 330) would give 140 completers per treatment group after 12 months, which was estimated to give 80% power to detect the equivalence within the margin of [−2.0, 2.0].

For the purpose of the regulatory submissions in other territories, the calculated overall sample size was higher. Therefore, the proposed sample size of 432 allowed enough power to detect the equivalence in both situations.

- **Randomisation and Blinding (masking)**

Randomisation

A unique randomisation number was assigned to each subject via the interactive web response system. Subjects eligible for enrolment were randomised 1:1 to receive either Prolia or SB16 at Month 0. At Month 12 subjects who previously received Prolia were again randomised 1:1 to continue to receive Prolia up to Month 18 or to receive SB16 up to Month 18. Patients who received SB16 in the first period also followed the re-randomisation procedure to maintain blinding. The study was conducted by multiple investigators at multiple centres internationally. Centre was included as a stratification factor in the randomisation scheme.

Blinding

The study was double blinded. Subjects, investigators and study personnel were blinded to treatment assignment. To ensure blinding, packaging and labelling was identical for the products and a blinding cap was applied to the pre-filled syringes.

Unblinding was to have been considered only when knowledge of the treatment assignment was deemed essential for the subject's safety by the Investigator or regulatory body. No subjects required unblinding of study treatment during the course of this study.

- **Statistical methods**

Analysis Sets

The full analysis set (FAS) contains all randomised subjects. Analysis is done according to the assigned treatment. Subjects who have no measurement of BMD and do not receive IP during the study period are excluded from the FAS.

The per protocol set (PPS) consists of all subjects in the FAS who have lumbar spine BMD measurements at baseline and Month 12, without any major protocol deviations that have an impact on the lumbar spine BMD measurement.

Major protocol deviations may include deviations from inclusion/exclusion criteria, withdrawal criteria, IP compliance, concomitant medication, and study procedure. Major protocol deviations that will lead to exclusion from this set will be pre-defined using the final version of merged protocol deviation list prior to unblinding the treatment group assignment for analyses. Subjects meeting of following criteria will be excluded from PPS as well even if it's not captured as a protocol deviation:

a. Lumbar spine BMD assessment (+/- 14 days) at Month 12 (including ET visit mapping to Month 12, when subject discontinued before Month 12) is out of visit window

Pharmacokinetic Analysis Set (PKS) consists of all subjects in the SAF1 who have at least one PK sample analysed.

Pharmacodynamic Analysis Set (PDS) consists of all subjects in the SAF1 who have at least one CTX or P1NP sample analysed without any major protocol deviations that have an impact on the pharmacodynamics results. Definition of PDS is revised from the definition specified in the protocol since some major protocol deviations impact the serum CTX and P1NP results. These subjects will not be included in PDS.

The PPS was used to assess efficacy in the primary analysis. The main analysis was repeated in the FAS as supportive analyses using multiple imputation and available cases respectively.

Primary Analysis

The primary analysis assessed similarity of SB16 and Prolia in precent change from baseline in lumbar spine BMD at Month 12. The population level summary of mean difference in percent change in lumbar spine BMD at Month 12 was estimated using ANCOVA with the baseline value of lumbar spine BMD as covariate and treatment group as factor. Similarity was to be concluded if the 95% CI from the ANCOVA model was contained within the pre-specified equivalence margins of [-2% to 2%].

Supportive / Sensitivity Analyses

The primary analysis was repeated in the FAS using multiple imputation for subjects who dropped out of the study prior to Month 12 under the missingness at random (MAR) assumption (Supportive Estimand 1). Multiple imputation methods replaced each missing primary efficacy endpoint value with a set of (m= 25) plausible values based on a prediction model. The prediction model was a regression model with the following covariates: treatment group, baseline lumbar spine BMD, and percent change from baseline in lumbar spine BMD at Month 6 and Month 12. The monotone regression imputation method was used to generate an imputed complete dataset (25 imputed datasets). If the MCMC monotone-data imputation was performed prior to using the monotone regression method, then the monotone regression imputation created a single imputed dataset based on each of the 25 imputed datasets from MCMC monotone-data imputation.

To evaluate the robustness of the supportive analysis a tipping point analysis was performed. Different delta-adjustments were applied to either treatment arm in the imputed datasets.

Available case analysis of the FAS was also performed (Supportive Estimand 2).

Secondary Analysis

Percent change from baseline in lumbar spine BMD at Month 6 and Month 18 was assessed with the same model as the primary endpoint (percent change from baseline in lumbar spine BMD at Month 12). A descriptive summary and plots were provided.

A descriptive summary and plots were generated for percent change from baseline in total hip and femoral neck BMD at each visit.

Pharmacokinetic Analysis

Serum PK concentrations were summarised descriptively by overall treatment group and scheduled visit. Below the limit of quantification (BLQ) values were treated as zero for the computation of descriptive statistics, and the generation of individual serum concentration-time profile, except for geometric mean, geometric SD, and geometric CV%, for which they were excluded. BLQ was presented as BLQ in the listings.

Pharmacodynamic Analysis

The PD analysis will be performed for the PDS. All PD assessment data will be reported and analysed with the same precision as the source regardless of how many significant figures or decimals the data carry. Values outside the limit of quantification will be imputed by the limit of quantification in descriptive statistics but will be reported as-is in the individual data listings.

Median and inter-quartile ranges of percent change from baseline in serum CTX and serum P1NP by visit and treatment group are provided for the PDS. Individual serum CTX and serum P1NP concentrations over time are provided for subjects in the SAF1.

The geometric mean of area under the effect curve (AUEC) from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX concentration will be analysed by main treatment group using ANOVA on the log-transformed $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX concentration with the main treatment group as a fixed effect. The ratio of least-squares geometric mean (SB16 vs. Prolia) will also be presented with corresponding 90% CI.

The AUEC will be computed by trapezoidal rule from Month 0 to Month 6 or the time serum CTX concentration becomes larger than baseline (denoted $AUEC_{0\text{-}M6}$). The AUEC from 0 to Month 6 irrespective of crossing of zero is denoted net $AUEC_{0\text{-}M6}$ and reported in the individual listings.

Error probabilities, adjustment for multiplicity and interim analyses

One primary endpoint has been defined for this study, with one critical treatment contrast (SB16 vs Prolia) and one time point of primary interest (Month 12). The secondary endpoints defined are intended to provide supportive evidence relating to the primary objective. No interim analyses were planned for the primary analysis. Hence no formal adjustments for multiplicity was performed.

Changes from protocol-specified analyses

The analysis for the main endpoint was changed from a linear mixed model with treatment as fixed effect and baseline lumbar spine BMD and site (or pooled centres) as covariates to an analysis of covariance with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor. Inclusion of the centre was no longer deemed necessary because the raw values of the BMD measurements were replaced by the values corrected for cross-calibration.

Results

Participant flow

A total of 998 subjects were screened in the study, 1 of which was re-screened. Out of which, 457 subjects were randomised, and 541 subjects were screen failed. The most common reason for screen failure was not meeting the eligibility criteria (423 subjects, 78.2% of screen failures).

Of the 457 subjects who were randomised, 456 (99.8%) subjects received IP and 417 (91.2%) subjects completed the main period. During the main period, one subject was transferred to other centre. The completion rate of the main period was comparable between the two treatment groups. Prior to re-randomisation, 50 (10.9%) subjects discontinued treatment (SB16: 19 [8.4%] subjects and Prolia Overall: 31 [13.4%] subjects). The most common primary reason for study discontinuation in the main period was withdrawal of consent (29 [6.3%] subjects).

At Month 12, 407 subjects who completed the scheduled Month 12 of the main period and were considered eligible entered into the transition period. The 206 subjects in the SB16 treatment group continued to receive SB16 at Month 12 and to be followed up to Month 18. The 201 subjects in the Prolia treatment group were further re-randomised at Month 12 into 2 treatment groups; continue Prolia treatment (Prolia+Prolia: 101 subjects) or transition to receive SB16 (Prolia+SB16: 100 subjects).

The completion rate of the transition period was comparable between the SB16 and Prolia Overall treatment groups. From the 201 subjects in the Prolia Overall treatment group, 99 (99.0%) subjects completed from the Prolia+SB16 treatment group; and 99 (98.0%) subjects completed from the Prolia+Prolia treatment group. Three (0.7%) subjects discontinued the study after Month 12. No subjects in the SB16 treatment group discontinued after Month 12 and 3 (1.5%) subjects in the Prolia Overall treatment group discontinued after Month 12, all due to withdrawal of consent (Prolia+SB16: 1 [1.0%] subject and Prolia+Prolia: 2 [2.0%] subjects).

Table 17. Subject disposition by treatment group (enrolled set)

		Prolia			
	SB16 n (%)	Overall n (%)	SB16 n (%)	Prolia n (%)	Total n (%)
Screened[a]					998
Screening failures					541
Major reasons for screening failures					
Does not meet eligibility criteria					423 (78.2)
Consent withdrawal					114 (21.1)
Other					4 (0.7)
Main Period					
Randomised at Month 0[b]	225 (100.0)	232 (100.0)			457 (100.0)
Treated in Main period[b]	225 (100.0)	231 (99.6)			456 (99.8)
Completed Main period (Month 12)[b]	212 (94.2)	205 (88.4)			417 (91.2)
Withdrew in Main period (before Transition period)[b]	19 (8.4)	31 (13.4)			50 (10.9)
Primary reasons for study discontinuation					
Consent withdrawal by subject	10 (4.4)	19 (8.2)			29 (6.3)
Adverse event	4 (1.8)	8 (3.4)			12 (2.6)
Protocol deviation	0 (0.0)	2 (0.9)			2 (0.4)
Lack of efficacy or disease progression	4 (1.8)	1 (0.4)			5 (1.1)
Investigator's discretion for any other reason	1 (0.4)	0 (0.0)			1 (0.2)
Other	0 (0.0)	1 (0.4)			1 (0.2)
Primary reasons for study discontinuation related with COVID-19	0 (0.0)	4 (1.7)			4 (0.9)
Consent withdrawal by subject	0 (0.0)	2 (0.9)			2 (0.4)
Adverse event	0 (0.0)	2 (0.9)			2 (0.4)
Transition Period					
Re-randomised at Month 12[c]	206 (100.0)	201 (100.0)	100 (100.0)	101 (100.0)	407 (100.0)
Treated in Transition period[c]	206 (100.0)	201 (100.0)	100 (100.0)	101 (100.0)	407 (100.0)
Completed Transition period (Month 18)[c]	206 (100.0)	198 (98.5)	99 (99.0)	99 (98.0)	404 (99.3)
Withdrew in Transition period (after Month 12 up to Month 18)[c]	0 (0.0)	3 (1.5)	1 (1.0)	2 (2.0)	3 (0.7)
Primary reasons for study discontinuation					
Consent withdrawal by subject	0 (0.0)	3 (1.5)	1 (1.0)	2 (2.0)	3 (0.7)

n = number of subjects with available data within each category
Percentages of screening failure reasons were based on the number of screening failures.
[a] The number of screened was 998, and 1 subject was re-screened.
[b] Percentages were based on the number of randomised subjects at Month 0.
[c] Percentages were based on the number of re-randomised subjects at Month 12.
If a subject was discontinued without re-randomisation at Month 12, but completed the Month 12 bone mineral density assessment, either at a scheduled visit or an early termination visit, the subject was considered as a completer of the Main period.

Protocol Deviations

A summary including the number and proportion of subjects with protocol deviations by Main treatment group for the RAN is presented in the table below.

Major protocol deviations were defined as deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

A total of 217 (47.5%) subjects had protocol deviations of any kind and 197 (43.1%) subjects had at least 1 major protocol deviation. A total of 44 subjects (9.6%) had major deviations that led to

exclusion from the PPS. The most common major deviations that led to exclusion from the PPS were related to concomitant medication criteria in 21 (4.6%) subjects, followed by violations of study procedures criteria in 14 (3.1%) subjects, and meeting an exclusion criterion in 8 (1.8%) subjects. A total of 14 subjects (3.1%) had major deviations that led to exclusion from the PDS. The major deviations that led to exclusion from the PDS were related to meeting an exclusion criterion in 13 (2.8%) subjects, followed by study procedures criteria (mis-randomisation) in 1 (0.2%) subject.

Table 18. Summary of protocol deviations by main treatment group for the overall study period (randomised set)

	SB16 N = 225 n (%)	Prolia N = 232 n (%)	Total N = 457 n (%)
Any protocol deviations	112 (49.8)	105 (45.3)	217 (47.5)
With at least one major protocol deviation	103 (45.8)	94 (40.5)	197 (43.1)
Excluded from Per-Protocol Set	24 (10.7)	20 (8.6)	44 (9.6)
Inclusion Criteria	1 (0.4)	2 (0.9)	3 (0.7)
Exclusion Criteria	5 (2.2)	3 (1.3)	8 (1.8)
Study Procedures Criteria	6 (2.7)	8 (3.4)	14 (3.1)
Concomitant Medication Criteria	14 (6.2)	7 (3.0)	21 (4.6)
Excluded from Pharmacodynamic Analysis Set	7 (3.1)	7 (3.0)	14 (3.1)
Exclusion Criteria	7 (3.1)	6 (2.6)	13 (2.8)
Study Procedures Criteria	0 (0.0)	1 (0.4)	1 (0.2)
Major protocol deviations not excluded from Per-Protocol Set	88 (39.1)	85 (36.6)	173 (37.9)
With at least one minor protocol deviation	26 (11.6)	29 (12.5)	55 (12.0)

N = total number of subjects in the Randomised Set in each treatment group; n = number of subjects with event
Percentages were based on the number of subjects in the Randomised Set.

Results

- **Recruitment**

Study Start Date: Nov 26, 2020

Study Completion Date: Jan 03, 2023

Date of Report Apr 28, 2023

SAP date of the document version: Jan 31, 2023

- **Conduct of the study**

Two amendments were made to the original protocol (dated Apr 06, 2020): One global amendment and one country-specific amendment (Republic of Korea).

Country-specific Amendment 1.1 - Republic of Korea (Version 1.1), Jul 28, 2020

This amendment was released to Republic of Korea only.

The major changes were:

• Added additional information of major protocol deviations of PPS definition

• Added the analysis method of primary objective for Korea MFDS and other regulatory agencies except EMA and FDA

Global Amendment 1 (Version 2.0), May 03, 2021

This amendment was released to all participating study sites.

The major changes were:

• Added additional information of major protocol deviations of PPS definition.

• Added the analysis method of primary objective for Korea MFDS and other regulatory agencies except EMA and FDA

• The secondary objective of percentage change from baseline in lumbar spine BMD at Month 6 was added.

• Efficacy analyses were revised to remove pooled centres and removed use of linear mixed model for BMD; information for missing data imputation was added.

• For PD, analysis method for $AUEC_{0\text{-}M6}$ of percent change from baseline in serum CTX was added.

• Immunogenicity endpoints were revised to separate ADA and NAbs.

• The Schedule of Activities was amended to add days from Month 0 and other clarifications.

• List of study staff was changed, and business address updated.

• Main CSR was deleted.

- **Baseline data**

Demographic characteristics by treatment group for the RAN are summarised in the table below.

Table 19. Demographic characteristics by treatment group (randomised set)

Characteristics	SB16 N = 225	Prolia Overall N = 232	Prolia SB16 N = 100[a]	Prolia Prolia N = 101[a]	Total N = 457
Age (years)					
Mean	66.5	66.3	65.8	66.4	66.4
SD	5.87	6.03	5.73	6.05	5.95
Age group, n (%)					
< 65 years	89 (39.6)	95 (40.9)	39 (39.0)	44 (43.6)	184 (40.3)
≥ 65 years	136 (60.4)	137 (59.1)	61 (61.0)	57 (56.4)	273 (59.7)
Race, n (%)					
Asian	18 (8.0)	23 (9.9)	10 (10.0)	11 (10.9)	41 (9.0)
White	207 (92.0)	208 (89.7)	89 (89.0)	90 (89.1)	415 (90.8)
Other	0 (0.0)	1 (0.4)	1 (1.0)	0 (0.0)	1 (0.2)
Ethnicity, n (%)					
Hispanic or Latino	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Other	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)
Country, n (%)					
Czech Republic	59 (26.2)	59 (25.4)	26 (26.0)	28 (27.7)	118 (25.8)
Denmark	5 (2.2)	6 (2.6)	2 (2.0)	2 (2.0)	11 (2.4)
Republic of Korea	18 (8.0)	23 (9.9)	10 (10.0)	11 (10.9)	41 (9.0)
Lithuania	13 (5.8)	12 (5.2)	4 (4.0)	5 (5.0)	25 (5.5)
Poland	130 (57.8)	132 (56.9)	58 (58.0)	55 (54.5)	262 (57.3)
Weight (kg)					
Mean	64.01	62.50	61.33	62.86	63.24
SD	9.940	9.443	9.299	9.514	9.709
Height (cm)					
Mean	159.58	158.54	158.06	158.70	159.05
SD	6.426	6.220	6.048	6.191	6.337
BMI (kg/m^2)					
Mean	25.17	24.86	24.55	24.95	25.01
SD	3.829	3.462	3.438	3.407	3.646
BMI level, n (%)					
< 25 kg/m^2	117 (52.0)	132 (56.9)	60 (60.0)	58 (57.4)	249 (54.5)
≥ 25 kg/m^2	108 (48.0)	100 (43.1)	40 (40.0)	43 (42.6)	208 (45.5)

N = total number of subjects in the Randomised Set in each treatment group; BMI = body mass index; n = number of subjects with available data within each category; SD = standard deviation
Age was calculated as the difference in years of informed consent form and birth year obtained.
BMI (kg/m^2) was calculated using baseline weight and height at Screening.
Percentages were based on the number of subjects in the Randomised Set.
[a] Based on subjects who had re-randomisation at Month 12, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.

Other baseline characteristics by treatment group for the RAN are summarised the table below.

