25 April 2025
EMA/CHMP/165386/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Denbrayce

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006199/0000

Note

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

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List of abbreviations

%CfB	Percentage change from baseline
%CfB-TF	Percentage change from baseline–treatment failure
25-OH	25-hydroxy
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, legible, contemporaneous, original, and accurate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Code
AUC	Area under the concentration-time curve
AUC0-6 months	Area under the concentration-time curve from time 0 to 6 months
AUC0-99	Area under the concentration-time curve from time 0 to Day 99
AUC0-last	Area under the concentration-time curve from time 0 to the last quantifiable concentration time point
AUC0-∞	Area under the concentration-time curve from time 0 extrapolated to infinity
AUEC	Area under the effect versus time curve
AUEC0-6 months	Area under the effect versus time curve from time 0 to 6 months
AUEC0-253	Area under the effect versus time curve from time 0 to Day 253
AUEC0-last	Area under the effect versus time curve from time 0 to the last quantifiable concentration
AUIC	Area under the % inhibition versus time curve
AUIC0-6 months	Area under the % inhibition versus time curve from time 0 to 6 months
AUIC0-253	Area under the % inhibition versus time curve from time 0 to Day 253
AUIC0-last	Area under the % inhibition versus time curve from time 0 to the last quantifiable concentration
BAN	British Approved Name
BDS	Bulk Drug Substance

BHT	Bulk harvest testing
BLQ	Below the limit of quantification
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
BSE	Bovine spongiform encephalopathy
BUN	Blood urea nitrogen
C1q	Complement component 1q
CAS	Chemical Abstract Service
CDR	Complementarity determining regions
CDC	Complement-dependent cytotoxicity
CE SDS	Capillary electrophoresis sodium dodecyl sulfate
CFB	Change from baseline
CFR	Code of Federal Regulations
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL/F	Apparent total body clearance following extravascular administration
Clast	Last quantifiable concentration
Cmax	Maximum observed serum concentration
Cmin	Minimum observed serum concentration
COA	Certificate of analysis
COVID-19	Coronavirus disease 2019
CPP	Critical process parameters
CPK	Creatine phosphokinase
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System

Ctrough	Trough (predose) serum concentration
CTX	Carboxy-terminal cross-linking telopeptide of type I collagen
CV	Coefficient of variation
DLS	Dynamic light scattering
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
DSM	Downscale model
DSMB	Data and Safety Monitoring Board
DSP	Downstream process
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoP	End of production
EOS	End of study
EOT	End of treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
Fab	Fragment antigen-binding
FAS	Full analysis set
Fc	Fragment crystallizable
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GCTB	Giant cell tumour of bone
GFR	Glomerular filtration rate
GIOP	Glucocorticoid-induced osteoporosis
GMP	Good Manufacturing Practice

HALT	Hormone ablation therapy
HAP	Hamster antibody production
HBV	Hepatitis B virus
HC	Heavy chain
HCP	Host cell protein
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HILIC	Hydrophilic interaction liquid chromatography
HIV	Human immunodeficiency virus
HMW	High molecular weight
HPLC	High-performance liquid chromatography
HPLC-SEC	High-performance liquid chromatography–size exclusion chromatography
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IEX-HPLC	Ion-exchange chromatography
IgG	Immunoglobulin G
IgG2	Immunoglobulin G2
IL	Interleukin
Imax	Maximum % inhibition
INN	International Nonproprietary Name
INR	International normalized ratio
IRT	Interactive response technology
IκB	Inhibitor of nuclear transcription factor κB
IV	Intravenous
JAN	Japanese Accepted Name
Kel	Elimination rate constant during terminal phase
LC	Liquid chromatography / Light chain
LC-MS	Liquid chromatography–mass spectrometry
LCM	Lymphocytic choriomeningitis virus

LLOQ	Lower limit of quantification
LMW	Low molecular weight
LRV	Log reduction value
LS	Least squares
mAb	Monoclonal antibody
MAA	Marketing Authorisation Application
MAP	Mouse antibody production
MAR	Missing at random
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of diet in renal disease
mDSC / µDSC	Micro differential scanning calorimetry
mFAS	Modified Full Analysis Set
MFI	Micro-flow imaging
MI	Multiple imputation
MLUXH	Million luxes per hour
MMRM	Mixed model for repeated measures
MMW	Medium molecular weight
MS	Mass spectrometry
MSD-ECL	Meso Scale Discovery electrochemiluminescence
MuLV	Murine leukemia virus
MVM	Minute virus of mice
N	Number of subjects in the treatment group
n	Number of evaluable values
N/A	Not applicable
nAb	Neutralising antibody
NFκB	Nuclear factor kappa-B
NOAEL	No observed adverse effect level
NOR	Normal operating range
NR	Non-reduced
OPG	Osteoprotegerin

PAR	Proven acceptable range
PC	Process characterisation
PCR	Polymerase chain reaction
PCS	Process control strategy
PD	Pharmacodynamic(s)
PES	Polyether sulfone
PETG	Polyethylene terephthalate copolyester
PFS	Prefilled syringe
Ph. Eur.	European Pharmacopeia
pH	Potential hydrogen
pI	Isoelectric point
PK	Pharmacokinetic(s)
PKCS	Pharmacokinetics Concentration Set for the Main Treatment Period
PKPS	Pharmacokinetics Parameter Set for the Main Treatment Period
PMDA	Pharmaceuticals and Medical Device Agency
PMO	Postmenopausal osteoporosis
PPQ	Process performance qualification
PRV	Pseudorabies virus
PS20	Polysorbate 20
PT	Preferred term / Prothrombin time / Peptide mapping (context-dependent)
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
PTM / PTMs	Post-translational modification(s)
q.s.	Quantum sufficit
QTcF	QT interval corrected using Fridericia's formula
QTL	Quality tolerance limit(s)
QTPP	Quality target product profile
R	Reduced
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
REC	Research Ethics Committee

RMP	Reference medicinal product
RN	Registry number
RP	Reference product / Reverse phase
RPM	Rounds per minute
RT	Room temperature
RT-PCR	Reverse transcription polymerase chain reaction
RU/RTU	Ready to use
s.c. / SC	Subcutaneous(ly)
SAE	Serious adverse event
SAF	Safety analysis set
SAL	Sterility assurance level
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety access system
sCTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	Standard deviation
SEC / SE-HPLC / SE HPLC	Size exclusion chromatography / high-performance liquid
SmPC	Summary of product characteristics
SOC	System organ class
SOE	Schedule of events
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Apparent terminal elimination half-life
TB-ADA	Treatment-boosted antidrug antibody
TEAE	Treatment-emergent adverse event
TEM	Transmission electron microscopy
TI-ADA / TIADA	Treatment-induced antidrug antibody
Timax / TImax	Time of occurrence of maximum % inhibition
Tmax	Time to reach maximum observed serum concentration
Tmin	Time of occurrence of minimum concentration
TNF	Tumour necrosis factor

TSE	Transmissible spongiform encephalopathy
US	United States
USAN	United States Adopted Name
USP / USP/NF	United States Pharmacopeia (and National Formulary)
UV	Ultraviolet
VH	Variable heavy
VL	Variable light
Vz/F	Apparent volume of distribution during terminal phase following extravascular administration
WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mabxience Research S.L. submitted on 23 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Denbrayce, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

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

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection in a vial
- Marketing authorisation holder: Amgen Europe B.V.
- 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 in a vial
- Marketing authorisation holder: Amgen Europe B.V.
- 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 bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xgeva 120 mg solution for injection in a vial
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 13-07-2011
- Marketing authorisation granted by:
  - Union

  Marketing authorisation number: EU/1/11/703
- Bioavailability study number(s): MB09-A-01-19

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
30 January 2020	EMEA/H/SA/4356/1/2019/II	Elina Rönnemaa, Juha Kolehmainen
24 March 2020	clarification letter EMA/133427/2020	Elina Rönnemaa, Juha Kolehmainen

The Scientific advice pertained to clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	23 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 August 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 February 2025
The CHMP agreed on a list of outstanding issues be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Denbrayce on	25 April 2025

2. Scientific discussion

2.1. About the product

Denbrayce was developed as a biosimilar product to Xgeva (INN: denosumab) and was developed with the same strength and presentation:

- Xgeva: 120 mg/1.7 mL single use vial

Denosumab is a fully human IgG2 monoclonal antibody produced in a mammalian cell line (CHO) by recombinant DNA technology. Denosumab mechanism of action consists of binding to RANKL, thereby preventing its binding to its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. RANKL is a TNF ligand superfamily member essential for the formation, activation, and function of osteoclasts. Denosumab does not possess any Fc-related effector activity as part of its functionality. Structurally, Denosumab consists of 2 heavy chains of γ-2 idiotype, and 2 light chains of the κ idiotype, yielding a molecular mass of approximately 147 kDa. Each heavy chain contains 447 amino acids with 4 intramolecular disulfide bonds, and an N-linked glycan at the consensus glycosylation site, N298. Additionally, each light chain contains 215 amino acids, with 2 intramolecular disulfide bridges. Denosumab contains 36 total cysteine residues, which are involved in both intrachain and interchain disulfide bonds.

Denbrayce is intended for all approved indications of Xgeva.

2.2. Type of application and aspects on development

Denbrayce (MB09) is a proposed biosimilar to EU-Xgeva.

The development has been conducted in line with EMA guidance documents for biosimilars. A comprehensive analytical comparability study according to EMA/CHMP/BWP/247713/2012 has been performed supporting the biosimilarity claim.

During the development of MB09, the applicant sought Scientific Advice (SA) from the EMA Scientific Advice Working Party. The SA was requested to discuss the clinical development of MB09.

The clinical development programme comprises two trials:

Pharmacokinetic aspects to support the similarity of MB09 to the respective originators EU-Xgeva/US-Xgeva or EU-Prolia have been evaluated in one Phase I comparative PK, PD, safety and immunogenicity study in healthy male subjects (**MB09-A-01-19**) and one Phase III comparative efficacy, safety, PK, PD and immunogenicity study (**MB09-C-01-19**).

2.3. Quality aspects

2.3.1. Introduction

This medicinal product has been developed as a biosimilar biological product to Xgeva (EMEA/H/C/2173). It contains the active substance denosumab (also referred to as MB09), a human monoclonal IgG2 antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as a solution for subcutaneous injection in a single-use vial where denosumab is formulated with acetic acid, sodium hydroxide, sorbitol, polysorbate 20 and water for injections. One vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL).

2.3.2. Active substance

2.3.2.1. General information

Denosumab is a fully human IgG2 monoclonal antibody (MAb) produced in CHO by recombinant DNA technology. Denosumab mechanism of action consists of binding to RANKL, thereby preventing its binding to its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. RANKL is a TNF ligand superfamily member essential for the formation, activation, and function of osteoclasts. Denosumab does not possess any Fc-related effector activity as part of its functionality. Structurally, denosumab consists of 2 heavy chains of γ-2 idiotype, and 2 light chains of the κ idiotype, yielding a molecular mass of approximately 147 kDa. Each heavy chain contains 447 amino acids with 4 intramolecular disulfide bonds, and an N-linked glycan at the consensus glycosylation site, N298. Additionally, each light chain contains 215 amino acids, with 2 intramolecular disulfide bridges. Denosumab contains 36 total cysteine residues, which are involved in both intrachain and interchain disulfide bonds.

2.3.2.2. Manufacture, characterisation and process controls

Description of the manufacturing process and process controls

The active substance is manufactured at GH GENHELIX S.A., Parque Tecnológico de León, Edifício GENHELIX, C/Julia Morros, s/n, Armunia, 24009 León, Spain. All sites involved in manufacture and quality control of the active substance operate in accordance with EU GMP.

MB09 is expressed in transfected CHO cells and produced in a fed-batch process. Material from bioreactor´s culture is harvested and purified to comprise a batch of active substance. Manufacture of a batch starts from the Working Cell Bank (WCB). After thawing, cells are expanded and a transferred into production bioreactors. The bulk harvest is clarified by depth filtration.

MB09 is purified from the clarified, cell-free harvest using chromatography steps. Multiple chromatography cycles are performed per batch.

Prior to filling, the active substance is ultrafiltered/diafiltered (UF/DF) and finally filtered into its final container with a 0.2 µm pore filter. The active substance is sealed, labelled, and stored for long-term storage.

The manufacturing process includes various dedicated orthogonal virus clearance steps.

The applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts and tables listing process parameters and in-process controls/tests (IPC/IPT) with their acceptable ranges. The composition of solutions and buffers for downstream purification is described. The composition of media and solutions in the cell culture process is provided.

Exemplary chromatograms of the chromatography steps are presented. Process parameters are classified into general process parameters (GPP), critical process parameters (CPP), non-critical process parameters (NCPP), and well-controlled critical process parameters (WC-CPP).

Definitions of batch and scale are provided; traceability of active substance batches is ensured by a unique batch code. Explanation of the batch numbering system is not provided in detail, but it is not identified as a concern.

Chromatography resins and filter membranes are re-used for multiple cycles. Maximum resins life-time – number of cycles allowed are provided.

Hold times have been established for process intermediates based on physicochemical and microbiological hold time studies. Provided studies support the proposed hold times and are sufficiently justified.

Reprocessing is proposed for various steps and performed in case if predefined failures occur (failed post-use filter integrity test).

The active substance is shipped frozen in qualified shipping containers between active substance and finished product manufacturing facilities.

In conclusion, the applicant provided a detailed description of the manufacturing process and controls that is in line with regulatory expectations.

Control of materials

Raw materials

Raw materials used for the cell culture and purification process are listed with their intended use. The in-house specifications are specified, which is considered sufficient. Compositions of buffers/stock solutions/media and components are provided. Specifications for resins and filters are also in place.

Except one animal-derived material that is used in the active substance manufacturing process, no other raw material of direct animal or human origin is used during manufacture of MB09. In addition, raw materials from indirect animal origin are used for active substance manufacturing. Respective TSE/BSE certificates were provided.

Filters and disposable containers used in cell culture and harvest process are provided.

Overall, the provided information is sufficient.

Cell Substrate

The construction of the expression plasmid of MB09 and their genetic elements are described in sufficient detail. The host cell line used for denosumab cell line creation is a Chinese Ovary (CHO) cell line. Construction of plasmids used to generate kappa and gamma chains of denosumab are presented and development of cell line is provided. The nucleotide sequence of the expression constructs was confirmed by sequencing. Host cells were transfected with expression plasmids.

A two-tiered cell bank system consisting of Master Cell Bank (MCB) and WCB has been established from the RCB in accordance with ICH Q5D and GMP requirements. The cell banking system is adequately described with sufficient details on manufacture and storage of the MCB and WCB.

A protocol describing the manufacture and qualification of new WCBs is provided.

MCB storage stability is monitored and the proposed intervals for cell bank stability testing are acceptable.

Characterisation of the cell banks (MCB, WCB, EOP) included an adequate demonstration of the genetic stability by sequencing, southern blotting, gene copy number determination and integration site stability.

A summary of analytical methods used to characterise and test MCB, WCB and EOP cell bank (excluding viral testing – already in place in A.2) is provided.

Characterisation of the cell banks satisfactorily demonstrates identity, purity, suitability, and genetic stability.

Control of critical steps and intermediates

This section defines process and performance parameters as well as acceptance limits. Parameters are classified into GPP, CPP, WC-CPP, NCPP. IPCs, IPTs and in-process parameters (IPP) with appropriate acceptance limits are listed for each parameter.

No critical intermediates are defined for the active substance manufacturing process.

The information provided in this section is sufficient.

Process validation

A traditional approach was chosen to verify process performance at commercial scale. Several process validation batches at commercial scale at the proposed commercial active substance manufacturing site Genhelix were included. All process validation batches were manufactured according to the intended commercial process.

Overall, the validation criteria are acceptable. A summary on the performed process performance qualification (PPQ) including the process and performance parameters per manufacturing step for each of the PPQ batches, has been provided. Deviations were sufficiently described and evaluated/justified. All other process and performance parameters met their acceptance criteria or acceptance range.

In summary, the presented process verification data demonstrate that the intended commercial manufacturing process performs consistently under commercial operating conditions and conforms to the guideline EMA/CHMP/BWP/187338/2014. The overall approach to validation is acceptable.

Hold times

Physicochemical hold time studies on the different active substance manufacturing steps have been performed at-scale during PPQ studies on several batches.

Microbial studies have been conducted in the worst-case condition selected.

The intermediate hold times for commercial manufacturing have been proposed based on the validated physicochemical studies.

The proposed hold times are sufficiently justified.

Resin and membrane reuse and cleaning

Resin lifetimes and potential carry-over have been investigated in small-scale studies. 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. The small-scale study on one of the chromatography resin reuse types is ongoing. Protocols for the ongoing at-scale verification studies have been provided.

Validation of re-usability of UF/DF membrane is ongoing. The maximum number of reuses was set according to industry technical reports, information from the supplier and process knowledge.

Impurity clearance

The MB09 manufacturing process has been shown to effectively and consistently remove process-related impurities to acceptable safety levels. For product-related proteins, no significant changes were seen through the downstream manufacturing process. This is acceptable. The manufacturing-scale data demonstrate consistent removal of product variants to acceptable levels.

Descriptions of the analytical methods used for the impurity detection are presented in the dossier and qualified.

Shipping validation

Frozen active substance is shipped from the manufacturing site in Leon, Spain to the finished product manufacturing site. The performance qualification confirmed that the shipping containers are suitable to maintain the shipping temperature and the validated time for the transport. Based on the outcome of the risk assessment extractable studies were performed for materials with high risk

The shipping process has been adequately qualified.

Single-use Equipment

The applicant performed a risk assessment to assess the risk for leachables from product contact components during manufacturing of MB09 and determine the need for leachables studies. The risk assessment approach is considered acceptable.

A report of the finalised leachable study for the container closure system was provided and no risks were identified.

Reprocessing

Reprocessing is described for various steps in the manufacturing process. Validation protocols were provided and found acceptable. Reprocessing is described in case of predefined failures; this is acceptable.

Manufacturing process development

Process design as a part of quality by design (QbD) approach involved process characterisation studies, comprising risk assessments for the identification of potential CPPs and WC-CPPs, followed by characterising the process parameters through statistically designed experimental studies as well as studies assessing the linkage of the unit operations using qualified scale-down model. The outcome of the studies resulted in identification of CPP and process parameter estimation of proven acceptable ranges (PARs) and defining process control strategy, which eventually were used for validating the active substance manufacturing process at commercial scale. Characterisation studies were conducted using design of experiments (DoE) and one factor at a time (OFAT) methodology and failure modes and effects analysis (FMEA) based risk assessment which was performed on each step of the process to identify CPPs.

Scale-down models (SDMs) were set and qualified. Results of these studies are provided. The assessed impact of investigated process parameters on identified critical quality attributes (CQAs) is shown. Results are analysed using ANOVA. Analysis of critical raw materials (for upstream and downstream process) is provided within process characterisation section. The qualifications of the SDMs are acceptable.

The quality attributes were evaluated for their criticality using a risk-based approach determined by impact score and uncertainty. The quality attributes (QAs) were assessed based on impact on pharmacokinetics (PK) / pharmacodynamics (PD), biological activity, immunogenicity, and safety. The information on the CQA assessment and its outcome that includes detailed assessment for each criticality category is satisfactory. Overall, criticality ratings and their justification appear reasonable. No questions are raised. The sufficiently detailed summary of risk assessment performed to identify CQAs is provided. The CQAs are identified in line with ICH Q8.

A post-process characterisation risk assessment was conducted. It summarises the outcome and assessments of several process characterisation studies. In addition, it includes an update on the criticality classification of the process parameters, which is based on data stemming from the process characterisation.

Clearance of process-related impurities has been sufficiently demonstrated by small-scale bypass studies and historical process data. The historical data demonstrate consistent reduction of impurities to or below the LOQ. These results are confirmed by the PPQ runs.

The presented approach is acceptable and the classification of the parameters and their specified ranges is reasonable.

Comparability Assessment

MB09 active substance manufacturing process was initially manufactured at small scale. Some adaptations and optimisations were conducted. A brief description of all changes was provided. Quality data from different steps were compared.

All scale-up related changes were described. Product quality results including clearance and process step yield recoveries were assessed. All analysed parameters were within established ranges.

Comparability between the small scales process was not assessed, however, considering that material from the first small scale has not been used in clinical studies, relevant stability studies or for analytical similarity studies, demonstration of comparability is not required.

A further scale up to the commercial scale was conducted at Genhelix. Material from the commercial scale was used for PPQ studies, analytical similarity, and stability studies. Analytical methods are described and qualified. Comparability approach is mainly in line with ICH Q5E.

Comparability between clinical phase and PPQ batches

A comprehensive comparability study was performed between clinical and PPQ including active substance release data comparison and an extended characterisation at finished product level.

The acceptance criteria for comparability were defined based on active substance release specifications and historical data from lots manufactured

An adequate comparability report was provided including representative chromatograms, individual data and analytical method descriptions. All tested parameters were within pre-defined acceptance criteria except for one of the assessed quality attributes. However, it is not considered a meaningful difference, which can be agreed.

In general, based on the provided data, comparability between active substance materials derived from the different process versions is demonstrated.

Characterisation

Elucidation of structure and other characteristics

The aim of the structural characterisation was to confirm the primary structure and the higher order structure of MB09. The structural and functional attributes of MB09 are described briefly for clinical batches. Additional characterisation data is provided for batches from the commercial process. Various orthogonal analytical techniques were used to characterise the primary structure, carbohydrate structure, mass heterogeneity, disulfide bridge patterns, size heterogeneity, charge heterogeneity, deamidation/oxidation and biological functions. Adequate and sufficient raw data (chromatograms, results) is provided.

In conclusion, the provided information is in line with the Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 and considered sufficient.

Impurities

A discussion of the potential impurities in MB09 active substance has been provided.

All product-related impurities are routinely controlled by in-process tests and release/shelf-life testing to assure consistency of MB09 manufacturing.

Data presented for, demonstrated that the process consistently and effectively removes impurities to very low levels

Adventitious contaminants were effectively removed during manufacturing process, which was demonstrated with the PPQ lots.

Overall, the information provided is satisfactory.

2.3.2.3. Specification

The release and shelf-life specifications for MB09 active substance comprise tests for general attributes (colour, clarity, pH, osmolality, polysorbate 20), identity, purity/impurity, heterogeneity, quantity, biological activity, quantity, and microbiological safety (bacterial endotoxins and bioburden).

In summary, the set of quality attributes tested at release complies with ICH Q6B, and EMA/CHMP/BWP/532517/2008 and is acceptable. Unique method identification numbers are included in the specifications.

Acceptance criteria have been established based on manufacturing capability, data from the analytical similarity exercise, product characterisation data, and batch release and stability data (clinical, consistency, and PPQ batches). Also, regulatory requirements from the Ph. Eur. and relevant guidelines were taken into account to justify the specifications. Evolution of the specifications throughout development is adequately described.

The proposed specifications are acceptable.

The applicant committed to re-evaluate the active substance specification limits for several specification parameters after a sufficient number of batches have been manufactured (after at least 30 batches) (Recommendation).

Analytical procedures

The general and microbial attributes are tested according to the respective Ph. Eur. monographs; all other attributes are tested using in-house analytical methods. For non-compendial methods, an overview of the method, sample preparation, reagents, equipment and operating conditions, representative chromatograms, assay and sample acceptance criteria, and the way of reporting results are described.

The analytical methods are adequate for their intended purpose and overall the implemented system suitability tests and sample acceptance criteria are suitable to provide adequate control over analytical method performance.

In general, adequate method validations were provided and the results demonstrate suitability of the analytical procedures for their intended use. The relevant parameters have been assessed in accordance with ICH Q2(R1).

During the procedure, the applicant proposed two minor changes to the analytical procedure for various parameters. The change proposed by the applicant is considered acceptable.

Batch analysis

Batch analysis data are presented for several development and PPQ batches. All results comply with the proposed commercial specifications.

In summary, the presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Reference standards

The applicant has described its reference standards used throughout the development of MB09. Different classes of reference standards including Interim Reference Standard (IRS), Primary Reference Standard (PRS), and Secondary Reference Standard (SRS) were defined. A two-tiered system with primary and secondary reference standards has been implemented.

The history of MB09 reference standards of MB09 was described. MB09 IRS preparation and qualification has been described.

The reference standards have been appropriately qualified.

A detailed stability programme is provided including discussion on potential potency drifts.

It is agreed that the two-tiered reference standard system in combination with stability monitoring of both primary and secondary reference standards ensures that potential drifts in potency are detected.

The qualification of future reference standards has been briefly described. The selected SRS will be qualified against the PRS including physicochemical and functional properties. 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 future reference standards is acceptable.

In summary, the information provided on the reference standards is satisfactory.

Container closure system

The container closure system (CCS) is adequately described. The materials comply with Ph. Eur. and/or USP requirements and Commission Regulation (EU) No. 10/2011 on plastic materials and articles in contact with food.

Specifications and drawings are provided, and compatibility of container closure system and active substance has been confirmed by stability studies.

The container closure system is suitable.

2.3.2.4. Stability

The shelf-life claim stored at long term conditions was proposed based on the stability data available from development batches and PPQ batches at long term, accelerated and stress conditions.

Based on the comparability study between clinical and commercial scale/PPQ batches, clinical batches can be considered as being representative of the PPQ/commercial batches and used as primary stability batches to support the shelf-life.

Considering this, the proposed shelf-life at the recommended storage conditions is sufficiently justified based on the results of clinical batches.

The stability sampling strategy applied is in line with ICH Q5C and the container closure system used for stability studies is representative for the commercial container closure system.

At long-term and accelerated conditions, all results comply with the acceptance criteria for the current studies as well as the proposed commercial specification limits. No obvious relevant trends are present at long-term or accelerated conditions.

In addition, stress and forced stress stability studies were performed to evaluate conditions that may be experienced during storage and use including photostability studies, temperature cycling, freeze/thaw studies, mechanical stress, temperature, pH, and oxidation stress.

Results demonstrated that the active substance is sensitive to certain stress conditions of pH, oxidation, high temperature and to forced light. For all other conditions, all acceptance criteria were met.

A commitment to complete the currently ongoing stability studies as well as the schedule for annual stability studies are provided.