Table 20. Other baseline characteristics by treatment group (randomised set)

Characteristics	SB16 N = 225	Prolia Overall N = 232	Prolia SB16 N = 100[a]	Prolia Prolia N = 101[a]	Total N = 457
Years since diagnosis of PMO					
Mean	3.34	2.86	2.59	2.96	3.10
SD	5.118	4.620	3.725	4.845	4.872
Years since menopause					
Mean	16.36	16.01	15.13	16.60	16.18
SD	7.371	7.643	7.274	7.728	7.504
Previous fracture history, n (%)					
Yes	74 (32.9)	68 (29.3)	33 (33.0)	33 (32.7)	142 (31.1)
No	151 (67.1)	164 (70.7)	67 (67.0)	68 (67.3)	315 (68.9)
Hip fracture history of the parents, n (%)					
Yes	21 (9.3)	27 (11.6)	15 (15.0)	7 (6.9)	48 (10.5)
No	204 (90.7)	205 (88.4)	85 (85.0)	94 (93.1)	409 (89.5)
Prevalent vertebral fracture, n (%)					
Yes	104 (46.2)	117 (50.4)	57 (57.0)	49 (48.5)	221 (48.4)
No	119 (52.9)	113 (48.7)	43 (43.0)	50 (49.5)	232 (50.8)
Not assessable[b]	2 (0.9)	2 (0.9)	0 (0.0)	2 (2.0)	4 (0.9)
Number of vertebral fractures, n (%)					
0	119 (52.9)	113 (48.7)	43 (43.0)	50 (49.5)	232 (50.8)
1	30 (13.3)	40 (17.2)	24 (24.0)	13 (12.9)	70 (15.3)

2	29 (12.9)	28 (12.1)	8 (8.0)	18 (17.8)	57 (12.5)
> 2	45 (20.0)	49 (21.1)	25 (25.0)	18 (17.8)	94 (20.6)
Not assessable[b]	2 (0.9)	2 (0.9)	0 (0.0)	2 (2.0)	4 (0.9)
Grade of most severe vertebral fracture, n (%)					
Normal	119 (52.9)	113 (48.7)	43 (43.0)	50 (49.5)	232 (50.8)
Mild	80 (35.6)	92 (39.7)	44 (44.0)	41 (40.6)	172 (37.6)
Moderate	24 (10.7)	25 (10.8)	13 (13.0)	8 (7.9)	49 (10.7)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not assessable[b]	2 (0.9)	2 (0.9)	0 (0.0)	2 (2.0)	4 (0.9)
Serum 25 (OH) vitamin D level (nmol/L)					
Mean	95.2240	92.1177	93.7370	92.9416	93.6470
SD	40.49865	34.84496	31.44580	39.33792	37.72497
Oral BP history, n (%)					
Yes	42 (18.7)	33 (14.2)	16 (16.0)	14 (13.9)	75 (16.4)
No	183 (81.3)	199 (85.8)	84 (84.0)	87 (86.1)	382 (83.6)
Total cumulated period prior to screening (months)					
Mean	15.4	13.0	10.6	14.6	14.4
SD	11.81	10.20	7.68	11.67	11.13
Duration of oral BP administration, n (%)					
Year ≤ 1	19 (8.4)	21 (9.1)	12 (12.0)	8 (7.9)	40 (8.8)
1 < Years ≤ 2	12 (5.3)	7 (3.0)	3 (3.0)	3 (3.0)	19 (4.2)
2 < Years ≤ 3	11 (4.9)	5 (2.2)	1 (1.0)	3 (3.0)	16 (3.5)
BMD of lumbar spine (g/cm^2)					
Mean	0.7687	0.7683	0.7728	0.7658	0.7685
SD	0.07170	0.07449	0.08193	0.06869	0.07305
BMD of total hip (g/cm^2)					
Mean	0.7592	0.7561	0.7515	0.7521	0.7576
SD	0.09822	0.09058	0.09159	0.08860	0.09433
BMD of femoral neck (g/cm^2)					
Mean	0.6896	0.6880	0.6888	0.6857	0.6888
SD	0.10002	0.09939	0.10021	0.10415	0.09959
T-score at lumbar spine					
Mean	–3.04	–3.05	–3.06	–3.07	–3.05
SD	0.474	0.496	0.534	0.484	0.484
T-score at total hip					
Mean	–1.81	–1.82	–1.88	–1.85	–1.81
SD	0.773	0.742	0.724	0.745	0.757
T-score at femoral neck					
Mean	–2.16	–2.16	–2.20	–2.17	–2.16
SD	0.615	0.632	0.570	0.670	0.623
Serum CTX (ng/mL)					
Mean	0.4423	0.4416	0.4085	0.4650	0.4420
SD	0.20367	0.20280	0.19461	0.21495	0.20300
Serum P1NP (ng/mL)					
Mean	60.189	59.915	57.904	60.909	60.050
SD	23.5823	24.7382	25.1357	25.3838	24.1490
Current smoking status, n (%)					
Yes	28 (12.4)	25 (10.8)	10 (10.0)	10 (9.9)	53 (11.6)
No	197 (87.6)	207 (89.2)	90 (90.0)	91 (90.1)	404 (88.4)
Current alcohol consumption status, n (%)					
Yes	56 (24.9)	64 (27.6)	34 (34.0)	25 (24.8)	120 (26.3)
No	169 (75.1)	168 (72.4)	66 (66.0)	76 (75.2)	337 (73.7)
Alcohol consumption amount, n (%)					
< 3 units/day	55 (24.4)	64 (27.6)	34 (34.0)	25 (24.8)	119 (26.0)
≥ 3 units/day	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

N = total number of subjects in the Randomised Set in each treatment group; BMD = bone mineral density; BP = bisphosphonate; CTX = c-telopeptide of type I collagen; n = number of subjects with available data within each category; P1NP = procollagen type I N-terminal propeptide; PMO = postmenopausal osteoporosis; SD = standard deviation
Years since diagnosis of PMO = (randomisation date – diagnosed date of PMO + 1) ÷ 365.25.
Years since menopause = (randomisation date – date of last menstruation + 1) ÷ 365.25.
Percentages were based on the number of subjects in the Randomised Set.

[a] Based on subjects who had re-randomisation at Month 12, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.
There are 3 types of measurements for the BMD result, original BMD measurement, instrument quality control (IQC) corrected BMD measurement, and IQC and cross-calibration (Xcal) corrected BMD measurement. IQC and Xcal corrected BMD measurement was used for analysis.
Original BMD T-score used for eligibility confirmation was used for analysis.

[b] Unknown fracture status at ≥ 1 vertebra with no fracture at remaining evaluable vertebrae.

The medical and surgical history by SOC reported in more than 5% of total subjects in the RAN is summarised in the table below.

Table 21. Most frequently reported (>5%) medical and surgical history by primary system organ class and treatment group (randomised set)

Primary System Organ Class	SB16 N = 225 n (%)	Prolia Overall N = 232 n (%)	Prolia SB16 N = 100[a] n (%)	Prolia Prolia N = 101[a] n (%)	Total N = 457 n (%)
Any medical and surgical history (regardless of 5% cut-off)	211 (93.8)	221 (95.3)	94 (94.0)	97 (96.0)	432 (94.5)
Cardiac disorders	33 (14.7)	38 (16.4)	17 (17.0)	14 (13.9)	71 (15.5)
Ear and labyrinth disorders	9 (4.0)	14 (6.0)	4 (4.0)	7 (6.9)	23 (5.0)
Endocrine disorders	78 (34.7)	67 (28.9)	27 (27.0)	31 (30.7)	145 (31.7)
Eye disorders	43 (19.1)	42 (18.1)	18 (18.0)	20 (19.8)	85 (18.6)
Gastrointestinal disorders	61 (27.1)	66 (28.4)	28 (28.0)	25 (24.8)	127 (27.8)
Hepatobiliary disorders	14 (6.2)	18 (7.8)	8 (8.0)	7 (6.9)	32 (7.0)
Immune system disorders	18 (8.0)	20 (8.6)	9 (9.0)	6 (5.9)	38 (8.3)
Infections and infestations	26 (11.6)	31 (13.4)	11 (11.0)	12 (11.9)	57 (12.5)
Injury, poisoning and procedural complications	78 (34.7)	75 (32.3)	36 (36.0)	35 (34.7)	153 (33.5)
Metabolism and nutrition disorders	95 (42.2)	113 (48.7)	46 (46.0)	50 (49.5)	208 (45.5)
Musculoskeletal and connective tissue disorders	111 (49.3)	107 (46.1)	46 (46.0)	45 (44.6)	218 (47.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (9.3)	21 (9.1)	10 (10.0)	7 (6.9)	42 (9.2)
Nervous system disorders	38 (16.9)	47 (20.3)	12 (12.0)	18 (17.8)	85 (18.6)
Psychiatric disorders	20 (8.9)	30 (12.9)	11 (11.0)	11 (10.9)	50 (10.9)
Renal and urinary disorders	26 (11.6)	22 (9.5)	10 (10.0)	7 (6.9)	48 (10.5)
Reproductive system and breast disorders	12 (5.3)	13 (5.6)	4 (4.0)	4 (4.0)	25 (5.5)
Respiratory, thoracic and mediastinal disorders	25 (11.1)	23 (9.9)	14 (14.0)	6 (5.9)	48 (10.5)
Surgical and medical procedures	38 (16.9)	46 (19.8)	19 (19.0)	19 (18.8)	84 (18.4)
Vascular disorders	110 (48.9)	110 (47.4)	53 (53.0)	40 (39.6)	220 (48.1)

N = total number of subjects in the Randomised Set in each treatment group; n = number of subjects with available data within each category

Percentages were based on the number of subjects in the Randomised Set.

Medical and surgical history were coded using MedDRA version 23.0.

Primary System Organ Class (SOC) were presented alphabetically.

If a subject had multiple conditions with the same primary SOC, the subject was counted only once.

[a] Based on subjects who had re-randomisation at Month 12, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.

If a subject had medical and surgical history, the subject was counted for the number of subjects for "any medical surgical history" in the 1st row.

Among all reported medical and surgical history, medical and surgical history with incidence by primary SOC > 5% in total subjects are presented in this table.

- **Numbers analysed**

The number of subjects included in each analysis set for the RAN is presented in the table below.

Of the 457 subjects randomised, 456 (99.8%) were included in the FAS and SAF1, 383 (83.8%) subjects satisfied the criteria for the PPS, 407 (89.1%) subjects were included in SAF2, 456 (99.8%) subjects were included in PKS, and 443 (96.9%) subjects were included in PDS.

Table 22. Number of subjects in the analysis sets by treatment group (randomised set)

	SB16 N = 225 n (%)	Prolia Overall N = 232 n (%)	Prolia SB16 N = 100[a] n (%)	Prolia Prolia N = 101[a] n (%)	Total N = 457 n (%)
Randomised Set	225 (100.0)	232 (100.0)	100 (100.0)	101 (100.0)	457 (100.0)
Full Analysis Set	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)
Per-Protocol Set	191 (84.9)	192 (82.8)	96 (96.0)	94 (93.1)	383 (83.8)
Safety Set 1	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)
Safety Set 2	206 (91.6)	201 (86.6)	100 (100.0)	101 (100.0)	407 (89.1)
Pharmacokinetic Analysis Set	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)
Pharmacodynamic Analysis Set	218 (96.9)	225 (97.0)	100 (100.0)	97 (96.0)	443 (96.9)

N = total number of subjects in the Randomised Set in each treatment group; n = number of subjects with available data within each category
Percentages were based on the number of subjects in the Randomised Set.
[a] Based on subjects who had re-randomisation at Month 12, Prolia+SB16, and Prolia+Prolia may not add up to Prolia Overall.

- **Outcomes and estimation**

Primary Efficacy Analysis

The primary efficacy analysis was performed for the PPS with percent change from baseline in lumbar spine BMD at Month 12 between the SB16 and Prolia treatment groups. The 95% CI of the least squares mean (LSmean) difference between the two treatment groups in relation to the percent change from baseline in lumbar spine BMD at Month 12 was estimated for the PPS; the results are summarised in the table below.

Table 23. Equivalence analysis of percent change from baseline in lumbar spine BMD at month 12 (per-protocol set)

				Difference (SB16 – Prolia)		
Timepoint	Treatment	n	LSmean (SE)	LSmean (SE)	90% CI	95% CI
Month 12	SB16 (N = 191)	191	5.71 (0.268)	0.39 (0.378)	[–0.24, 1.01]	[–0.36, 1.13]
	Prolia (N = 192)	192	5.32 (0.267)			

N = total number of subjects in the Per-Protocol Set in each treatment group; BMD = bone mineral density; CI = confidence interval; LSmean = least squares mean; n = number of subjects with available data at Month 12; SE = standard error
Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor.

The primary efficacy analysis was also performed for the FAS with percent change from baseline in lumbar spine BMD at Month 12 between the SB16 and Prolia treatment groups. The results are summarised in the table below.

Table 24. Equivalence analysis of percent change from baseline in lumbar spine BMD at month 12 (full analysis set)

				Difference (SB16 – Prolia)		
Timepoint	Treatment	n	LSmean (SE)	LSmean (SE)	90% CI	95% CI
Month 12	SB16 (N = 225)	225	5.63 (0.250)	0.33 (0.354)	[–0.25, 0.91]	[–0.36, 1.03]
	Prolia (N = 231)	231	5.30 (0.254)			

N = total number of subjects in the Full Analysis Set in each treatment group; BMD = bone mineral density; CI = confidence interval; LSmean = least squares mean; n = number of subjects with available data at Month 12; SE = standard error
Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor. Missing data was imputed using multiple imputation method under the assumption of missing at random.
Source: Table 14.2-2.1

Secondary Efficacy Analyses

Percent Change from Baseline in Lumbar Spine BMD at Month 6 and Month 18

The analysis of percent change from baseline in lumbar BMD at Month 6 and Month 18 for the FAS is summarised in the table below.

Table 25. Analysis of Percent change from baseline in lumbar spine BMD at month 6 and month 18 (full analysis set)

Timepoint	Treatment	n	LSmean (SE)	Difference (A – B)		
				LSmean (SE)	90% CI	95% CI
Month 6	SB16 (N = 225) [A]	225	3.69 (0.238)	–0.12 (0.337)	[–0.68, 0.43]	[–0.78, 0.54]
	Prolia (N = 231) [B]	231	3.81 (0.240)			
Month 18	SB16+SB16[a] (N = 206) [A]	206	6.77 (0.286)	0.23 (0.408)	[–0.44, 0.90]	[–0.57, 1.03]
	Prolia Overall (N = 201) [B]	201	6.54 (0.291)			
	SB16+SB16[a] (N = 206) [A]	206	6.77 (0.286)	–0.03 (0.501)	[–0.85, 0.79]	[–1.01, 0.95]
	Prolia+Prolia[a] (N = 101) [B]	101	6.80 (0.411)			
	Prolia+SB16[a] (N = 100) [A]	100	6.28 (0.412)	–0.52 (0.582)	[–1.48, 0.43]	[–1.66, 0.62]
	Prolia+Prolia[a] (N = 101) [B]	101	6.80 (0.411)			

N = total number of subjects in the Full Analysis Set in each treatment group; BMD = bone mineral density; CI = confidence interval; LSmean = least squares mean; n = number of subjects with available assessment results at each timepoint; SE = standard error

Prolia Overall include subjects who had randomised to Prolia at Month 0 and had re-randomisation at Month 12 among the Full Analysis Set.

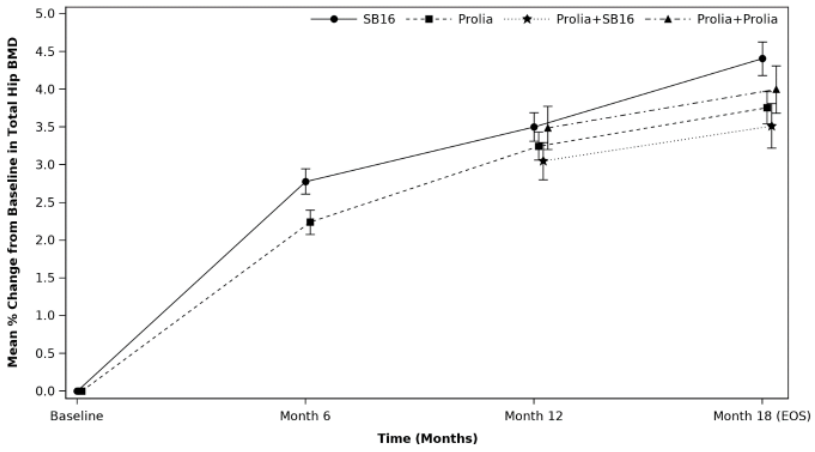
[a] Based on subjects who had re-randomisation at Month 12 among the Full Analysis Set.

Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor. Missing data was imputed using multiple imputation method under the assumption of missing at random.

Percent Change from Baseline in Total Hip BMD

The analysis of percent change from baseline in total hip BMD Month 6, Month 12 and Month 18 for the FAS is presented in the figure below.

Figure 12. Mean percent change from baseline in total hip BMD up to month 18 (full analysis set)



BMD = bone mineral density; % Change = [(value – baseline) / baseline] × 100; EOS = end of study

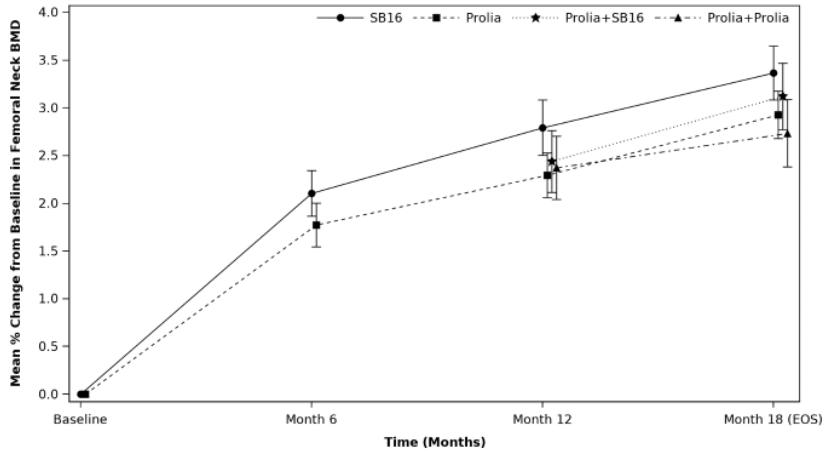
There are three types of measurements for the BMD result, original BMD measurement, instrument quality control (IQC) corrected BMD measurement, and IQC and cross-calibration (Xcal) corrected BMD measurement. IQC and Xcal corrected BMD measurement was used for analysis.

The symbol and error bar represented mean and standard error at each timepoint.

Percent Change from Baseline in Femoral Neck BMD

The analysis of percent change from baseline in femoral neck BMD at Month 6, Month 12 and Month 18 for the FAS is presented in the figure below.

Figure 13. Mean percent change from baseline in femoral neck BMD up to month 18 (full analysis set)



BMD = bone mineral density; % Change = [(value – baseline) / baseline] × 100; EOS = end of study

There are three types of measurements for the BMD result, original BMD measurement, instrument quality control (IQC) corrected BMD measurement, and IQC and cross-calibration (Xcal) corrected BMD measurement. IQC and Xcal corrected BMD measurement was used for analysis.

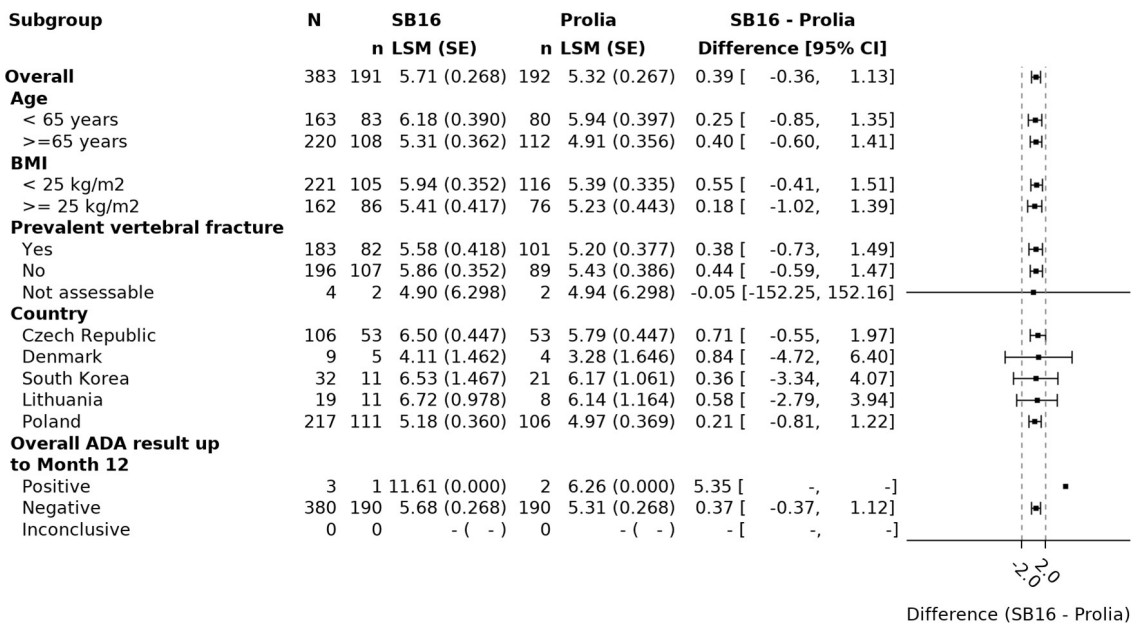
The symbol and error bar represented mean and standard error at each timepoint.

Subgroup Analyses

The primary efficacy endpoint, percent change from baseline in lumbar spine BMD at Month 12, was summarised and analysed for the following subgroups: ages (< 65 years and ≥ 65 years); country; BMI (< 25 kg/m^2 and ≥ 25 kg/m^2), presence of prevalent vertebral fracture, and the overall ADA results up to Month 12.

Confidence intervals were contained in the equivalence margins for the larger subgroups.

Figure 14. Forest plot for treatment difference of mean percent change from baseline in lumbar spine BMD at month 12 by subgroups per-protocol set



- BMD: bone mineral density; BMI: body mass index; ADA: anti-drug antibody; CI: confidence interval; LSM: least square mean; SE: standard error.
- Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor.

- **Ancillary analyses**

Sensitivity Analysis

To evaluate the robustness of the result for the percent change from baseline in lumbar spine BMD at Month 12 for the FAS under the assumption of missing at random, a tipping point analysis was performed. The tipping point is denoted as the delta adjustment that would have to be imputed to overturn a statistically significant result. Clinical judgement was also applied to the plausibility of the tipping point (delta adjustment).

The results of the sensitivity analyses performed in the FAS are summarised the table below. It is observed that generally, the missing Prolia population would have to have at least −4 to −6% less lumbar spine BMD improvement from baseline than the non-missing population average in order to result in non-equivalence. Since the average lumbar spine BMD improvement is around 5%, this would mean that the Prolia patients with missing data would have almost no improvement in lumbar spine BMD from baseline while the missing SB16 patients would have to show at least some improvement to result in non-equivalence.

Table 26. Tipping point analysis of percent change from baseline in lumbar spine BMD at month 12 (full analysis set)

	Prolia						
SB16	Delta=-6	Delta=-4	Delta=-2	Delta=0	Delta=2	Delta=4	Delta=6
Delta=-6							
LSM (SE)	0.66 (0.388)	0.43 (0.377)	0.21 (0.370)	-0.02 (0.367)	-0.24 (0.370)	-0.47 (0.377)	-0.69 (0.389)
90% CI	[0.02, 1.30]	[-0.19, 1.05]	[-0.40, 0.82]	[-0.62, 0.59]	[-0.85, 0.37]	[-1.09, 0.15]	[-1.33, -0.05]
95% CI	[-0.10, 1.42]	[-0.30, 1.17]	[-0.52, 0.93]	[-0.74, 0.70]	[-0.97, 0.48]	[-1.21, 0.27]	[-1.45, 0.07]
Delta=-4							
LSM (SE)	0.77 (0.382)	0.55 (0.370)	0.32 (0.363)	0.10 (0.361)	-0.13 (0.363)	-0.35 (0.371)	-0.58 (0.383)
90% CI	[0.15, 1.40]	[-0.06, 1.16]	[-0.27, 0.92]	[-0.49, 0.69]	[-0.72, 0.47]	[-0.96, 0.26]	[-1.21, 0.05]
95% CI	[0.03, 1.52]	[-0.18, 1.28]	[-0.39, 1.04]	[-0.61, 0.81]	[-0.84, 0.59]	[-1.08, 0.38]	[-1.33, 0.17]
Delta=-2							
LSM (SE)	0.89 (0.378)	0.67 (0.366)	0.44 (0.359)	0.22 (0.356)	-0.01 (0.359)	-0.23 (0.366)	-0.46 (0.379)
90% CI	[0.27, 1.51]*	[0.06, 1.27]	[-0.15, 1.03]	[-0.37, 0.80]	[-0.60, 0.58]	[-0.84, 0.37]	[-1.08, 0.16]
95% CI	[0.15, 1.63]	[-0.05, 1.38]	[-0.26, 1.14]	[-0.48, 0.91]	[-0.71, 0.69]	[-0.95, 0.48]	[-1.20, 0.28]
Delta=0							
LSM (SE)	1.01 (0.376)	0.78 (0.364)	0.56 (0.357)	0.33 (0.354)	0.11 (0.357)	-0.12 (0.365)	-0.34 (0.377)
90% CI	[0.39, 1.62]*	[0.18, 1.38]	[-0.03, 1.14]	[-0.25, 0.91]	[-0.48, 0.69]	[-0.72, 0.48]	[-0.96, 0.28]
95% CI	[0.27, 1.74]	[0.07, 1.49]	[-0.14, 1.26]	[-0.36, 1.03]	[-0.59, 0.81]	[-0.83, 0.60]	[-1.08, 0.39]
Delta=2							
LSM (SE)	1.12 (0.377)	0.90 (0.365)	0.67 (0.358)	0.45 (0.355)	0.22 (0.358)	-0.00 (0.366)	-0.23 (0.378)
90% CI	[0.50, 1.74]*	[0.30, 1.50]*	[0.08, 1.26]	[-0.14, 1.03]	[-0.37, 0.81]	[-0.61, 0.60]	[-0.85, 0.39]
95% CI	[0.38, 1.86]	[0.18, 1.61]	[-0.03, 1.37]	[-0.25, 1.14]	[-0.48, 0.92]	[-0.72, 0.71]	[-0.97, 0.51]
Delta=4							
LSM (SE)	1.24 (0.380)	1.01 (0.368)	0.79 (0.361)	0.56 (0.359)	0.34 (0.362)	0.11 (0.369)	-0.11 (0.381)
90% CI	[0.61, 1.86]*	[0.41, 1.62]*	[0.19, 1.38]	[-0.03, 1.15]	[-0.26, 0.93]	[-0.50, 0.72]	[-0.74, 0.51]
95% CI	[0.49, 1.98]	[0.29, 1.73]	[0.08, 1.50]	[-0.14, 1.27]	[-0.37, 1.05]	[-0.61, 0.84]	[-0.86, 0.63]
Delta=6							
LSM (SE)	1.35 (0.386)	1.13 (0.375)	0.90 (0.367)	0.68 (0.365)	0.45 (0.368)	0.23 (0.375)	0.00 (0.387)
90% CI	[0.72, 1.99]*	[0.51, 1.74]*	[0.30, 1.51]*	[0.08, 1.28]	[-0.15, 1.06]	[-0.39, 0.84]	[-0.63, 0.64]
95% CI	[0.60, 2.11]*	[0.39, 1.86]	[0.18, 1.62]	[-0.04, 1.39]	[-0.27, 1.17]	[-0.51, 0.96]	[-0.76, 0.76]

Source: Listing 16.2.6-1.1
- BMD: bone mineral density; CI: confidence interval; LSM: least square mean; SE: standard error.
- Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor. Missing primary endpoint was imputed using multiple imputation method under the assumption that subjects with missing data had, on average, worse or better BMD compared to those who had data observed. Difference in LSM between SB16 and Prolia, 90% CI, 95% CI were presented for each scenario.
- *: indicates the 90% CI for the difference in LSM between SB16 and Prolia is not fully within the pre-defined equivalence margin of [-1.45%, 1.45%] or 95% CI for the difference in LSM between SB16 and Prolia is not fully within the pre-defined equivalence margin of [-2.0%, 2.0%].

The results based on the available case using the FAS with 90% CI is reported in the table below.

Table 27. Available case analysis of percent change from baseline in lumbar spine BMD at month 12 (full analysis set)

				Difference (SB16 - Prolia)		
Timepoint	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
Month 12	SB16 (N=225)	212	5.65 (0.252)	0.35 (0.359)	[-0.24, 0.95]	[-0.35, 1.06]
	Prolia (N=231)	205	5.29 (0.256)			

Source: Listing 16.2.6-1.1
- BMD: bone mineral density; CI: confidence interval; LSM: least square mean; SE: standard error.
- Inferential statistics were based on analysis of covariance model with the baseline value of lumbar spine BMD as a covariate and treatment group as a fixed factor.

- **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 28. Summary of efficacy for trial SB16-3001

Title: A Phase III, Randomised, Double-blind, Multicentre Clinical Study to Compare the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity between SB16 (proposed denosumab biosimilar) and Prolia in Postmenopausal Women with Osteoporosis		
Study identifier	SB16-3001	
Design	Randomised, double-blind, multicentre clinical study <u>Main period</u> The main period was a clinical Phase III, randomised, double-blind, parallel group, multicentre, equivalence study to evaluate the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of SB16 compared to Prolia in PMO. Patients were randomised in a 1:1 ratio to receive either SB16 or Prolia subcutaneously at Months 0 and 6. <u>Transition period</u> At Month 12, patients who received Prolia in the main period of the SB16-3001 study were randomised again in a 1:1 ratio to either continue on Prolia (Prolia+Prolia) or were transitioned to SB16 (Prolia+SB16). Patients who received SB16 in the main period of the SB16-3001 study continued to receive SB16, but they also followed the randomisation procedure to maintain blinding. Patients were followed up to Month 18.	
	Duration of treatment:	Patients were administered subcutaneous 60 mg SB16 or Prolia once every 6 months for up to 18 months (total of 3 doses).
Hypothesis	Equivalence	
Treatment Group	SB16 (N = 225 randomised)	Patients were randomised to receive SB16 subcutaneously at Month 0, 6, and 12. At Month 12, patients who completed the scheduled Month 12 of the main period and were considered eligible entered into the Transition period. In the transition period, patients received SB16 in the main period continued to receive SB16, but they also followed the randomisation procedure to maintain blinding. Patients were followed up to Month 18.
	Prolia Overall (N = 232 randomised)	Patients were randomised to receive Prolia subcutaneously at Month 0, 6, and 12. At Month 12, patients who completed the scheduled Month 12 of the main period and were considered eligible entered into the transition period. In the transition period, patients who had received Prolia in the main period were randomised again in a 1:1 ratio to either continue on Prolia (Prolia+Prolia) or transitioned to SB16 (Prolia+SB16).
	Prolia+SB16 (N = 100 randomised)	At Month 12, patients who completed the scheduled Month 12 of the main period and were considered eligible entered into the transition period. In the transition period, half of the patients who received Prolia were randomised to transition to SB16 at Month 12.
	Prolia+Prolia (N = 101 randomised)	At Month 12, patients who completed the scheduled Month 12 of the main period and were considered eligible entered into the transition period. In the transition period, half of the patients who received Prolia were randomised to continue on Prolia at Month 12.
Endpoints and definitions	Primary endpoint	Percent change from baseline in lumbar spine BMD at Month 12
	Secondary efficacy endpoints	Percent change from baseline in lumbar spine BMD at Month 6 and 18 Percent change from baseline in total hip BMD at Month 6, 12 and 18 Percent change from baseline in femoral neck BMD at Months 6, 12 and 18

Database lock	Feb 13, 2023		
Results and Analysis			
Analysis description	**Primary Analysis** **Primary Endpoint: Percent change from baseline in lumbar spine BMD at Month 12**		
Analysis population	Per-protocol Set (PPS): PPS consisted of all Full Analysis Set (FAS) patients who have lumbar spine BMD assessment results at baseline and Month 12 without any major protocol deviations that have impact on the lumbar spine BMD assessment results.		
Descriptive statistics	Treatment group	SB16	Prolia
	Number of patients (n)	191	192
	LSMeans (Standard Error [SE]) of percent change from baseline in lumbar spine BMD at Month 12	5.71 (0.268)	5.32 (0.267)
Effect estimate per comparison	Adjusted difference [95% CI] (SB16 – Prolia)	0.39 [−0.36, 1.13]	
Notes	The clinical equivalence is demonstrated if the two-sided 95% confidence interval (CI) of the mean difference in percent change from baseline in lumbar spine BMD at Month 12 between SB16 and Prolia was within the pre-defined equivalence margin of [−2.0, 2.0].		
Analysis description	**Supportive Analysis for Primary Efficacy Variable**		
Analysis population	Full Analysis Set (FAS): FAS consisted of all Randomised Set (RAN) patients. Patients were analysed according to the treatment assigned at randomisation. However, patients who did not have any lumbar spine BMD assessment result after randomisation by accident and did not receive any IP during the study period were excluded from this analysis set.		
Descriptive statistics	Percent Change from Baseline in Lumbar Spine BMD at Month 12		
	Treatment group	SB16	Prolia
	Number of patients (n)	225	231
	Method: Multiple imputation (for missing values) LSMeans (SE) of percent change from baseline in lumbar spine BMD at Month 12	5.63 (0.250)	5.30 (0.254)
Effect estimate per comparison	Adjusted difference [95% CI] (SB16 – Prolia)	0.33 [−0.36, 1.03]	
Analysis description	**Secondary Efficacy Analysis**		
Analysis population	Full Analysis Set (FAS)		
Analysis description	Secondary Efficacy Endpoint: Percent Change from Baseline in Lumbar Spine BMD at Month 6		
Descriptive statistics	Treatment group	SB16	Prolia
	Number of patients (n)	225	231
	LSMeans (Standard Error [SE]) of percent change from baseline in lumbar spine BMD at Month 6	3.69 (0.238)	3.81 (0.240)
Effect estimate per comparison	Adjusted difference [95% CI] (SB16 – Prolia)	−0.12 [−0.78, 0.54]	

Analysis description	Secondary Efficacy Endpoint: Percent Change from Baseline in Lumbar Spine BMD at Month 18				
Analysis population	Full Analysis Set (FAS)				
Descriptive statistics	Treatment group	SB16+SB16	Prolia Overall	Prolia+SB16	Prolia+Prolia
	Number of patients (n)	206	201	100	101
	LSMeans (Standard Error [SE]) of percent change from baseline in lumbar spine BMD at Month 18	6.77 (0.286)	6.54 (0.291)	6.28 (0.412)	6.80 (0.411)
Effect estimate per comparison	Adjusted difference [95% CI]	-	0.23[a] [−0.57, 1.03]	−0.52[b] [−1.66, 0.62]	−0.03[c] [−1.01, 0.95]
Analysis description	Secondary Efficacy Endpoint: Percent Change from Baseline in Total Hip BMD at Month 6, 12 and 18				
Analysis population	Full Analysis Set (FAS)				
Descriptive statistics and timepoint	Treatment group	SB16	Prolia Overall	Prolia+SB16	Prolia+Prolia
	Number of patients (n)	225	231	100	101
	Mean (± Standard Deviation [SD]) of percent change from baseline in total hip BMD at Month 6	2.779 (2.4628)	2.239 (2.3691)	-	-
	Mean (± SD) of percent change from baseline in total hip BMD at Month 12	3.503 (2.7537)	3.247 (2.6638)	3.049 (2.4572)	3.491 (2.8743)
	Mean (± SD) of percent change from baseline in total hip BMD at Month 18	4.407 (3.1586)	3.758 (3.0155)	3.517 (2.9258)	3.999 (3.0986)
Analysis description	Secondary Efficacy Endpoint: Percent Change from Baseline in Femoral Neck BMD at Month 6, 12 and 18				
Analysis population	Full Analysis Set (FAS)				
Descriptive statistics and timepoint	Treatment group	SB16	Prolia Overall	Prolia+SB16	Prolia+Prolia
	Number of patients (n)	225	231	100	101
	Mean (± SD) of percent change from baseline in femoral neck BMD at Month 6	2.106 (3.5558)	1.773 (3.3493)	-	-
	Mean (± SD) of percent change from baseline in femoral neck BMD at Month 12	2.794 (4.2197)	2.296 (3.3633)	2.439 (3.2580)	2.373 (3.3197)
	Mean (± SD) of percent change from baseline in femoral neck BMD at Month 18	3.365 (4.0452)	2.928 (3.4800)	3.121 (3.4521)	2.735 (3.5145)

- = not applicable
[a] Difference (A – B), A: SB16+SB16, B: Prolia Overall
[b] Difference (A – B), A: SB16+SB16, B: Prolia+Prolia
[c] Difference (A – B), A: Prolia+SB16, B: Prolia+Prolia

2.5.5.3. Clinical studies in special populations

Not applicable

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

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

Not applicable

2.5.5.6. Supportive study(ies)

Not applicable

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study SB16-3001 was a randomised, double-blind, multicentre, phase III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of SB16 and EU-authorised Prolia. The study was conducted in 40 investigational sites across five countries (Czech Republic, Denmark, Lithuania, Poland, Republic of Korea). Subjects were randomised in a 1:1 ratio for the main treatment period (12 months). In the transition period (Month 12-18) subjects receiving EU-Prolia were re-randomised to receive either SB16 or EU-Prolia. The subjects received in total three subcutaneous doses of SB16 or EU-Prolia. Overall, the design of study SB16-3001 is acceptable and is generally in agreement with previous Scientific Advice received from EMA (EMEA/H/SA/4025/1/2018/III). Specific design aspects will be discussed below.

The study was conducted in the PMO indication. For all indications of Prolia/Xgeva, the mechanism of action of denosumab is identical, i.e. binding to RANK-L and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalised bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Because of the same mechanism of action, it is considered that the efficacy results can be extrapolated to all indications. This is endorsed.