In conclusion, the presented data support the proposed shelf-life.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Description of the finished product

MB09 finished product is a clear, colourless to slightly yellow, sterile and preservative-free solution for injection. MB09 vial finished product is presented as a single-use 2R Type I clear glass vial with a bromobutyl coated with fluoropolymer film stopper and an aluminium seal with a plastic flip-off cap containing 120 mg/1.7 mL of denosumab for subcutaneous injection. MB09 vial is formulated at a target concentration of 70 mg/mL with acetic acid, sorbitol, polysorbate 20, sodium hydroxide and water for injections. The formulation of MB09 is identical to that of EU-approved Xgeva. The suitability of the formulation for MB09 was justified by data derived from stability studies as well as data from formulation robustness. All excipients used are of compendial quality.

Pharmaceutical development

Mainly narrative and data description of the manufacturing process development has been presented. Based on these studies it can be concluded that all batches are comparable, irrespectively from the composition and manufacturing process.

Presented information on container closure system is sufficient. Results of extractables and leachables studies have been presented.

The applicant has outlined manufacturing process changes that occurred between development and commercial production. The proposed manufacturing process applied to produce material for the pivotal clinical studies and the commercial process differ with respect to the batch size. Additional adaptions were mostly related to change of equipment.

Comparability between development and PPQ batches has been sufficiently demonstrated. Observed differences are discussed and underlying reasons as well as potential influence on product activity and safety have been addressed.

Development of the primary CCS for denosumab finished product has been described. The suitability of the CCS used for MB09 finished product was demonstrated by the studies assessing the appropriateness of materials (compliance to standards and extractable assessment), compatibility of materials of construction with dosage form, and container closure integrity. It has been stated that extractables and leachables studies were conducted, the results available have been presented and found acceptable.

2.3.3.2. Manufacture of the product and process controls

Manufacture

The manufacturer responsible for batch release is at GH GENHELIX S.A., Parque Tecnológico de León, Edifício GENHELIX, C/Julia Morros, s/n, Armunia, 24009 León, Spain. All sites involved in manufacture and control of the finished product operate in accordance with EU GMP.

The commercial manufacturing process of the finished product is a standard manufacturing process which comprises active substance mixing, filtration, aseptic filling, sealing and capping. Then the vials are visually inspected and stored at the manufacturing site. The manufacturing process is appropriately described. Pooling of active substance is reflected in the manufacturing process description and the maximum number of active substance batches and bottles pooled for finished product manufacture are defined. The filter flush volume is included in the process description and flow diagram. The holding times have been investigated during process validation.

Batch composition has been presented. The applicant has established a control strategy to ensure that CQAs consistently remain within acceptable limits. CPPs are outlined and are controlled or monitored with an acceptable range, which has been defined based on product development studies and existing product knowledge.

Process validation

Validation of the finished product manufacturing process at the commercial manufacturing site included several commercial scale MB09 120 mg/1.7 mL batches originating from independent active substance batches Therefore, active substance variability is sufficiently covered.

Critical steps identified during product development activities have been addressed during process validation and results were compared to pre-defined validation criteria. All process parameters operated well within defined values and ranges and all in-process controls met pre-defined criteria. Analytical release testing was performed in line with specifications proposed for release of commercial batches. The release test results were well within pre-defined specifications for all process validation batches. Hold times have been evaluated and justifications are considered sufficient.

Sterile filter validation was performed. The studies presented demonstrated that no leachable are present, the formulation does not compromise the integrity of the filters, and the filters have an adequate bacterial

retention capability. Test procedures are well described and results from validation activities demonstrate suitability of the chosen filter. Filter validation is considered accepted.

The applicant presented data on media fill for several batches, which gave satisfactory results.

Sufficient information on transport validation has been provided in order to be considered successful. Nevertheless, as the quality testing of the winter shipping campaign is ongoing, the applicant committed to submit the respective results once available (Recommendation).

2.3.3.3. Product specification

Specifications

The proposed finished product release and shelf-life specifications were defined considering ICH Q6B guidance, Ph. Eur. monograph "Monoclonal Antibodies for Human Use" and finished product manufacturing experience.

Panel of release specifications includes tests for identity, potency, purity and impurities, microbiological quality, content and general properties.

The list of MB09 finished product specifications is acceptable. Wider shelf-life limits are justified by presented stability studies results. The applicant committed to re-evaluate the finished product specification limit after a sufficient number of batches have been manufactured (after at least 30 batches) for several specifications parameters (Recommendation).

Analytical procedures

Finished product-specific methods are controlled by compendial methods and are suitable for their intended purpose.

Non-compendial analytical methods for the finished product were validated. In general, the validation of non-compendial analytical procedures has been done according to relevant guidelines. The methods validation information provided is adequate and sufficient.

Batch analysis

Batch analyses data have been presented for several batches from development and commercial manufacturing process and scale. Results have also been presented for the clinical batches.

The respective results comply with the specifications valid at time of release testing and indicate a consistent manufacturing process.

Reference materials

Reference is made to the active substance section for information on "Reference Standards or Materials".

Characterisation of impurities

The absence of risk assessment report on elemental impurities at initial submission triggered a Major Objection. 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. This risk assessment was provided later during the procedure. No elements relevant for parenteral administration listed in classes 1 – 3 according to ICH Q3D are used in the manufacturing process and actual levels of elemental impurities assessed as part of the leachable study are well below 30% of permitted daily exposure (PDE). Based on the risk assessment it

can be concluded that it is not necessary to include any elemental impurities control in the finished product specification. This matter is considered satisfactorily addressed. The risk as regards nitrosamines can be considered as low based on the provided risk assessment.

Container closure

The primary packaging components (type I borosilicate clear glass vial, bromobutyl rubber coated with fluoropolymer film are of compendial quality and tested according to the respective monographs: Ph. Eur. 3.2.1 and Ph. Eur. 3.2.9. The stopper is covered with an aluminium seal and plastic flip-off cap, which are not in direct product contact. Specifications, drawings and certificates of analysis have also been provided. Furthermore, all primary packaging components and seal are sterile and ready-to-use. The information and data regarding sterilisation in accordance with the EMA/CHMP/CVMP/QWP/850374/2015 guideline are provided.

2.3.3.4. Stability of the product

Stability at the long-term storage condition, at the accelerated storage conditions and at stressed and forced degradation storage conditions have been performed in line with relevant guidance.

Based on a comparability study the development batches are considered as being representative of the PPQ/commercial batches. As such and in accordance with Q5C and Q1A(R2) these batches can be used as primary stability batches in order to support the shelf life.

The batches were tested against the stability specifications valid at the time of testing. At the intended storage condition of 5 ± 3°C all test results complied with the shelf-life specifications. Potency results were relatively stable over time and no trends were observed for any tested QA.

At accelerated conditions presented stability data are comparable. Potency results remained stable over time. All results remained within end of shelf-life acceptance criteria.

Stress storage conditions resulted in minor changes; however product specifications were not exceeded.

Photostability studies conducted according to ICH Q1B resulted in product degradation at intense light exposure. Based on the study results, it can be concluded that MB09 should be stored protected from light. Other tested stress conditions did not induce significant changes.

The presented stability studies are considered in line with ICH Q5C and ICH Q1A requirements. The provided data indicate that MB09 is stable when stored for up to 36 months at the intended storage conditions (i.e. 5 ± 3°C, protected from light). The proposed 36-month shelf-life is acceptable.

Once removed from the refrigerator, the product may be stored at room temperature (up to 25°C) for up to 30 days in the original container. It must be used within this 30-day period.

2.3.3.5. Biosimilarity

This product has been developed as a biosimilar biological product to Xgeva (EMEA/H/C/2173). In general, a very comprehensive and sound biosimilarity assessment has been conducted. Since both, EU-sourced reference product and US-sourced comparator product, have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product, based on three-pairwise analytical comparisons has been established.

The described and applied methodology is considered state-of-the-art. If any individual value exceeded the quality range, the magnitude and the criticality of the observed differences were discussed and justified. It can be agreed that the EMA reflection paper on statistical methodology (EMA/CHMP/138502/2017) has been taken into account for analytical assessment and the rational for the acceptance criteria.

Several finished product lots, each originating from a different active substance lot were used in the similarity assessment. Both presentations and material from development and PPQ lots representative of the commercial process were included, and the age of the material has been taken into account. Regarding reference product material, several lots of Prolia and Xgeva source from EU and US were used with a sufficient range of expiration dates. It is agreed that a sufficient number of batches from both, the proposed biosimilar as well as from the reference product has been included to enable a robust and reliable similarity assessment.

All analytical methods were either validated, qualified, or demonstrated fit for purpose. Analytical method descriptions and validation/qualification summaries were provided. Overall, the descriptions and validation/qualification data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and indicate that the methods are suitable for the intended purpose.

The study results and their evaluation are well presented in the dossier. Figures and tables showing the individual results and data distribution for each parameter, chromatographs, spectra, etc. have been included in the analytical similarity report.

To further support the demonstration of biosimilarity between MB09 and Prolia/Xgeva, a comparative forced degradation study and a comparative accelerated study was conducted.

In principle, the provided results support, the biosimilarity claim. For most of the quality attributes similarity was demonstrated. A more detailed discussion on general properties, primary structure, higher order structure, charge variants, glycosylation profile, purity, biological activity, degradation studies and comparative stability studies is given below.

Overall design of analytical comparability studies is in line with the quality guideline for biosimilars (EMEA/CHMP/BWP/49348/2005 and EMA/CHMP/BWP/247713/2012) and the guideline on development, production, characterisation and specifications for monoclonal antibodies and related products (CHMP/BWP/157653/2007).

Comparability between MB09, EU-RMP and US-RMP

General

Protein concentration was adequately demonstrated to be comparable for MB09 PFS with EU- and US-Prolia and for MB09 vial with EU- and US-Xgeva.

Primary structure

Several orthogonal methods were applied to demonstrate that the primary structure of MB09 is similar to that of the reference products, EU- and US-Prolia and Xgeva.

Molecular mass was analysed by LC-MS and representative spectra were shown. The mass spectra of MB09 and RMP are comparable.

A reduced mass analysis was performed and showed comparable spectra and masses between MB09 and EU and US RMP. Lower glycation was detected for MB09 compared to the RMP, however, the results met the acceptance criteria. Primary structure was confirmed.

N- and C-terminal integrity was evaluated.

Higher order structure

Several orthogonal methods were applied to demonstrate that the higher order structure of MB09 is similar to EU and US RMP. High similarity was found between MB09 and EU and US RMP and all expected disulfide bridges were confirmed.

IgG2 isoforms were compared. Overlays of chromatograms were presented, and no significant differences were observed.

The spectral profiles of MB09 lots were comparable.

Assessment of conformational stability was determined. Slight differences between MB09 and EU and US RMP that were observed were within method variability, which can be agreed.

Post-translational modifications

Charge variant profile was analysed.

Slightly less oxidation was observed for MB09, however, all lots were within the acceptance criteria.

Deamidation was shown to be comparable between MB09 and EU and US RMP.

The glycosylation profile was assessed.

Purity

Purity was assessed using several orthogonal methods. MB09 and EU and US RMP were acceptably demonstrated to be comparable with respect to all the evaluated attributes.

Biological activity

RANKL binding and affinity was evaluated by several orthogonal methods. All MB09 lots were within acceptance criteria of EU and US RMP. Absence of binding to TNFα and TNFβ was confirmed by ELISA.

Relative potency was assessed by several orthogonal methods.

Epitope mapping confirmed same epitope binding of MB09 and EU and US RMP on human RANKL.

Fc-related activity was evaluated by binding to FcRn, FcγRIIa, FcγRI, FcγRIIb/c, FcγRIIIa V, and FcγRIIIb. MB09 binding to FcRn and FcγRIIa was comparable to EU and US RMP and low binding to other FcγR receptors was similar.

Low C1q binding and lack of ADCC activity was demonstrated and comparable to EU and US RMP. Lack of CDC activity also showed comparable results between MB09 and EU and US RMP.

Comparative stability – Forced degradation

To evaluate the comparability of degradation behaviour and pathways, a head-on-head comparison study was conducted under multiple stress conditions including thermal, oxidative, mechanical, alkaline and acidic stress conditions. In addition, a separate study to evaluate photostability was conducted. General properties, conformational stability, purity, product variants, potency and post-translational modifications were analysed.

In summary, MB09 and EU and US RMP show highly similar degradation pathways regarding forced degradation and photostability.

Comparative stability – Accelerated stability at 25°C and freeze/thaw stability

Overall, MB09 and EU and US RMP show similar behaviour under accelerated stability and after F/T cycles.

Comparability between PFS and vial

An extensive comparability study was performed to establish a quality bridge between PFS and vial presentations of MB09, EU and US RMP to justify pooling of data for the three-pairwise biosimilarity evaluation. The applicant provided the results of supportive comparability studies, demonstrating comparability of PFS and vial presentations.

Regarding EU-Prolia/EU-Xgeva and US-Prolia/US-Xgeva, comparability was assessed for primary, secondary, tertiary, and higher order structure, charge variants, purity, potency and Fc effector functions. Regarding MB09, quality attributes that potentially could be affected by fill and finish process were included in the comparability assessment.

Pairwise comparisons between PFS and vial presentations were performed against quality ranges.

In summary, based on the totality of presented data it is agreed that PFS and vial presentations of MB09, EU-Prolia/EU-Xgeva and US-Prolia/US-Xgeva are considered analytically comparable and the results support pooling of data for PFS and vial presentations.

Conclusion

Overall, it is concluded that provided results demonstrate that MB09 and EU reference products are highly similar in terms of quality attributes, compared in comprehensive analytical similarity exercise. Moreover, EU RP and US RP are highly similar. The biosimilarity claim is demonstrated.

This section covers also data that substantiates comparability between vials and PFS (EU vial vs. EU PFS, US vial vs. US PFS and MB09 vial vs. MB09 PFS). The comparability between both finished product presentations (vial and PFS) for MB09 and denosumab RPs sourced from EU and US has been evaluated. Based on demonstration of comparability, data from both presentations have been pooled for each product type (MB09, EU-approved and US-licensed RP) to generate the dataset for this analytical similarity assessment.

The comparability exercise results provided demonstrated that analytical similarity between MB09 and the RMP is sufficient to allow a firm conclusion on the physicochemical and biological similarity between the products.

The following table summarises the outcome of the analytical similarity exercise:

Table 1: Analytical similarity between MB09, EU and US RMP results summary

Molecular parameter	Attribute	Key Findings
General test	Protein content	Similar
Primary structure	Intact mass	Similar
	Reduced mass (HC)	Similar
	Reduced and de-N-glycosylated mass (HC and LC)	Similar

Molecular parameter	Attribute	Key Findings
	Glycation (HC and LC)	Similar
	Primary structure confirmation	Similar
	N-terminal integrity	LC -Similar HC- minor differences justified and with no clinical relevance
	C-terminal integrity	Minor differences justified and with no clinical relevance
High Order Structure	Disulfide bridges	Similar
	Free Thiols	Minor differences justified and with no clinical relevance
	IgG2 isoforms	Similar profile Minor differences in IgG content justified and with no clinical relevance
	Secondary structure	Similar
	Tertiary structure	Similar
	Higher Order Structure	Similar
	Structural stability	Similar profile Non meaningful minor differences shown in melting temperatures justified without clinical relevance and related with method variability.
Post translational modifications	Charge variants	Similar profile. Minor differences in charge variants content variants justified and without clinical relevance
	Oxidation	Similar, with MB09 showing overall lower oxidation level
	Deamidation	Similar, with MB09 showing overall lower deamidation level
	Glycosylation assessment	Similar profile Differences shown in glycoforms content (lower levels of afucosylation and slightly higher sialylation) justified without clinical relevance.
Product purity	Size heterogeneity	Similar
	Particles assessment	Similar

Molecular parameter	Attribute	Key Findings
Biological activity (Fab region)	RANKL binding	Similar
	mRANKL binding	Similar
	Absence of TNFα and TNFβ binding	Similar
	Relative potency	Minor differences justified without clinical relevance and related to method variability.
	Epitope mapping	Similar
Biological activity (Fc region)	FcRn binding	Similar
	FcγRIIa binding	Minor differences justified and related with method variability.
	FcγRI binding	Similar
	FcγRIIb/c binding	Similar
	FcγRIIIa binding	Similar
	FcγRIIIb binding	Similar
	C1q binding	Similar.
	Lack of ADCC activity	Similar
	Lack of CDC activity	Similar

2.3.3.6. Adventitious agents

Multiple complementing measures are implemented to ensure product safety regarding non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks and process intermediates, 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 and adequate sanitisation procedures.

Animal-derived materials

Except for one material (coming from a no TSE relevant species), no other raw materials of direct animal or human origin are used during manufacture of MB09. Two recombinant materials, that are produced without direct animal/human-derived materials, are used in the manufacturing process of MB09. Based on the information provided, it is agreed that the risk regarding TSE or viral contamination is low.

Microbial agents

MCB, WCB and EOP cells were tested according to compendial methods for the absence of bacterial, fungal, or mycoplasma contamination. Bioburden and endotoxin tests are performed.

Adventitious viruses

Absence of viruses in MCB, WCB, and EOP cells was determined by a battery of tests covering a broad range of potentially contaminating viruses. In addition, unprocessed bulk batches were tested for potential viral contamination.

The testing programme for the cell banks and unprocessed harvest applied to demonstrate the absence of non-viral and viral adventitious agents is in line with guideline ICH Q5A and relevant Ph. Eur. monographs. Satisfactory descriptions of the respective virus testing methods are available. In addition, descriptions and validation summaries for the methods routinely performed as IPCs on each unprocessed bulk have been filed in 3.2.S.2.4.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using downscaled models of the respective large-scale manufacturing steps. The design of the studies is in line with the guidance documents ICH Q5A and CPMP/BWP/268/95.

The downscaled models are representative for the large-scale process.

The virus clearance capacity of several orthogonal process steps including the dedicated virus clearance steps, and virus filtration), was evaluated using a suitable panel of model viruses. Generally, parameters considered critical for virus clearance were set. Potential carry-over of viruses into the subsequent run was investigated for the chromatography steps. The process intermediates used in the virus studies originated from several active substance batches are representative of the intended commercial process. The virus titration assays and associated controls are described in sufficient detail. The original viral clearance study reports have been submitted**.**

The dedicated virus clearance steps in combination with the chromatography steps provide for an effective and robust clearance capacity.

In summary, the risk for potential contamination and transmission of bacterial, viral, or TSE agents is acceptably low.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

MB09 has been developed as a proposed biosimilar to Xgeva. MB09 is manufactured using a typical manufacturing process for monoclonal antibodies. The active substance denosumab is expressed in a CHO cell line and subsequently purified by several chromatography steps and ultra/diafiltration. Various dedicated virus clearance steps are implemented in the active substance manufacturing process.

The applicant provided a description of the manufacturing process and controls including process parameters and in-process controls as well as potential re-processing

Raw and starting materials and their use in manufacture of active substance are sufficiently described. The expression system and cell banks intended for commercial manufacture are sufficiently described, and in the main characterised and qualified in accordance with ICH guidelines.

The overall control strategy was established in accordance with ICH Q11 using an enhanced development approach. The relevant critical quality attributes have been determined using risk assessment tools. The methodology as well as the proposed classification of quality attributes in critical and non-critical attributes can be agreed. The in-process controls and their acceptance criteria/action limits are considered adequate and sufficiently described.

Process characterisation and process verification (PPQ) data from several batches at commercial scale generally support the conclusion that the active substance manufacturing process reliably generates active substance (and subsequently finished product) meeting its predetermined specifications and quality attributes.

Hold times are listed and sufficiently justified for the respective manufacturing step.

Process development and process changes implemented with the different process versions of the active substance manufacturing process are described and justified. Based on the provided data, comparability between active substance materials derived from the different process versions is demonstrated.

A comprehensive characterisation of structural and functional features of MB09 has been performed based on broad panel of standard and state-of-the-art methods. In addition, a discussion of the potential impurities in MB09 active substance has been provided.

The proposed active substance specifications are acceptable. The descriptions of the analytical methods applied for release and stability testing of active substance are satisfactory. Overall, the analytical methods are appropriately validated.

Reference standards are described and characterised. The container closure system is suitable for its intended use.

Based on the submitted stability data, the proposed shelf-life at the recommended conditions is acceptable.

Finished product

The formulation of MB09 is identical to that of EU-approved Xgeva. The suitability of the formulation for MB09 was justified by data derived from stability studies as well as data from formulation robustness. All excipients used are of compendial quality.

MB09 vial finished product is manufactured according to a standard process including the following steps: Mixing sterile filtration, aseptic filling, sealing and capping, visual inspection and storage for later secondary packaging.

The manufacturing process is appropriately described. It is described how the development programme identified the critical parameters that impact on product performance and how they are controlled ensuring that the product is of the desired quality. CPP and CQA are clearly specified and justified – batches, on which studies have been performed are clearly described. Process validation and batch data (several PPQ batches) demonstrate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes. Sufficient information is presented for MB09 transport validation. Information according to the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015) have been presented and sterile filtration can be considered successfully validated.

The development finished product batches are considered representative of the commercial batches and therefore can be used for shelf-life claim. Although there were limited number of process changes between the development and PPQ/commercial finished product manufacturing process, all of those changes were assessed to have low risk. Furthermore, the comparability between development and PPQ batches has been sufficiently demonstrated. Observed differences were discussed addressing underlying reasons as well as potential influence on product activity and safety.

Specifications were defined considering ICH Q6B guidance, Ph. Eur. monograph "Monoclonal Antibodies for Human Use" and finished product manufacturing experience. The list of MB09 finished product specifications is acceptable.

Finished product-specific methods are controlled by compendial methods and are suitable for their intended purpose.

Risk assessment regarding the presence of elemental impurities and nitrosamines were provided and are acceptable. No specific controls are considered necessary.

The presented stability studies are considered in line with ICH Q5C and ICH Q1A requirements. The provided data indicate that MB09 is stable when stored for up to 36 months at the intended storage conditions (i.e. 5 ± 3°C, protected from light).

Biosimilarity

In general, a very comprehensive and sound biosimilarity assessment has been conducted. Since both, EU-sourced reference product and US-sourced comparator product, have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product, based on 3 pairwise analytical comparisons has been established. MB09 has been developed as vial (this product) and as PFS presentation (Izamby) similar to the reference product presentations. Comparability between the two presentations was demonstrated, supporting pooling of data for the biosimilarity evaluation.

A broad panel of orthogonal state-of-the-art methods has been applied for biosimilarity evaluation to address general properties, primary structure, secondary, tertiary and higher order structure, post-translational modifications, product purity, and biological activity. Degradation profiles have been analysed in comparative stability studies. All individual test results of the analytical similarity exercise are provided and based on the provided information, it is concluded that the analytical methods are suitable for the intended purpose.

In principle, the provided results support the biosimilarity claim. In addition, comparability of US sourced comparator with EU sourced reference product was demonstrated.

Adventitious agents

The risk of contamination and for transmission of adventitious agents is adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

The Major Objections raised during the procedure regarding Module 3 (see above) were adequately addressed.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance and intermediates is adequately described, controlled and validated. The active substance and intermediates are well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents safety including TSE have been sufficiently assured.

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application is considered approvable from the quality point of view. Recommendations have been agreed (see below).

2.3.6. Recommendations for future quality development

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

2.4. Non-clinical aspects

2.4.1. Introduction

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

Denbrayce is indicated in adults for: Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. 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 the prevention of skeletal related events in adults with advanced malignancies involving bone, the recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.

For Giant cell tumour of bone, the recommended dose of Denbrayce is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.

Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present.

2.4.2. Non-clinical studies

The applicant conducted *in vitro* studies to demonstrate biosimilarity between the biosimilar MB09 candidate and the EU and US reference medicinal products, Prolia and Xgeva.

The *in vitro* studies regarding binding and function included *in vitro* pharmacodynamics Fab-dependent biological activities, Fc binding activities, Fc effector function characterisation assays.

Overall, the undertaken *in vitro* studies are considered adequate for evaluation of biosimilarity between MB09 and the approved RMP.

The similarity in Fab-related effector functions was demonstrated by similar binding to RANKL assessed by various orthogonal methods, with minimal differences, within the expected variability of the method.

The similarity in biofunctional properties was further confirmed with orthogonal binding and bioassay methods. It can be considered that MB09 and the RMP product have similar mechanisms of action involving Fab-related function with similar *in vitro* biological potencies.

The assessment of Fc related bio-functional properties shows that MB09 and RMP batches show similar binding response to FcγRIIa and to FcRn. Lack of binding to C1q and FcγRIIIb, as well as low binding to other FcγRs (FcγRI, FcγRIIb/c and FcγRIIIa) was observed for MB09 and RMP as expected for IgG2 molecules. Lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities were also confirmed.

Generally, based on the provided *in vitro* studies, MB09 and the RMP can be considered biosimilar.

No stand-alone secondary pharmacodynamic, safety pharmacology, pharmacodynamic drug interactions, pharmacokinetics and toxicology studies were conducted by the applicant. This is in line with the Guideline for biosimilar development (EMEA/CHMP/BMWP/42832/2005 Rev. 1) and is considered acceptable.

2.4.3. Ecotoxicity/environmental risk assessment

An adequate justification for the absence of ERA studies has been provided. Since the active substance denosumab is a protein monoclonal antibody, it is not anticipated to pose risk to the environment.

2.4.4. Discussion on non-clinical aspects

Based on the *in vitro* studies provided, MB09 and the RMP can be considered biosimilar.

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

On 04.11.2019 the applicant requested EMA scientific advice on the development of this product. Although the applicant raised no explicit questions on the acceptability of the waiver of non-clinical *in vivo* studies, the CHMP endorsed a development programme which includes a full analytical similarity exercise and clinical data to demonstrate similarity.

Accordingly, no non-clinical *in vivo* studies were provided by the applicant. This is endorsed.

With reference to "Environmental Risk Assessment" the applicant declares that: "approval of Denosumab MB09 60 mg DP is not expected to cause increase in environmental exposure and any additional hazards to the environment during storage, distribution, use and disposal. An environmental risk assessment is therefore not deemed necessary. In addition, denosumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00, and its updated draft version, denosumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment."

This view is supported.

2.4.5. Conclusion on the non-clinical aspects

Based on the *in vitro* studies provided, MB09 and the RMP can be considered biosimilar.

No non-clinical *in vivo* studies were provided by the applicant, which is acceptable.