Study SB16-3001 was conducted in 40 study centres in five countries (Czech Republic, Denmark, Lithuania, Poland and Republic of Korea). The inclusion of Asian and White subjects within one study could have reduced the sensitivity of the studied population as there could have been potential differences between the Asian and White population. However, the baseline characteristics and the country-specific efficacy analyses do not give rise to concerns regarding differences in the Asian and White population that could have affected the sensitivity of the studied population. Therefore, the selection of countries and study centres is regarded acceptable.

For study SB16-3001, a population consisting of postmenopausal women with osteoporosis was selected. The main inclusion criteria were "postmenopausal women", "age between 55-80 years", "body weight between 50.0 and 90.0 kg". These inclusion criteria are regarded adequate for the intended purpose. Another inclusion criterion was "absolute bone mineral density consistent with T-score at the total hip or lumbar spine of ≥-4.0 and ≤-2.5. In general, the inclusion of postmenopausal women with a T-score of ≥-4.0 and ≤-2.5 is in line with state of art definition of the WHO. However, for the inclusion criterion, it would have been preferable to limit T-score measurement to the lumbar spine. The definition including total hip or lumbar spine led to a situation where patients with a T-score ≤-4.0 or ≥-2.5 at the lumber spine and therefore representing a population of more/less severe patients were included in the study. This reduced the homogeneity of the studied population. However, as only

a small number of patients with a T-score ≤-4.0 or ≥-2.5 at the lumbar spine were included and baseline characteristics regarding T-score at lumber spine were overall comparable between groups, no further concern is raised on this issue. The exclusion criteria were chosen to recruit a population without previous exposure to denosumab or ongoing use of any osteoporosis treatment. The washout periods for previous osteoporosis treatments are also adequately reflected. For the participation in the transition period, subjects must have been enrolled and completed the month 12 visit of the main period. This is also acceptable. Overall, the inclusion and exclusion criteria are considered appropriate for recruitment of a population consisting of postmenopausal women with a diagnosis of osteoporosis. In addition, it is agreed that the chosen study population is appropriate to conduct a biosimilar study with denosumab as it is regarded a sensitive population to identify, or exclude, differences between the test and the reference product, if existent.

At month 0, subjects were randomised in a 1:1 ratio to one of the two treatments groups SB16 or EU sourced Prolia. For the transition period, subjects in the EU-Prolia group were re-randomised in a 1:1 ratio to further receive EU-Prolia or switch to SB16 after month 12. Subjects in the initial SB16 group continued their initial treatment. Overall, the process of randomisation was adequately described and is considered acceptable. A subject randomisation list was also provided, which is endorsed. In the Scientific Advice received from EMA (EMEA/H/SA/4025/1/2018/III), the applicant was recommended to stratify for age, body weight/BMI and previous oral BP use. However, the applicant did not follow this advice regarding stratification factors and only stratified for study centre. Nonetheless, the baseline characteristics were well balanced between the SB16 and EU-Prolia group and no concerns arise.

Study SB16-3001 was a double-blind study, with subjects, investigators and other study personnel being blinded throughout the study. In order to ensure blinding, a blinding cap was applied to the IP PFS (SB16 or Prolia) and packaging and labelling was identical. The process of blinding was adequately described and is considered acceptable.

The participants from study SB16-3001 each received three subcutaneous doses of study drug (SB16 or EU sourced Prolia) at 6-month intervals. The route of administration is in line with the recommendations of the Prolia SmPC. The chosen dose of 60 mg every 6 months is also according to the posology recommendations from the Prolia SmPC for the treatment of osteoporosis and is regarded adequate for the assessment of biosimilarity of the test and reference product. All enrolled subjects received calcium (1 g/day) and vitamin D (800 IU/day) supplementation from screening until the end of the study, which is endorsed. In the clinical efficacy and safety studies for the initial marketing authorisation of the reference product, women received 1g/day calcium and 400 IU/day vitamin D. However, the higher supplementation with vitamin D in this study is not of concern.

Several medications were prohibited during the study. These included Xgeva, drugs used for treatment of osteoporosis, drugs affecting bone metabolism and any kind of monoclonal antibodies. This is endorsed.

The applicant provided a definition of the primary and supportive estimands of the study, which is acknowledged. Of note, the IEs and strategies how to handle those were not addressed for the EMA submission. However, as results were presented both for the PPS and FAS, no issue arises for this biosimilar application.

The primary endpoint of this study was the percent change from baseline in lumbar spine BMD at Month 12. This is principally acceptable. However, as also discussed in EMA Scientific Advice procedure EMEA/H/SA/4025/1/2018/III, it would have been preferable to include both lumbar BMD and serum CTX as co-primary endpoints. BMD is a quantitative predictor of osteoporotic fractures in postmenopausal women without previous fracture. However, the causal link (surrogacy) between the marker and longer-term endpoints has not been unequivocally proven. (GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PRIMARY OSTEOPOROSIS,

CPMP/EWP/552/95 Rev. 2). After denosumab treatment, the changes in BMD are slow and modest, while the changes in serum CTX are large and dynamic. Thus, serum CTX might be more sensitive to compare test and reference product in terms of biosimilarity, however, the clinical relevance might be higher for BMD, which is often used in clinical trials. Thus, the choice of these endpoints as co-primary endpoints for study SB16-3001 would have been more appropriate. Of note, the area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX was included as a secondary PD endpoint and the analysis of "Area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX" was pre-specified in the protocol. However, the fact that this has not been defined as a co-primary endpoint is addressed in this assessment by treating the results on serum CTX as co-primary. Thus, the applicant was asked to present the ratio of least-squares geometric mean (SB16 vs. Prolia) with the corresponding 95% CI. The applicant provided the requested analyses, which support the main analysis.

The equivalence margin for the efficacy analysis was derived from a meta-analysis of three historical studies with Prolia. According to the applicant, a margin of 2% retains at least 60% of the minimum treatment effect. Of note, in the EMA-Scientific advice (EMEA/H/SA/4025/1/2018/III), a margin of 2.29% was deemed principally acceptable, but it was preferred by CHMP to have a smaller margin of e.g. 2%. Thus, the margin chosen by the applicant is in line with the recommendations of the CHMP and is thereby accepted.

The efficacy parameter BMD was assessed using only GE Lunar or Hologic machines. The DXA device had to be certified by the central reading centre. Subjects had to be scanned on the same DXA machines at each timepoint. The assessments were performed equally between treatment arms. This is regarded acceptable. Additionally, the applicant provided a well-structured schedule of activities, which is endorsed.

The secondary objectives included PK, PD, efficacy, safety and immunogenicity aspects of SB16 and the reference product. The objectives also included an evaluation of PK, PD, efficacy, safety and immunogenicity aspects after a transition of subjects from Prolia to SB16. Overall, the secondary objectives of the study are endorsed.

The secondary efficacy endpoints were the percent change from baseline in BMD at lumbar spine, femoral neck, and total hip at month 6 and the percent change from baseline in femoral neck BMD and total hip BMD at month 12. This is considered adequate to support the primary efficacy endpoint.

The secondary PD endpoints consisted of CTX and P1NP serum concentrations at months 0, 0.5, 1, 3, 6, 9, and 12. In addition, the area under the effect curve from time zero to Month 6 ($AUEC_{0\text{-}M6}$) of percent change from baseline in serum CTX was defined as a secondary PD endpoint. The secondary PD endpoints are considered acceptable to support the demonstration of PD similarity of SB16 and EU-Prolia.

The PK endpoint in this study was the serum drug concentration at month 0, 0.5, 1, 3, 6, 9, and 12. No further analyses on PK parameters were foreseen in this study and the PK sampling was also sparse. However, for the assessment of the PK profile in a Phase 3 study in patients and in light of the availability of the PK/PD study SB16-1001, this is regarded acceptable.

Fracture incidence during the study was not assessed as a secondary endpoint, which would have been preferable. Instead, fractures were monitored as an adverse event of special interest (AESI), see below discussion on clinical safety. Vertebral fractures can affect the measurement of BMD at the lumbar spine, i.e. false increase in BMD may be observed due to compression of the bone. Only one patient in the Prolia group had a vertebral fracture and thus a false high BMD value in that patient would have been in favour of Prolia rather than SB16 and thus not of concern.

The planned main analysis is adequate to test the primary hypothesis of similarity of SB16 to Prolia with respect to percent change in lumbar spine BMD after 12 months. The supportive analyses provide value in assessing the robustness of the main analysis. The impact of a deviation from the missing at random assumption is assessed in a tipping-point analysis and results for pre-defined subgroups are presented.

The sample size was based on the analyses for the marketing authorisation application submitted to the FDA. The primary analysis for the marketing authorisation submitted to the EMA would have required fewer subjects under the same assumptions. The sample size is therefore adequate to assess the primary endpoint of the European MAA.

The main analysis was changed from a linear mixed model to an analysis of covariance and the values for lumbar spine BMD were adjusted for cross-calibration of the DMX devices in protocol version 2.0, before unblinding. It was requested to include centre effect in the analysis to reflect the stratification applied at randomisation (Guideline on adjustment for baseline covariates in clinical trials). The applicant provided the requested analysis. The results were within the equivalence margin of -2 to 2 thus confirming the main analysis.

The primary efficacy analysis was performed for the per protocol (PP) analysis set (number of patients 191 and 192 in the SB16 and Prolia treatment groups, respectively for the 12-month treatment period) using an analysis of covariance (ANCOVA) with the baseline value of lumbar spine BMD as a covariate and treatment group as a factor. The applicant argued that inclusion of the centre in the model is not necessary after cross-calibration of BMD measurements. The applicant was requested to repeat the primary analysis adjusting for centre in the ANCOVA model. The applicant provided the requested analysis. The results were within the equivalence margin of -2 to 2 thus confirming the main analysis.

The analyses applied for the pharmacokinetic and pharmacodynamic endpoints are adequate to assess similarity in the respective endpoints. The calculation of the $AUEC_{0\text{-}6M}$ for serum CTX change from baseline would not capture different extent of rebound in the treatment arms. The applicant was therefore asked to repeat the analysis for the pharmacodynamic parameter using $netAUEC_{0\text{-}6M}$. The applicant provided the requested analysis. Use of net AUEC in place of AUEC did not meaningfully change the estimated mean ratio and confirmed similarity within the conventional margin of 0.8-1.25. Rebound occurred in few subjects (3 in the SB16 group and 6 in the Prolia group) and the rebound area was highly variable but small with respect to the total net AUEC.

The protocol of the study was amended twice. One amendment was specific for the Republic of Korea and the other was a global amendment. The major changes of the global amendment were the addition of information on major protocol deviations, addition of BMD evaluation at month 6 as secondary objective, addition of the analysis method for PD assessment and a revision of the immunogenicity endpoints. This is acceptable.

The study started on 26-Nov-2020 with the first subject signing informed consent and was completed on 03-Jan-2023 with the last subject last assessment. Of note, date of the document version for the SAP was 31-Jan-2023. Thus, the SAP was finalised after the last subject last assessment. This is acceptable, as the database lock was on 13-Feb-2023 and therefore after the SAP finalisation and prior to unblinding for this double-blind study.

Overall, the participant flow is described in sufficient detail. Of the 998 screened subjects, 457 subjects were randomised in a 1:1 ratio. Major reasons for screen failures were not meeting the eligibility criteria (423 subjects), consent withdrawal (114 subjects) and other (4 subjects). This is regarded acceptable. Of the 457 randomised subjects, 417 completed the main period. 50 subjects withdrew in main period before transition period. The reasons for discontinuation were consent withdrawal (10 subject in the SB16 group; 19 subjects in the EU-Prolia group), adverse event (4 subject in the SB16

group; 8 subjects in the EU-Prolia group), protocol deviation (0 subject in the SB16 group; 2 subjects in the EU-Prolia group), lack of efficacy or disease progression (4 subjects in the SB16 group; 1 subject in the EU-Prolia group), investigator's discretion (1 subject in the SB16 group; 0 subjects in the EU-Prolia group) and other (0 subject in the SB16 group; 1 subject in the EU-Prolia group). Thus, the number of subjects completing the main period was high. In addition, the number of subjects discontinuing the study and reasons for discontinuation were similar between the groups. Of the 407 subjects re-randomised for the transition period, 404 completed the transition period. The primary reasons for discontinuation during transition period was consent withdrawal (1 subject in the Prolia/SB16 group and 2 subjects in the Prolia/Prolia group). Thus, the number of subjects completing the transition period was high.

The number of subjects with any protocol deviation during the study was 217. The numbers were similar between the treatment groups. 197 subjects had at least one major protocol deviation. 24 subjects in the SB16 group and 20 subjects in the Prolia treatment group were excluded from the per-protocol set due to major protocol deviations (inclusion criteria, exclusion criteria, study procedure criteria or concomitant medication criteria). Exclusion from the per-protocol set due to concomitant medication criteria concerned 14 subjects in the SB16 group and 7 subjects in the Prolia group. The applicant was asked to explain this imbalance. The applicant provided a listing of the patients excluded from the PPS due to concomitant medication criteria with the specific reason for medication. Most of the prohibited medications were glucocorticoids or heparin use. The AE leading to medication were not related to IP. Thus, it is agreed to the applicant that the imbalance in exclusion from the per-protocol set due to concomitant medication criteria between SB16 and Prolia group (14 versus 7 subjects) might be a chance finding.

Furthermore, the applicant provided an overview of the number of subjects per analysis set. The number of subjects randomised to the study was 457. The Full analysis set included 456 subjects. The PPS set included 383 subjects. According to table 21, 24 subjects in the SB16 group and 20 subjects in the Prolia group were excluded from the PPS due to major protocol deviations and the reasons for exclusion were also provided in detail. In addition, the applicant provided a listing with protocol deviations by subject and a listing with subjects excluded from any analysis set with reason. This is acknowledged.

There were several subjects with major protocol deviations (39.1% in the SB16 group and 36.6% in the Prolia group) who were not excluded from the per-protocol set. The reasons why some major protocol deviations led to exclusion from PPS, while others did not, were not obvious. After request, the applicant clarified that the major protocol deviations leading to exclusion from the PPS were pre-defined in the PD definition list. Final decision on exclusion from the PPS, based on the PD definition list, was confirmed through a blind data review meeting. The applicant also provided a report of this blinded data review meeting. This is acknowledged.

Overall, the demographic characteristics were well balanced between the SB16 and EU-Prolia group for the randomised set. The mean age was 66.5 and 66.3 years, respectively. Most of the subjects in the study were "White" (90.8%), 9% were of Asian origin. The race and ethnicity aspects were well balanced between the groups. In addition, the height, weight and BMI of the subjects was comparable among the groups. Thus, the demographics data show that a very homogeneous population of female subjects with a diagnosis of osteoporosis was recruited. Additionally, the demographic characteristics were also similar among the groups in the transition period. This is appropriate. The applicant also provided an overview of the baseline characteristics for the pharmacokinetic and pharmacodynamic analysis sets. Also in these sets, the baseline characteristics were well balanced between the SB16 and EU-Prolia group and no concerns arise. The applicant also provided an overview of other baseline characteristics. The mean years since menopause, previous fracture history, vitamin D levels, BMD of lumbar spine/total hip/femoral neck, T-score at lumbar spine/total hip/femoral neck, current smoking

status and current alcohol consumption status are comparable between the SB16 and EU-Prolia group. Similarly, these factors are also comparable among the groups in the transition period.

Patients with prevalent vertebral fractures constituted about half of the patients, about 12% had 2 prevalent fractures and about 20% had a history of > 2 vertebral fractures. Stratification of patients at inclusion was not done but would have been preferable to reduce imbalance between treatment groups. Stratification by weight should also have been considered, instead the applicant choose to limit the weight range which is acceptable.

The mean years since diagnosis of PMO was 3.34 years for the SB16 group and 2.86 years for the Prolia group. Thus, there is a slight imbalance with subjects in the SB16 group having their diagnosis about half a year longer than the subjects in the Prolia group. In addition, 18.7% in the SB16 group and 14.2% in the Prolia group had a history of oral BP. The total cumulated period of oral BP treatment prior to screening was also longer for the SB16 group (15.4 months in the SB16 group versus 13 months in the Prolia group). This is further reflected in the duration of oral BP administration, with a higher percentage of subjects in the SB16 group having more than 1 year and more than 2 years of oral BP administration compared to the Prolia group. The applicant was asked to reflect on this issue and provide data in how far these discrepancies might have had an impact on the efficacy analysis. The applicant has provided sensitivity analyses to assess the impact of the imbalance in "mean years since diagnosis" and "use of oral BP prior to screening" between the groups. The sensitivity analyses support the results of the main analysis. Thus, no further concern is raised on this issue.

Efficacy data and additional analyses

The percent change from baseline in lumbar spineBMD at Month 12 was 5.71% for the SB16 group and 5.32% for the EU-Prolia group. The primary efficacy analysis revealed that the difference between the SB16 and the EU-Prolia group for the per protocol set was 0.39% with the corresponding 95% CI being -0.36% and 1.13%. Thus, the 95% CI was within the pre-specified equivalence range of [-2.0%, 2.0%] and the primary efficacy endpoint was met. The 95% confidence interval for the primary endpoint also lies entirely within this equivalence range for the full analysis set, supporting biosimilarity.

For the primary efficacy endpoint, subgroup analyses by age (< 65 years and ≥ 65 years); country; BMI (< 25 kg/m^2 and ≥ 25 kg/m^2), presence of prevalent vertebral fracture, and overall ADA results up to Month 12 were provided. These are generally consistent with the primary endpoint analysis, although for smaller subgroups (e.g. country) the confidence intervals were not contained within the pre-specified margin. Results were similar for the PPS and FAS. The predefined subgroup analyses support the conclusion of the main analysis and no concerns arise from these subgroup analyses. Moreover, the applicant provided several sensitivity analyses which all supported the primary efficacy endpoint analysis. In a tipping point analysis, the missing Prolia population would have to have at least −4 to −6% less lumbar spine BMD improvement from baseline than the non-missing population average in order to result in non-equivalence. Since the average lumbar spine BMD improvement is around 5%, this would mean that the Prolia patients with missing data would have almost no improvement in lumbar spine BMD from baseline while the missing SB16 patients would have to show at least some improvement to result in non-equivalence. This is considered an unlikely scenario and therefore this is accepted.

The secondary endpoint percent change from baseline in lumbar spine BMD at month 6 was 3.69% for the SB16 group and 3.81% for the EU-Prolia group. Thus, the percent change from baseline in lumbar spine BMD at month 6 was similar for both groups, supporting the primary endpoint analysis. Similar results were seen for the per protocol set and the full analysis set. In addition, the percent change from baseline in lumbar spine BMD at month 18 was similar among the different treatment groups.

Thus, the switch from Prolia to SB16 does not seem to cause any difference in terms of lumbar spine BMD compared to staying on the same product.

The percent change from baseline in total hip BMD at month 6 was 2.78% for the SB16 group and 2.24% for the EU-Prolia group. The percent change from baseline in total hip BMD at month 12 was 3.5% for the SB16 group and 3.25% for the EU-Prolia group. Thus, the percent change from baseline in total hip BMD at month 6 was slightly lower for the EU-Prolia group compared to the SB16 group. The same holds true for month 12. Nevertheless, no concern arises from these secondary endpoint results, which are overall comparable between the groups. Thus, the results in the total hip BMD support the results seen in the lumbar spine BMD. In addition, the percent change from baseline in total hip-BMD at month 18 was similar among the different treatment groups. Thus, the switch from Prolia to SB16 does not seem to cause any difference in terms of total hip-BMD compared to staying on the same product.

The percent change from baseline in femoral neck BMD at month 6 was 2.11% for the SB16 group and 1.77% for the EU-Prolia group. The percent change from baseline in femoral neck BMD at month 12 was 2.79% for the SB16 group and 2.29% for the EU-Prolia group. Thus, the percent change from baseline in femoral neck BMD at month 6 was slightly lower for the EU-Prolia group compared to the SB16 group. The same holds true for month 12. Nevertheless, no concern arises from these secondary endpoint results, which are overall comparable between the groups. Thus, the results in the femoral neck BMD support the results seen in the lumbar spine BMD. In addition, the percent change from baseline in femoral neck BMD at month 18 was similar among the different treatment groups. Thus, the switch from Prolia to SB16 does not seem to cause any difference in terms of femoral neck BMD compared to staying on the same product.

2.5.7. Conclusions on the clinical efficacy

In study SB16-3001, the primary efficacy analysis based on the percent change from baseline in lumbar spine BMD at month 12 was met as the 95% CI of the difference between the SB16 and the EU-Prolia group was within the pre-specified equivalence criteria. This was further supported by secondary endpoint and sensitivity analyses. The provided efficacy data support the biosimilarity of SB16 and EU-Prolia.

Taking into account the common mechanism of action across all indications, the CHMP considers that the results of the study using Prolia as comparator are relevant for the demonstration of comparable efficacy between Xbryk and Xgeva. Thus, the provided efficacy data support the biosimilarity of Xbryk and Xgeva.

2.5.8. Clinical safety

The clinical safety of SB16 has been assessed in two clinical studies, a clinical Phase I PK study in healthy male subjects (SB16-1001) and a clinical Phase III efficacy and safety study in patients with postmenopausal osteoporosis (PMO) (SB16-3001). Safety of SB16 in these studies was assessed by monitoring adverse events (AEs), serious AEs (SAEs), adverse events special interest (AESI) (e.g. 'hypocalcaemia', 'hypersensitivity to IP', 'osteonecrosis of the jaw', 'atypical femoral fractures', and 'skin infections'), vital signs, and laboratory evaluations as well as immunogenicity, which is an important safety aspect of therapeutic proteins.

As SB16 is a proposed biosimilar to Prolia, the safety and tolerability profiles of SB16 have been compared against those of Prolia. Key safety data are derived from the clinical Phase III study (SB16-3001) in patients with PMO, with additional safety data from the clinical Phase I study (SB16-1001) in

healthy male subjects. Due to the heterogeneity of the study populations and differences in the treatment regimens including the duration of exposure, a pooled safety analysis of two studies was not performed.

Following the posology of the originator Prolia, patients were supplemented with calcium (at least 1000 mg/day) and vitamin D (at least 400 IU/day in study 1001 and at least 800 IU/day in study 3001) during the treatment period and patients. Supplementation of calcium and vitamin D in Phase 1 started on day -1 and in phase 3 at randomisation. In both the phase 1 and phase 3 trial, calcium levels were regularly investigated, and serum vitamin D levels were assessed in regular intervals in the phase 1 trial, and in phase 3 at screening, and at the 6 & 12 month visit prior to dosing. Additionally, the following exclusion criteria were implemented to address the risk of hypocalcaemia:

Trial 1001 (healthy volunteers)

- Albumin-adjusted serum calcium levels below the lower limit of normal (LLN) or above the upper limit of normal (ULN)
- Intolerance to calcium or vitamin D supplements

Trial 3001 (patients with PMO)

- Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L]) at Screening
- Hypercalcaemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcaemia > 2.62 mmol/L [10.5 mg/dL]) at Screening
- Inability to tolerate long-term calcium or vitamin D supplementation or malabsorption of calcium or vitamin D supplements, in the opinion of the Investigator, at Screening

Subjects with presence, risk, or history of osteonecrosis of the jaw were excluded from both trials. Risk factors for ONJ leading to exclusion included invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) or active periodontal disease within 180 days prior to Randomisation.

In study 1001, safety assessments after a single subcutaneous dose of 60 mg study drug included continuous adverse event monitoring, physical examination, 12-lead ECG, vital signs (blood pressure, pulse rate and body temperature), clinical laboratory tests (serology, haematology and chemistry including calcium and vitamin D, urinalysis), injection site assessment and blood sampling for immunogenicity analysis (ADAs and NAbs).

<u>Study 1001 - safety endpoints</u>

- Adverse events (AEs) and serious AEs (SAEs)
- Clinical laboratory tests including haematology, chemistry, and urinalysis
- 12-lead ECG
- Vital signs
- Physical examination
- Injection site assessment

<u>Study 1001 - immunogenicity endpoints</u>

- Incidence of anti-drug antibodies (ADAs) to denosumab
- Incidence of neutralising antibodies (NAbs) to denosumab

In study 3001 safety assessments after dosing included vital signs (body temperature measurement, blood pressure, and heart rate), physical examination, haematology, biochemistry tests, ISRs, and immunology assessment (ADAs and NAbs). 12-lead ECG was performed at screening. Study 3001 consisted of two treatment periods: a 12 month main period, during which patients were randomised 1:1 to either SB16 or Prolia; and a 6 month transition period during which patients in the SB16 group continued SB16 treatment and patients in the Prolia group were randomised 1:1 to either SB16 or Prolia. After randomisation, the subjects received the first dose of SB16 or Prolia 60 mg via subcutaneous injection (Month 0) and the second dose at Month 6 in the main period. A third dose was administered in the transition period (Month 12).

The safety analyses for the Screening, Main, and Overall study periods were carried out using the SAF1, which was defined as all subjects who received at least 1 dose of IP. SAF2 consisted of all subjects in the SAF1 who received IP after re-randomisation at Month 12. Subjects were analysed according to the treatment received.

Study 3001 - safety endpoints

- Incidence of adverse events (AEs)
- Incidence of serious AEs (SAEs)

Study 3001 – immunogenicity endpoints

- Incidence of anti-drug antibodies (ADAs) at Months 0, 0.5, 1, 3, 6, 9, and 12 and at month 18
- Incidence of neutralising antibodies (NAbs) at Months 0, 0.5, 1, 3, 6, 9, and 12 and at month 18

For the purpose of this document, the following definitions apply:

'*Adverse event – AE*' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'*Serious adverse event – SAE*' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'*Adverse Drug Reaction – ADR*' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

Table 29. Overview of the clinical development plan for evaluation of safety similarity

Type of Study Identifier (Country) Status	Objective(s) of the Study	Subjects/Patients	Study Design Duration	Treatments	Safety Endpoints
Phase I **SB16-1001** (1 center in France 2 centers in US) Completed	Primary objective: To demonstrate the pharmacokinetic (PK) similarity between SB16 and EU Prolia, between SB16 and US Prolia, and between EU Prolia and US Prolia in healthy male subjects. Secondary objective: To investigate and compare the pharmacodynamic (PD), safety, tolerability, and immunogenicity between SB16 and EU Prolia, between SB16 and US Prolia, and between EU Prolia and US Prolia in healthy male subjects.	Healthy male subjects Randomized Set (RAN): N = 168 SB16: 56; US Prolia: 56; EU Prolia: 56 Safety Set (SAF): N = 168 SB16: 56; US Prolia: 56; EU Prolia: 56	Randomized, double-blind, three-arm, parallel group, single-dose study Approximately 32 weeks (including 28 days of Screening period).	A single-dose 60 mg of either SB16 or US Prolia or EU Prolia subcutaneous (SC) injection	• Adverse events (AEs) and serious adverse events (SAEs) • Clinical laboratory tests including hematology, chemistry, and urinalysis • 12-lead electrocardiogram (ECG) • Vital signs • Physical examinations • Injection site assessment
Phase III **SB16-3001** 40 investigational centers in 5 countries (Czech Republic, Denmark, Lithuania, Poland, Republic of Korea) Completed	Primary objective: The primary objective of this study was to demonstrate the equivalence of SB16 to Prolia, in terms of percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12 in patients with postmenopausal osteoporosis (PMO). Secondary objective: To evaluate the efficacy of SB16 compared to Prolia by percentage change from baseline in lumbar spine BMD, percentage change from baseline in total hip BMD, percentage change from baseline in femoral neck BMD. To evaluate the PK profile, PD profile, immunogenicity, and safety and tolerability of SB16 compared to Prolia. To evaluate the safety, tolerability, immunogenicity, PK, PD, and efficacy in patients with PMO who transitioned to SB16 from Prolia compared to patients who maintained Prolia from the Main period.	Patients with PMO Randomized Set (RAN): N = 457 (SB16: 225, Prolia overall: 232, Prolia+SB16: 100, Prolia+Prolia: 101) Full Analysis Set (FAS): N = 456 (SB16: 225, Prolia overall: 231, Prolia+SB16: 100, Prolia+Prolia: 101) Safety Set 1 (SAF1): N = 456 (SB16: 225, Prolia overall: 231, Prolia+SB16: 100, Prolia+Prolia: 101) Safety Set 2 (SAF2): N = 407 (SB16: 206, Prolia overall: 201, Prolia+SB16: 100, Prolia+Prolia: 101)	Randomized, double-blind, parallel group, multicenter clinical study Total duration of treatment of approximately 18 months.	Patients were administered SC 60 mg SB16 or Prolia once every 6 months for up to 18 months (total of 3 doses).	• Incidence of adverse events (AEs) • Incidence of serious AEs (SAEs)

AE = adverse event; BMD = bone mineral density; ECG = electrocardiogram; PD = pharmacodynamic(s); PMO = postmenopausal osteoporosis; PK = pharmacokinetic(s); SAE = serious AE; SC = subcutaneous

Study 1001 – healthy volunteers:

Physical examination, 12-lead ECG, vital signs, clinical laboratory tests, immunogenicity data and injection site assessment was performed at regular intervals throughout the study period. Non IP administration and adverse events were continuously assessed.

Study 3001 – patients with PMO:

Physical examination, vital signs, haematology, biochemistry tests, urinalysis, immunogenicity data and injection site assessment were performed at regular intervals throughout the study period. ECG evaluation was performed at baseline. Non-IP administration and adverse events were continuously assessed, the method of data collection is not specified in the CSR. In the SAF1, safety data was provided separately for the main study period and transition study period as well as for the overall period and in the SAF2, data was reported for each of the three treatment groups (SB16+SB16, Prolia+SB16, Prolia+Prolia).

2.5.8.1. Patient exposure

Exposure data are available for the following studies and populations:

Study 1001: Healthy male volunteers received a single subcutaneous injection of 60 mg study drug (SB16, EU-Prolia, or US-Prolia). To minimise the risk of hypocalcaemia, subjects received daily calcium

(at least 1,000 mg) and vitamin D (at least 400 IU) during the treatment period. A total of 438 subjects were screened, of whom 168 subjects were randomised. 56 subjects each received one dose of SB16, EU Prolia, and US Prolia. The Safety Set (SAF) consisted of all subjects who received investigational product (IP). The duration of study participation was approximately 32 weeks including 28 days of screening period per subject.

Study 3001: Female patients with postmenopausal osteoporosis initially received two subcutaneous injections of 60 mg of either SB16 or EU-Prolia at 6-month intervals (Main study period). Then, patients who received SB16 received an additional dose of SB16, and patients who received EU-Prolia were randomised 1:1 to receive either one dose of SB16, or EU-Prolia (transition period). The duration of study participation was 18 months per subject.

- SAF1: The Safety Set 1 (SAF1) consisted of all patients who received at least one IP n= 456 (SB16: 225, Prolia overall: 231, Prolia+SB16: 100, Prolia+Prolia: 101).
- SAF2: The Safety Set 2 (SAF2) consisted of all patients in the SAF1 who received IP after re-randomisation at Month 12. N=407
  (SB16: 206, Prolia overall: 201, Prolia+SB16: 100, Prolia+Prolia: 101)

Table 30. Study 3001 - Patient exposure

Exposure	SB16 N = 225	Prolia			Total N = 456
		Overall N = 231	SB16[a] N = 100[a]	Prolia[a] N = 101[a]	
Number of IP administration, n (%)					
1 injection	9 (4.0)	20 (8.7)	-	-	29 (6.4)
2 injections	10 (4.4)	10 (4.3)	-	-	20 (4.4)
3 injections	206 (91.6)	201 (87.0)	100 (100.0)	101 (100.0)	407 (89.3)
Duration of Exposure to IP (days) in Main period (up to Month 12)					
n	225	231	-	-	456
Mean	351.8	338.2	-	-	344.9
SD	45.74	74.50	-	-	62.31
Median	359.0	359.0	-	-	359.0
Min, Max	16, 372	6, 372	-	-	6, 372
Duration of exposure to IP (days) in Overall study period (up to Month 18)					
n	225	231	100	101	456
Mean	518.5	496.4	543.4	542.9	507.3
SD	88.04	129.03	3.99	4.29	111.15
Median	541.0	541.0	542.0	541.0	541.0
Min, Max	16, 553	6, 561	540, 561	523, 554	6, 561

IP = investigational product; Max = maximum; Min = minimum; N = total number of patients in Safety Set 1 in each treatment group; SD = standard deviation; - = not applicable
[a] Based on patients in the SAF2, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.
Percentages were based on the number of patients in the Safety Set 1.
Exposure duration (days) in the Main period and the Overall study period were calculated as follows:
Duration of exposure (days) in the Main period = minimum of (maximum of [study discontinuation decision date, early termination (ET) visit date], IP administration date at Month 12, [last IP administration date before Month 12 + 182]) – first IP administration date + 1
Duration of exposure (days) in the Overall study period = minimum of (maximum of [study discontinuation decision date, ET visit date], end of study [EOS] visit date, [last IP administration date + 182]) – first IP administration date + 1
Source: Section 5.3.5.1 CSR Study SB16-3001, Table 12-1

2.5.8.2. Adverse events

TEAEs were defined as any AEs which started after IP administration or pre-existed before IP administration with increase in severity after IP administration. Only TEAEs are discussed in this report, unless specified otherwise. Baseline value was defined as the last available measurement value recorded prior to IP administration.

In both studies, all AEs were coded according to the MedDRA® version 23.0 and assigned to a primary SOC and PT.

Study 1001

A total of 90 (53.6%) subjects had 170 TEAEs. Comparable number of subjects had TEAEs in each treatment group . The majority of TEAEs were mild or moderate in intensity and not related to the IP (138 events were not related out of a total of 170 TEAEs). A total of 12 TEAEs related to COVID-19 was reported in 12 (7.1%) subjects.

Three SAEs were reported for 3 (5.4%) subjects in the SB16 treatment group, which were considered not related to the IP. Of the 3 SAEs reported, there was 1 death leading to study discontinuation. No other subject discontinued the study due to TEAEs during the study.

Table 31. Study 1001: summary of adverse events (safety set)

Treatment	SB16 N=56		EU sourced Prolia N=56		US sourced Prolia N=56		Total N=168	
Category	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any AEs	35 (62.5)	69	25 (44.6)	51	31 (55.4)	56	91 (54.2)	176
Any TEAEs	35 (62.5)	66	25 (44.6)	51	30 (53.6)	53	90 (53.6)	170
TEAE severity								
Mild	19 (33.9)	44	17 (30.4)	38	18 (32.1)	35	54 (32.1)	117
Moderate	14 (25.0)	20	8 (14.3)	13	11 (19.6)	16	33 (19.6)	49
Severe	2 (3.6)	2	0 (0.0)	0	1 (1.8)	2	3 (1.8)	4
TEAE causality								
Related	8 (14.3)	10	4 (7.1)	11	7 (12.5)	11	19 (11.3)	32
Not related	27 (48.2)	56	21 (37.5)	40	23 (41.1)	42	71 (42.3)	138
Any SAEs	3 (5.4)	3	0 (0.0)	0	0 (0.0)	0	3 (1.8)	3
Serious TEAE	3 (5.4)	3	0 (0.0)	0	0 (0.0)	0	3 (1.8)	3
Serious non-TEAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Serious TEAE causality								
Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Not related	3 (5.4)	3	0 (0.0)	0	0 (0.0)	0	3 (1.8)	3
TEAEs related to COVID-19	6 (10.7)	6	2 (3.6)	2	4 (7.1)	4	12 (7.1)	12
TEAEs leading to study discontinuation	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1
TEAEs leading to death	1 (1.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.6)	1

N = number of subjects in the Safety Set; n = number of subjects with event; E = frequency of adverse events; AE = adverse event; TEAE = treatment-emergent adverse event; SAE = serious adverse event
Percentages were based on the number of subjects in the Safety Set
If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n)
Source: Table 14.3.1-1.1

The most frequently reported TEAEs in the SB16 treatment group were COVID-19, blood creatine phosphokinase increased, nasopharyngitis, headache, and back pain. The most frequently reported TEAEs in the EU sourced Prolia treatment group were constipation, nasopharyngitis, blood creatine phosphokinase increased, headache, and arthralgia The most frequently reported TEAEs in the US sourced Prolia treatment group were blood creatine phosphokinase increased, COVID-19, nasopharyngitis, arthralgia, and headache. No hypocalcaemia was reported during the study.

Table 32. Study 1001: treatment-emergent adverse events with incidence > 5% of subjects (safety set)

Treatment	SB16 N=56		EU sourced Prolia N=56		US sourced Prolia N=56		Total N=168	
Preferred term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE with incidence of > 5% of subjects	21 (37.5)	28	16 (28.6)	21	19 (33.9)	21	56 (33.3)	70
COVID-19	6 (10.7)	6	2 (3.6)	2	4 (7.1)	4	12 (7.1)	12
Blood creatine phosphokinase increased	5 (8.9)	6	3 (5.4)	3	5 (8.9)	5	13 (7.7)	14
Nasopharyngitis	5 (8.9)	6	3 (5.4)	4	4 (7.1)	4	12 (7.1)	14
Headache	4 (7.1)	4	3 (5.4)	3	3 (5.4)	3	10 (6.0)	10
Back pain	4 (7.1)	4	1 (1.8)	1	1 (1.8)	1	6 (3.6)	6
Arthralgia	2 (3.6)	2	3 (5.4)	3	3 (5.4)	4	8 (4.8)	9
Constipation	0 (0.0)	0	5 (8.9)	5	0 (0.0)	0	5 (3.0)	5

N = number of subjects in the Safety Set; n = number of subjects with event; E = frequency of TEAEs; TEAE = treatment-emergent adverse event
Percentages were based on the number of subjects in the Safety Set.
Adverse events were coded to primary system organ class and preferred term using MedDRA® coding dictionary version 23.0.