No ecotoxicity/environmental risk assessment was submitted. This is accepted given the product characteristics.

The proposed text for section 4.6 and 5.3 of the SmPC is in line with that of the reference product.

From a non-clinical perspective Denbrayce is approvable as proposed 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.

- **Tabular overview of clinical studies**

Pharmacokinetic aspects to support the similarity of MB09 to the respective originators EU-Xgeva/US-Xgeva or EU-Prolia have been evaluated in one Phase I comparative PK, PD, safety and immunogenicity study in healthy male subjects (**MB09-A-01-19**) and one Phase III comparative efficacy, safety, PK, PD and immunogenicity study (**MB09-C-01-19**).

Table 2: Clinical studies investigating PK of MB09

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
MB09-A-01-19	Double blind, randomised, parallel arm, comparator.	257 healthy male volunteers (n=85 in the MB09 arm, 86 in the EU-Xgeva arm, 86 in the US-Xgeva arm)	Single dose of 35 mg MB09, US-Xgeva or EU-Xgeva, s.c.	Primary PK endpoints: • AUC0-last • Cmax Secondary PK endpoints: • AUC0-inf • Tmax • CL/F • t1/2
MB09-C-01-19	Double blind, randomised, parallel arm, comparator.	558 postmenopausal women (n=281 in the MB09 arm, 277 in the Prolia arm)	MB09, EU-Prolia, one 60 mg dose every 6 months, s.c.	Secondary PK endpoints: • AUC0-6 months • Cmax • Ctrough at Month 6 and Month 12

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

2.5.2.1.1. Bioanalytical methods

Pharmacokinetics

The concentration of denosumab in human serum samples was determined using a validated MesoScale Discovery (MSD) ECL method. The same analytical method was used in the Phase I study MB09-A-01-19 and the Phase III study MB09-C-01-19 and has been validated according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

Overall, the PK assay for denosumab quantification is considered to be suitable for its purpose.

PD biomarkers

The serum concentration of C-terminal telopeptide of type I Collagen (CTx-1) was determined using a validated ELISA. The same analytical method was used in the Phase I study MB09-A-01-19 and the Phase III study MB09-C-01-19 and has been validated according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

Overall, the PD assay for determination of serum CTx-1 is considered to be appropriate for its intended purpose.

Immunogenicity

ADA assay

The applicant presents a bioanalytical method for the detection, confirmation and titration of anti-MB09 (anti-denosumab) antibodies in human serum which has been developed and validated by a central laboratory.

This is a qualitative assay designed to detect anti-MB09 (anti-denosumab) antibodies in human serum. Anti-drug antibodies (ADA) against denosumab in human serum are detected using an electrochemiluminescent (ECL) immunoassay. A full validation of the assay was performed with the principal objective of demonstrating the reliability of the assay to detect anti-MB09 and anti-Xgeva (both ES- and US-Xgeva) and anti-Prolia (EU-Prolia) ADAs in human serum.

NAb assay

The applicant presents a bioanalytical method for the detection of neutralising antibodies against denosumab in human serum which has been developed and validated by a central laboratory.

This qualitative assay is designed to detect neutralizing anti-MB09 (anti-denosumab) antibodies in human serum. Using affinity capture elution (ACE), neutralizing antibodies (NAb) against denosumab in human serum are detected with electrochemiluminescence (ECL).

2.5.2.1.2. Pharmacokinetic data analysis

Study MB09-A-01-19

The PK parameters of denosumab were to be analysed based on the actual sampling times. In cases where an actual time was not recorded, the nominal time was to be used.

The following plasma PK parameters were to be calculated for denosumab:

$AUC_{0\text{-last}}$	Area under the plasma concentration versus time curve from time zero to the last quantifiable concentration time point, calculated using the linear up log down trapezoidal rule.
$AUC_{0\text{-}\infty}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity calculated per the formula: $AUC_{0\text{-}\infty} = AUC_{0\text{-last}} + C_{last} / K_{el}$,, where C_{last} is the concentration of the last quantifiable concentration timepoint sample and K_{el} is the first order rate constant of the terminal phase.
C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach maximum observed plasma concentration.
K_{el}	Elimination rate constant (λ_z) during terminal phase
$t_{1/2}$	Terminal phase half-life, calculated as $t_{1/2} = \ln 2/K_{el}$
CL/F	Apparent total body clearance following extravascular administration, calculated as $CL/F = Dose/AUC_{0\text{-}\infty}$
V_z/F	Apparent volume of distribution during the terminal phase following extravascular administration, calculated as $V_z/F = (CL/F)/K_{el}$

An analysis of variance (ANOVA) model with treatment and stratification factors (i.e., Body Weight) as fixed effects was to be performed on the natural log-transformed values of Cmax, AUC0-last, and AUC0-∞ to assess the relative bioequivalence between MB09 (test) versus EU-sourced or US-sourced Xgeva (reference), as well as comparing EU-sourced Xgeva (test) to US-sourced Xgeva (reference). The geometric least squares means, ratios of the geometric least squares means, and corresponding 90% confidence intervals (CIs) for the ratios were to be computed for Cmax, AUC0-t, and AUC0-∞ by taking the antilog of the least squares means from the ANOVA model on the natural logarithms of the corresponding PK parameters for the following comparisons:

- MB09 / EU-sourced Xgeva
- MB09 / US-sourced Xgeva
- EU-sourced Xgeva / US-sourced Xgeva

No adjustment was to be made for multiplicity.

Biosimilarity was to be concluded if the 90% CIs for the test to reference ratios of the geometric least square means for Cmax, AUC0-last, and AUC0-∞ are entirely contained within the [80.00%, 125.00%] interval.

Nonparametric methods (Wilcoxon signed-rank test) were to be performed to examine median differences in Tmax for MB09 versus EU-sourced Xgeva, MB09 versus US-sourced Xgeva, and EU-sourced Xgeva versus US-sourced Xgeva comparisons. The Hodges-Lehmann estimate, and its 90% CI were calculated for the median difference between treatments, and a p-value was generated by the Wilcoxon signed-rank test.

Study MB09-C-01-19

To assess the denosumab PK profile of MB09 compared with EU-Prolia, Cmax and AUC0-6 months were to be analysed on the log scale by ANCOVA. The model was to include treatment and stratification variables (baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (< 68 years versus ≥ 68 years) and prior bisphosphonate medication use at study entry (yes versus no) as fixed effects. The estimated mean difference with 95% CI was to be back-transformed to give the ratio of geometric means (MB09/EU-Prolia) with 95% CI following the first dose in the Main Treatment Period.

2.5.2.1.3. Bioequivalence

Study MB09-A-01-19

Study design

Study MB09-A01-19 was a Phase I, randomised, double-blind, 3-arm, single-dose, parallel design bioequivalence study to compare the PK, PD, safety, and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-/US-Xgeva in healthy male volunteers. Subjects were randomly assigned to receive either 35 mg of MB09 SC (Study Arm 1) or 35 mg of EU-Xgeva SC (Study Arm 2) or 35 mg of US-Xgeva SC (Study Arm 3) in 1:1:1 ratio. This study was planned as a single-centre study conducted at 1 site in Poland. Approximately 255 subjects were planned to be enrolled to achieve 204 evaluable subjects.

The study consisted of a screening period (Days -30 to -2), check-in (Day -1), treatment period (Day 1), follow-up period (Days 2 to 252) and an end of study (EOS) visit (Day 253). The duration of the study, excluding screening, was approximately 36 weeks.

PK/PD Sampling Timepoints

Blood samples for PK analysis of the study treatment (MB09 or Xgeva) in serum and PD analysis of area under the effect curve were collected up to 2 hours prior to study treatment dosing and after dosing at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), Days 6, 8, and 11 (± 1 day), Days 15, 22, and 29 (± 2 days), Days 43, 57, 71, 85, 99, 113, 141, 169, 197, 225, and 253 (± 3 days). At each time point, blood samples were collected after overnight fasting of at least 10 hours.

Study population

Key inclusion Criteria

1. The subject was a male of any race, between **28 and 55 years of age**, inclusive, at screening.
2. The subject had a body mass index (BMI) between **18.5 and 29.9 kg/m^2**, inclusive, (total body weight between **60 and 95 kg**, inclusive) at screening and check-in.
3. The subject was considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results (congenital non-haemolytic hyperbilirubinemia [e.g., Gilbert's syndrome] was acceptable), vital sign measurements (systolic blood pressure [BP] ≥90 mm Hg and ≤140

mm Hg, diastolic BP ≥50 mm Hg and ≤90 mm Hg), 12-lead electrocardiogram (ECG) results, and physical examination findings at screening and check-in.

4. Adequate method of contraception for both male participants and their female partners (WOCBP).

Exclusion Criteria

1. The subject had **previous exposure to denosumab**.
2. The subject had a significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the investigator.
3. The subject had a history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the investigator.
4. The subject had any current or recent history of infections, including localised infections (within 2 months prior to screening for any serious infection that required hospitalisation or intravenous anti-infective or within 14 days prior to screening for any active infection which required oral treatment).
5. The subject had a dental or jaw disease requiring oral surgery or dental surgery within 6 months prior to study product administration or planned to have dental surgery within 6 months after dosing.
6. The subject had a history of osteomyelitis or osteonecrosis of the jaw requiring suturing within 30 days before dosing, or within 30 days after the last study visit.
7. The subject had a medically significant dental disease or dental neglect, with signs and/or symptoms of local or systemic infection that required a dental procedure during the course of the study. Standard dentistry treatments (e.g., dental filling or prophylaxis/cleaning) were allowed.
8. The subject had clinically relevant history of alcoholism, addiction or drug/chemical abuse prior to check-in, and/or positive urinary test for alcohol or drugs of abuse at screening or check-in.
9. The subject had positive hepatitis panel (hepatitis B virus [HBV] and hepatitis C virus [HCV]) or positive human immunodeficiency virus (HIV) test. Subjects whose results were compatible with prior immunisation and not infection could be included at the discretion of the investigator.
10. The subject had participated in a clinical study involving administration of an investigational drug (new chemical entity), with dosing in the past 90 days prior to Day 1, or within 5 half-lives of the investigational drug used in the study, whichever was longer.
11. The subject had used or intended to use slow-release medications/products considered to still be active within 30 days prior to check-in, unless deemed acceptable by the investigator.
12. The subject had used or intended to use any non-prescription medications/products (except paracetamol [up to 2 g/day] and ibuprofen [800 mg/day]), including vitamins, minerals, supplements (e.g., Biotin), and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator. Vitamin C, vitamin D, and calcium in daily recommended doses (≤1000 mg elemental calcium and 1000 IU vitamin D based on screening levels of vitamin D) were allowed.
13. The subject had received the coronavirus disease 2019 (COVID-19) vaccine within 14 days before Day 1 or planned to receive a COVID-19 vaccine within 12 weeks after study treatment dosing or had positive test for COVID-19 during screening or presence of COVID-19 symptoms within 4 weeks prior to Day -1.

14. The subject had received a live or attenuated vaccine within 3 months prior to screening or had the intention to receive a vaccine during the study. The subject intended to travel to a region where a vaccination was required due to endemic disease during the study.
15. The subject had used tobacco- or nicotine-containing products within 1 year prior to check-in or anytime during the study, or had a positive cotinine test upon screening or check-in.
16. The subject had donated blood within 60 days prior to dosing, plasma from 14 days prior to screening, or platelets from 42 days prior to dosing.
17. The subject had poor peripheral venous access.
18. Subjects who, in the opinion of the investigator, was not eligible to participate in this study.

Description of Trial intervention

Treatment/ Posology

Subjects were randomly assigned to receive either a 35 mg s.c. dose of MB09 (Study Arm 1), EU-Xgeva (Study Arm 2) or US-Xgeva (Study Arm 3) on Day 1, administered in the upper arm. Subjects remained semi-supine for the first 4 hours after administration unless moving was medically necessary, for required procedures, or subject was going to the washroom.

Table 3: Investigational products used in the study

Product	Formulation	Lot Number
MB09 (Study Arm 1, test)	Vial containing 70 mg/mL	21A49C
EU-sourced Xgeva® (Study Arm 2, reference)	Vial containing 70 mg/mL	1133897
US-sourced Xgeva® (Study Arm 3, reference)	Vial containing 70 mg/mL	1130402

Prohibited/allowed medications

Regarding prohibited medications for study MB09-A-01-19, the following treatments have been excluded. Previous exposure to denosumab; treatment of serious infections via i.v. anti-infective medications; administration of an investigational drug (new chemical entity), slow-release medications/products considered to still be active within 30 days prior to check-in; use of any nonprescription medications/products (except paracetamol [up to 2 g/day] and ibuprofen [800 mg/day]), including vitamins, minerals, supplements (e.g., Biotin), and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to check-in, unless deemed acceptable by the investigator. Vitamin C, vitamin D, and calcium in daily recommended doses (≤1000 mg elemental calcium and 1000 IU vitamin D based on screening levels of vitamin D) were allowed. Furthermore, subjects that received a COVID-19 vaccine within 14 days before Day 1 or plans to receive a COVID-19 vaccine within 12 weeks after study drug dosing; a live or attenuated vaccine within 3 months prior to screening or has the intention to receive a vaccine during the study were also excluded.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator.

Objectives and Endpoints

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

- MB09 vs. EU-Xgeva
- MB09 vs. US-Xgeva
- EU-Xgeva vs. US-Xgeva

in healthy subjects.

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

- To evaluate and compare the derived pharmacokinetics and pharmacodynamics of single s.c. doses of MB09 and EU-Xgeva and MB09 and US-Xgeva in healthy subjects.
- To evaluate the safety, tolerability, and immunogenicity of single s.c. doses of MB09, EU-Xgeva, and US-Xgeva in healthy subjects.

Primary PK endpoints:

- Area under the serum concentration vs. time curve from time 0 to the last quantifiable concentration time point (**$AUC_{0\text{-}last}$**)
- Maximum observed serum concentration (**C_{max}**)

Secondary PK endpoints:

- AUC from time 0 to Day 99 (**$AUC_{0\text{-}99}$**)
- Area under the serum concentration vs. time curve from time 0 extrapolated to infinity (**$AUC_{0\text{-}\infty}$**)
- Time of reach the maximum observed serum concentration (**T_{max}**)
- Apparent total body clearance following extravascular administration (**CL/F**)
- Apparent terminal elimination half-life (**$t_{1/2}$**)

For **PD endpoints** refer to section "Primary pharmacology"

Immunogenicity Endpoint: Immunogenicity samples were analysed for anti-MB09 antibodies and neutralising antibodies using validated Meso Scale Discovery® electrochemiluminescence (MSD-ECL) assay.

Safety Endpoints: Safety and tolerability endpoints included monitoring and recording of AEs, clinical laboratory test results (haematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and targeted physical examination.

Randomisation

The Contract Research Organisation (CRO) generated the randomisation schedule. Subjects who met all inclusion and none of the exclusion criteria were randomly assigned to 1 of the 3 study arms by a ratio of 1:1:1. on Day -1 or Day 1 prior to initiating any study procedures. Randomisation numbers (in sequential order) were assigned before the study treatment was administered on Day 1.

Randomisation was stratified based on the subject's body weight: 60 to <80 kg and 80 to 95 kg.

Blinding

This study employed a double-blind study design. MB09 and Xgeva were packed in identical boxes. The unblinded pharmacists were responsible for preparing and dispensing the study treatment in a manner

consistent with maintaining the blind. Study treatment was administered by the blinded clinical unit personnel at the clinical unit according to the schedule of events (SOE).

The site was responsible for maintaining the blind throughout the study. If a subject became seriously ill during the study, the blind would be broken upon the investigator's approval only if knowledge of the administered study treatment affected that subject's available treatment options.

The unblinded personnel was predefined and documented before breaking the study blind. The investigator was responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. Subjects who were unblinded, were able to continue in the study at the investigator's discretion.

The study remained blinded to the investigators, subjects, and predefined Sponsor and CRO personnel until all subjects had completed the study and the database had been finalised for study closure.

Sample Size

The sample size for this study was based on a statistical power calculation. A coefficient of variation (%CV) value of 33% was estimated for the area under the serum concentration versus time curve (AUC) parameter. Assuming a ratio of AUC and Cmax between 0.95 and 1.05, 68 PK-evaluable subjects per arm were required to provide at least 90% power to conclude bioequivalence of MB09 and Xgeva. Thus, 204 evaluable subjects were required in all. Assuming a 20% dropout rate, approximately 255 subjects were planned to be enrolled in this study.

Statistical methods

- Safety population: The safety population included all subjects who received the study treatment.
- PK population: The PK population included subjects, who received the study treatment, did not have major protocol deviations and had sufficient data to calculate primary PK endpoints.
- PD population: The PD population included subjects, who received the study treatment, did not have major protocol deviations, and had sufficient data to calculate secondary PD endpoints.

Results

Participant flow

A total of 257 subjects were enrolled (MB09, EU-Xgeva, US-Xgeva: 85 (100.0%), 86 (100.0%), 86 (100.0) subjects). A total of 255 (99.2%) subjects was treated (before study treatment administration 2 (0.8%) subjects were discontinued, 1 subject in the EU-Xgeva arm withdrew, while the other subject in the US-Xgeva arm was discontinued due to an adverse event [AE]). 254 (98.8%) subjects completed the study (1 subject in the US-Xgeva arm was lost to follow-up).

The end of the study was defined as the date on which the last subject completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

Table 4: Summary of subject disposition (all subjects)

	MB09 (N=85) n (%)	EU-sourced Xgeva (N=86) n (%)	US-sourced Xgeva (N=86) n (%)	Overall (N=257) n (%)
Total Number of Subjects				
Enrolled	85 (100.0)	86 (100.0)	86 (100.0)	257 (100.0)
Treated	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)
Completed	85 (100.0)	85 (98.8)	84 (97.7)	254 (98.8)
Discontinued	0	1 (1.2)	2 (2.3)	3 (1.2)
Reason for Discontinuation from Study				
Adverse Event	0	0	1 (1.2)	1 (0.4)
Lost to Follow-Up	0	0	1 (1.2)	1 (0.4)
Withdrawal y Subject	0	1 (1.2)	0	1 (0.4)
Analysis Populations				
Safety Population[1]	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)
PK Population[2]	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test)
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference)
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference)
Percentages are based on the number of subjects that entered the trial.
Subject with screening number 00166 was enrolled and randomised to US-sourced Xgeva but discontinued before drug intake due to adverse event.
Subject with screening number 00237 was enrolled and randomised to EU-sourced Xgeva but withdrew before drug intake.
Subject with screening number 00488 was enrolled and randomised to US-sourced Xgeva, completed treatment but was lost during follow-up.
[1] Safety population includes all subjects who received the study treatment.
[2] Pharmacokinetic (PK) population includes subjects who received the study treatment, who did not have major protocol deviations, and had sufficient data to calculate primary PK endpoints.
Source: End-of-Text Table 14.1.1.

Recruitment

Study initiation date: 01 March 2022
Study completion date: 18 March 2023
Database lock date: 23 May 2023

Conduct of the study

For study MB09-A-01-19, there were 2 administrative letters (Administrative Letter 1, dated 23 August 2021 and Administrative Letter 3, dated 10 February 2022) and 1 protocol amendment (dated 30 November 2021) to the original study protocol (dated 17 August 2021). Both letters and the protocol amendment were issued before the enrolment of any study subjects.

Protocol deviations

In total, protocol deviations have been reported for 60 (23.5%) subjects (MB09; EU-Xgeva; US-Xgeva group: 20 (24.7%); 22 (25.9%); 17 (20.0%) subjects).

The most prominent protocol deviation reported was "PK, PD and immunogenicity sample not performed within the allowed window" (MB09; EU-Xgeva; US-Xgeva group: 20 (23.54%); 17 (20.0%); 14 (16.5%) subjects).

Other protocol deviations were "safety/tolerability sample/assessment not performed within the allowed window or mishandled (not per protocol/safety lab requirements). Including AEs, SAEs PEs, vital signs, 12-lead ECGs, injection site evaluation, clinical laboratory safety test, review of concomitant medications and procedures" (MB09; EU-Xgeva; US-Xgeva group: 8 (9.4%); 9 (10.6%); 7 (8.2%) subjects), "fasting period not followed" (1 (1.2%); 3 (3.5%); 0 subjects), "visit not completed" (3 (3.5%); 0; 0 subjects), "missing PK, PD and immunogenicity sample" (3 (3.5%); 0; 0 subjects), and "missing safety/tolerability sample/assessment. Including AEs, SAEs PEs, vital signs, 12-lead ECGs, injection site evaluation, clinical laboratory safety test, review of concomitant medications and procedures" (1 (1.2%); 0; 0 subjects).

One subject was reported with an admission criteria deviation (repeat BP measurement values were not reported - inadequate source documentation - attributable, legible, contemporaneous, original, and accurate [ALCOA] principle not met).

No subjects were reported with significant protocol deviations during the study.

Baseline Data

Demographics

Table 5: Summary of subject demographics and baseline characteristics (safety population)

	MB09 (N=85)	EU-sourced Xgeva (N=85)	US-sourced Xgeva (N=85)	Overall (N=255)
Age (years)				
Mean (SD)	40.5 (6.93)	38.8 (6.59)	39.4 (7.15)	39.5 (6.90)
Median	39.0	37.0	39.0	39.0
Min, Max	28, 54	28, 52	28, 55	28, 55
Sex, n (%)				
Male	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Race, n (%)				
White	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Ethnicity, n (%)				
Not Hispanic or Latino	85 (100.0)	85 (100.0)	85 (100.0)	255 (100.0)
Height (cm)				
Mean (SD)	179.07 (6.098)	179.20 (6.662)	177.72 (5.857)	178.66 (6.227)
Median	179.00	179.20	177.00	179.00
Min, Max	163.0, 194.0	157.0, 198.0	164.0, 194.0	157.0, 198.0
Weight (kg)				
Mean (SD)	83.68 (8.550)	82.74 (8.334)	82.48 (8.643)	82.97 (8.492)
Median	84.70	83.50	83.20	83.50
Min, Max	63.6, 95.0	60.1, 95.0	60.0, 95.0	60.0, 95.0
Body Mass Index (kg/m2)				
Mean (SD)	26.13 (2.441)	25.76 (2.344)	26.05 (2.415)	25.98 (2.396)
Median	26.40	25.90	26.70	26.30
Min, Max	18.9, 29.9	20.5, 29.8	18.8, 29.8	18.8, 29.9

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test)
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference)
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference)
Percentages are based on the number of subjects in the safety population.
Source: End-of-Text Table 14.1.2.

Medical/surgical history

A total of 193 (75.7%%) patients had at least one item listed under medical history (MB09, EU-Xgeva, US-Xgeva: 62 (72.9%), 62 (72.9%), 69 (81.2%). No numbers for the items of the medical history by SOC have been provided. However, according to the respective Listing provided, most common medical history (Safety population) by SOC were surgical and medical procedures; respiratory, thoracic and mediastinal disorders; and eye disorders.

Prior/Concomitant medication

No numbers for prior or concomitant medications have been provided. However, according to the respective Listing, most common prior and concomitant medication was vitamin D.

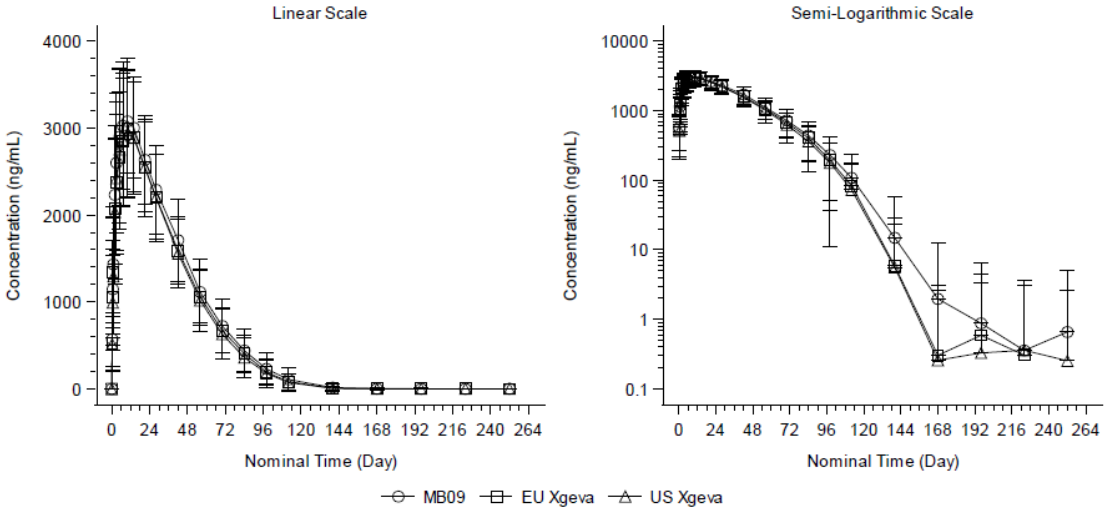
Numbers analysed

All 255 subjects in the safety population were included in the PK and PD populations (MB09, EU-Xgeva, US-Xgeva: 85 (100.0%), 85 (98.8%), 85 (98.8%) subjects).

Outcomes - PK

Serum Concentration – Denosumab

Figure 1: Mean (+/-SD) denosumab serum concentration versus time following single subcutaneous administration PK population



MB09: 35 mg subcutaneous MB09 (Study Arm 1, test); EU Xgeva: 35 mg subcutaneous of EU-sourced Xgeva (Study Arm 2, reference); US Xgeva: 35 mg subcutaneous of US-sourced Xgeva(Study Arm 3, reference).
All values below the limit of quantification (20.0 ng/mL) were taken as zero for calculation of summary statistics.
Concentrations collected outside the predefined collection windows have been excluded.
Source Data: Table 14.2.1.1
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PK-Parameters – Denosumab

Table 6: Serum pharmacokinetic parameters of denosumab (pharmacokinetic population)

PK Parameter (unit)	MB09 (N=85)	EU-sourced Xgeva (N=85)	US-sourced Xgeva (N=85)
$AUC_{0\text{-}99}$ (day*ng/mL)	143000 (25.3)	136000 (23.1)	133000 (26.3)
$AUC_{0\text{-}last}$ (day*ng/mL)	146000 (26.8)	138000 (24.1)	134000 (27.4)
$AUC_{0\text{-}\infty}$ (day*ng /mL)	147000 (26.9)	139000 (24.3)	136000 (27.4)

C_{max} (ng/mL)	3240 (22.0)	3090 (25.4)	3100 (27.0)
T_{max} (day)	10.00 (1.95 – 43.04)	9.99 (2.97 – 28.02)	9.95 (3.02 – 27.99)
$t_{1/2}$ (days)	12.5 (38.6)	12.4 (37.6)	12.1 (37.2)
CL/F (L/day)	0.238 (26.9)	0.251 (24.3)	0.258 (27.4)
Vz/F (L)	4.28 (34.2)	4.48 (33.0)	4.48 (35.1)

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test).
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference).
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference).
Geometric mean and geometric CV presented for all parameters except T_{max}; median (minimum – maximum) presented for T_{max}.
Source: End-of-Text Table 14.2.2.1.