The proportion of subjects who experienced TEAEs considered to be related to the IPs was 14.3% of the subjects in the SB16 treatment group, 7.1% of the subjects in the EU Prolia treatment group, and 12.5% of the subjects in the US Prolia treatment group. The most frequently reported TEAE related to IP by PT was 'headache' (3.0% of subjects): 3.6% of subjects in the SB16 treatment group, 1.8% of subjects in the EU Prolia treatment group, and 3.6% of subjects in the US Prolia treatment group.

Study 3001

Main period

A total of 323 (70.8%) subjects experienced at least one TEAE in the main period. The majority of TEAEs were mild or moderate in intensity. Additionally, the majority of TEAEs were considered not related to the IP (795 events out of a total of 876 TEAEs).

A total of 55 (12.1%) subjects experienced 61 treatment-emergent AESIs in the main period. The most frequently reported AESI was hypocalcaemia in 49 (10.7%) subjects overall. The incidence of hypocalcaemia was comparable between the SB16 (22 [9.8%] subjects) and Prolia (27 [11.7%] subjects) treatment groups. No events of osteonecrosis of jaw or atypical femoral fracture were reported during the main period.

Three (1.3%) subjects in the SB16 treatment group and 1 (0.4%) subject in the Prolia treatment group reported injection site reactions.

A total of 16 (3.5%) subjects had 20 SAEs in the main period. Of these 20 SAEs, 12 events were severe, 7 events were moderate, and 1 event was mild. None of the SAEs were considered related to the IP. There were no TEAEs that resulted in death in the main period.

Table 33. Study 3001: Summary of all adverse events in the main period (safety set 1)

Number of Subjects Experiencing	SB16 N = 225 n (%) E	Prolia N = 231 n (%) E	Total N = 456 n (%) E
No adverse event	66 (29.3)	67 (29.0)	133 (29.2)
TEAEs	159 (70.7) 424	164 (71.0) 452	323 (70.8) 876
TEAEs severity			
Mild	91 (40.4) 296	80 (34.6) 311	171 (37.5) 607
Moderate	62 (27.6) 120	78 (33.8) 135	140 (30.7) 255
Severe	6 (2.7) 8	6 (2.6) 6	12 (2.6) 14
TEAEs causality with IP			
Related	26 (11.6) 33	33 (14.3) 48	59 (12.9) 81
Not related	133 (59.1) 391	131 (56.7) 404	264 (57.9) 795
TEAEs causality with non-IP			
Related	8 (3.6) 8	17 (7.4) 18	25 (5.5) 26
Not related	151 (67.1) 416	147 (63.6) 434	298 (65.4) 850
TEAEs of special interest	24 (10.7) 26	31 (13.4) 35	55 (12.1) 61
Hypocalcaemia	22 (9.8) 24	27 (11.7) 29	49 (10.7) 53
Hypersensitivity to IP	1 (0.4) 1	3 (1.3) 5	4 (0.9) 6
Osteonecrosis of the jaw	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Atypical femoral fractures	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Skin infections	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Injection site reactions	3 (1.3) 4	1 (0.4) 1	4 (0.9) 5
Serious TEAEs	8 (3.6) 10	8 (3.5) 10	16 (3.5) 20
Serious TEAEs severity			
Mild	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
Moderate	1 (0.4) 1	4 (1.7) 6	5 (1.1) 7
Severe	6 (2.7) 8	4 (1.7) 4	10 (2.2) 12
Serious TEAEs causality with IP			
Related	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not related	8 (3.6) 10	8 (3.5) 10	16 (3.5) 20
Serious TEAEs causality with non-IP			
Related	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not related	8 (3.6) 10	8 (3.5) 10	16 (3.5) 20
TEAEs leading to death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

N = total number of subjects in the Safety Set 1 in each treatment group; AESI = adverse event of special interest; E = frequency of events; IP = investigational product; n = number of subjects with event; TEAE = treatment-emergent adverse event
Percentages were based on the number of subjects in the Safety Set 1.
If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n).
Source: Table 14.3.1-1.1.1

TEAEs were most frequently reported in the following SOCs: Infections and Infestations (135 [29.6%] subjects total; SB16: 62 [27.6%] subjects and Prolia: 73 [31.6%] subjects), musculoskeletal and connective tissue disorders (103 [22.6%] subjects total; SB16: 53 [23.6%] subjects and Prolia: 50 [21.6%] subjects), metabolism and nutrition disorders (85 [18.6%] subjects total; SB16: 42 [18.7%] subjects and Prolia: 43 [18.6%] subjects), and nervous system disorders (71 [15.6%] subjects total; SB16: 39 [17.3%] subjects and Prolia: 32 [13.9%] subjects).

Overall, the most frequently reported PTs in the main period were 'hypocalcaemia', 'COVID-19', 'headache', and 'arthralgia'.

Table 34. Study 3001: treatment-emergent adverse events with incidence > 5% of patients by system organ class or preferred term in the main period (safety set 1)

System Organ Class	SB16 N = 225			Prolia N = 231			Total N = 456		
Preferred Term	n	%	E	n	%	E	n	%	E
Any TEAEs with incidence > 5% of patients	**84**	**37.3**	**110**	**80**	**34.6**	**96**	**164**	**36.0**	**206**
Infections and infestations	**42**	**18.7**	**53**	**43**	**18.6**	**46**	**85**	**18.6**	**99**
COVID-19	16	7.1	16	15	6.5	15	31	6.8	31
Urinary tract infection	12	5.3	15	5	2.2	5	17	3.7	20
Upper respiratory tract infection	11	4.9	12	12	5.2	12	23	5.0	24
Nasopharyngitis	10	4.4	10	14	6.1	14	24	5.3	24
Metabolism and nutrition disorders	**22**	**9.8**	**24**	**27**	**11.7**	**29**	**49**	**10.7**	**53**
Hypocalcaemia	22	9.8	24	27	11.7	29	49	10.7	53
Musculoskeletal and connective tissue disorders	**16**	**7.1**	**17**	**9**	**3.9**	**10**	**25**	**5.5**	**27**
Arthralgia	16	7.1	17	9	3.9	10	25	5.5	27
Nervous system disorders	**16**	**7.1**	**16**	**10**	**4.3**	**11**	**26**	**5.7**	**27**
Headache	16	7.1	16	10	4.3	11	26	5.7	27

E = frequency of events; n = number of patients with event; N = total number of patients in the Safety Set 1 in each treatment group; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 23.0.
Percentages were based on the number of patients in the Safety Set 1.
SOC was sorted by descending frequency in the SB16 treatment group, then alphabetically if tied. PT was sorted within SOC by descending frequency in the SB16 treatment group, then alphabetically if tied.

transition period

A total of 137 (33.7%) subjects experienced at least one TEAE in the Transition period. The majority of TEAEs were mild or moderate in intensity. The majority of TEAEs were not considered related to the IP (215 events out of a total of 218 TEAEs).

A total of 2 (0.5%) subjects experienced 2 treatment-emergent AESIs in the transition period; both were in the SB16+SB16 treatment group (1.0%). The only AESI reported in the transition period was hypocalcaemia. No events of osteonecrosis of jaw or atypical femoral fracture were reported during the transition period.

A total of 7 (1.7%) subjects had 9 SAEs in the transition period (SB16+SB16: 4 [1.9%] subjects, Prolia Overall: 3 [1.5%] subjects, Prolia+SB16: 2 [2.0%] subjects, and Prolia+Prolia: 1 [1.0%] subjects). Of these 9 SAEs, 8 events were severe, 1 event was moderate, and no events was mild. None of the SAEs were considered related to IP. There were no TEAEs that resulted in death in the transition period.

Table 35. Study 3001: summary of all adverse events in the transition period (safety set 2)

Number of Subjects Experiencing	SB16+SB16 N = 206 n (%) E	Prolia Overall N = 201 n (%) E	Prolia SB16 N = 100 n (%) E	Prolia Prolia N = 101 n (%) E	Total N = 407 n (%) E
No adverse event	133 (64.6)	137 (68.2)	71 (71.0)	66 (65.3)	270 (66.3)
TEAEs	73 (35.4) 121	64 (31.8) 97	29 (29.0) 34	35 (34.7) 63	137 (33.7) 218
TEAEs severity					
Mild	49 (23.8) 86	42 (20.9) 49	19 (19.0) 21	23 (22.8) 28	91 (22.4) 135
Moderate	21 (10.2) 31	19 (9.5) 43	8 (8.0) 11	11 (10.9) 32	40 (9.8) 74
Severe	3 (1.5) 4	3 (1.5) 5	2 (2.0) 2	1 (1.0) 3	6 (1.5) 9
TEAEs causality with IP					
Related	3 (1.5) 3	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	3 (0.7) 3
Not related	70 (34.0) 118	64 (31.8) 97	29 (29.0) 34	35 (34.7) 63	134 (32.9) 215
TEAEs causality with non-IP					
Related	1 (0.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.2) 1
Not related	72 (35.0) 120	64 (31.8) 97	29 (29.0) 34	35 (34.7) 63	136 (33.4) 217
TEAEs of special interest	2 (1.0) 2	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (0.5) 2
Hypocalcaemia	2 (1.0) 2	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (0.5) 2
Hypersensitivity to IP	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Osteonecrosis of the jaw	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Atypical femoral fractures	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Skin infections	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Injection site reactions	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

Number of Subjects Experiencing	SB16+SB16 N = 206 n (%) E	Prolia Overall N = 201 n (%) E	Prolia SB16 N = 100 n (%) E	Prolia Prolia N = 101 n (%) E	Total N = 407 n (%) E
Serious TEAEs	4 (1.9) 4	3 (1.5) 5	2 (2.0) 2	1 (1.0) 3	7 (1.7) 9
Serious TEAEs severity					
Mild	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Moderate	1 (0.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.2) 1
Severe	3 (1.5) 3	3 (1.5) 5	2 (2.0) 2	1 (1.0) 3	6 (1.5) 8
Serious TEAEs causality with IP					
Related	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not related	4 (1.9) 4	3 (1.5) 5	2 (2.0) 2	1 (1.0) 3	7 (1.7) 9
Serious TEAEs causality with non-IP					
Related	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Not related	4 (1.9) 4	3 (1.5) 5	2 (2.0) 2	1 (1.0) 3	7 (1.7) 9
TEAEs leading to death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

N = total number of subjects in the Safety Set 2 in each treatment group; AESI = adverse event of special interest; E = frequency of events; IP = investigational product; n = number of subjects with event; TEAE = treatment-emergent adverse event
Percentages were based on the number of subjects in the Safety Set 2.
If a subject had multiple events with different severity (or causality), then the subject was counted only once at the worst severity (or causality) for the number of subjects (n).
Source: Table 14.3.1-1.1.2

Overall period

Skeletal fractures

In Study SB16-3001, there was a numerical difference in TEAEs of skeletal fractures between the SB16 and Prolia treatment groups (11 [4.9%] patients in the SB16 and 4 [1.7%] patients in the Prolia treatment groups). This study was not designed to measure the difference of fractures, in contrast with pivotal osteoporosis studies such as FREEDOM, and since the nature of fracture occurrence does not reflect what was observed in pivotal studies, the applicant believes that the numerically higher incidence of TEAEs with skeletal fractures in the SB16 treatment group was not attributable to any potential difference in treatment effect of SB16 and Prolia, with the following explanations.

The numerical difference in skeletal fracture mainly resulted from the numerical difference in 'non-vertebral fracture' between the SB16 and Prolia treatment groups (8 [4.9%] patients in the SB16 and 1 [1.3%] patients in the Prolia treatment groups) specifically during the main period (up to Month 12). All fractures except for 1 (0.4%) patient ('spinal compression' in the Prolia+Prolia treatment group during the transition period) were non-vertebral fractures.

Table 36 Study 3001. Summary of skeletal fracture treatment-emergent adverse events in the overall study period (safety set 1, study SB16-3001)

Number of Patients Experiencing	SB16 N = 225			Prolia									Total N = 456		
				Overall N = 231			SB16[a] N = 100			Prolia[a] N = 101					
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any skeletal fracture[b]	11	4.9	14	4	1.7	4	0	0.0	0	4	4.0	4	15	3.3	18
Vertebral fracture	0	0.0	0	1	0.4	1	0	0.0	0	1	1.0	1	1	2.0	1
Non-vertebral fracture[c]	11	4.9	13	3	1.3	3	0	0.0	0	3	3.0	3	14	3.1	16
AE occurred period															
Main period	8	3.6	9	1	0.4	1	0	0.0	0	1	1.0	1	9	2.0	10
Transition period	4	1.8	5	3	1.3	3	0	0.0	0	3	3.0	3	7	1.5	8
Anatomical region															
Rib	3	1.3	3	0	0.0	0	0	0.0	0	0	0.0	0	3	0.7	3
Ankle	2	0.9	3	1	0.4	1	0	0.0	0	1	1.0	1	3	0.7	4
Forearm	2	0.9	2	0	0.0	0	0	0.0	0	0	0.0	0	2	0.4	2
Foot (metatarsal bone)	1	0.4	1	1	0.4	1	0	0.0	0	1	1.0	1	2	0.4	2
Hip (femoral neck)	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Patella	1	0.4	2	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	2
Radius	1	0.4	1	1	0.4	1	0	0.0	0	1	1.0	1	2	0.4	2
Skull	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Spine	0	0.0	0	1	0.4	1	0	0.0	0	1	1.0	1	1	0.2	1

AE = adverse event; E = frequency of events; N = total number of subjects in the Safety Set 1 in each treatment group; n = number of subjects with event

[a] Based on subjects in the Safety Set 2, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.

The applicant did not describe adverse drug reactions.

2.5.8.3. Serious adverse event/deaths/other significant events

Study 1001: healthy volunteers

There was 1 death (completed suicide) during the study in the SB16 treatment group. In addition to 1 death, 2 SAEs were reported, i.e., a total of 3 SAEs were reported for 3 (5.4%) subjects in the SB16 treatment group. Two subjects were reported with facial bones fracture (following a sporting accident) and depression, respectively, and none were considered to be related to the IP.

Study 3001: patients with PMO

Adverse events of special interest (AESI) categories were 'hypocalcaemia', 'hypersensitivity to IP', 'osteonecrosis of the jaw', 'atypical femoral fractures', and 'skin infections'. In the Overall study period, 56 (12.3%) patients experienced at least one AESI, and the proportion of patients experiencing AESIs

was comparable across the treatment groups for the SAF1: 25 (11.1%) in the SB16, 31 (13.4%) in the Prolia Overall, 12 (12.0%) in the Prolia+SB16, and 13 (12.9%) in the Prolia+Prolia treatment groups.

Table 37. Treatment-emergent adverse events of special interest (AESI) by system organ class in the overall study period (safety set 1, study SB16-3001)

AESI Category	SB16 N = 225			Prolia									Total N = 456		
				Prolia Overall N = 231			Prolia+SB16[a] N = 100			Prolia+Prolia[a] N = 101					
System Organ Class	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any TEAE of special interest	**25**	**11.1**	**28**	**31**	**13.4**	**35**	**12**	**12.0**	**13**	**13**	**12.9**	**14**	**56**	**12.3**	**63**
Hypocalcaemia	**23**	**10.2**	**26**	**27**	**11.7**	**29**	**11**	**11.0**	**12**	**13**	**12.9**	**14**	**50**	**11.0**	**55**
Metabolism and nutrition disorders	23	10.2	26	27	11.7	29	11	11.0	12	13	12.9	14	50	11.0	55
Hypersensitivity to IP	**1**	**0.4**	**1**	**3**	**1.3**	**5**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**4**	**0.9**	**6**
General disorders and administration site conditions	1	0.4	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Eye disorders	0	0.0	0	1	0.4	1	0	0.0	0	0	0.0	0	1	0.2	1
Skin and subcutaneous tissue disorders	0	0.0	0	2	0.9	3	0	0.0	0	0	0.0	0	2	0.4	3
Vascular disorders	0	0.0	0	1	0.4	1	1	1.0	1	0	0.0	0	1	0.2	1
Skin infections	**1**	**0.4**	**1**	**1**	**0.4**	**1**	**1**	**1.0**	**1**	**0**	**0.0**	**0**	**2**	**0.4**	**2**
Infections and infestations	1	0.4	1	1	0.4	1	1	1.0	1	0	0.0	0	2	0.4	2

E = frequency of adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with events; N = number of patients in the Safety Set 1 in each treatment group; TEAE = treatment emergent adverse event

[a] Based on patients in the Safety Set 2, Prolia+SB16 and Prolia+Prolia may not add up to Prolia Overall.
Percentages were based on number of patients in the Safety Set 1.
AEs were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
SOC was sorted by descending frequency in the SB16 treatment group, then alphabetically if tied. PT was sorted within SOC by descending frequency in the SB16 treatment group, then alphabetically if tied.
Source: Section 5.3.5.1 CSR Study SB16-3001, Table 14.3.1-1.11.3

The incidence of serious TEAEs was comparable across the treatment groups in the main period. A total of 16 (3.5%) patients (8 [3.6%] patients in the SB16 treatment group, and 8 [3.5%] patients in the Prolia treatment group) had 10 SAEs in the main period.

A total of 7 (1.7%) patients had 9 SAEs in the transition period (4 [1.9%] patients in the SB16+SB16, 3 [1.5%] patients in the Prolia Overall, 2 [2.0%] patients in the Prolia+SB16, and 1 [1.0%] patients in the Prolia+Prolia treatment groups). Of these 9 SAEs, 8 events were severe, 1 event was moderate, and no event was mild in severity. No SAEs were considered related to IP. There were no TEAEs that resulted in death in the transition period.

No deaths occurred over the course of the trial.