Table 7: Statistical analysis of serum pharmacokinetic parameters of denosumab (pharmacokinetic population)

PK Parameter (unit)	Treatment	Geometric LS Means (n)	Comparison	%Ratio	90% CI of the %Ratio
$AUC_{0\text{-last}}$ (day*ng/mL)	MB09	150000 (85)	MB09 / EU-Xgeva	105.93	(99.54, 112.73)
	EU-Xgeva	142000 (85)	MB09 / US-Xgeva	108.87	(102.30, 115.86)
	US-Xgeva	138000 (85)	EU-Xgeva / US-Xgeva	102.77	(96.58, 109.37)
C_{max} (ng/mL)	MB09	3290 (85)	MB09 / EU-Xgeva	105.13	(98.86, 111.80)
	EU-Xgeva	3130 (85)	MB09 / US-Xgeva	104.75	(98.50, 111.40)
	US-Xgeva	3140 (85)	EU-Xgeva / US-Xgeva	99.64	(93.69, 105.96)
$AUC_{0\text{-}\infty}$ (day*ng/mL)	MB09	152000 (85)	MB09 / EU-Xgeva	105.92	(99.51, 112.76)
	EU-Xgeva	144000 (85)	MB09 / US-Xgeva	108.62	(102.03, 115.62)
	US-Xgeva	140000 (85)	EU-Xgeva / US-Xgeva	102.54	(96.33, 109.15)

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test).
EU-Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference).
US-Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference).
An ANOVA model was fitted to the natural log transformed PK parameters with treatment and stratification factor (body weight) as fixed effects.
Source: End-of-Text Table 14.2.3.1.

Restricting the ANOVA model to data on MB09 and EU-sourced Xgeva as requested during the assessment, gave the following results.

Table 8: Statistical analysis of serum pharmacokinetic parameters of denosumab (restricting the ANOVA model to data on MB09 and EU-sourced Xgeva)

PK Parameter (unit)	Treatment	Geometric LS Means (n)	Comparison	%Ratio of Geometric LS Means	90% CI of the Geometric LS Means
Cmax (ng/mL)	MB09	3300 (85)	MB09 / EU Xgeva	105.15	(98.04, 112.78)
	EU Xgeva	3140 (85)			
AUC0-last (day*ng/mL)	MB09	151000 (85)	MB09 / EU Xgeva	105.95	(98.63, 113.82)
	EU Xgeva	142000 (85)			
AUC0-∞(day*ng/mL)	MB09	153000 (85)	MB09 / EU Xgeva	105.95	(98.58, 113.87)
	EU Xgeva	144000 (85)			

MB09: 35 mg subcutaneous MB09 (Study Arm 1, test); EU Xgeva: 35 mg subcutaneous of EU-sourced Xgeva (Study Arm 2, reference).
ANOVA = Analysis of variance; AUC0-∞= Area under concentration,time curve from time 0 extrapolated to infinity; AUC0,last = Area under concentration,time curve from time 0 to the last quantifiable concentration; CI = Confidence interval; Cmax = Maximum observed concentration; LS = Least squares; n = Number of evaluable values.
An ANOVA model was fitted to the natural log transformed PK parameters with treatment and stratification factor (body weight) as fixed effects.

Pharmacokinetics in the target population

Study MB09-C-01-19

This was a Randomised, Double-Blind, Parallel, Multicentre, Multinational Study to Compare the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of MB09 Versus Prolia (EU-sourced) in Postmenopausal Women with Osteoporosis (SIMBA Study).

This study was comprised of two periods: a Main Treatment Period (Day 1 to Month 12, including two doses of study treatment on Day 1 and at Month 6) and a Transition/Safety Follow-up Period (Month 12 to Month 18 or End of Study [EOS], including the third dose of the study treatment at Month 12).

For the overall design of study MB09-C-01-19 refer to section "Main study(ies)".

For PK data analysis (statistics) refer to section "Pharmacokinetic data analysis".

The following PK endpoints were assessed in the main period:

- AUC0-6 months and Cmax following the first dose
- Ctrough of serum denosumab at Month 6 and Month 12.

The following PK endpoints were assessed in the transition period:

- Transition Period AUC0-6 months and Cmax following the third dose at Month 12.
- Ctrough of serum denosumab at Transition Period Month 6.

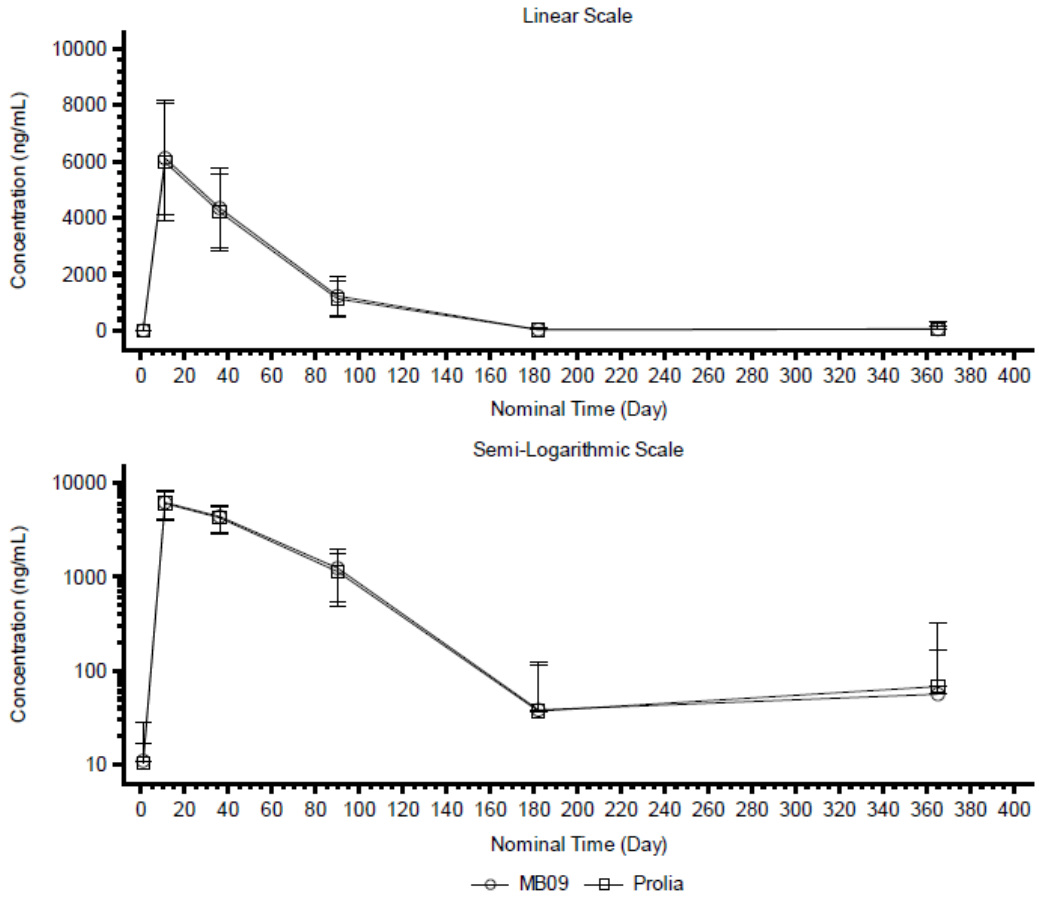
During the Main period, PK samples were collected on Day 1 (0 pre-dose), Day 11 and at Month 1 (Day 36), Month 3 (Day 90), Month 6 (Day 182, pre-dose) and Month 12 (Day 365) (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug).

During the Transition Period, additional PK samples were taken at 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (i.e., Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

Outcomes - PK (Main Treatment Period)

Serum Concentration – Denosumab

Figure 2: Mean (±SD) denosumab serum concentrations versus time following SC administration (linear and semilogarithmic scales) – Main treatment period (pharmacokinetic concentration analysis set)



Abbreviations: LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation.
Note: All values below the limit of quantification (20.0 ng/mL) were taken as half of the LLOQ value for summary statistics. Negative error bars below half of LLOQ are not displayed.
Source: Figure 14.3.5.1.

PK-Parameters – Denosumab

Table 9: Geometric mean (geometric CV%) serum pharmacokinetic parameters of denosumab by treatment – Main treatment period (pharmacokinetic parameter analysis set)

	Denosumab Treatment	
Parameter (unit)	**MB09 (N=269)**	**Prolia (N=274)**
C_{max} (ng/mL) (geometric CV%)	5960 (31.1) n =269	5700 (35.9) n =273
$AUC_{0\text{-}6\ months}$ (day*ng/mL) (geometric CV%)	360,000 (36.5) n =256	337,000 (39.5) n =260
Month 6 C_{trough} (ng/mL) (geometric CV%)	17.2 (137) n = 266	16.5 (130) n = 265
Month 12 C_{trough} (ng/mL) (geometric CV%)	21.6 (181) n =252	20.7 (181) n = 259

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; C_{max}, observed maximum serum concentration after study treatment administration; C_{trough}, trough (predose) serum concentration; CV, coefficient of variation; LLOQ, lower limit of quantification; PK, pharmacokinetics.

Note 1: Samples below the limit of quantification were treated as zero prior to the first quantifiable concentration and considered as half of LLOQ when below the limit of quantification after the first quantifiable sample for PK parameter analysis.

Note 2: Data were excluded when the baseline concentrations were >5% C_{max}.

Source: Table 14.3.5.3.

Table 10: Statistical analysis of denosumab PK parameters – Main treatment period pharmacokinetic parameter analysis set

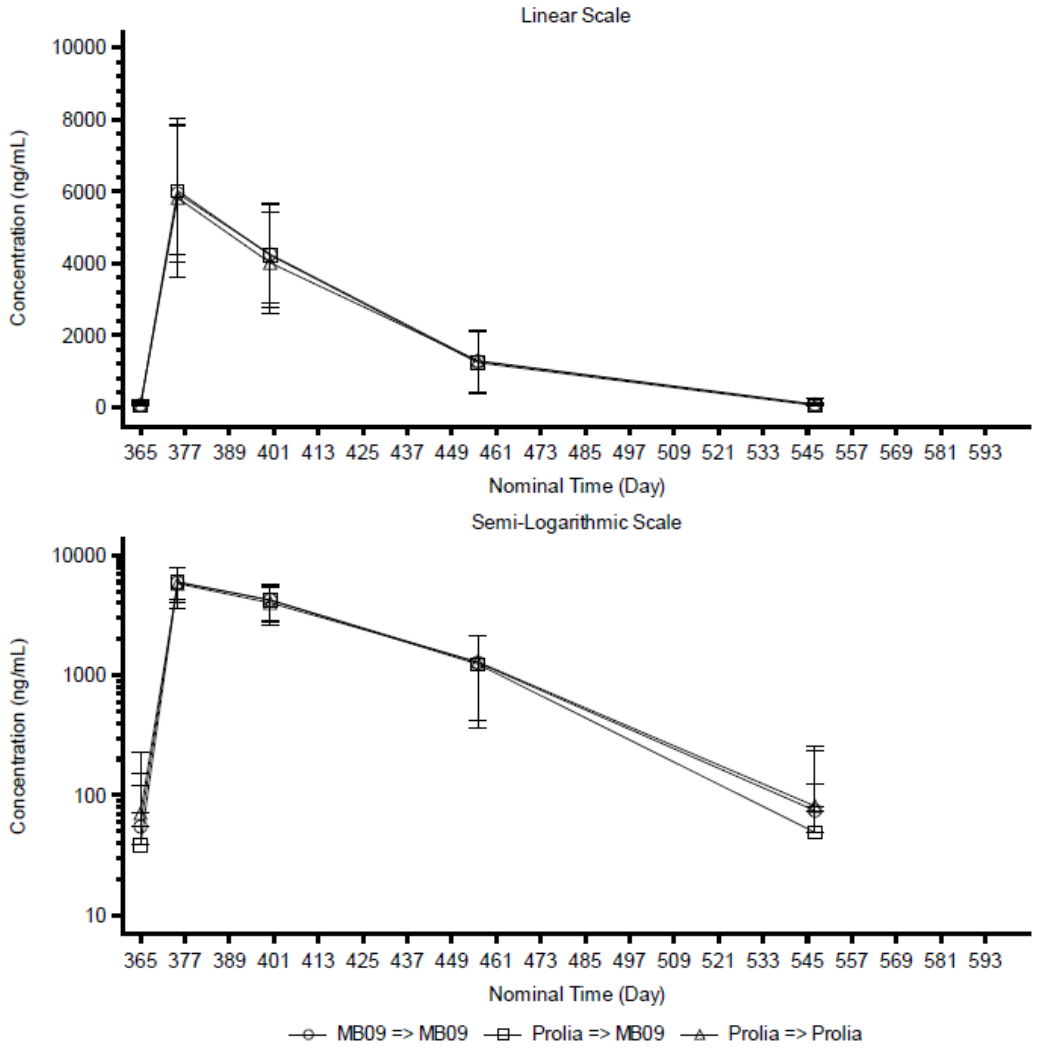
Parameter	Treatment	N	n	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio	95% CI of the Ratio
Cmax (ng/mL)	MB09	269	269	5890	MB09/Prolia	104.13	(99.66 ,108.79)	(98.83 ,109.71)
	Prolia	274	273	5650				
AUC0-6 months (day*ng/mL)	MB09	269	256	363000	MB09/Prolia	106.06	(100.82 ,111.57)	(99.84 ,112.66)
	Prolia	274	260	342000				
M6 Ctrough (ng/mL)	MB09	269	266	20.2	MB09/Prolia	103.10	(89.47 ,118.81)	(87.06 ,122.10)
	Prolia	274	265	19.6				
M12 Ctrough (ng/mL)	MB09	269	252	25.4	MB09/Prolia	103.25	(86.84 ,122.75)	(84.00 ,126.90)
	Prolia	274	259	24.6				

Note:
A linear model was fitted to ln-transformed data with treatment and stratification variables: baseline BMD T-score at the lumbar spine (<= -3.0 and > -3.0 SD), body mass index (< 25 and >= 25 kg/m2), age at study entry (>= 55 to < 68 years versus >= 68 to <= 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonates); results are presented as percentages.
AUC0-6 months = Area under the concentration-time curve from time zero to 6 months; Cmax = Observed maximum serum concentration after administration; Ctrough = Predose concentration; CI = Confidence interval, LS = Least squares; N = Number of Subjects in the treatment group; n = number of evaluable values.
Source Data: Listing 16.2.10.2.

<u>Outcomes - PK</u> (transition/safety follow-up period)

<u>Serum Concentration – Denosumab</u>

Figure 3: Mean (±SD) denosumab serum concentrations versus time following SC administration (linear and semilogarithmic scales) – Transition period (pharmacokinetic concentration analysis set for transition period)



Abbreviations: LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation.

Note: All values below the limit of quantification (20.0 ng/mL) were taken as half of the LLOQ value for summary statistics. Negative error bars below half of LLOQ are not displayed.

Source: Figure 14.3.5.2.

PK-Parameters – Denosumab

Table 11: Geometric mean (geometric CV%) serum pharmacokinetic parameters of denosumab by treatment – Transition period (pharmacokinetic parameter analysis set for transition period)

PK Parameter (unit)	Denosumab Treatment		
	MB09-MB09 (N=242)	Prolia-MB09 (N=130)	Prolia-Prolia (N=122)
C_{max} (ng/mL) (geometric CV%)	5840 (32.1) n =228	5800 (32.2) n =125	5630 (37.1) n =111
$AUC_{0\text{-}6\ months}$ (day*ng/mL) (geometric CV%)	360,000 (36.2) n =214	350,000 (37.0) n =115	353,000 (38.6) n =104
Month 6 C_{trough} (ng/mL) (geometric CV%)	24.8 (210) n = 227	22.8 (166) n = 123	27.0 (240) n = 110

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; C_{max}, observed maximum serum concentration after study treatment administration; C_{trough}, trough (predose) serum concentration; CV, coefficient of variation; LLOQ, lower limit of quantification; PK, pharmacokinetics.

Note 1: Samples below the limit of quantification were treated as zero prior to the first quantifiable concentration and considered as half of LLOQ for samples below the limit of quantification after the first quantifiable sample for PK parameter analysis.

Note 2: Data were excluded when the baseline concentration was >5% C_{max}.

Source: Table 14.3.5.4.

Table 12: Statistical analysis of denosumab PK parameters – Transition period pharmacokinetic parameter analysis set for transition period

Parameter	Arm	N	n	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	95% CI of the Ratio
Cmax (ng/mL)	MB09-MB09	229	228	5900	MB09 => MB09 vs Prolia => Prolia	103.40	(96.28 ,111.04)
	Prolia-MB09	126	125	5910	Prolia => MB09 vs Prolia => Prolia	103.65	(95.66 ,112.31)
	Prolia-Prolia	110	111	5710			
TP AUC0-6 months (day*ng/mL)	MB09-MB09	229	214	364000	MB09 => MB09 vs Prolia => Prolia	101.57	(93.68 ,110.12)
	Prolia-MB09	126	115	356000	Prolia => MB09 vs Prolia => Prolia	99.48	(90.80 ,108.99)
	Prolia-Prolia	110	104	358000			
TPM6Ctrough (ng/mL)	MB09-MB09	229	227	27.9	MB09 => MB09 vs Prolia => Prolia	91.60	(68.36 ,122.75)
	Prolia-MB09	126	123	26.3	Prolia => MB09 vs Prolia => Prolia	86.17	(61.93 ,119.90)
	Prolia-Prolia	110	110	30.5			

Note: MB09 => MB09 (Arm 1), Prolia => MB09 (Arm 2), Prolia => Prolia (Arm 3)
A linear model was fitted to ln-transformed data with arm and stratification variables: baseline BMD T-score at the lumbar spine (<= -3.0 and > -3.0 SD), body mass index (< 25 and >= 25 kg/m2), age at study entry (>= 55 to < 68 years versus >= 68 to <= 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate; results are presented as percentages.
AUC0-6 = Area under the concentration-time curve from time zero to 6 months; Cmax = Observed maximum serum concentration after administration; Ctrough = Predose concentration; CI = Confidence interval, LS = Least squares; N = Number of Subjects in the treatment group; n = number of evaluable values, TP = Transition period.
Source Data: Listing 16.2.10.2.

2.5.2.2. Pharmacodynamics

Mechanism of action

Mode of action

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

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

Extrapolation of indications

Furthermore, the applicant seeks approval for all indications that are currently approved for Prolia and Xgeva. These are:

Prolia [Prolia SmPC, 2023]

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Xgeva [Xgeva SmPC, 2024]

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

Primary and Secondary pharmacology

The pharmacodynamics of MB09 and the respective reference product have been investigated in 2 clinical studies, a Phase I PK study MB09-A-01-19 and a Phase III efficacy and safety study MB09-C-01-19.

Study MB09-A-01-19

PD parameters were estimated using absolute serum C-terminal telopeptide of type I collagen (sCTX) concentration values (without baseline-adjustment):

- Minimum serum concentration (which represents the maximum PD effect) (Cmin)
- Time of occurrence of the minimum serum concentration (Tmin)

- Area under the effect versus time curve (AUEC) from time 0 to the last quantifiable sCTX concentration time point using the linear trapezoidal rule (AUEC0-last).
- AUEC from time 0 to Day 253 (i.e., the last planned sampling time) using the linear trapezoidal rule (AUEC0-253). Where the last observation was observed before Day 253, the AUEC until Day 253 was to be extrapolated from AUEC0-last, where possible. If extrapolation was not possible, AUEC0-253 was to be set to missing. Where the last observation was observed after Day 253, the AUEC until Day 253 was to be interpolated.

PD parameters estimated using %change from baseline (%CfB) sCTX values:

- Maximum % inhibition (Imax).
- Time of occurrence of the maximum % inhibition (TImax).
- Area under the % inhibition curve (AUIC) from time 0 to the last quantifiable sCTX concentration time point using the linear trapezoidal rule (AUIC0-last).
- AUIC from time 0 to Day 253 (i.e., the last planned sampling time) using the linear trapezoidal rule ($AUIC_{0-253}$). Where the last observation was observed before Day 253, the AUIC until Day 253 was to be extrapolated from AUIC0-last, where possible. If extrapolation was not possible, AUIC0-253 was to be set to missing. Where the last observation was observed after Day 253, the AUIC until Day 253 was to be interpolated.

Sampling

Serial blood samples for serum PD analysis were collected before up to 2 hours before dosing (Predose) and at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), and on Days 6 (120 hours, ± 1 day), 8 (168 hours, ± 1 day), 11 (240 hours, ± 1 day), 15 (336 hours, ± 2 days), 22 (504 hours, ± 2 days), 29 (672 hours, ± 2 days), 43 (1008 hours, ± 3 days), 57 (1344 hours, ± 3 days), 71 (1680 hours, ± 3 days), 85 (2016 hours, ± 3 days), 99 (2352 hours, ± 3 days), 113 (2688 hours, ± 3 days), 141 (3360 hours, ± 3 days), 169 (4032 hours, ± 3 days), 197 (4704 hours, ± 3 days), 225 (5376 hours, ± 3 days), and 253 (6048 hours, ± 3 days) after dosing.

Pharmacodynamic data analysis

The PD population was to include all subjects who received the study drug, who did not have major protocol deviations, and had sufficient data to calculate secondary PD endpoints.

An analysis of covariance (ANCOVA) model with treatment and stratification factors (i.e. body weight) as fixed effects and logged pre-dose sCTX concentrations (baseline) fitted as a covariate was performed on the natural log-transformed values of AUEC0-253 and AUIC0-253 to assess the relative bioequivalence between MB09 (test) versus EU- or US-Xgeva (reference), as well as comparing EU-Xgeva (test) to US-Xgeva (reference). The geometric least squares means, ratios of the geometric least squares means, and corresponding 90% confidence intervals (CIs) for the ratios were to be computed by taking the antilog of the least squares means from the ANCOVA model on the natural logarithms of the corresponding PD parameters for the following comparisons:

- MB09 / EU-sourced Xgeva
- MB09 / US-sourced Xgeva
- EU-sourced Xgeva / US-sourced Xgeva

A 90% CI for the ratio was to be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity. Biosimilarity in PD biomarker was to be reported as the test to reference ratio of geometric means and its corresponding 90% CI for AUEC0- 253 and AUIC0-253 PD parameters.

Changes from protocol-specified analyses

According to the second version of the protocol the PD parameters were to be calculated without baseline adjustment, in particular only the area under the effect versus time curve (AUEC) but not the area under the inhibition curve (AUIC) was to be analysed. Moreover, only treatment was to be included in the ANOVA for the AUEC. In the SAP, the analysis strategy was revised to include the stratification factor body weight and logged pre-dose sCTX concentration as variables. According to the footnote of Table 11-6 in the CSR, the logged pre-dose sCTX concentration was only included in the model for AUEC0-253 but not into the model for AUIC0-253.

In addition, while the protocol listed AUEC0-last as the only PD parameter and specified an ANOVA model for it, the SAP contained more PD parameters as listed in the tables above and specified that ANCOVAs should be performed for AUEC0-253 and AUIC0-253. This change was not listed in section 9.8.2 (Changes in the Planned Analyses) in the CSR.

Study MB09-C-01-19

PD variables – Main Treatment Period:

- AUEC0-6months, AUEC0-181days and sCTX at Month 12.
- Mean difference in sCTX at 11 days and 1, 3, and 6 months after the first dose; and 6 months after the second dose of study treatment.

Furthermore, the following has been presented in the current CSR for the evaluation of PD:

- Absolute sCTX concentration vs. nominal time profile
- %CfB sCTX vs. nominal time profile
- AUIC0-6 months and AUIC0-181days
- Imax
- TImax

PD variables – Transition/Safety Follow-up Period:

- Transition Period sCTX AUEC up to Transition Period Month 6.
- Ctrough of sCTX at Month 12 and Transition Period Month 6.

Sampling

During the Main Treatment Period, blood samples for PD analysis of area under the effect curve were collected at Day 1 (predose), Day 11, Day 36 (Month 1), Day 90 (Month 3), Day 182 (Month 6, predose), Day 365 (for those subjects entering the Transition Period, this sample was to be taken prior to the third

dose of the study drug). Samples for PD testing have been taken in the morning after fasting overnight for 8 hours prior to assessment.

During the Transition/Safety Follow-Up Period, samples for PD assessments were taken at Month 12 (predose), Day 11 (M12 + 10 days), Week 5 (M12 + 5 weeks), Day 456 (Month 3) and Day 547 (Month 6).

Pharmacodynamic data analysis

In study MB09-C-01-19, PD parameters have been assessed in the Modified Full Analysis Set. This subset of the FAS included all subjects who met all eligibility criteria.

All PD parameters were to be calculated for each individual subject if data permit by the noncompartmental analysis. AUEC0-6months was to be estimated for sCTX using absolute sCTX concentrations. The following PD parameters were to be estimated for sCTX using %CFB in sCTX values: Imax (the maximum % inhibition), TImax (the time of occurrence of the maximum % inhibition) and AUIC0-6months (area under the % inhibition curve from time zero to month 6 using %CFB data). AUEC0-6 months and AUIC0-6months were to be calculated by the linear trapezoidal method provided there were at least baseline, and three post-dose time points between Day 11 and Month 6, inclusive. Interpolation or extrapolation was to be used if the last time point is not at exactly Day 182 whereby concentrations were estimated based on the slope of elimination. If the slope could not be characterised and the Month 6 sample was missing the AUEC0-6 months or AUIC0-6 months were not to be reported. In such cases, additional PD parameters, such as truncated AUECs or AUICs over a common time period across all subjects, might have been calculated as required. If sCTX baseline values were close to the LLOQ of the sCTX assay the effect of denosumab on sCTX in terms of %CFB could not be measured and would have led to unreliable %CFB values (ie, within the assay precision of 16.3% for LLOQ level). Therefore, for baseline PD values of <1.163 fold the LLOQ, the AUIC of %CFB in serum CTX was still to be calculated but excluded from further analysis.
During the procedure additional data was provided. The area under the effect curve for absolute sCTX concentrations from time zero to 181 days
(AUEC0-181 days) and area under the inhibition curve from time zero to 181 days
(AUIC0-181 days) were also calculated using the slope based on the last 2 timepoints in the 6-month dosing interval to interpolate or extrapolate to exactly 181 days post dose.

'Estimand 5' was defined for sCTX AUEC0-6months as the ratio of geometric means (MB09/EU-Prolia) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming all women received their first denosumab dose without any errors in dosing and without receipt of any prohibited therapies or other osteoporosis medications up to 6 months after first dose. No estimand was defined for AUIC0-6months.

To assess the denosumab sCTX PD profile of MB09 compared with EU-Prolia, AUEC0-6 months and AUIC0-6 months were to be analysed on the log scale by ANCOVA. The geometric least squares means, ratios of the geometric least squares means (MB09 compared with EU-Prolia), and corresponding 90% CIs for the ratios were to be computed by taking the antilog of the least squares means from the ANCOVA model on the natural logarithms of the corresponding PD parameters including log transformed baseline sCTX as a continuous covariate with treatment and stratification variables (baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use) as fixed effects.
Biosimilarity was to be concluded if the 90% CIs for the test (MB09) to reference (EU-Prolia) ratios of the geometric least square means is entirely contained within the [80.00%, 125.00%] interval for AUEC and AUIC.
If deemed necessary by the Sponsor, a supplementary analysis was to be performed to assess the impact of missing data. A mixed model for repeated measures (MMRM) was to be fitted to the unlogged sCTX (mFAS) allowing for different variability at each time point (up to Month 12). The model was to include fixed effect

terms for visit by treatment, baseline sCTX and classification factors for each stratum. An estimate statement was to be used to calculate a weighted average across the scheduled visits where the weights correspond to the weights used in calculating AUEC. Thus, this was to give an estimate of mean AUEC and difference between mean AUEC with 95% CI.

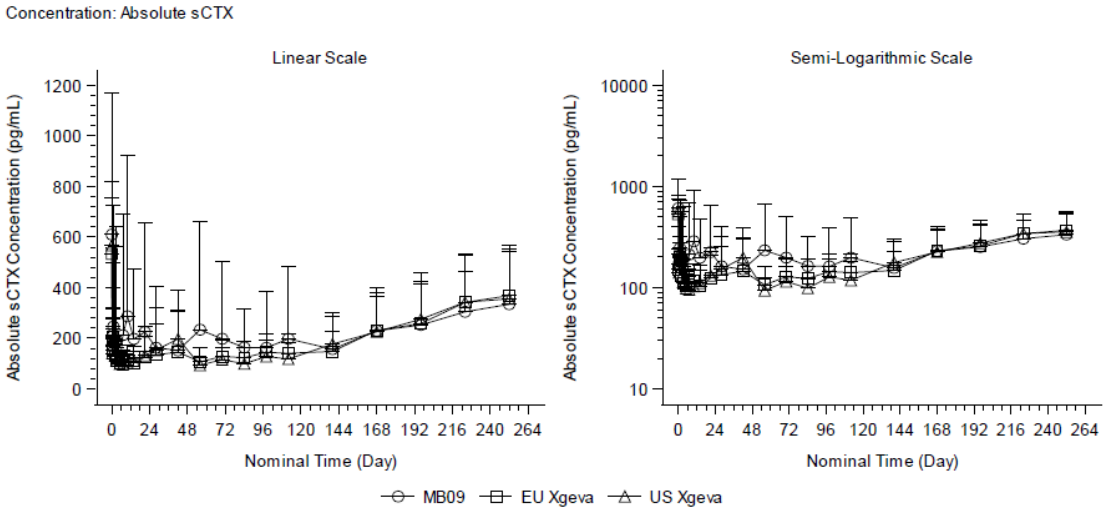
Results

Study MB09-A-01-19

PD parameters were estimated for sCTX using absolute (without baseline-adjustment) serum concentration values or percent change from baseline (%CFB) values.

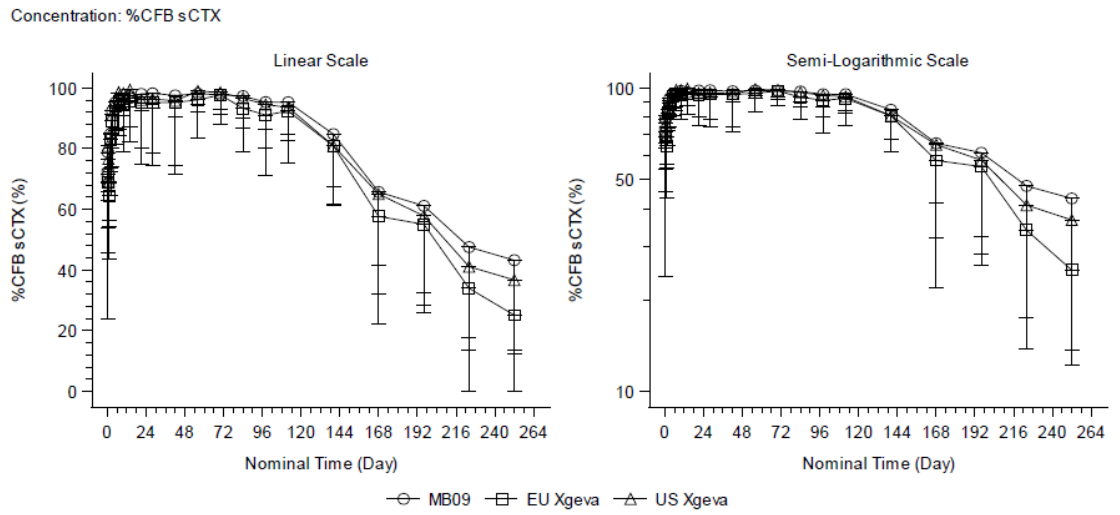
Serum Concentration – sCTX

Figure 4: Mean (+/-SD) sCTX serum concentration versus time following single subcutaneous administration PD population



MB09: 35 mg subcutaneous MB09 (Study Arm 1, test); EU Xgeva: 35 mg subcutaneous of EU-sourced Xgeva (Study Arm 2, reference); US Xgeva: 35 mg subcutaneous of US-sourced Xgeva(Study Arm 3, reference).
%CFB = Percentage change from baseline; CFB = Change from baseline; sCTX = serum C-terminal telopeptide of Type 1 collagen.
% Change from baseline calculated as ((Predose concentration – concentration at timepoint)/Predose concentration)*100%; values < 70.0 pg/mL were treated as zero for derivations.
All absolute sCTX values below the limit of quantification (70.0 pg/mL) were treated as missing; %CFB = 0 included as 0 in the calculation of all summary statistics for %CFB.Concentrations collected outside the predefined collection windows have been excluded.
Source Data: Table 14.2.1.3
\\wilbtia\wilbtia02\mAbxience MB09A0119_PK\Trunk\TLF\f140203.sas.SAS Executed: 11JUL2023 19:26

Figure 5: Mean (+/-SD) sCTX serum concentration versus time following single subcutaneous administration PD population



MB09: 35 mg subcutaneous MB09 (Study Arm 1, test); EU Xgeva: 35 mg subcutaneous of EU-sourced Xgeva (Study Arm 2, reference); US Xgeva: 35 mg subcutaneous of US-sourced Xgeva(Study Arm 3, reference).
%CFB = Percentage change from baseline; CFB = Change from baseline; sCTX = serum C-terminal telopeptide of Type 1 collagen.
% Change from baseline calculated as ((Predose concentration − concentration at timepoint)/Predose concentration)*100%; values < 70.0 pg/mL were treated as zero for derivations.
All absolute sCTX values below the limit of quantification (70.0 pg/mL) were treated as missing; %CFB = 0 included as 0 in the calculation of all summary statistics for %CFB.Concentrations collected outside the predefined collection windows have been excluded.
Source Data: Table 14.2.1.3
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Table 13: Absolute sCTX pharmacodunamic parameters (pharmacodynamic population)

PD Parameter (unit)	MB09 (N=85)	EU-sourced Xgeva (N=85)	US-sourced Xgeva (N=85)
$AUEC_{0\text{-}last}$ (day*ng/mL)	30000 (57.2)	33400 (45.8)	31800 (61.5)
$AUEC_{0\text{-}253}$ (day*ng /mL)	29400 (81.1)	32200 (54.1)	33200 (77.5)
C_{min} (ng/mL)	35.0 (0)[1]	35.6 (14.9)	35.5 (11.9)
T_{min} (day)	2.92 (0.33 – 112.02)	3.00 (0.33 – 195.88)	2.96 (0.33 – 112.03)

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test).
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference).
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference).
Absolute sCTX concentrations below the limit of quantification were taken as ½ lower limit of quantificatio (LLOQ) for parameter estimation (LLOQ: 70.0 pg/mL).
Geometric mean and geometric CV presented for all parameters except T_{min}; median (minimum – maximum presented for T_{min}.
[1] All C_{min} values were <LLOQ; therefore, all values were set to ½ LLOQ in the analysis.
Source: End-of-Text Table 14.2.2.3.

Table 14: Percent change from baseline sCTX pharmacodynamic parameters (pharmacodynamic population)

PD Parameter (unit)	MB09 (N=85)	EU-sourced Xgeva (N=85)	US-sourced Xgeva (N=85)
$AUIC_{0\text{-last}}$ (day*%)	18700 (16.2)	17800 (16.3)	18000 (19.5)
$AUIC_{0\text{-}253}$ (day*%)	18700 (19.8)	17900 (15.8)	18300 (15.9)
I_{max} (%)	92.4 (3.82)	91.4 (7.55)	92.5 (3.58)
TI_{max} (day)	2.92 (0.33 – 112.02)	3.00 (0.33 – 195.88)	2.96 (0.33 – 112.03)

Note:

MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test).

EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference).

US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference).

Absolute sCTX concentrations below the limit of quantification were taken as ½ LLOQ for parameter estimation (LLOQ: 70.0 pg/mL).

Geometric mean and geometric CV presented for all parameters except TI_{max}; median (minimum – maximum) presented for TI_{max}.

Source: End-of-Text Table 14.2.2.3.

Table 15: Statistical analysis of sCTX pharmacodynamic parameters (pharmacodynamic population)

PD Parameter (units)	Treatment	Geometric LS Means (n)	Comparison	%Ratio	90% CI of the %Ratio
$AUEC_{0\text{-}253}$ (day*pg/mL)	MB09	28500 (85)	MB09 / EU Xgeva	84.71	(64.79, 110.74)
	EU-Xgeva	33600 (85)	MB09 / US Xgeva	82.64	(65.28, 104.62)
	US-Xgeva	34500 (85)	EU Xgeva / US Xgeva	97.56	(75.45, 126.15)
$AUIC_{0\text{-}253}$ (day*%)	MB09	18700 (85)	MB09 / EU Xgeva	103.68	(99.30, 108.24)
	EU-Xgeva	18000 (85)	MB09 / US Xgeva	101.69	(97.42, 106.15)
	US-Xgeva	18400 (85)	EU Xgeva / US Xgeva	98.08	(93.95, 102.41)

Note:

MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test).

EU-Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference).

US-Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference).

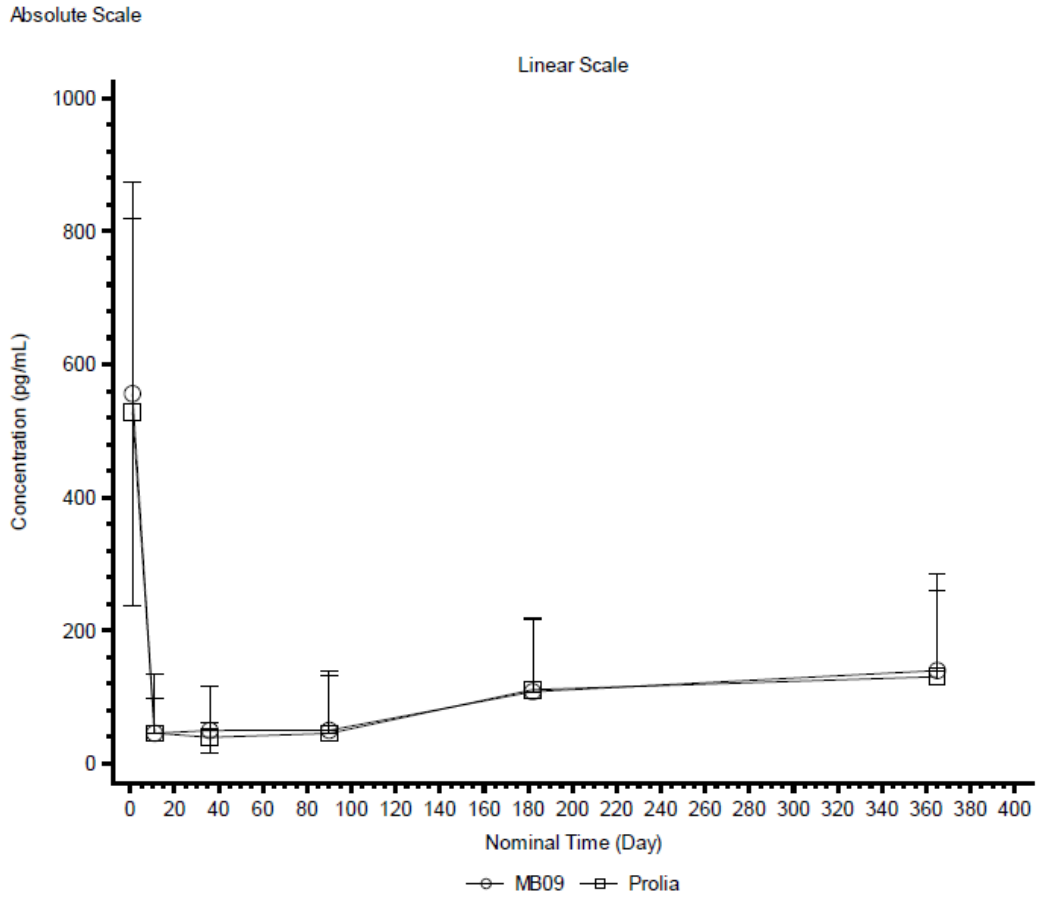
An ANCOVA model was fitted to the natural log transformed PD parameters with treatment and stratification factor (body weight) as fixed effects. For AUEC, the logged pre-dose sCTX concentration (i.e., baseline) was also fitted as a covariate.

Source: End-of-Text Table 14.2.3.3.

Study MB09-C-01-19

Serum Concentration – sCTX – Main Treatment Period

Figure 6: Mean (±SD) Absolute sCTX concentrations versus time following SC Administration (Linear Scale) – Main Treatment period (Modified Full Analysis Set)

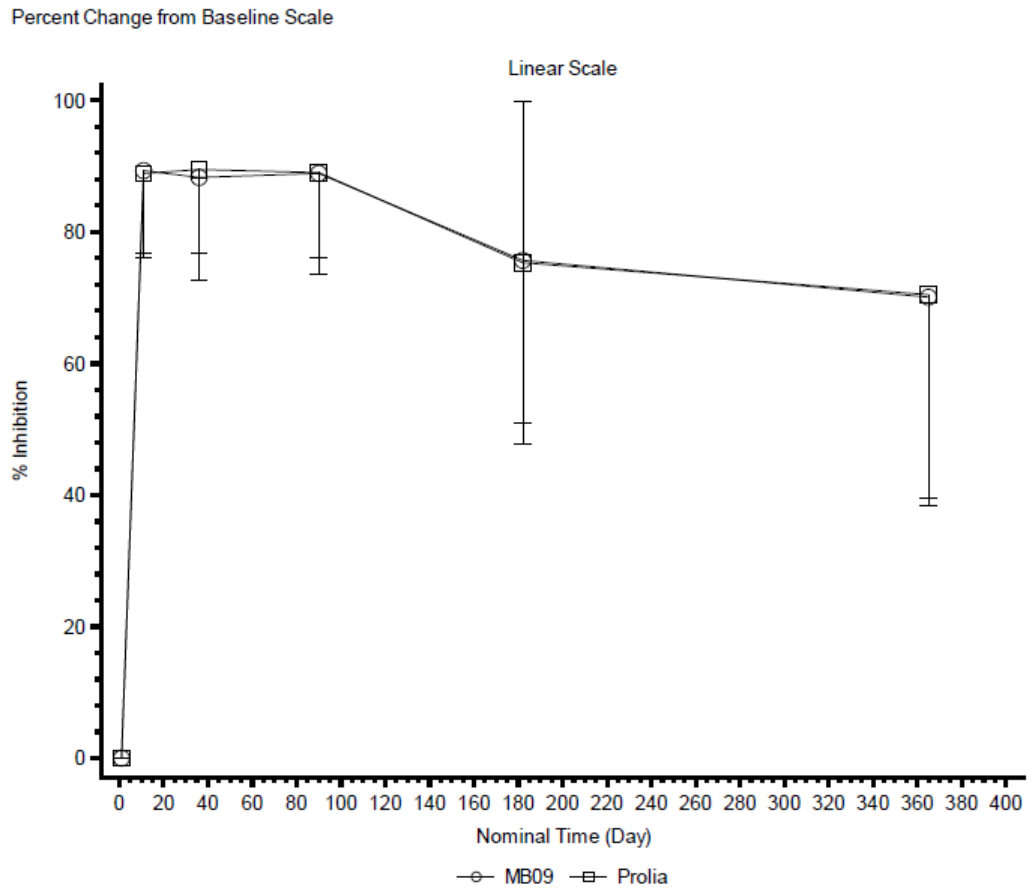


Abbreviations: sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation.

Note: All values below the limit of quantification (70.0 pg/mL) were taken as half of the LLOQ value for summary statistics. Negative error bars below half of LLOQ are not displayed.

Source: Figure 14.3.6.1.

Figure 7: Mean (±SD) Percent Change from baseline sCTX concentrations versus time following SC Administration (Linear Scale) – Main Treatment period (Modified Full Analysis Set)



Abbreviations: sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SC, subcutaneous; SD, standard deviation.

Note: Percent change from baseline was determined by subtracting each postdose concentration from the Day 1 predose concentration divided by the Day 1 predose concentration × 100. Positive error bars above 100% are not displayed.

Source: Figure 14.3.6.1.

PD-Parameters – sCTX – Main Treatment Period

Table 16: Geometric mean (geometric CV%) sCTX pharmacodynamic parameters – Main treatment period (modified full analysis set)

Absolute scale	Denosumab Treatment	
Parameter (unit)	**MB09 (N=258)**	**Prolia (N=266)**
$AUEC_{0\text{-}6\ months}$ (geometric CV%), day*pg/mL	12,300 (49.3) n = 218	12,400 (44.1) n = 228
$AUEC_{0\text{-}181days}$ (geometric CV%), day*pg/mL	11,900 (47.9) n = 240	12,000 (44.7) n = 242
Percentage change from baseline scale		
Parameter (unit)	**MB09 (N=258)**	**Prolia (N=266)**
$AUIC_{0\text{-}6\ months}$ (geometric CV%), day*%	15,100 (17.4) n = 218	15,300 (13.6) n = 228
$AUIC_{0\text{-}181\ days}$ (geometric CV%), day*%	15,100 (17.3) n = 240	15,200 (13.6) n = 242
I_{max} (geometric CV%), %	91.0 (7.76) n = 241	91.5 (6.01) n = 242
TI_{max} (median days)	10.93 n = 241	10.91 n = 242

Abbreviations: $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; $AUEC_{0\text{-}181\ days}$, area under the effect curve for absolute sCTX concentrations from time zero to 181 days calculated by interpolation/extrapolation; $AUIC_{0\text{-}6\ months}$, area under the inhibition curve from zero to 6 months; $AUIC_{0\text{-}181\ days}$, area under the inhibition curve from time zero to 181 days calculated by interpolation/extrapolation; CV, coefficient of variation; I_{max}, maximum percentage inhibition; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SD, standard deviation; TI_{max}, time of occurrence of the maximum percentage inhibition.

Note: Due to limitations of Phoenix WinNonlin, a regression slope could not be estimated in some subjects. $AUEC_{0\text{-}6\ months}$ and $AUIC_{0\text{-}6\ months}$ were calculated using the actual time at the Month 6 visit (± 10 days). $AUEC_{0\text{-}181\ days}$ and $AUIC_{0\text{-}181\ days}$ were calculated by interpolation/extrapolation of the last 2 timepoints.

Source: Table 14.3.6.3.

Table 17: Statistical analysis of pharmacodynamic parameters of sCTX – Main treatment period (modified full analysis set)

Absolute scale			Ratio of Geometric Means MB09/Prolia (%)		
PD Parameter (units)	Treatment	Geometric LS Means (n)	Estimate[1]	90% CI	95% CI
$AUEC_{0\text{-}6\ months}$ (day*pg/mL)	MB09	11,700 (218)	99.91	(93.22, 107.08)	(91.99, 108.52)
	Prolia	11,700 (228)			
$AUEC_{0\text{-}181\ days}$ (day*pg/mL)	MB09	11,600 (240)	99.37	(92.98, 106.20)	(91.79, 107.56)
	Prolia	11,700 (242)			
$AUIC_{0\text{-}6\ months}$ (day*%)	MB09	14,900 (218)	99.13	(96.76, 101.55)	(96.31, 102.02)
	Prolia	15,100 (228)			
$AUIC_{0\text{-}181\ days}$ (day*%)	MB09	14,900 (240)	99.81	(97.51, 102.16)	(97.07, 102.62)
	Prolia	15,000 (242)			

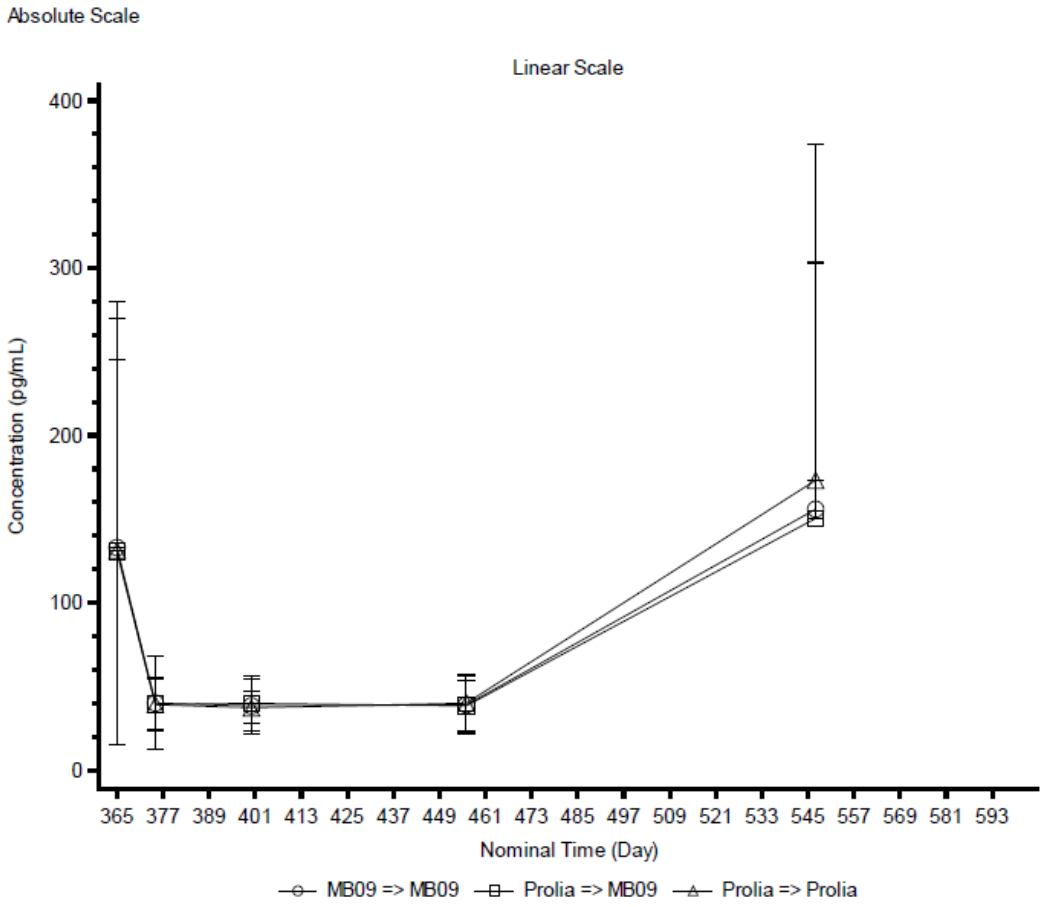
Abbreviations: $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; $AUIC_{0\text{-}6\ months}$, area under the inhibition curve from zero to 6 months; $AUEC_{0\text{-}181\ days}$, area under the effect curve from zero to 181 days calculated by interpolation/extrapolation; $AUIC_{0\text{-}6\ months}$, area under the inhibition curve from zero to 6 months; $AUIC_{0\text{-}181\ days}$, area under the inhibition curve from zero to 181 days calculated by interpolation/extrapolation; CI, confidence interval, LS, least squares; PD, pharmacodynamics; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

[1] Results of $AUEC_{0\text{-}6\ months}$ and $AUEC_{0\text{-}181\ days}$ are estimates of estimand 5: Ratio of geometric means (MB09/Prolia) in sCTX $AUEC_{0\text{-}6\ months}$ in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming all women received their first denosumab dose without any errors in dosing and without receipt of any prohibited therapies or other osteoporosis medications up to 6 months after first dose.

Source: Table 14.3.6.5.