Table 38. Treatment-emergent adverse events of special interest (AESI) by system organ class and preferred term in main period (safety set 1)

AESI Category System organ class Preferred term	SB16 N=225 n (%) E		Prolia N=231 n (%) E		Total N=456 n (%) E	
Any TEAEs of special interest	24 (10.7)	26	31 (13.4)	35	55 (12.1)	61
[AESI Category: Hypocalcaemia]	22 (9.8)	24	27 (11.7)	29	49 (10.7)	53
Metabolism and nutrition disorders	22 (9.8)	24	27 (11.7)	29	49 (10.7)	53
Hypocalcaemia	22 (9.8)	24	27 (11.7)	29	49 (10.7)	53
[AESI Category: Hypersensitivity to IP]	1 (0.4)	1	3 (1.3)	5	4 (0.9)	6
General disorders and administration site conditions	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Injection site erythema	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Eye disorders	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Swelling of eyelid	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Skin and subcutaneous tissue disorders	0 (0.0)	0	2 (0.9)	3	2 (0.4)	3
Erythema	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Pruritus	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Rash	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
[AESI Category: Hypersensitivity to IP] (cont.)						
Vascular disorders	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
Hot flush	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1
[AESI Category: Skin infections]	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Infections and infestations	1 (0.4)	1	1 (0.4)	1	2 (0.4)	2
Herpes zoster	1 (0.4)	1	0 (0.0)	0	1 (0.2)	1
Erysipelas	0 (0.0)	0	1 (0.4)	1	1 (0.2)	1

Source: Listing 14.3.2-1.4
- TEAE: treatment-emergent adverse event; n: number of subjects with event; E: frequency of events; IP: investigational product.
- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA coding dictionary version 23.0.
- Percentages were based on the number of subjects in the safety set 1.
- SOC was sorted by descending frequency in SB16 group, then alphabetically if tied. PT was sorted within SOC by descending frequency in SB16 group, then alphabetically if tied.

Table 39. Treatment-emergent adverse events of special interest (AESI) by system organ class and preferred term in main period (safety set 2)

AESI Category System organ class Preferred term	SB16+SB16 N=206 n (%) E		Prolia Overall N=201 n (%) E		Prolia SB16 N=100 n (%) E		Prolia Prolia N=101 n (%) E		Total N=407 n (%) E	
Any TEAEs of special interest	2 (1.0)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.5)	2
[AESI Category: Hypocalcaemia]	2 (1.0)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.5)	2
Metabolism and nutrition disorders	2 (1.0)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.5)	2
Hypocalcaemia	2 (1.0)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (0.5)	2

Source: Listing 14.3.2-1.4
- TEAE: treatment-emergent adverse event; n: number of subjects with event; E: frequency of events; IP: investigational product.
- Adverse events were coded to system organ class (SOC) and preferred term (PT) using MedDRA coding dictionary version 23.0.
- Percentages were based on the number of subjects in the safety set 2.
- SOC was sorted by descending frequency in SB16+SB16 group, then alphabetically if tied. PT was sorted within SOC by descending frequency in SB16+SB16 group, then alphabetically if tied.

2.5.8.4. Laboratory findings

Study 1001

In study 1001, clinical laboratory evaluations for haematology, clinical chemistry and urinalysis were performed. Mean and median values of all parameters of Haematology did not show any clinically relevant changes over time. A few subjects had shifts from normal haematology values at baseline to values outside the normal range post-baseline. However, there were no clinically significant changes from baseline in haematology values in any treatment group. Mean and median values of all parameters of chemistry did not show any clinically relevant changes over time.

There were 15 subjects with clinically significant abnormalities in chemistry parameters identified by the Investigator; 5 subjects in the SB16, 5 subjects in the EU Prolia, and 5 subjects in the US Prolia treatment groups. Relevant AEs reported in these subjects included 'blood creatine phosphokinase', 'alanine aminotransferase increased', 'aspartate aminotransferase increased', and 'blood creatinine increased', all of which were assessed not to be related to the IP and all the events resolved.

'Blood creatine phosphokinase' was reported as TEAE in 13 subjects (5 subjects in the SB16, 3 subjects in the EU Prolia, and 5 subjects in the US Prolia treatment groups). 'Alanine aminotransferase increased' was reported as TEAE in 3 subjects (1 subject each in the SB16, EU Prolia, and US Prolia treatment groups). 'Aspartate aminotransferase increased' was also reported as TEAE in 3 subjects (1 subject each in the SB16, EU Prolia, and US Prolia treatment groups). 'Blood creatinine increased' was reported as TEAE in 1 subject in the EU Prolia treatment group.

Mean and median values of all continuous parameters of urinalysis did not show any clinically relevant changes over time.

Study 3001

Haematology, biochemistry tests, and urinalysis assessments were performed at Screening, Months 0, 0.5, 1, 3, 6, 9, 12 and Month 18 (EOS)/early termination (ET) visit. Blood samples for serum vitamin D (25-hydroxyvitamin D) assessment were collected at screening and prior to dosing at Months 6 and 12.

Clinically significant abnormal laboratory results were infrequent and rarely reported for more than 1 patient in any treatment group. No trends in clinically meaningful changes or shifts from baseline in haematology (parameters: haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count [total and differential), were observed in any treatment groups at any timepoints during the study.

10 patients in total had at least clinically significant abnormal haematology value at any timepoint. The majority of haematology values were CTCAE Grade 1 or 2 and the abnormalities were similar between the treatment groups.

No trends in clinically meaningful changes from baseline in biochemistry were observed in any treatment groups at any timepoints during the study. The distribution of normal, abnormal not clinically significant, abnormal clinically significant by each parameter was comparable between the SB16 and Prolia treatment groups during the main period and among the SB16+SB16, Prolia Overall, Prolia+SB16, and Prolia+Prolia treatment groups during the transition period.

Low albumin corrected serum calcium, high cholesterol, low calcium, and high aspartate aminotransferase were the most frequently reported clinically significant biochemistry parameters per patient. The majority of biochemistry values were CTCAE Grade 1, including albumin corrected serum calcium and the abnormalities were comparable between the two treatment groups.

No trends in clinically meaningful changes from baseline in serum vitamin D were observed in any treatment groups at any timepoints during the study. Up to Month 12, 16 patients (7 [3.2%] patients in the SB16 treatment group and 9 [4.3%] in the Prolia treatment group) reported abnormal clinically significant low serum vitamin D.

2.5.8.5. Safety in special populations

Safety in special populations was not investigated as it is not required for the investigation of bioequivalence.

2.5.8.6. Immunological events

The applicant has adopted an electrochemiluminescence immunoassay (ECLIA) bridging assay to screen, confirm and quantify denosumab specific antibodies in human serum matrix. The adopted three-tiered approach for determination of ADAs was well described and developed and is considered state of the art.

Further, the applicant presented an electrochemiluminescence assay for the detection of neutralising ADA's in human serum. The presented assay was well described and established.

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

Not applicable for biosimilars

2.5.8.8. Discontinuation due to adverse events

Study 1001:

There was 1 death leading to study discontinuation. No other subject discontinued the study due to TEAEs during the study 1001.

Study 3001:

All AEs leading to discontinuation occurred during the main period. Four (1.8%) subjects in the SB16 treatment group experienced TEAEs that led to permanent discontinuation of the IP (arachnoid cyst, headache, acute phase reaction, tooth fracture, and alopecia). Eight (3.5%) subjects in the Prolia Overall treatment group experienced TEAEs that led to permanent discontinuation of the IP (presyncope, alopecia, dental caries, haemorrhoids, noninfective gingivitis, COVID-19, diverticulitis, upper respiratory tract infection, breast cancer, and lung adenocarcinoma).

2.5.8.9. Post marketing experience

Not applicable for initial application

2.5.9. Discussion on clinical safety

The safety of SB16 was evaluated in a pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity study of denosumab (SB16, EU-sourced Prolia, and US-sourced Prolia) in healthy male subjects (Study SB16-1001) and in an efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity study in female subjects with PMO (Study 16-3001). The comparator drugs in Study 1001 were EU-Prolia and US-Prolia. The comparator drug in Study 3001 was EU-Prolia. In accordance with the Prolia and Xgeva label recommendations, adequate measures were taken for the prevention of hypocalcaemia by adequate intake of calcium and vitamin D before initiating denosumab therapy, as well as clinical monitoring of calcium levels before each dose and throughout treatment in both studies at regular intervals.

As described in the sections above, the mechanism of action of denosumab is identical for all indications of Prolia/Xgeva. Therefore, safety and immunogenicity results can be extrapolated from patients with PMO to all indications. This extrapolation is further supported by the known safety and immunogenicity profile of denosumab as summarised in the product information for Prolia/Xgeva which is comparable across the approved indications and patient populations.

In study 1001, safety assessments were made after administration of a single subcutaneous injection of 60 mg SB16, EU sourced Prolia, and US sourced Prolia in healthy male volunteers. Safety endpoints consisted of adverse events (AEs) and serious AEs (SAEs), clinical laboratory tests (haematology, chemistry, and urinalysis), 12-lead ECG, vital sign assessment, physical examination and injection site assessment. Immunogenicity, incidence of anti-drug antibodies (ADAs) and neutralising antibodies (nAbs) was evaluated at regular intervals and at EoS/ET.

In study 3001, safety assessments after study drug administration consisted of AEs, SAEs, vital signs, physical examination, clinical laboratory tests (haematology, chemistry, and urinalysis), bone mineral density (lumbar spine, total hip, and femoral neck) and serum vitamin D. Most assessments were made at regular intervals over the entirety of the 18-month study duration. BMD and serum vitamin D were assessed at screening, month 6, 12, 18 and at ET and AEs were assessed continuously. 12-lead ECG was only performed at baseline, which is not considered concerning as the most likely driver of potential QT prolongation was hypocalcaemia, which was assessed regularly. Immunogenicity, incidence of anti-drug antibodies (ADAs) and neutralising antibodies (nAbs) was evaluated at regular intervals and EoS/ET.

Both studies took place during the COVID-19 pandemic, but the impact on compliance of study visit from the COVID-19 pandemic was low. Additionally, only 4 patients in total withdrew from both studies due to COVID-19 which is regarded as non-influential.

In trial 1001, the safety set (SAF) consisted of all subjects who received IP. In total, the SAF consisted of all 168 subjects who were randomised, with 56 being allocated to each treatment arm (SB16, EU-sourced Prolia, US-sourced Prolia). Each subject received one subcutaneous dose of 60 mg study drug.

In trial 3001, two separate safety sets were analysed based on IP administration in the main and transition period of the trial. SAF1 consisted of all patients who received at least one dose of IP, while SAF2 consisted of all subjects in SAF1 who received study drug after re-randomisation at month 12. Patients who finished the main period in the Prolia treatment arm were re-randomised to receive one dose of either SB16 or Prolia, and patients in the SB16 arm continued to receive one additional dose of SB16. The SAF1 consisted of 456 subjects, with 407 subjects continuing the trial in the transition period for inclusion in the SAF2. Summaries were presented for the main period, the transition period, and the overall period separately. In total, 225 female patients with PMO received at least one dose of SB16 over the course of the trial, which is considered sufficient to enable detection of differences in safety between SB16 and Prolia.

Overall, the design of the clinical studies is considered adequate for a comprehensive safety and immunogenicity similarity assessment of SB16 and Prolia. The safety assessments performed during Studies 1001 and 3001 were designed to capture the known safety issues listed in the Prolia and Xgeva labels and are considered appropriate. The available safety data and extent of exposure is considered adequate to assess the safety of SB16 in comparison to Prolia.

For a discussion of demographic and baseline characteristics, see the discussions on pharmacology and efficacy above.

There are small imbalances in exposure noted in trial 3001 with 20 (8.7%) patients in the Prolia group receiving only one injection vs. 9 (4.0%) patients in the SB16 group. This is not considered overly concerning, as the mean and median duration of exposure was similar in the main and overall study period between the treatment groups.

In Study 1001, 90 of subjects experienced a total of 170 TEAEs, with 68.8% of events rated as mild, and 28.8% rated as moderate. The proportion of patients who experienced AEs were overall similar between the three treatment groups, although both the proportion of subjects who experienced AEs and the number of AEs was highest in the SB16 group (SB16: 62.5% of subjects with 66 AEs; EU-

Prolia 44.6% of subjects with 51 AEs; US-Prolia 53.6% of subjects with 53 AEs in SB16). The applicant was asked to discuss this discrepancy between the three treatment groups, and argued that the numerical difference of the proportion of subjects with TEAEs between the treatment groups in total, as well as on SOC level, was mainly driven by small differences on PT level by one or two patients. It is acknowledged that the numerical differences in TEAEs in the phase 1 trial are not clinically relevant, and this observation in the end does not raise a concern.

Notably, 4 TEAEs were rated 'severe' occurring in 4 subjects in total, two subjects each in the SB16 and US-Prolia groups. The TEAE rate in the US Prolia group was 53.6%. Furthermore, moderate to severe TEAEs were more frequently reported for the SB16 treatment group (25% and 3.6% for moderate and severe TEAEs, respectively) compared with EU Prolia (14.3% and 0.0%, for moderate TEAEs and severe TEAEs, respectively). Causality was assessed as related for 14.3% and 7.1% of the TEAEs for the SB16 and Prolia groups, respectively. For all serious TEAEs that occurred in 3 patients in the SB16 group, causality was assessed as non-related.

On SOC level, most AEs were well balanced between the treatment groups, although for 4 SOC classes, imbalances of >5% were reported: Infections, musculoskeletal and connective tissue disorders, renal and urinary disorders were higher in the SB16 group and gastrointestinal disorders occurred in more EU-Prolia group, but these AEs are not considered clinically meaningful as they occurred in a small number of patients with few events. On patient level, the most frequent AEs were COVID-19, increase in blood creatinine phosphatase, nasopharyngitis, headache, back pain, arthralgia and constipation. Blood creatine phosphokinase (CPK) increased was reported in 8.9% of patients treated with SB16 compared to 5.4% in the EU Prolia group. The rate of CPK increased in the US Prolia group was the same as the rate in the SB16 group. The relevance of these findings is uncertain but is conceivably related to the subjects being healthy volunteers and thus confounded by physical activity. Importantly, the number of subjects behind these rates is low in each group and only one was reported as severe and assessed as not related to study drug. AEs were overall well balanced between the treatment groups and discrepancies are not considered clinically relevant as subject and event numbers in these cases are very low. No hypocalcaemia was reported during the study.

In study 3001, in the main period, 323 (70.8%) subjects experienced at least one TEAE, with the proportion of patients experiencing AEs, as well as the total number of AEs between the treatment groups being similar. In the Prolia group, a slightly higher proportion of AEs was considered related with IP (14.4% vs. 7.1% of subjects for SB16 and Prolia, respectively) and non-IP, compared to SB16, although this difference is not considered to be significant based on the low number of patients involved (8 vs. 4 subjects for SB16 and Prolia, respectively).

The most frequent AEs by SOC were infections and infestations (in 29.6% of patients), musculoskeletal and connective tissue disorders (in 22.6% of patients), metabolism and nutrition disorders (in 18.6% of patients) and nervous system disorders (in 15.6% of patients), all of which were similar between the two treatment groups. By PT, the most frequent AEs were hypocalcaemia (in 10.7% total), COVID-19 (in 6.8% total), headache (in 5.7% total), and arthralgia (in 5.5% total), the proportions of patients being similar between the treatment groups. The small differences in occurrence of AEs can be attributed to few patients and are not considered clinically relevant. Most events were considered mild (70.8%) or moderate (30.7%) in severity, with 14 severe TEAES occurring in a total of 12 patients (6 in each treatment group).

Most AEs were not considered related to study drug (795/876), with the proportion of AEs related to study drug being comparable between the two treatment groups. Among the AEs associated with study drug, hypocalcaemia was the most common, being related to study drug in 41/53 cases of hypocalcaemia in the main period with similar proportions between SB16 and Prolia. None of the

hypocalcaemia events were graded as 'severe'. AEs in the main period are largely considered supportive of biosimilarity, with the exception of non-vertebral fractures, which is discussed below.

In the transition period, the number of patients with AEs and the number of events were overall similar between the three groups (SB16, Prolia + SB16, Prolia + Prolia), with the lowest occurrence in Prolia + SB16 group (29.0% of subjects for Prolia + SB16 vs. 35.4% for SB16 and SB16, and 34.7% of subjects for Prolia + Prolia). In terms of TEAE severity and causality, no notable differences were observed between the treatment groups. Two cases of hypocalcaemia were observed, both in the SB16 group. This is not considered concerning due to the similarity of occurrence of hypocalcaemia in the main period and the low numbers observed in the transition period. No other TEAEs of special interest occurred in the transition period. AEs in the transition period are largely considered supportive of biosimilarity, with the exception of non-vertebral fractures, which is discussed below.

Over the entirety of study 3001, 11 subjects in the SB16 group and 4 subjects in the Prolia Overall treatment group reported skeletal fractures with the main phase accounting for 9 and 1 fractures for SB16 and Prolia respectively. None of these fractures were considered related to IP, and only one was a vertebral fracture. This dissimilarity in fractures between the treatment groups was nevertheless considered concerning, and the applicant was asked to provide narratives for all fractures, report whether these were pathological or non-pathological fractures, and discuss the implications on clinical significance. Additionally, the applicant was asked to provide details of these cases, including baseline characteristics such as baseline BMD, concomitant and previous medication, previous fractures and nature of the fractures (non-traumatic vs traumatic). The difference in number of fractures was mainly driven by a larger number of traumatic fractures in the SB16 group, compared to the Prolia group (10 vs. 3 or 2 traumatic fractures for SB16 and Prolia, respectively. Note: one fracture in the Prolia group was deemed traumatic but also influenced by osteoporosis). The number of subjects with osteoporotic fractures was 4 vs. 2 or 1 subjects for SB16 and Prolia, respectively.

In study 1001, three serious TEAEs occurred in the SB16 group, and none in the EU-Prolia and US-Prolia groups: One death occurred during the course of the study due to subject committing suicide, one incidence of depression and one incidence of facial bone fracture following a sporting accident. These events were not considered related to the IP by the applicant, which is supported by the provided narratives and is therefore not considered concerning from a safety perspective.

In study 3001, in the main period, the most frequent treatment emergent AESI was hypocalcaemia, which was observed in 49 subjects overall. The proportion of subjects who developed hypocalcaemia was similar between the treatment groups. Skin infections were reported in one subject each in both treatment groups, and hypersensitivity to IP in 3 patients in the Prolia group, and 1 in the SB16 group. The rate of AEs observed during the main period of the trial is in line with historical information on Prolia, was similar between the treatment groups, and therefore does not give rise to concern. In the transition period, a total of 2 (0.5%) patients in the SB16 arm experienced 2 treatment-emergent AESIs, in both cases hypocalcaemia. Due to the low proportion of subjects with hypocalcaemia, this discrepancy is not considered concerning. No events of osteonecrosis of jaw, atypical femoral fracture or death were reported during the entirety of the study duration.