Serum Concentration – sCTX – Transition/Safety Follow-up Period

Figure 8: Mean (±SD) Absolute sCTX concentrations versus time following SC Administration (Linear Scale) – Transition period (Modified Full Analysis Set for Transition period)

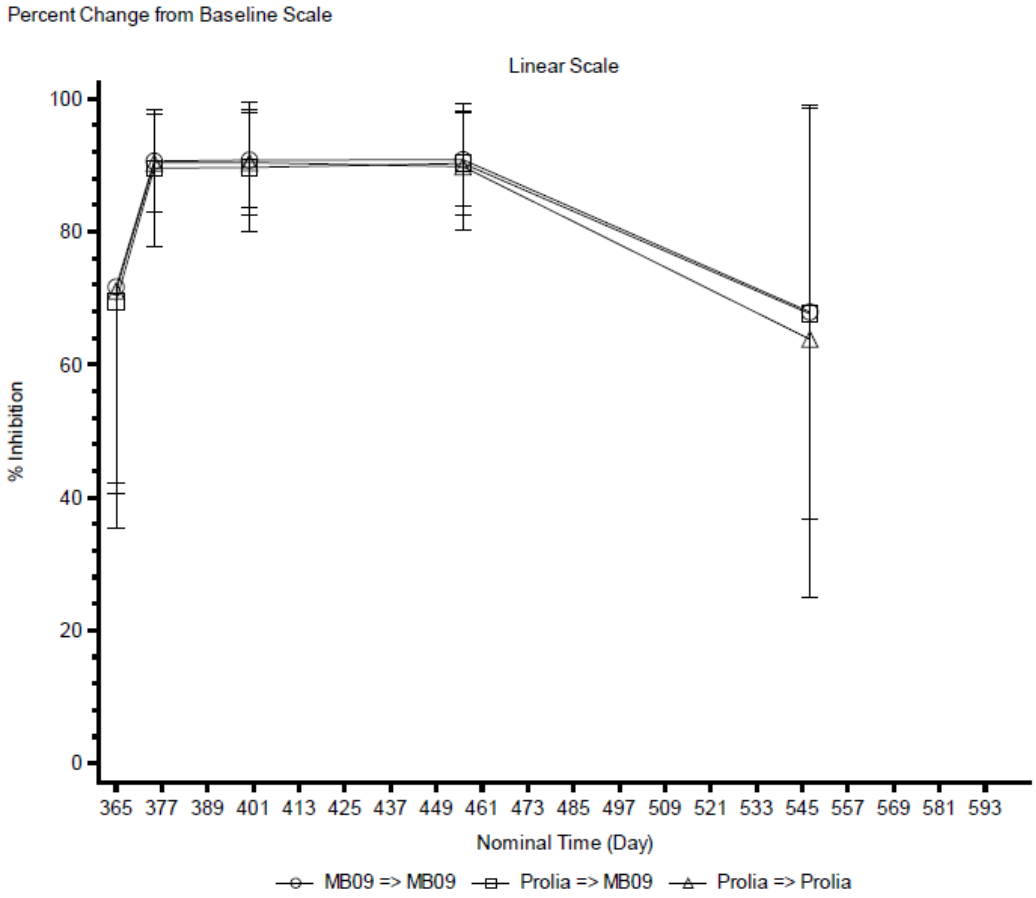


Abbreviations: sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation.

Note: All values below the limit of quantification (70.0 pg/mL) were taken as half of the LLOQ value for summary statistics. Negative error bars below half of the LLOQ are not displayed.

Source: Figure 14.3.6.2.

Figure 9: Mean (±SD) Percent change from Baseline sCTX concentrations versus time following SC Administration (Linear Scale) – Transition period (Modified Full Analysis Set for Transition period)



Abbreviations: sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; LLOQ, lower limit of quantification; SC, subcutaneous; SD, standard deviation.

Note: Percent change from baseline (% inhibition) was determined by subtracting each postdose concentration from the Day 1 predose concentration divided by the Day 1 predose concentration × 100. Positive error bars above 100% are not displayed.

Source: Figure 14.3.6.2.

PD-Parameters – sCTX – Transition/Safety Follow-up Period

Table 18: Geometric mean (Geometric CV%) sCTX pharmacodynamic parameters – Transition period (modified full analysis set for transition period)

	Denosumab Treatment		
Absolute scale **Parameter (unit)**	**MB09-MB09 (N=233)**	**Prolia-MB09 (N=127)**	**Prolia-Prolia (N=121)**
$AUEC_{0\text{-}6\ months}$ (geometric CV%), day*pg/mL	10,700 (56.2) n =184	11,000 (45.0) n = 101	9770 (52.2) n = 93
$AUEC_{0\text{-}181days}$ (geometric CV%), day*pg/mL	10,300 (54.4) n = 211	10,400 (43.5) n = 115	9650 (51.2) n = 106
Percentage change from baseline scale **Parameter (unit)**	**MB09-MB09 (N=233)**	**Prolia-MB09 (N=127)**	**Prolia-Prolia (N=121)**
$AUIC_{0\text{-}6\ months}$ (geometric CV%), day*%	15,500 (11.4) n = 184	15,500 (10.7) n = 101	15,600 (11.6) n = 93
$AUIC_{0\text{-}181\ days}$ (geometric CV%), day*%	15,300 (17.5) n = 211	15,500 (10.3) n = 115	15,200 (27.9) n = 106
I_{max} (geometric CV%), %	91.4 (7.35) n = 208	91.2 (7.88) n = 115	90.9 (7.97) n = 105
TI_{max} (median), days	6.98 n = 208	9.00 n = 115	6.98 n = 105

Abbreviations: $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; $AUEC_{0\text{-}181\ days}$, area under the effect curve for absolute sCTX concentrations from time zero to 181 days calculated by interpolation/extrapolation; $AUIC_{0\text{-}6\ months}$, area under the inhibition curve from zero to 6 months; $AUIC_{0\text{-}181\ days}$, area under the inhibition curve from time zero to to 181 days calculated by interpolation/extrapolation; CV, coefficient of variation; I_{max}, maximum percentage inhibition; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen; SD, standard deviation; TI_{max}, time of occurrence of the maximum percentage inhibition.

Note: Due to limitations of Phoenix WinNonlin, a regression slope could not be estimated in some subjects. $AUEC_{0\text{-}6\ months}$ and $AUIC_{0\text{-}6\ months}$ were calculated using the actual time at the Month 6 visit (± 10 days). $AUEC_{0\text{-}181\ days}$ and $AUIC_{0\text{-}181\ days}$ were calculated by interpolation/extrapolation of the last 2 timepoints.

Source: Table 14.3.6.4.

2.5.3. Discussion on clinical pharmacology

Analytical methods

PK Assay

A single assay approach was chosen for determination of denosumab in serum samples drawn from study subjects treated with MB09, Xgeva or Prolia. The same validated MesoScale Discovery (MSD)-based ECL method was used across Phase I study MB09-A-01-19 and Phase III study MB09-C-01-19. The acceptance criteria for analytical runs are in accordance with ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019).

Method validation and analysis of clinical samples was performed by a central laboratory.

The method has been validated in 2022, i.e. before the revised Guideline EMA/CHMP/ICH/172948/2019/ICH M10 came into effect. However, overall, the requirements of the revised ICH M10 are met.

Overall, the PK assay for denosumab quantification is considered adequately validated and suitable for its intended use. Analysis of the study samples is described in detailed analytical reports.

PD assay

A validated ELISA method was used to determine the concentration of CTx-1 in serum samples collected in the Phase I study MB09-A-01-19 and Phase III study MB09-C-01-19. The method has been validated in 2022. The acceptance criteria for analytical runs essentially resemble the requirements of ICH guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019) and are deemed appropriate to ensure consistent method performance and validity of results.

Method validation and analysis of clinical samples was performed by a central laboratory. Overall, it is concluded that the method is adequately validated and suitable for its intended use.

Analysis of the study samples is described in detailed analytical reports.

Pharmacokinetics

Pharmacokinetics of MB09 and respective reference products was thoroughly investigated in a Phase I PK/PD study in healthy subjects (MB09-A-01-19). Supportive PK data was generated in a Phase III efficacy and safety study in patients with postmenopausal osteoporosis (PMO) (MB09-C-01-19). This approach was discussed and agreed during a scientific advice (EMA/CHMP/SAWP/25066/2020).

MB09-A-01-19 (PK in healthy subjects)

Study design/methods

Study MB09-A-01-19 was a Phase I, randomised, double-blind, 3-arm, single-dose, parallel study to compare the PK, PD, safety, and immunogenicity profile of MB09, EU-Xgeva and US-Xgeva in healthy male volunteers.

Eligibility criteria pertaining to gender (men only), age (exclusion of subjects <25 years of age to ensure bone maturity), body weight (60.0-95.0 kg) and BMI (18.5-29.9 kg/m2) are appropriate to decrease PK variability in these parameters. Other eligibility criteria, e.g. not excluding subjects with prior use of medications that affect bone metabolism (e.g., bisphosphonates, selective oestrogen receptor modulator (SERMs), post-menopausal hormone replacement therapy) and could influence the PD marker sCTX, were not optimised. This design deficiency is, however, superseded by the fact that the enrolled subjects had no history of using these medications, except a small proportion of subjects who used vitamin D supplementation in clinically relevant doses [>1000 IU/day]. Given the small number of affected subjects, the impact on PD parameters is not expected to be significant, especially given the supportive nature of the PD analysis. Confirmatory evidence is generated in the Phase III study, therefore, no issues are raised. The impact on the PK is not expected to be relevant. Study subjects who met all inclusion and none of the exclusion criteria were randomised 1:1:1 to receive either MB09, EU- or US-sourced Xgeva. Randomisation was stratified based on the subject's body weight: 60 to <80 kg and 80 to 95 kg. The process of randomisation and blinding were adequately described and are considered acceptable.

Denosumab was administered as a single 35 mg (subtherapeutic) s.c. dose. Denosumab displays non-linear PK due to target-mediated drug elimination at lower doses (>20 mg and <60 mg). However, for doses of ≥60 mg, approximately dose proportional increases in exposure are seen (linear non-target-mediated drug disposition). Consequently, the use of a subtherapeutic dose of 35 mg is considered more sensitive to detect PK differences between MB09 and Xgeva. Also, the use of the lower dose of 35 mg is considered justified based on the healthy volunteers' safety. The use of Xgeva at a dosage of 35 mg is deemed appropriate for reasons of practicality, as the Xgeva vial contains 120 mg of drug product in 1.7 mL solution (35 mg of drug

product corresponds to 0.5 mL). Thus, an accurate administration of this subtherapeutic dose is enabled. In consequence, the use of Xgeva as reference product in study MB09-A-01-19 is endorsed. The dose selection for the Phase 1 study is acceptable.

Due to the long half-life of denosumab (mean half-life 28 days), a parallel design is appropriate. The study consisted of a screening period (Days -30 to -2), check-in (Day -1), treatment period (Day 1), follow-up period (Days 2 to 252) and an end of study visit (Day 253). The duration of the study was approximately 36 weeks/9 months, which covers 5 half-lives and captures the entire PK and PD profile including the target-mediated clearance of denosumab.

Blood samples for PK/PD analysis have been collected up to 2 hours prior to study treatment dosing and after dosing at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), Days 6, 8, and 11 (± 1 day), Days 15, 22, and 29 (± 2 days), Days 43, 57, 71, 85, 99, 113, 141, 169, 197, 225, and 253 (± 3 days). The timepoints are acceptable to characterise the PK and PD profile of denosumab.

In study MB09-A-01-19, the primary objective was to assess the PK equivalence of a single s.c. dose of MB09 vs. EU-Xgeva, MB09 vs. US-Xgeva and EU-Xgeva vs. US-Xgeva. The secondary objectives were to evaluate and compare PK, PD, safety, tolerability, and immunogenicity. The objectives are endorsed. The co-primary PK endpoints were area under the serum concentration versus time curve from time 0 to the last quantifiable concentration time point (AUC0-last) and the maximum observed serum concentration (Cmax). The co-primary endpoint AUC0-last is not in line with the EMA "*Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues* (EMA/CHMP/BMWP/403543/2010)", which states that in case of a single dose PK study with s.c. administration, AUC0-inf and Cmax should be evaluated as co-primary PK parameters.

Nonetheless, the applicant included AUC0-inf as a secondary endpoint and provided respective results (with corresponding 90% CIs), and therefore the necessary information is available. It is noted that other than specified by the applicant, AUC0-inf is regarded as a co-primary endpoint for the purpose of the assessment. Other secondary PK endpoints included are acceptable.

The secondary endpoints were area under the serum concentration versus time curve from time 0 extrapolated to infinity (AUC0-∞), time to reach the maximum observed serum concentration (Tmax), apparent total body clearance following extravascular administration (CL/F) and apparent terminal elimination half-life (t1/2).

Statistical methods:

An analysis of variance (ANOVA) model with treatment group and stratification factors (i.e., Body Weight) as fixed effects was to be performed on the natural log-transformed values of Cmax, AUC0-last, and AUC0-inf to assess the relative bioequivalence between MB09 (test) versus EU- or US-Xgeva (reference), as well as comparing EU-Xgeva (test) to US-Xgeva (reference). Equivalence was to be concluded if the 90% CIs for the test to reference ratios of the geometric least square (LS) means for Cmax, AUC0-last, and AUC0-∞ were entirely contained within the [80.00%, 125.00%] interval, which is in line with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). This is supported. However, it is understood that the analysis model for the PK parameters Cmax, AUC0-last, and AUC0-inf included data from all three treatment arms MB09, EU-Xgeva and US-Xgeva, which is not in accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Revised analyses were requested for the PK parameters Cmax, AUC0-last, and AUC0-inf following the strategy outlined in the statistical analysis plan but restricting to data on MB09 and EU-Xgeva. No adjustment was made for multiplicity, which is considered appropriate.

A Wilcoxon signed rank-test should have been used for comparing Tmax, but it is unclear how this test, which requires paired samples, could be applied to the data of study MB09-A-01-19. Information on which method was finally used was not provided in the CSR. For the comparison of Tmax the descriptive measures as provided in the CSR are considered sufficient, and the comparative analyses are not essential for this endpoint, thus this issue is not further pursued.

The PK population included subjects, who received the study treatment, did not have major protocol deviations and had sufficient data to calculate primary PK endpoints. The PD population included subjects, who received the study treatment, did not have major protocol deviations, and had sufficient data to calculate secondary PD endpoints. The definition of the PK and PD populations are considered not accurate enough, as they leave open which data are necessary for calculating the endpoints or what is considered a major protocol deviation. As the PK population is identical to the Safety population, no concern is raised for the definition of the PK population. The appropriateness of the definition of the PD population is discussed in more detail below.

Results

A total of 257 subjects were enrolled in study MB09-A-01-19 (85, 86 and 86 subjects in the MB09, EU-Xgeva, US-Xgeva arm, respectively). A total of 255 (99.2%) subjects was treated and 254 (98.8%) subjects completed the study. The number of subjects completing the study was high and well balanced between treatment arms [85 (100.0%), 85 (98.8%) and 84 (97.7%) subjects in the MB09, EU-Xgeva and US-Xgeva arm, respectively).

In total, protocol deviations have been reported for 60 (23.5%) subjects [MB09; EU-Xgeva; US-Xgeva group: 20 (24.7%); 22 (25.9%); 17 (20.0%) subjects]. The most prominent protocol deviation reported was "PK, PD and immunogenicity sample not performed within the allowed window" (MB09; EU-Xgeva; US-Xgeva group: 20 (23.54%); 17 (20.0%); 14 (16.5%) subjects). In line with the Study protocol, the PK parameters of denosumab for each treatment arm (MB09, EU-sourced Xgeva, and US-sourced Xgeva) were analysed based on the actual sampling times. In cases where an actual time was not recorded, the nominal time was used. According to the applicant, no protocol deviations have been considered significant. No deviation led to discontinuation from the study. No significant implications on PK/PD results are expected.

The baseline characteristics were overall balanced across treatment arms. All subjects were male, white, and not Hispanic or Latino. The mean age was 40.5, 38.8 and 39.4 years (MB09, EU-Xgeva and US-Xgeva, respectively). Mean height, weight (83.68 kg, 82.74 kg and 82.48 kg) and BMI (26.13 kg/m^2, 25.76 kg/m^2 and 26.05 kg/m^2) were comparable between treatment arms. No relevant imbalances between study arms were noted regarding medical/surgical history or prior and concomitant medication.

All 255 subjects in the safety population were also included in the PK and PD populations (MB09, EU-Xgeva, US-Xgeva: 85 (100.0%), 85 (98.8%), 85 (98.8%) subjects).

Overall, denosumab serum concentration vs. time profiles were comparable between the treatment arms.

There was no significant difference in the time to attain maximum serum concentrations of denosumab (Tmax) between all 3 treatment groups. In addition, remaining PK parameters (AUC_{0-99}, $t_{1/2}$, CL/F, Vz/L) were similar between treatment groups and support the PK similarity of the test and reference products.

The 90% CIs around the geometric LS mean ratio (MB09/EU-Xgeva) for Cmax, AUC0-inf and AUC0-last were entirely contained within the [80.00%, 125.00%] equivalence range. The geometric LS mean ratios [90% CI] (MB09/EU-Xgeva) for Cmax, AUC0-last and AUC0-inf were 105.15% [98.04%, 112.78%], 105.95%

[98.63%, 113.82%], and 105.95% [98.58%, 113.87%], respectively, using the model restricted to data on MB09 and EU-Xgeva. The results support equivalence of MB09 to EU-Xgeva.

The review of individual denosumab concentrations revealed fluctuations in concentrations around expected Tmax (double peaking) and at later time points (albeit to a lesser extent) in a small number of participants. This phenomenon was observed with both the biosimilar candidate and the reference product. The fact that some of these fluctuations were observed around the expected Tmax introduces uncertainty for the equivalence conclusion on Cmax (one of two co-primary endpoints).

For most of the identified profiles, a reasonable likelihood exists that the actual Tmax is in close vicinity of the time point where the implausible drop was observed. This finding has two consequences: First, Cmax measurement as planned appears (generally) cumbersome from a methodological perspective for some profiles, which brings uncertainty on Cmax equivalence testing.

Phenomena of huge short-term PK fluctuations were discussed by Reijers et al. (Clin Pharmacokinet, 2017). This paper shows that the plasma concentration–time course of selected monoclonal antibodies can show considerable fluctuations with no straightforward explanations based on physiology or assay variability.

Although the reasons for these fluctuations are currently not understood, the frequency and magnitude of concentration fluctuations observed in this application were sufficiently low/small to not raise concerns about the overall biosimilarity conclusion, and similarity in PK is considered demonstrated for Cmax. The other co-primary endpoint AUC, which is less affected by these fluctuations compared to Cmax, did also entirely lie within the standard equivalence range and similarity in PK between the two treatments is considered demonstrated.

MB09-C-01-19 (PK in the target population)

Study design/methods

This was a randomised, Double-Blind, Parallel, Multicentre, Study to Compare the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of MB09 Versus EU-Prolia in postmenopausal women with osteoporosis. The study consisted of two periods: a Main Treatment Period (Day 1 to Month 12), during which patients received 2 doses of denosumab 60 mg s.c. at a 6-month interval (Day 1 and Month 6); and a Transition/Safety Follow-up Period (Month 12 to Month 18/End of Study), during which patients received an additional dose of 60 mg s.c. (at Month 12).

The following PK endpoints were assessed in the Main period: AUC0-6 months and Cmax following the first dose, Ctrough of serum denosumab at Month 6 and Month 12. Additional PK endpoints were assessed in the Transition period. The selected endpoints are acceptable; the PK during the Main period is of main interest. During the main treatment period, PK samples were collected on Day 1 (0 pre-dose), Day 11 and at Month 1 (Day 36), Month 3 (Day 90), Month 6 (Day 182, pre-dose) and Month 12 (Day 365, prior to the third dose). During the transition period, PK samples were collected at 10 days, 5 weeks, 3 months and 6 months. PK sampling timepoints were chosen sparse. However, given that PK was thoroughly assessed in the Phase I study, this approach can be accepted. The sampling time points are adequate for characterizing the PK endpoints.

Cmax and AUC0-6 months were analysed on the log scale by ANCOVA. The model included treatment and stratification variables (baseline BMD T-score at the lumbar spine (≤-3.0 and >-3.0 SD), BMI (< 25 and ≥ 25 kg/m2), age (≥ 55 to < 68 years vs. ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use (prior use of BP vs. no prior BP) as fixed effects. The estimated mean difference with 95% CI was back-transformed to give the ratio of geometric means (MB09/EU-Prolia) with 95% CI following the first dose in the Main

Treatment Period. Ctrough was also compared at Month 6 and Month 12 in the Main Treatment Period and at Month 6 in the Transition Period. According to the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) 90% CI should have been provided instead of the presented 95% CI. However, using 95% CI results in a more conservative criterion for equivalence, thus equivalence with respect to PK parameters can be concluded from the 95% CI. In addition, in contrast to PK data from the Phase I study, PK data from the Phase III study are considered supportive rather than pivotal.

Results

Main Treatment Period

Following the first dose, denosumab concentrations were highest at Day 11 and declined slowly through Month 6 for both treatments. The concentration-time curves of the products were overall comparable.

Cmax, AUC0-6months, Ctrough at Month 6, Ctrough at Month 12 were slightly higher for the MB09 group compared to the Prolia group, however overall comparable. The Cmax observed with both treatments in this study was nearly double that of the Cmax in the Phase I study, corresponding to the nearly 2-fold higher administered dose (35 mg in the Phase I study vs. 60 mg in the Phase III study).

Although no confirmatory testing was foreseen for the PK endpoints in this study, the 90% CIs for Cmax, AUC0-6months, Ctrough at Month 6, and Ctrough at Month12 were contained within the 80-125% range, which supports that the PK between MB09 and EU-Prolia is similar also in the target population.

No PK-related issues have been identified in the Phase III study. Overall, the PK data from the Phase III study in the target population support equivalence of MB09 to EU-Prolia.

Transition/Safety Follow-up Period

Following the third dose, denosumab concentrations were highest around Day 11 of the Transition Period and declined slowly through Month 6. The concentration-time curves were overall comparable for all treatments. Cmax, AUC0-6months, Ctrough at Month 6 were comparable between groups.

Pharmacodynamics

Pharmacodynamics of MB09 and respective reference products was investigated in two clinical studies, a Phase I PK/PD study in healthy subjects (MB09-A-01-19) and a Phase III efficacy and safety study in patients with postmenopausal osteoporosis (PMO) (MB09-C-01-19). The investigation of PD in both studies included serum C-terminal telopeptide of Type 1 collagen (sCTX), a biochemical marker of bone turnover, particularly bone resorption. No other PD markers were used. The additional investigation of P1NP (Procollagen Type I N-terminal Propeptide) would have been beneficial and could strengthen the biosimilarity claim, however it is not considered indispensable, therefore its omission can be accepted.

MB09-A-01-19 (PD in healthy volunteers)

Study design/methods

Blood sampling timepoints for PD were the same as for the PK (for details see the PK part). The frequency and duration of sampling was adequate from the PD perspective.

PD parameters were estimated using absolute serum C-terminal telopeptide of type I collagen (sCTX) concentration values (without baseline-adjustment): Cmin, Tmin, AUEC0-last, AUEC0-253; whereas: Imax, TImax, AUIC0-last, AUIC0-253 were estimated using %CFB sCTX values.

AUEC0-last was defined as "Area under the effect-time curve from time zero to the last quantifiable sCTX concentration time point using absolute data (without baseline-adjustment) and the linear trapezoidal rule". **AUEC0-253** was defined as "Area under the effect-time curve from time zero to Day 253 (i.e., the last planned sampling time) using absolute data (without baseline-adjustment), and the linear trapezoidal rule. Where the last observation is observed before Day 253, the AUEC until Day 253 will be extrapolated from AUEC0-last, where possible. If extrapolation is not possible, AUEC0-253 will be set to missing. Where the last observation is observed after Day 253, the AUEC until Day 253 will be interpolated."

AUIC0-last and AUIC0-253 were defined analogously but using the %CFB sCTX instead of the absolute data.

During the assessment it was clarified that 'last quantifiable sCTX concentration' in the definition of AUEC0-last and AUIC0-last refers to the last available sCTX values, as sCTX is a physiologically present bone turnover marker, whose concentration decreases following administration of denosumab but later increases again following diminishing of the denosumab effect.

Furthermore, the applicant clarified that AUEC0-253 and AUIC0-253 were derived from AUEC0-last and AUIC0-last by using extrapolation or interpolation based on the regression slope. If the slope was negative for an individual, there were technical issues with the implementation in WinNonlin and the parameter was set to missing. This approach might be reasonable when calculating the area under a concentration curve, which is known to be decreasing after maximum was reached and where an increasing slope might be an indicator for erroneous measurements. For sCTX, whose concentration decreases following administration of denosumab and later increases again following diminishing of the denosumab effect, excluding subjects with a negative slope at the end of the observation period from the analysis set of AUEC0-253 is not acceptable and is expected to result in a biased sample. Excluding subjects with a negative slope is also not in accordance with what was prespecified in the SAP. As AUEC0-253 has only limited relevance in the description of sCTX compared to AUIC0-253 and as additional analyses are presented for AUEC0-last, which is understood to be very similar to AUEC0-253, the inadequacy of the analysis of AUEC0-253 is not pursued further.

The clarification on the origin of missing values in the analysis of AUEC0-253 raises questions concerning the analysis of AUIC0-253. According to Table 14.2.3.3 this analysis was based on almost all enrolled patients (85 out of 85 for MB09, 83 out of 86 for EU Xgeva). However, the patients who were included in the analysis of AUEC0-253 (25 with MB09 and 18 for EU Xgeva) needed to have decreasing sCTX values at the end of the profile, which implies that their change from baseline sCTX values were increasing. Assuming that the same WinNonlin model was used for AUIC0-253 as for AUEC0-253, it was unclear why the analysis of AUIC0-253 could take into account patients with increasing profiles while this was not possible for the analysis of AUEC0-253. In the D180 LoOI the applicant was asked to clarify this issue but instead of providing an explanation, the applicant presented analyses of additional parameters AUEC0-253R and AUIC0-253R, where the concentration at day 252 was imputed using an estimate of slope based on the last two values only and this imputed concentration was included in the WinNonlin analysis as additional data record. These new parameters can be calculated independently of whether the slope is increasing or decreasing at the end of the observation period and respective results will be considered as supportive information for the assessment.

Finally, the applicant clarified that negative CfB values have been included in the derivation of AUIC0-last and AUIC0-253 so long as negative values did not preclude the ability to extrapolate to 253 where necessary.