The proportion of subjects with severe TEAEs and the number of severe TEAE events were generally similar between SB16 and Prolia. Nonetheless, two subjects in the SB16 group and none in the Prolia group experienced fractures designated as serious TEAE. In conjunction with the occurrence of other fractures that were not designated 'serious TEAEs', this was seen as potentially clinically relevant. However, as discussed above, the difference in number of fractures was mainly driven by a larger number of traumatic fractures in the SB16 group, compared to the Prolia group. Overall, in conjunction with the other safety and efficacy, this does not raise further concerns.

No discontinuations due to AEs were reported in study 1001 in either group. In study 3001, the overall incidence of AEs leading to discontinuation was similar across both treatment groups. The relation of IP administration to AEs leading to discontinuation was not discussed by the applicant, which will not be followed further as the number of AEs leading to discontinuation is too low to draw meaningful conclusions (1.8% and 3.4 for SB16 and Prolia respectively).

With respect to laboratory findings, there we no observed trends in clinically meaningful changes across treatment groups for any laboratory parameter in any of the studies and clinically significant abnormalities were overall rare. Laboratory measurement results raise no concerns.

Immunogenicity

In Study 1001 in healthy volunteers, the overall incidence of post-dose ADAs to denosumab was 2 (3.6%), 0 and 4 (7.1%) for SB16, EU Prolia and US Prolia respectively and none of the patients with ADAs had a positive result for Nabs. There were no statistically significant differences in ADA occurrence between the treatment groups. Subgroup analysis for primary PK parameters (AUC_{inf}, C_{max}) was performed for ADA positive subjects, with consistent results to the primary PK analysis in the PK set. Thus, in the Phase 1 study, the incidence of ADA in the SB16 and the US Prolia group far exceeds the reported ADA incidence for denosumab of < 1%. The number of patients contributing to these rates is, however, low. ADA positivity did not result in difference in primary PK endpoints compared to the main analysis set.

In Study 3001 in patients with PMO, the overall incidence of post-dose ADAs to denosumab was 3 patients overall, 1 for SB16 and 2 patients in the Prolia overall group (i.e. < 1% at all timepoints) which was lower compared to Study 1001 and in line with what would be expected. None of the patients positive for ADAs were positive for NAbs. Separate analyses for influence on PK, safety and efficacy were not performed, as the number of patients with positive results was considered too low to derive meaningful conclusions. This is considered acceptable.

Overall, due to the low historical rate of ADAs for Prolia (<1%) and the number of detected ADAs over the course of both trials, the results of the immunogenicity assessment are considered supportive of biosimilarity with no remaining questions.

2.5.10. Conclusions on the clinical safety

Throughout the two clinical trials, the safety observations made were consistent with the established safety profiles of the reference drugs Prolia and Xgeva.

The submitted safety data are considered supportive of biosimilarity.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 40. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Osteonecrosis of the jaw Atypical femoral fracture Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	Cardiovascular events

Summary of safety concerns	
	Malignancy Delay in diagnosis of primary malignancy in giant cell tumour of bone Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Safety with long-term treatment and with long-term follow up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 41. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation SmPC sections 4.3, 4.4, 4.8, and 5.1 PL sections 2 and 4 Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities None
Atypical femoral fracture	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Recommendation for examining the contralateral femur in denosumab-treated patients who have sustained a femoral shaft fracture is included in SmPC section 4.4. Recommendation for evaluating patients presenting with new or unusual thigh, hip or groin pain for an incomplete femoral fracture is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	Specific adverse reaction follow-up questionnaire 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 SmPC sections 4.4 and 4.8 PL sections 2 and 4 Recommendation for monitoring patients for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium, and re-evaluation of the patients' calcium and vitamin D supplementation requirements is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Cardiovascular events	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Malignancy	Routine risk minimisation SmPC sections 4.4, 4.8. and 5.1 PL section 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Recommendation for monitoring patients for radiological signs of malignancy, new radiolucency or osteolysis is included in SmPC section 4.4. Subject to restricted medical prescription Additional risk minimisation None	Additional pharmacovigilance activities None
Delay in diagnosis of primary malignancy in giant cell tumour of bone	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Hypercalcemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation SmPC sections 4.5 and 5.1 PL section 2 Subject to restricted medical prescription Additional risk minimisation 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 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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 Subject to restricted medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

PL = package leaflet; SmPC = summary of product characteristics.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Pyzchiva (EMEA/H/C/006183) and Xgeva (EMEA/H/C/002173). The bridging report submitted by the applicant has been found acceptable.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Xbryk/SB16 was developed as a biosimilar product to Xgeva (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation (Xgeva: 120 mg/1.7mL single use vial). Xgeva is indicated for:

- The prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone

- The treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

For this MAA, the applicant intends to claim all of the indications of the reference product.

Summary of Clinical Data

SB16 was developed as a biosimilar product to Amgen's denosumab, which is contained in two different products, Prolia and Xgeva, containing the same active ingredient but at two different strengths with two different presentations. Prolia was used in the clinical development program for the comparative assessment between SB16 and Amgen's denosumab.

The aim of the clinical development for SB16 120 mg vial as part of the biosimilarity exercise was to demonstrate the similarity between SB16 (60 mg PFS and 120 mg vial) and Prolia/Xgeva in terms of PK, pharmacodynamic (PD), efficacy, safety, and immunogenicity profiles.

For this purpose, two clinical studies have been conducted:

• Clinical Phase I study (SB16-1001): A randomised, double-blind, three-arm, parallel group, single-dose study to compare the PK, PD, safety, tolerability, and immunogenicity of denosumab (SB16, European Union [EU]-sourced Prolia [hereafter referred to as, 'EU Prolia'], and US-sourced Prolia [hereafter referred to as, 'US Prolia']) in healthy male subjects. This was the pivotal PK similarity study designed in accordance with the European Medicines Agency (EMA) guideline [EMA/CHMP/BMWP/403543/2010].

• Clinical Phase III study (SB16-3001): Study SB16-3001 was a randomised, double-blind, multicentre phase III study in postmenopausal women with osteoporosis to compare the pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity of SB16 and EU-authorised Prolia. The study was conducted in 40 investigational sites across five countries (Czech Republic, Denmark, Lithuania, Poland, Republic of Korea). Subjects were randomised in a 1:1 ratio for the main treatment period (52 weeks). In the transition period (week 52-78) subjects receiving EU-Prolia were re-randomised to receive either SB16 or EU-Prolia. The subjects received in total three s.c. doses of SB16 or EU-Prolia. Overall, the design of the study SB16-3001 is acceptable and has been discussed in EMA Scientific Advice procedure (EMEA/H/SA/4025/1/2018/III). Generally, the design is in agreement with the advice received and supports the biosimilarity development.

3.2. Results supporting biosimilarity

Quality

Clinical

PK/PD

Study SB16-1001

Biosimilarity was demonstrated in healthy male subjects, since the geometric LSMean ratios (90% CI) for SB16 and EU-Prolia for AUC_{inf}, C_{max}, and AUC_{last} were 1.01 (0.93 to 1.10), 1.02 (0.95 to 1.10), and 1.02 (0.94 to 1.12), respectively. Similar to the SB16/EU-Prolia comparison, all 90% CIs for the ratios (SB16/US-Prolia and EU-Prolia/US-Prolia) of the geometric means for AUC_{inf}, C_{max} and AUC_{last} were within the prespecified equivalence criteria. Thus, all primary PK endpoints were met as all results were within the pre-defined equivalence margin of (0.8, 1.25).

PK parameters AUC_{inf}, AUC_{last}, C_{max}, $T_{1/2}$, $AUC\%_{extrap}$, Lambda_z and T_{max} were similar among the three treatment groups SB16, EU-Prolia and US-Prolia. Overall, mean serum concentration vs nominal time curves were comparable between all groups.

Descriptive statistics of pharmacodynamic parameters Imax (%inhibition) and $AUEC_{0\text{-}D197}$ (%inhibition*h) of serum CTX levels show similar PD profiles between the treatment groups.

Study SB16-3001

The mean serum concentration-time profiles over the whole study period were similar for the SB16 and EU-Prolia group for the main period. Additionally, the profiles were comparable among the groups in the transition period. Thus, the PK profiles from the osteoporosis patients support PK similarity of the test and reference product.

Biosimilarity in pharmacodynamics was also demonstrated in osteoporosis patients in study SB16-3001. The "$AUEC_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" was evaluated as a secondary endpoint. The point estimate of the geometric mean ratio (SB16/EU-Prolia) for AUEC was 0.98 with the corresponding 90% CI being (0.94; 1.03). Thus, the results observed support the PD similarity of the test and reference product. An analysis with the corresponding 95% CIs also supported the results of the main analysis.

PD similarity of the test and reference product was further supported by similar median percent change from baseline in CTX concentration time profiles for the SB16 and EU-Prolia groups. Moreover, also the median percent change from baseline in P1NP concentration time profiles were comparable between the groups.

Efficacy

Study SB16-3001

The biosimilarity of SB16 and EU-Prolia in terms of efficacy was demonstrated in osteoporosis patients. The primary efficacy analysis on the percent change from baseline in lumbar spine BMD at Month 12was performed on the PPS set and revealed that the difference between the SB16 and the EU-Prolia group was 0.39% with the corresponding 95% CI being -0.36% and 1.13%. Thus, the primary efficacy endpoint was met. The 95% confidence limits (-0.36%; 1.13%) are very well within the pre-defined and accepted equivalence range of [-2%, 2%] and estimate a 'maximum' difference of 1.13%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments. Additionally, the primary efficacy endpoint analysis was also conducted with the full analysis set and the 95% confidence interval also lies entirely within the equivalence, thus also showing equivalent efficacy. Moreover, the applicant provided several sensitivity and subgroup analyses which also support the primary efficacy endpoint analysis.

Similarity in efficacy was further supported by the secondary efficacy endpoints. The summary statistics of the percent change from baseline in BMD at lumbar spine at month 6 and the percent change from baseline in BMD at total hip and femoral neck at month 6 and month 12 showed comparable mean BMD and percent change from baseline between the SB16 and EU-Prolia group. Additionally, the applicant could demonstrate that there is no difference between those subjects who switched from EU-Prolia to SB16 and those who continued on EU-Prolia for the third dose, as the month 18 data for the lumbar spine BMD, femoral neck BMD and total hip BMD were similar among the groups.

Safety

In terms of safety, the biosimilarity of SB16 and Prolia was demonstrated in two trials, one in healthy male volunteers and one in patients with PMO. In study 1001, SB16, EU-Prolia and US-Prolia showed a

comparable safety profile. The incidence of AEs was similar between the treatment groups and most AEs were of mild or moderate severity. SAEs that occurred during the trial were not related to study drug and are considered chance findings. In study 3001, SB16 and EU-Prolia showed similar incidences of AEs, most which were mild in severity and not considered related to study drug. The incidences of SAEs and AESIs were comparable between the treatment groups.

In both trials, there were no relevant changes in vital signs or laboratory data. Hypocalcaemia incidences were similar between the treatment groups in trial 1001 and 3001 and none of the events were graded severe.

Immunogenicity

A well described and developed three-tiered assay was employed to determine ADAs and NAbs. In study 3001 in patients with PMO, the observed incidence of ADAs was <1%, which is in line with the Prolia and Xgeva labels. None of the patients positive for ADAs developed NAbs. In healthy volunteers in study 1001, the proportion of patients who developed ADAs was similar between the treatment groups, and none of the ADA-positive subjects developed NABs. Taken together, the immunogenicity results are considered supportive of biosimilarity.

3.3. Uncertainties and limitations about biosimilarity

Quality

Clinical

PK/PD

Study SB16-1001

Limitations of the study were the short study duration (6.6 months) and administration of a (single) 60 mg therapeutic dose. This may hamper the appropriate characterisation of PD at lower concentrations. To assess the terminal target-mediated clearance of denosumab, pAUCs were provided upon request.

From 3360 h (Day 141) to 4032 h (Day 169), mean concentrations of SB16 only marginally decreased from 194.10 ng/ml to 175.92 ng/ml, while EU-Prolia and US-Prolia concentrations decreased from 194.94 ng/ml to 91.90 ng/ml, and from 277.07 ng/ml to 163.86 ng/ml, respectively, between the same time points. On the other hand, most subjects had denosumab levels BLQ during the terminal elimination phase, which were not included in the statistical analyses. Sensitivity analyses setting terminal BLQ concentrations to 'zero' showed similar results to the main analyses.

Regarding PD, at the last sampling timepoint (4704 h or Day 197), serum CTX levels have not yet returned to baseline, but were similar between treatment groups (mean -58.73%, -58.95%, and -65.47% change from baseline for SB16, EU-Prolia and US-Prolia, respectively).

Study SB16-3001

There were some uncertainties relating to the PK assay and abnormal values at baseline. In relation to this the applicant was asked to discuss and refer to assay validation and if those measurements or values are likely to be related to assay function. The applicant provided a root cause analysis and ad-hoc analyses. The applicant further provided compelling argumentation and reasoning behind the claim that, despite the unknown reason for the measurable denosumab levels at baseline, it should not affect the PK similarity outcome. This also applies to trustworthiness of the assay and data analysis. Taken together the impact is negligible and because of the thorough answer it is deemed that these abnormal baseline values are not indicative of a general fault with sample measurements or analysis. Furthermore, there is an uncertainty regarding the sparse PK sampling in study SB16-3001, with PK

samples being collected only at month 0, 0.5, 1, 3, 6, 9, 12 and 18. Furthermore, beside mean serum concentrations, no further analyses on PK parameters were foreseen in this study. Thus, there is an uncertainty around PK analysis in patients. However, this issue is alleviated due to the available PK data in healthy volunteers and therefore no concern is raised.

Regarding PD, the "AUEC $_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" would have been expected to be a co-primary endpoint in study SB16-3001. After denosumab treatment, the changes in BMD (defined as primary endpoint) are slow and modest, while the changes in serum CTX are large and dynamic. Thus, serum CTX might be more sensitive to compare test and reference product in terms of biosimilarity, however, the clinical relevance might be higher for BMD, which is often used in clinical trials. Therefore, the applicant was asked to present the ratio of least-squares geometric mean (SB16 vs. Prolia) with the corresponding 95% CI. The analysis provided in response to the request supported the results of the main analysis.

Efficacy

Study SB16-3001

Baseline data revealed that there is an imbalance in oral BP use and years since diagnosis of PMO between the SB16 and EU-Prolia group. Subjects in the SB16 group had their osteoporosis diagnosis about half a year longer than the subjects in the Prolia group. The total cumulated period of oral BP treatment prior to screening was 15.4 months in the SB16 group versus 13 months in the Prolia group. After request, the applicant provided several sensitivity analyses to assess the impact of the imbalance in "mean years since diagnosis" and "use of oral BP prior to screening" between the groups. The sensitivity analyses support the results of the main analysis.

3.4. Discussion on biosimilarity

Quality

Clinical

In study SB16-1001 PK similarity was demonstrated in healthy male subjects. The geometric LSMean ratios (90% CI) for SB16 and EU-Prolia for AUC_{inf}, C_{max}, and AUC_{last} were 1.01 (0.93 to 1.10), 1.02 (0.95 to 1.10), and 1.02 (0.94 to 1.12), respectively. Thus, all primary PK endpoints were within the pre-defined equivalence margin of (0.8, 1.25). Similar to the SB16/EU-Prolia comparison, all 90% CIs for the ratios (SB16/US-Prolia and EU-Prolia/US-Prolia) of the geometric means for AUC_{inf}, C_{max} and AUC_{last} were within the prespecified equivalence criteria. Limitations of the study were the short study duration (6.6 months) and administration of a single therapeutic dose (60 mg) only. Therefore, the characterisation of PD at lower concentrations may be hampered.

PK similarity is further supported by study SB16-3001, where similar mean serum concentration-time profiles over the whole study period were shown for the SB16 and EU-Prolia group. However, this was not fully informative as only sparse PK sampling was performed in this study.

PD similarity has been demonstrated in both clinical studies. In study SB16-3001 the 90% CI for the ratio of geometric mean for AUEC of percent change from baseline in serum CTX was within the pre-specified acceptance criteria of 0.8 to 1.25. This was further supported by comparable median percent change from baseline in CTX/P1NP concentration time profiles for the SB16 and EU-Prolia groups. However, the secondary endpoint "AUEC $_{0\text{-}6M}$ of percent change from baseline in serum CTX concentration" would have been expected to be a co-primary endpoint and therefore, the ratio of least-squares geometric mean (SB16 vs. Prolia) with the corresponding 95% CI was requested, which also supports the main analysis. PD similarity is further supported by similar descriptive PD profiles of

serum CTX levels between the treatment groups in study SB16-1001. However, there remains an uncertainty as due to the short study duration, the serum CTX levels have not yet returned to baseline at the last sampling timepoint.

In study SB16-3001 efficacy similarity was demonstrated in osteoporosis patients. The primary efficacy analysis on the percent change from baseline in lumbar spine BMD at Month 12 was performed on the PPS set and revealed that the difference between the SB16 and the EU-Prolia group was 0.39% with the corresponding 95% CI being -0.36% and 1.13%. The 95% confidence limits (-0.36%; 1.13%) are very well within the pre-defined and accepted equivalence range of [-2%, 2%] and estimate a 'maximum' difference of 1.13%. This size of a difference between the treatments is thereby convincingly supporting clinical equivalence of the treatments. Additionally, the primary efficacy endpoint analysis was also conducted with the full analysis set, also supporting clinical equivalence. Similarity in efficacy was further supported by the secondary efficacy endpoints. However, an imbalance in oral BP use and years since diagnosis of PMO between the SB16 and EU-Prolia group was revealed. After request, the applicant provided several sensitivity analyses to assess the impact of the imbalance in "mean years since diagnosis" and "use of oral BP prior to screening" between the groups. The sensitivity analyses support the results of the main analysis.

Safety and immunogenicity

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

3.5. Extrapolation of safety and efficacy

SB16 was developed as a biosimilar product to Prolia and Xgeva. The mechanism of action is identical to the reference products. The monoclonal antibody Denosumab targets and binds to RANKL, thus preventing interaction of RANKL with RANK. Block of interaction of RANKL with RANK leads to reduced osteoclast formation and function. Thus, bone resorption and cancer induced bone destruction is decreased.

The mechanism of action is identical across all indications, i.e. binding to RANKL and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalised bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Thus, based on the same mechanism of action, extrapolation to all indications might be allowed.

The extrapolation is further supported by the fact that the known PK, safety and immunogenicity profile of denosumab as summarised in the product information for Prolia/Xgeva is comparable across the approved indications and patient populations.

Furthermore, the clinical data were derived from healthy volunteers and female post-menopausal osteoporosis patients. These are regarded sensitive populations in terms of evaluating biosimilarity of SB16 and the reference product.

Based on the above, the safety and efficacy profile of SB16 as assessed in the PMO indication can be extrapolated to all indications applied for SB16.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Xbryk 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 Xbryk is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the < marketing authorisation 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

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.