There were less than 2% of samples with negative CfB and the mean rebound area (defined as the area that is below 0 and above the %CFB in sCTX curve) was less than 2% of the mean area above baseline. Thus, the impact of the handling of negative values is considered negligible.

The AUEC0-253 and AUIC0-253 were to be compared in a similar way as the PK parameters between MB09, EU- and US-sourced Xgeva using ANCOVA models. As for the primary PK parameters revised analyses restricting to data on MB09 and EU-sourced Xgeva including 95% CI instead of 90% CI were requested.

The analysis performed for AUIC0-253 did not include logarithmised pre-dose sCTX concentration as adjustment variable as defined in the SAP. However, as AUIC0-253 is only a secondary parameter in MB09-A-01-19 and the differences between the analyses are not expected to be substantial, this issue is not pursued further.

Results

Baseline levels of sCTX were somewhat higher in the MB09 arm compared to EU- and US-Xgeva arm, with higher inter-subject variability noted for the MB09 arm. Baseline arithmetic mean and CV were 610 pg/mL (91.6%) for MB09, 533 pg/mL (41.5%) for EU-sourced Xgeva arm, and 567 pg/mL (44.9%) for US-sourced Xgeva arm. This considered, PD parameters calculated based on %CFB are considered more relevant.

Following a single dose of denosumab, sCTX concentrations decreased quickly in all three arms. The concentration/time curves for all three treatments seem overall similar, with somewhat higher concentrations observed for MB09 until around Day 144. Thereafter sCTX concentrations started increasing again, similarly in all treatment arms. A similar trend was observed as expected from the originator and it is considered to be associated with waning of denosumab effect. The mean %CFB sCTX concentrations were similar in all three study arms over time.

The minimum concentration was first attained (Tmin) at approximately 3 days post-dose for all treatment groups (median estimates). The minimum sCTX concentration (Cmin) was observed to be below the limit of quantification (BLQ; 70.0 pg/mL) in the majority of subjects across all 3 treatment groups. Cmin was comparable between treatment groups.

The maximum inhibition (Imax) was similar between treatment arms (92.4%, 91.4% and 92.5% in the MB09, EU-Xgeva and US-Xgeva arm, respectively). Imax was attained at approximately 3 days post-dose (median TImax estimates). Imax and TImax were comparable between treatment groups.

As described above, the analysis of AUEC0-253 is not considered adequate due to problems with inter- and extrapolation. For AUEC0-253R the estimated geometric mean ratio of MB09/EU-sourced Xgeva was 86.45 with 95% confidence interval of (76.91, 97.17), which is very similar to the results obtained for AUEC0-last.

In line with these results for the absolute values, the analyses of the %CfB data resulted in geometric mean ratios larger than 100% for MB09 versus EU-sourced Xgeva. For AUIC0-253 the geometric mean ratio was 103.82 with 95% CI of [98.58; 109.35]; for AUIC0-last it was 104.56 with 95% CI of [99.86; 109.48] and for AUIC0-253R it was 107.85 with 95% CI of [97.30; 119.54], estimated from ANOVA models restricted to data on MB09 and EU Xgeva.

These results indicate that there was stronger suppression of sCTX in the MB09 arm than in the EU-sourced Xgeva arm. However, as the PD data from the Phase I study are only considered supportive and no dissimilarity was observed for the PD marker in the Phase III study in a more relevant patient model, this issue is not further pursued.

As previously mentioned, for the Phase I study no specific acceptance criterion needs to be met for the PD biomarker. Moreover, the parameters based on the absolute values (AUEC0-253, AUEC0-last and AUEC0-253R), which showed more extreme results, are considered less reliable and less important than their counterparts based on %CfB values.

MB09-C-01-19

Study design/methods

Blood sampling timepoints for PD were the same as for the PK (for details see the PK part).

AUEC0-6months was estimated for sCTX using absolute sCTX concentrations. The following PD parameters were estimated for sCTX using %CFB in sCTX values: Imax (the maximum % inhibition), TImax (the time of occurrence of the maximum % inhibition) and AUIC0-6months (area under the % inhibition curve from time zero to month 6 using %CFB data). sCTX AUEC up to Transition Period Month 6 (Month 18 in total), Ctrough of sCTX at Month 12 and Transition Period Month 6 were presented as well.

In a Scientific Advice (EMA/CHMP/SAWP/25066/2020) the applicant was advised to include the AUEC of % change from baseline in s-CTX after the first dose as a co-primary endpoint, alongside the mean % change in BMD of lumbar spine at Week 52. BMD is of greater clinical relevance, while sCTX offers a better dynamic response, justifying the need for both as co-primary endpoints. Although this advice was not followed and AUEC of sCTX at Month 6 (based on %change from baseline, referred to as AUIC by the applicant) was included only as a secondary endpoint, it has been regarded as a co-primary endpoint for the purpose of this assessment and is assessed with more stringent criteria in line with the estimand framework.

From the provided definition of AUIC0-6months it remained unclear how a potential rebound effect was handled. As the AUIC0-6months was described to be not necessarily positive in the D120 responses, it is understood to be defined as the net area, i.e. with areas below zero subtracted from the area above zero. The applicant was asked to additionally investigate the AUIC as the area above zero and below the change from baseline sCTX curve until the sCTX values return to the baseline values, i.e. the CFB sCTX curve crosses zero for the first time. In addition, the applicant was asked to present comparative summary statistics for the rebound area, defined as the area that is below 0 and above the %CFB in sCTX curve (% x day) from the first time the %CFB in sCTX curve crosses 0 up to 253 days.

For AUIC0-6months, no estimand was defined. However, the estimand defined for the area under the absolute sCTX values (AUEC0-6months) based on a hypothetical strategy for errors in dosing and administration of prohibited therapy is understood to be equally applicable to AUIC0-6months and was considered its primary estimand for the assessment.

The PD parameters AUEC and AUIC only were to be analysed using a complete-case analysis. In face of the high relevance of the PD parameters, additional sensitivity analyses based on multiple imputation and tipping point approach were requested.

The SAP states that for the PD analysis the 90% confidence interval was to be compared with the acceptance range but the CSR finally shows the 95% confidence interval, which is the one expected for the PD analysis.

Results

Main Treatment Period

Baseline levels of sCTX were comparable across both treatment groups with arithmetic mean and CV values of 556 pg/mL (57.3%) for MB09 and 529 pg/mL (55.1%) for Prolia. Following the first dose of denosumab, sCTX concentrations decreased quickly in both arms. The sCTX concentration/time as well as %change from baseline in sCTX/time curves for sCTX were similar for both treatment arms. Levels of sCTX at Month 6 were comparable between MB09 and Prolia, 108 pg/mL and 111 pg/mL, respectively. The maximum inhibition of sCTX (Imax) was comparable between treatments (91.0% vs. 91.5% for MB09 and Prolia, respectively). The median time to achieve Imax was similar in both treatment groups (10.93 and 10.91 days). AUEC0-6months (based on absolute sCTX conc) was comparable for MB09 vs. EU-Prolia (12.300 day*pg/mL vs. 12.400 day*pg/mL). Also, AUIC0-6months (based on %CFB sCTX conc) was comparable between study arms (15.100 day*% vs. 15.300 day*pg/mL).

Co-primary Endpoint – AUIC0–6 months of %CFB in sCTX

The applicant was asked to discuss the reasons to exclude 53 subjects (10.1% of mFAS) from the ANCOVA model for the AUIC0-6months and 36 subjects (6.9% of mFAS) from the ANCOVA model for the AUEC0-6months as reported in the main treatment period CSR.

It was clarified that some of the issues causing missing values for AUIC0-6months were associated with interpolation or extrapolation based on regression slopes requiring at least three data points excluding Imax and resulting in technical problems with positive slopes.

During the assessment, the applicant has provided an additional, more robust parameter AUIC0-181days for which the inter- or extrapolation is performed based on the slope between the last two values instead of a regression slope. AUIC0-181days is considered an acceptable approximation of the co-primary endpoint AUIC0-6months defined in the SAP. The analysis of AUIC0-181days included 501 (95.6%) patients out of 524 patients in the mFAS. Out of the 23 excluded study participants, 8 participants were excluded due to baseline sCTX concentration below LLOQ and one participant because of negative AUIC. Other reasons for exclusion were missing baseline or Day 181 sCTX sample, fewer than 3 samples between Day 10 and Day 182, prohibited therapy, incorrect treatment and missing baseline T-score. The number of excluded patients is considered sufficiently small with reasons for missingness not of further concern to allow assessment of the results. The revised analysis gave an estimated ratio of geometric means for AUIC0-181days for MB09 versus Prolia of 100.92 with 95% confidence interval of (96.90, 105.12), which is considered sufficiently narrow and close enough to 1 to support the claim of biosimilarity.
A similarly revised analysis of AUEC0-181days included 509 (97.1%) of 524 patients in the mFAS and resulted in an estimated ratio of geometric means for MB09 versus Prolia of 100.02 with 95% confidence interval of (93.11, 107.44). These analyses are considered suitable to conclude on similarity with respect to PD markers.

The results of the multiple imputation analysis are similar to the results of the complete case analysis, which is reassuring.

Levels of sCTX at Month 12 (6 months following second administration) were also comparable between MB09 and Prolia, 140 pg/mL and 131 pg/mL, respectively.

Transition/Safety Follow-up Period

During the Transition Period, levels of sCTX and the maximum inhibition of sCTX were overall comparable across treatment groups.

Immunogenicity

In both studies, the overall incidence of post-dose ADAs to denosumab was very low. None of the patients with ADAs had a positive result for Nabs. Overall, the observed low immunogenicity with both treatments is in line with the low immunogenicity profile of the reference product. The results of the immunogenicity assessment support similarity of MB09 to the reference product.

2.5.4. Conclusions on clinical pharmacology

The investigated product can be considered similar to the reference product Prolia/Xgeva regarding the pharmacokinetic and pharmacodynamic properties.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

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

2.5.5.2. Main study(ies)

Study MB09-C-01-19

Methods

Study MB09-C-01-19 s a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, PK, PD, safety and immunogenicity of MB09 vs. EU-Prolia in postmenopausal women with osteoporosis.

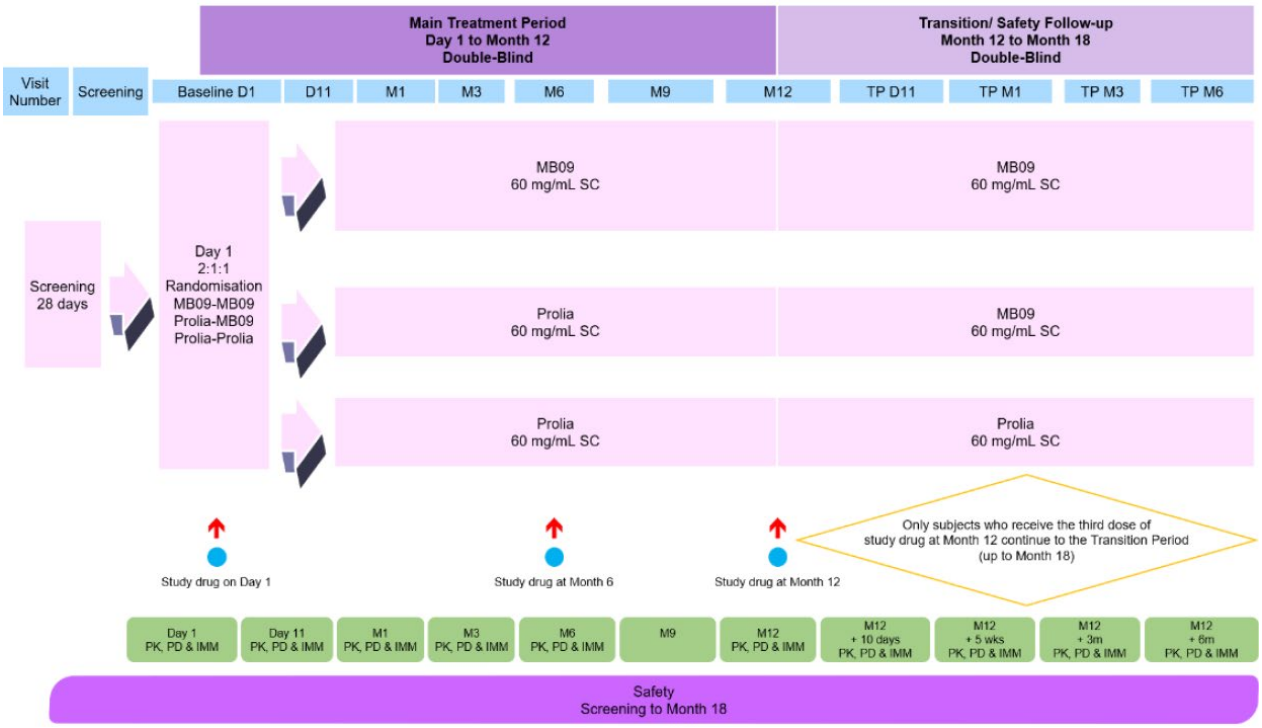
Study phases & Study duration

The current Phase III study was designed to compare the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety, and immunogenicity of MB09 with EU-Prolia in women with postmenopausal osteoporosis. This study was comprised of a Screening Period (28 Days) and two treatment periods: a Main Treatment Period (Day 1 to Month 12, including two doses of study treatment on Day 1 and at Month 6) and a Transition/Safety Follow-up Period (Month 12 to Month 18 or End of Study [EOS], including the third dose of the study treatment at Month 12).

Study initiation date was the date of the first visit of the first patient: 16 March 2022. Main Treatment Period Completion Date was the last subjects last visit of the Main Treatment Period: 14 December 2023. Transition Period Completion Date was the last subjects last visit of the Transition Period: 22 May 2024. Final Database Lock: 26 June 2024.

During the Main Treatment Period, therapeutic equivalence between MB09 and EU-Prolia was evaluated based on lumbar spine bone mineral density (BMD) measured at Month 12, after administration of two doses of study drug (primary objective). The Transition/Safety Follow-up Period focussed on the safety of MB09 and EU-Prolia.

Figure 10: Study schema



Abbreviations: D, Day, IMM, immunogenicity; M, Month; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous, TP, Transition Period.

Study Participants

Study MB09-C-01-19 is a multinational, multicentre trial. A total of 62 sites in 8 countries participated in the study.

The study population consisted of postmenopausal women between the ages of 55 to 80 years with body weight ≥50 and ≤99.9 kg and a BMI of ≤30 kg/m2 at screening. Enrolled patients were to have a BMD T-score of ≤-2.5 and ≥-4.0 at the lumbar spine or total hip as measured by DXA during the Screening Period with at least two intact, nonfractured vertebrae in the L1 to L4 region and at least one hip joint evaluable by DXA.

This population aligns with the approved denosumab indication and the reference studies for PMO. This population is likely to not receive any immunosuppressive therapies. Also, PMO represents an immunocompetent group of subjects well suited for assessment of comparative PK, PD, efficacy, safety, and immunogenicity.

Main Inclusion Criteria

1. Postmenopausal women. Postmenopausal status is defined as at least 12 consecutive months of amenorrhea prior to date of screening with a follicle-stimulating hormone level of ≥30 mIU/mL or surgical menopause (bilateral oophorectomy with or without hysterectomy) ≥12 months prior to the screening visit when follicle-stimulating hormone is not required.
2. Aged ≥55 and ≤80 years at screening (based on age rounded down to the nearest year).

3. Body weight ≥50 kg and ≤99.9 kg, and a body mass index of ≤30 kg/m2 at screening.
4. Absolute BMD consistent with T-score ≤ -2.5 and ≥ -4 at the lumbar spine or total hip as measured by DXA during the Screening Period.
5. At least two intact, nonfractured vertebrae in the L1 to L4 region (vertebrae to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint is evaluable by DXA.
6. Adequate organ function as defined by the following criteria:
   - Normal levels of vitamin D (≥20 to ≤64 ng/mL) and albumin-adjusted total serum calcium (≥8.5 to ≤10.5 mg/dL) at screening.
   - Serum aspartate aminotransferase, alanine aminotransferase and bilirubin ≤2.0 × ULN in the absence of any evidence of viral hepatitis.
   - Platelets ≥100 × 109/L.
   - Haemoglobin ≥9.0 g/dL.
   - Albumin 3.4 to 5.4 g/dL.
   - Glomerular filtration rate >30 mL/min.
   - Adequate coagulation parameters such as: INR ≤2.0 and aPTT ≤1.5 × ULN.

Main Exclusion Criteria

1. Previous exposure to denosumab (Prolia, Xgeva, or denosumab biosimilar) or any other monoclonal antibody (e.g., romosozumab) or fusion protein containing IgG or other biologic agent targeting IgG.
2. History and/or presence of one severe or more than two moderate vertebral fractures or hip fracture (as determined from the subject's medical history or by the central imaging centre during the Screening Period). Note: All subjects will have an X-ray performed at screening and this radiograph will be used as the reference radiograph that all radiographs performed during the study will be compared to.
3. Recent long bone fracture (within 6 months). Presence of active healing fracture according to assessment of investigators.
4. History and/or presence of bone metastases, bone disease, or metabolic disease other than osteoporosis, which could interfere with the interpretation of the findings, e.g., osteogenesis imperfecta, osteopetrosis, osteomalacia, rheumatoid arthritis, Paget's disease, ankylosing spondylitis, Cushing's disease, hyperprolactinaemia, malabsorption syndrome, hypoparathyroidism or hyperparathyroidism (irrespective of current controlled or uncontrolled status), hypocalcaemia or hypercalcaemia (based on albumin-adjusted total serum calcium). Current hyperthyroidism or hypothyroidism are not allowed unless they are well-controlled with stable therapy for at least 3 months prior to baseline and no change of start of therapy for hyperthyroidism or hypothyroidism is anticipated during the study. Subclinical hyperthyroidism (thyroid-stimulating hormone levels <0.1 μU/mL) due to its effect on bone metabolism is not allowed.
5. Malignancy within the 5 years before enrolment (except cervical carcinoma in situ or basal cell carcinoma, which are not prohibitive).
6. Drugs being investigated for osteoporosis.

7. Intravenous bisphosphonate, strontium or fluoride administered for osteoporosis within 5 years of screening.
8. Oral bisphosphonates ≥12 months cumulative use prior to screening. If used <12 months cumulatively and the last dose was ≥12 months before screening, the subject can be enrolled.
9. Ongoing use of any osteoporosis treatment (excluding calcium and vitamin D supplements) taken within the past 5 years prior to screening, with the exception of the medications listed below that are required to adhere to rules for the following washout periods:
    - Tibolone, oestrogen/progesterone containing products including any oestrogen/progesterone contraceptives or hormone-replacement therapy, selective oestrogen receptor modulators, received within 3 months prior to screening.
    - Calcitonin, calcitriol, maxacalcitol, falecalcitriol or alfacalcidol: dose received within 3 months prior to screening.
    - Cinacalcet: dose received within 3 months prior to screening.
    - Parathyroid hormone or parathyroid hormone derivatives within the last 3 months before initial administration of the study drug.
10. Other bone active drugs including heparin, warfarin, antiplatelet therapy (clopidogrel), anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin-releasing hormone agonists, anabolic steroids, aluminium, aromatase inhibitors, protease inhibitors, methotrexate and thiazolidinediones within the past 3 months before initial administration of the study drug. Note: Direct oral anticoagulants are allowed as they have no effect on bone metabolism.
11. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening.
12. Use of certain immunosuppressants (e.g., calmodulin and calcineurin inhibitors) within the past 3 months prior to screening.
13. Chronic treatment of protein pump inhibitors if used continuously for longer than a year within the past 3 months prior to screening.
14. Use of other investigational drugs within five half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline or within 30 days prior to screening, whichever is longer, or longer if required by local regulations.
15. Oral or dental conditions: osteomyelitis or history and/or presence of osteonecrosis of the jaw, presence of risk factors for osteonecrosis of the jaw (e.g., periodontal disease, poorly fitting dentures, invasive dental procedures such as tooth extractions in 6 months before screening), active dental or jaw condition which requires oral surgery and/or planned invasive dental procedure at the discretion of the investigator. Note: Subjects may be further examined by a dental specialist at the investigator's discretion.
16. Vitamin D deficiency (25-OH vitamin D serum level <20 ng/mL). Vitamin D repletion is permitted at the investigator's discretion and subjects will be rescreened to re-evaluate vitamin D level post repletion. Vitamin D levels will be re-tested once within the Screening Period.
17. Known intolerance to, or malabsorption of calcium or vitamin D supplements.

18. Has an active infection that required the use of oral antibiotics within 2 weeks or parenteral antibiotics used within 4 weeks prior to randomisation. Has an HBV, HCV, HIV-1/HIV-2 or SARS-CoV-2 positive test result at screening. If a positive test result is obtained, a confirmatory test is required.
19. Received a COVID-19 vaccine within 14 days prior to randomisation to study drug or is planning to receive a COVID-19 vaccine within 14 days prior to study drug administration at Month 6 or Month 12.
20. History and/or presence of significant cardiac disease as per investigator's discretion, including but not restricted to: ECG abnormalities at screening indicating significant risk of safety for subjects participating in the study, history and/or presence of myocardial infarction within 6 months before screening, history and/or presence of NYHA class III or IV heart failure, any unstable pulmonary disease (eg, chronic obstructive disease), haematologic, neurological, psychiatric, endocrine (eg, diabetes), autoimmune disease (eg, Crohn's disease or coeliac disease), gastrointestinal, renal, urinary, skeletal or dermatologic disease, which can be judged as clinically significant at the investigator's discretion.
21. Have major surgery (including surgery to bone), or significant traumatic injury occurring within 4 weeks before randomisation or if one is planned during the study.

Treatments

During the Main Treatment Period, patients received 60 mg of either MB09 or EU-Prolia on Day 1 and at Month 6 as s.c. injections in the upper arm, upper thigh, or abdomen by unblinded clinical staff members (e.g., nurse/physician) who were not involved in any other study-related procedures.

A third dose of either 60 mg MB09 or EU-Prolia was administered at the beginning of the Transition/Safety Follow-up Period at Month 12.

Table 19: Batch numbers and expiry dates of the study treatment

Batch Numbers	Expiry Dates
MB09	
21A60C	Initial expiry date: Jun 2022 Extended expiry date: Sep 2022
22A31C	Initial expiry date: Mar 2023 Extended expiry date: Sep 2023 Extended expiry date: Mar 2024
Prolia	
1136812	29 Feb 2024
1142161	31 Aug 2024
1153835	30 Apr 2025

Permitted concomitant medications

Any concomitant medication deemed necessary for the welfare of the subject during the study could be given at the discretion of the investigator. It was the investigator's responsibility to ensure recording of details of all concomitant medications, any changes in concomitant medications, especially the use of all prior and

concomitant medications for the treatment of osteoporosis, from the diagnosis of the disease until the End of Study visit and any COVID-19 vaccination.

Prohibited concomitant medications

For study MB09-C-01-19, prohibited concomitant therapy was defined as the bundle of medication compound, indication, dose, frequency and duration of the therapy, or any other consideration which could have had an impact on bone metabolism, BMD, and/or denosumab mechanism of action. Prohibited concomitant medications were:

- Denosumab (Prolia, Xgeva, or a denosumab biosimilar) or any other monoclonal antibody (e.g., romosozumab) or fusion protein containing IgG or other biologic agent targeting IgG.
- Drugs being investigated for osteoporosis.
- Intravenous bisphosphonate, strontium or fluoride administered for osteoporosis within 5 years of screening.
- Oral bisphosphonates ≥12 months cumulative use prior to screening.
- Ongoing use of any osteoporosis treatment (excluding calcium and vitamin D supplements) taken within the past 5 years prior to screening, with the exception of the medications listed below that were required to adhere to rules for the following washout periods:
    - Tibolone, oestrogen/progesterone containing products including any oestrogen/progesterone contraceptives or hormone-replacement therapy, selective oestrogen receptor modulators, received within 3 months prior to screening.
    - Calcitonin, calcitriol, maxacalcitol, falecalcitriol or alfacalcidol: dose received within 3 months prior to screening.
    - Cinacalcet: dose received within 3 months prior to screening.
    - Parathyroid hormone or parathyroid hormone derivatives within the last 3 months before initial administration of the study drug.
- Other bone active drugs including heparin, warfarin, antiplatelet therapy (clopidogrel), anticonvulsives (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin-releasing hormone agonists, anabolic steroids, aluminium, aromatase inhibitors, protease inhibitors, methotrexate and thiazolidinediones within the past 3 months before initial administration of the study drug. Note: Direct oral anticoagulants are allowed as they have no effect on bone metabolism.
- Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days or a total cumulative dose of ≥50 mg) within the past 3 months before screening.
- Use of certain immunosuppressants (e.g., calmodulin and calcineurin inhibitors) within the past 3 months prior to screening.
- Chronic treatment of protein pump inhibitors if used continuously for longer than a year within the past 3 months prior to screening.

- Use of other investigational drugs within five half-lives of the drug or until the expected pharmacodynamic effect of the drug has returned to baseline or within 30 days prior to screening, whichever is longer, or longer if required by local regulations.
- Received a COVID-19 vaccine within 14 days prior to randomisation to study drug or is planning to receive a COVID-19 vaccine within 14 days prior to study drug administration at Month 6 or Month 12.

When a listed prohibited medication was started during the study, a medical assessment was performed to distinguish whether this was clinically significant and whether or not could impact the efficacy evaluation.

In addition, time to first prohibited or other osteoporosis medication was to be presented by treatment group (MB09 or Prolia) using a Kaplan-Meier curve on the SAF where the first dose date of prohibited or other osteoporosis medication was set as the event date. Subjects who did not have an event were censored.

Patients who have received or planned to receive these prohibited medications or treatments were not enrolled in the study. Patients who received any prohibited therapy during the Screening Period were to be considered a screen failure. Intake of prohibited therapy by the patients after randomisation were to be considered as a protocol deviation. If a patient had taken a prohibited medication, they remained in the study in order to collect safety follow-up information as well as the efficacy assessments at Month 6 and Month 12.

Co-administration of Calcium and Vitamin D

All subjects received daily supplementation of at least 1000 mg elemental calcium. The dosage of vitamin D was adjusted based on baseline levels. If screening levels of 25-OH vitamin D were >20 ng/mL at least 400 IU/d was administered. If screening levels were 12 to 20 ng/mL at least 800 IU/d was administered.

Patients with screening levels of 25-OH vitamin D of <20 ng/mL were permitted to undergo vitamin D repletion at the investigator's discretion and could be rescreened to reevaluate vitamin D level after repletion. Ergocalciferol was the preferable supplement (for at least two weeks), although any other vitamin D supplement could have been used according to the local clinical practice. Information about calcium and vitamin D administration was recorded for data analysis purposes.

If a subject was intolerant to the daily calcium or vitamin D supplementation, the investigator was allowed to change the formulation to a preferred product that the subject tolerated well earlier or lower the dose. The intolerance as well as the resolution (e.g., change in formulation or dosage) were to be recorded for data analysis purposes.

Objectives

Main Treatment Period

Primary objective: To demonstrate equivalent efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12.

Key secondary objectives:
- To assess the efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 6 and hip and femur neck BMD at Month 6 and Month 12.
- To assess the PD profile of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of sCTX AUEC up to Month 6 and sCTX at Month 12.

Other secondary objectives:

- To assess the PK profile of MB09 compared with EU-Prolia.
- To evaluate the safety profile of MB09 compared with EU-Prolia.
- To assess the immunogenicity of MB09 compared with EU-Prolia assessed through ADAs.

Transition/Safety Follow-Up Period

Key secondary objectives: To assess the PK/PD profile, the risk of hypersensitivity and AEs and the risk of immunogenicity through formation of ADAs after the single transition from EU-Prolia to MB09 or receiving MB09 throughout the study. Each group compared with those patients receiving EU-Prolia throughout the study.

Outcomes/endpoints

Primary Efficacy Endpoint: **%CfB in lumbar spine BMD** after 52 weeks

Key secondary endpoints:

Efficacy

- Difference in means (MB09 minus EU-Prolia) in composite endpoint of %CfB (zero was taken for anyone who died) in
  - lumbar spine BMD after 6 months.
  - hip BMD after 6 and 12 months.
  - femur neck BMD after 6 and 12 months.

PD

- Ratio of geometric means (MB09/EU-Prolia) in sCTX **$AUEC_{0\text{-}6\ months}$**
- Mean difference in sCTX at 11 days and 1, 3, and 6 months after the first dose; and 6 months after the second dose of study treatment.

Other secondary endpoints:

PK

- **$AUC_{0\text{-}6\ months}$** and **C_{max}** following the first dose.
- **C_{trough}** of serum denosumab at Month 6 and Month 12.

Safety

- Subject incidence of TEAEs up to and including Month 12.
- Subject incidence of AESIs (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of jaw, dermatologic reaction, and atypical femoral fracture) up to and including Month 12.
- Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG, and vital signs from baseline up to and including Month 12.
- Subject incidence of deaths and SAEs up to Month 12.

Immunogenicity

- Binding and neutralising serum denosumab antibodies from baseline up to and including Month 12.

Transition/Safety Follow-Up Period

Key secondary endpoints:

PK

- Transition Period **$AUC_{0\text{-}6\ months}$** and **C_{max}** following the third dose at Month 12.
- **C_{trough}** of serum denosumab at Transition Period Month 6.

PD

- Transition Period sCTX **AUEC** up to Transition Period Month 6.
- **C_{trough}** of sCTX at Month 12 and Transition Period Month 6.

Safety

- Subject incidence of TEAEs from third dose at Month 12 and up to and including Transition Period Month 6.
- Subject incidence of AESIs (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of jaw, dermatologic reaction, and atypical femoral fracture) from the third dose at Month 12 and up to and including Transition Period Month 6.
- Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG, and vital signs from third dose at Month 12 and up to and including Transition Period Month 6.
- Subject incidence of deaths and SAEs from third dose at Month 12 and up to and including Transition Period Month 6.

Immunogenicity

- Binding and neutralising serum denosumab antibodies from Month 12 and up to and including Transition Period Month 6.

Table 20: Primary objective and estimands with rationale for strategies to address intercurrent events

	Estimand 1a (Primary)	**Estimand 1b (Supportive)**
Estimand Description (summary below)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications.	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.
Treatment Conditions of Interest	MB09 versus EU-Prolia	
Target Population	Postmenopausal women with osteoporosis	

Endpoint	Percentage change from baseline in lumbar spine bone mineral density (*%CfB* lumbar spine BMD) to Month 12 and taking *%CfB* value of zero for someone who dies.	
Population Level Summary	Difference between treatments in population mean *%CfB* BMD at Month 12.	
ICEs and Strategies to Handle ICEs	**Hypothetical strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. **Treatment policy strategy** for: • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.	**Treatment policy strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.
Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; ICE, intercurrent event.
Note: The screening BMD assessment will be taken as the baseline BMD assessment

Estimands for key secondary endpoints

Estimand 2a\3a\4a: Difference in means (MB09 minus EU-Prolia) in composite endpoint of %CFB (zero was taken for anyone who died) in

- (2a) lumbar spine BMD after 6 months.
- (3a) hip BMD after 6 and 12 months.
- (4a) femur neck BMD after 6 and 12 months.

in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.

Estimand 2b\3b\4b: Same as Estimand 1b for each endpoint above irrespective of discontinuation of treatment for any reason, errors or deviations in dosing, and whether any prohibited therapies or other osteoporosis medications were taken.

Sample size

A sample size of 448 subjects (224 subjects on each of MB09 and EU-Prolia [Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia pooled] at Month 12) approximately achieves 85% statistical power for the demonstration of equivalence in the %CfB lumbar spine BMD at Month 12, based on the two one-sided 2.5% significance level and an equivalence margin of ± 1.45%. In this sample size calculation, the common SD is assumed to be 4.5% and the true mean difference of %CfB is assumed to be zero. Therefore, allowing for a 15% dropout, 528 subjects will be randomised 2:1:1 to the MB09-MB09, Prolia-MB09 and Prolia-Prolia treatment arms.
A meta-analysis of available clinical studies with Prolia gave the pooled denosumab treatment effect 5.35% (95% CI: 4.83% to 5.87%). Based on the lower bound of the 95% CI, a 1.45% margin will preserve 70% of the treatment effect (0.3*4.83%).

Randomisation and blinding (masking)

Randomisation

Interactive response technology was to be used to administer the randomisation schedule. Biostatistics were to generate the randomisation schedule for IRT, which linked sequential subject randomisation numbers to treatment codes. Permuted block randomisation with block size of 4 was used. The randomisation schedule was to be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use). IRT system was to dynamically allocate stratification combination of the stratification factors in order to allocate a subject to a treatment arm in a blinded manner.
Eligible subjects were to be randomised in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2), or Prolia-Prolia (Arm 3) on Day 1.
Subjects who withdraw the study were not to be replaced.

Blinding and Unblinding

The study is to remain blinded to the investigators, subjects, and predefined Sponsor and contract research organisation (CRO) personnel until all subjects have completed the study and the database has been finalised for study closure.
The randomisation codes are not to be revealed to study subjects, investigators, or study site personnel, except for delegated unblinded staff who handle the study treatment and predefined unblinded Sponsor and CRO personnel, until all final clinical data have been entered into the database and the database is locked and released for final analysis.
During the Main Treatment Period, the trained clinical staff members responsible for study treatment administration (e.g., nurse/physician) were designated as unblinded study site personnel and were not involved in any clinical or safety evaluations that were part of the blinded protocol or had other subject contact. Subjects were blinded by using a blindfold, screen, or similar method during the dosing procedure so that the injection syringe was not visible to them. Unblinded staff were required to visually inspect the study treatment prior to its use. The solution may have contained trace amounts of translucent to white proteinaceous particles. The study treatment was not to be injected if it was cloudy or discoloured or if it contained many particles or foreign particulate matter. Blinded staff were absent during study treatment administration and will remain blinded throughout the study.

Breaking the Blind

The blind was not broken until all final clinical data have been entered into the database and the database was locked and released for final analysis.

Provision to break the blind was available only if specific emergency treatment that required the knowledge of study treatment assignment was required for medical management. In such cases, the investigator, in an emergency, was allowed to determine the identity of the study treatment by using the applicable procedure in the IRT. The date, time, and reason for the unblinding were to be documented in the appropriate field of the eCRF, and the medical monitor was to be informed as soon as possible. All calls resulting in an unblinding event were to be recorded and reported by the IRT to the medial monitor and Sponsor. The identity of the person responsible for breaking the blind was also to be documented. Any subject for whom the blind was broken could continue in the study and receive study treatment (per protocol) at the investigator's discretion. Sponsor´s Pharmacovigilance Department had access to the randomisation code, if suspected unexpected serious adverse reactions, which were subject to expedited reporting, were to be unblinded before submission to the regulatory authorities.
For reporting the Main Treatment Period results, partial unblinding took place after database lock for data up to the end of Month 12 for all subjects (interim database lock with data cut on 19 Jan 2024). The unblinded personnel were predefined and documented before breaking the study blind and involved a separate unblinded project team at Sponsor and CRO. Datasets (and related tables, listings, figures) containing unblinding data were exclusively handled by the unblinded project team members at the CRO. However, for the blinded CSR (Document Version 1.0, dated 25 March 2024), for the primary efficacy analysis, only cumulative summary results (tables and figures) that did not contain information about individual subject study treatment or other unblinding data were provided to unblinded and blinded project teams at Sponsor and CRO.
The database was locked for the final analysis on 26 Jun 2024 followed by unblinding of individual subject treatment assignment. The final CSR (Document Version 2.0, dated 30 August 2024) includes the unblinded results of the complete study up to Week 78, i.e., the Main Treatment Period and the Transition/Safety Follow-up Period.

Statistical methods

Primary analysis

For the primary efficacy analysis, an MMRM was to be fitted to the composite %CfB lumbar spine BMD at Month 6 and Month 12 on the mFAS. The MMRM was to include terms for visit by treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. Subject was to be included as a random effect. The estimated mean difference in %CfB lumbar spine BMD at Month 12 was to be presented with 95% CI and equivalence was to be concluded if this falls within the predefined equivalence margins of [-1.45%, 1.45%]. Of note, the main analysis was on the mFAS and, therefore, did not use data after any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.

Sensitivity and supplementary analyses for the primary analysis

The following two sensitivity analyses were to be performed

1. A multiple imputed data set (30 imputations) produced under MAR was to be applied to the mFAS. The composite %CfB lumbar spine BMD was to be calculated as a post processing step from BMD values. In a first step, any intermittent missing data at Month 6 (i.e. Screening and Month 12 data available) were imputed and subsequently monotone regression was used to impute the remaining missing data. The imputation models included (in this specific order) age, BMI at baseline, prior use of bisphosphonates, baseline sCTX, lumbar spine BMD at baseline, sCTX (at Day 11, M1, M3, M6), Lumbar spine BMD (M6), hip BMD (M6), femur BMD (M6), sCTX (M12), Lumbar spine BMD (M12), hip BMD (M12), femur BMD (M12). The imputation model for the intermittent missing data was fitted by treatment, while the model for the monotone missing data included treatment as additional first

term. An MMRM model with the same variables as in the primary analysis was fitted on each imputed data set and the results were combined using Rubin's formula.

2. A tipping point penalty was added to the Month 12 imputed BMD values. The tipping point will add penalties of delta1 and delta2 to %CfB BMD values for EU-Prolia and MB09, respectively, in a matrix of values (delta1 = -6 to 6 by delta2 = -6 to 6 in steps of 1.5). For each combination of delta values, ANCOVA is performed for each multiply imputed dataset and then result pooled using Rubin's method.

As a supplementary analysis the log-transformed BMD data was analysed using a similar MMRM model as in the primary analysis.

Primary analysis of estimand 1b

In order to estimate Estimand 1b an ANCOVA will be fit to the composite %CfB lumbar spine BMD at Month 12 to each multiple imputed data set on the FAS where a treatment failure offset penalty is applied to imputed Month 12 BMD values of those not receiving the 2nd dose. The multiple imputed data set was to be generated similarly as described in the first sensitivity analysis for the primary analysis. The treatment failure offset was to be chosen such that the resulting %CfB BMD values for a subject considered as 'treatment failure' were centred around zero. The ANCOVA was to include terms for treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. The estimated mean difference in %CfB lumbar spine BMD results was to be pooled using Rubin's method and will be presented with 95% CI.

A tipping point analysis was to be conducted for the primary analysis of estimand 1b, using the same methods as the tipping point analysis for the primary analysis of estimand 1a.
In addition, the ANCOVA analysis was to be performed on the FAS without multiple imputation, both on the non-transformed and the log-transformed data.

Analysis of secondary endpoints

For the endpoints

- Lumbar spine BMD after 6 months.
- Hip BMD after 6 and 12 months.
- Femur neck BMD after 6 and 12 months.

estimands 2a-4a, which employ a hypothetical strategy, were to be analysed using MMRM as per the main analysis of the primary endpoint for the composite endpoint of %CfB (zero was taken for anyone who dies) on the mFAS.
Estimands 2b-4b, which are based on treatment policy strategies, were to be analysed using an ANCOVA on the FAS (without any multiple imputation methods) for the composite endpoint of %CfB (zero was taken for anyone who dies).

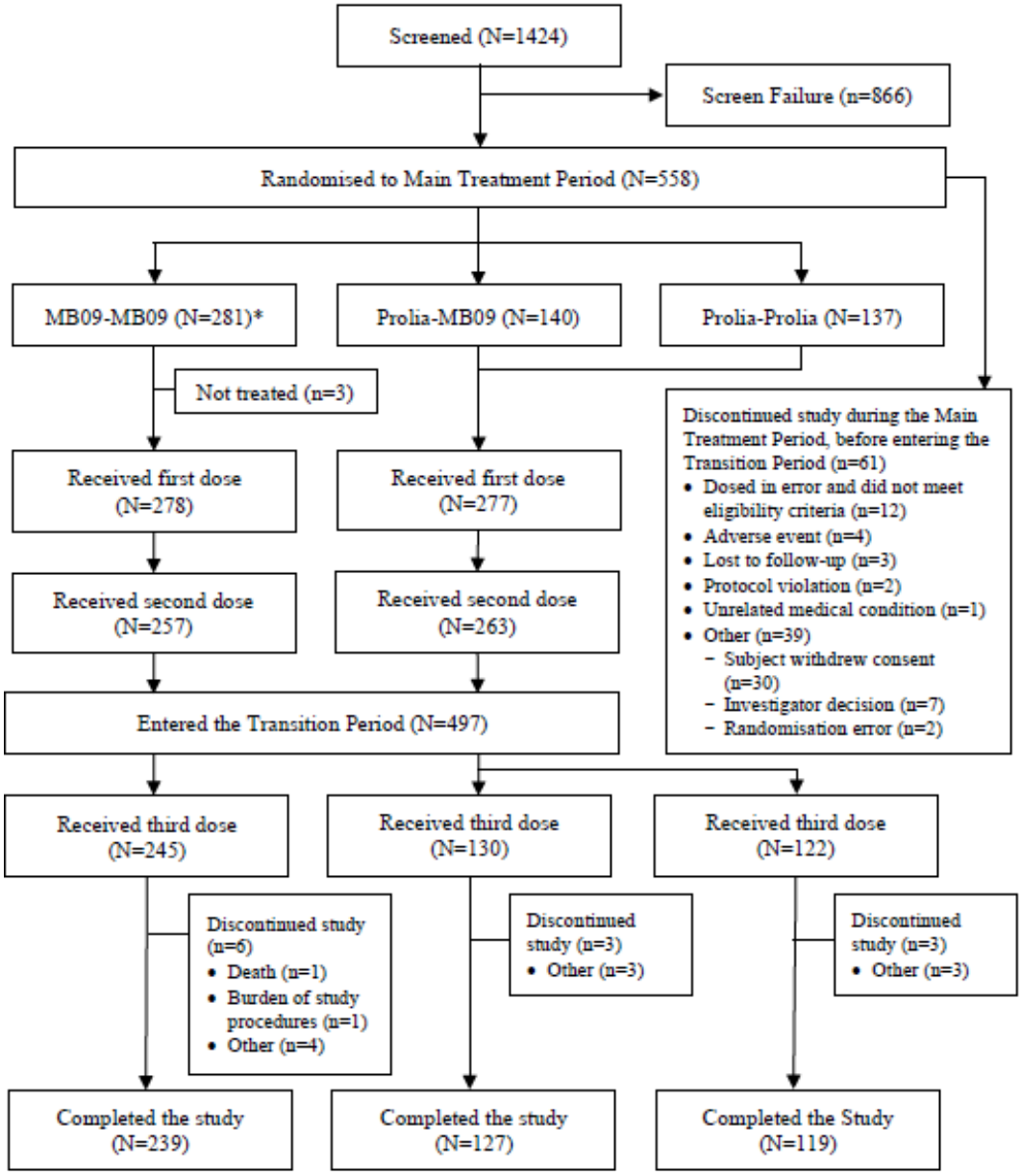
Planned subgroup analyses

Subgroup analyses were to be conducted for the primary estimand 1a and the secondary estimand 2a in the mFAS and the below subgroups were to be examined.
· Baseline lumbar spine BMD T-score (as per Clario) (≤ -3.0 versus > -3.0 SD).
· Body mass index at baseline (< 25 versus ≥ 25 kg/m2).
· Age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years).
· Prior bisphosphonate medication use at study entry (Yes/No).
· Body weight at baseline (≥ 50 to < 70 kg versus ≥ 70 to ≤ 99.9 kg).
· Smoker (Yes/No).
· Region (Latin America/Europe)

Results

Participant flow

Figure 5-1 Subject Disposition



* N as randomised. One subject (Subject RS001106) randomly assigned to the MB09-MB09 arm did not receive the assigned treatment, and instead received study treatment assigned to the Prolia-Prolia arm throughout the study. This subject was analysed for efficacy per the treatment as randomised (MB09-MB09) and for safety per the actual treatment received (Prolia-Prolia).
Source: Adapted from Table 14.1.2.1; Table 14.1.2.2; and Table 14.1.2.3.

Of the 866 screen failures, 41 patients have been rescreened resulting in 558 randomised patients.

Three of the randomised subjects did not receive the assigned study treatment as they were discontinued early: one subject was diagnosed with COVID-19 on Day 1 before receiving the study treatment and therefore was considered ineligible; one subject withdrew consent before receiving the study treatment; and one subject did not receive the study treatment due to technical issues.

Thus, a total of 555 subjects (99.5%) received the first dose and a total of 520 subjects (93.2%) received the first and second doses (Day 1 and Month 6) of the study treatment. A total of 497 subjects (89.1%) received the third dose (Month 12) of the study treatment.

All dosed subjects, including those who only received the first dose, were allowed to perform Month 12 visit assessments for safety and efficacy reasons.

Table 21: Subject disposition – Main treatment period (all enrolled analysis set)

	MB09 (N=281) n (%)	Prolia (N=277) n (%)	Total (N=1424) n (%)
Total number of subjects			
Screen failures			866 (60.8)
Randomised	281 (100)	277 (100)	558 (39.2)
Treated[1,2]	278 (98.9)	277 (100)	555 (99.5)
Received study treatment on Day 1 and at Month 6[2]	257 (91.5)	263 (94.9)	520 (93.2)
Received 3 doses of study treatment[2]	245 (87.2)	252 (91.0)	497 (89.1)
Discontinued from treatment prior to Month 12[2]	21 (7.5)	14 (5.1)	35 (6.3)
Completed Month 6 BMD assessment[2,3]	264 (94.0)	270 (97.5)	534 (95.7)
Completed Month 12 BMD assessment[2,3]	255 (90.7)	260 (93.9)	515 (92.3)
Received study treatment only on Day 1[2]	5 (1.8)	1 (0.4)	6 (1.1)
Received study treatment on Day 1 and Month 6[2]	250 (89.0)	259 (93.5)	509 (91.2)
Discontinued from study during Main Treatment Period[2]	36 (12.8)	25 (9.0)	61 (10.9)
Withdrawal prior to Month 12 (not returning for Month 12 visit)[2]	24 (8.5)	15 (5.4)	39 (7.0)
Withdrawal at Month 12 or partial withdrawal (returning for Month 12 visit)[2]	10 (3.6)	7 (2.5)	17 (3.0)
Withdrawal after Month 12[2]	2 (0.7)	3 (1.1)	5 (0.9)
Primary reasons for discontinuation from treatment prior to Month 12[2]			
Adverse event	3 (1.1)	0	3 (0.5)
Lost to follow-up	0	1 (0.4)	1 (0.2)
Subject dosed in error and did not meet eligibility criteria	7 (2.5)	6 (2.2)	13 (2.3)
Other[4]	11 (3.9)	7 (2.5)	18 (3.2)
Withdrawal of consent	8	7	15
Investigator's decision	3	0	3
Primary reasons for discontinuation from study during the Main Treatment Period[2]			
Adverse event	4 (1.4)	0	4 (0.7)
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)
Subject dosed in error and did not meet eligibility criteria	6 (2.1)	6 (2.2)	12 (2.2)
Protocol violation	1 (0.4)	1 (0.4)	2 (0.4)
Unrelated medical conditions	1 (0.4)	0	1 (0.2)
Other[4]	23 (8.2)	16 (5.8)	39 (7.0)
Withdrawal of consent	18	12	30
Investigator's decision	4	3	7
Randomised in error	2	0	2

Abbreviation: BMD, bone mineral density; eCRF, electronic case report form.

Note: Screen failures included 41 subjects who initially failed screening but were later successfully rescreened.

1 All randomised subjects who received at least one dose of study treatment.

2 Numbers are shown according to the planned treatment arm, and percentages are based on the number of subjects randomised.

3 Includes subjects with at least one of lumbar spine, hip, or femur neck BMD assessment collected by Clario.

4 The "Other" category was collected from free text field in the eCRF and data were extracted from listings.

Source: Adapted from Table 14.1.2.1. and Listing 16.2.1.3.

Table 22: Subject disposition – Transition period (full analysis set for transition period)

	MB09-MB09 (N=245) n (%)	Prolia-MB09 (N=130) n (%)	Prolia-Prolia (N=122) n (%)	Total (N=497) n (%)
Total number of subjects				
Treated[1]	245 (100)	130 (100)	122 (100)	497 (100)
Discontinued from study during Transition Period	6 (2.4)	3 (2.3)	3 (2.5)	12 (2.4)
Completed study	239 (97.6)	127 (97.7)	119 (97.5)	485 (97.6)
Primary reasons for discontinuation from study during Transition Period				
Death	1 (0.4)	0	0	1 (0.2)
Burden of study procedures	1 (0.4)	0	0	1 (0.2)
Other[2]	4 (1.6)	3 (2.3)	3 (2.5)	10 (2.0)
Withdrawal of consent	4	3	2	9
Subject left the country	0	0	1	1

[1] All randomised subjects who received a dose of study treatment at Month 12.

[2] The "Other" category was collected from free text field in the eCRF and data were extracted from listings. The category "withdrawal of consent" included subjects who withdrew consent, withdrew due to personal reasons, and refused to continue study participation.

Source: Adapted from Table 14.1.2.2 and Listing 16.2.1.3.

Recruitment

First patient first visit (Study Initiation Date): 16/03/2022

Main Treatment Period Completion Date: 14/12/2023

Data Cut-Off for the Main Treatment Period CSR: 19/01/2024

Transition Period Completion Date: 22/05/2024

Database-lock date: 26/06/2024

Conduct of the study

The original protocol (Version 1.0), dated 30/09/2021, was amended resulting in protocol version 2.0, dated 07/11/2022. Three protocol clarification letters (dated 12/11/2021, 10/12/2021 and 31/03/2022) have been incorporated into the final version of the study protocol. The latter are memos that intend to correct the information presented in the initial protocol version 1.0.

Study initiation date was on 16/03/2022 (first subject first visit), Main Treatment Period completion date was on 14/12/2023 and the date of data cut-off for the Main Treatment Period CSR was 19/01/2024. So, the last protocol clarification letter and the date of protocol version 2.0 lie after the start of the study.

The following amendments have been implemented:

Protocol Clarification Letter (12/11/2021)

- It was clarified that the upper age cut-off of inclusion criterion #3 was to be based on age rounded down to the nearest year ("Aged ≥55 and **<80** years" was changed to "Aged ≥55 and **≤80** years").
- Correction of the age stratification factor of "≥68 to <80 years" throughout the protocol to match the upper age cut-off in inclusion criterion #3 ("≥55 to <68 years versus ≥68 to **<80** years" was changed to "(≥55 to <68 years versus ≥68 to **≤80** years).

Protocol Clarification Letter (10/12/2021)

- Correction: All DXA scans performed during the study must be performed during screening.
- Update: The validity time of the DXA scan performed at screening has been extended to 3 months to be valid at rescreening.
- Correction: Any DXA scan performed as per standard of care cannot serve as an eligibility scan.

Protocol Clarification Letter (31/03/2022)

- It was clarified that albumin-adjusted total serum calcium instead of total calcium was used to determine eligibility and to monitor hypocalcaemia and hypercalcaemia.
- The threshold of subclinical hyperthyroidism in exclusion criterion #6 was defined by the thyroid stimulating hormone level cut-off of "<0.1 µU/mL"
- The only antiplatelet therapy considered prohibited was clopidogrel, other antiplatelet drugs were allowed.
- It was clarified that ergocalciferol was the preferred vitamin D supplement (for at least two weeks), although any other vitamin D supplement could be used according to the local clinical practice.

Protocol amendment 1 (07/11/2022)

Major changes implemented were:

- Subjects that had been discontinued from the study drug due to "dosing despite not meeting the eligibility criteria", were allowed to continue in the study if they had osteoporosis and no safety concerns per principal investigator's discretion.
- It was clarified that injection site reactions were to be recorded and severity would be collected as an AESI.
- It was clarified that subjects who experience or develop life-threatening treatment-related hypersensitivity/allergic reactions, should be permanently discontinued from the study drug and should be asked to complete the scheduled visits until the end of the Main Treatment Period at Month 12.

Baseline data

Demographic Data

Table 23: Demographics – Main treatment period (safety analysis set)

	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Age (years)			
n	277	278	555
Mean (SD)	65.8 (6.00)	65.9 (5.90)	65.8 (5.94)
Median	66.0	66.0	66.0
Min, Max	55, 80	55, 80	55, 80
Age group, n (%)			
≥55 to <68 years	170 (61.4)	172 (61.9)	342 (61.6)
≥68 to ≤80 years	107 (38.6)	106 (38.1)	213 (38.4)
Sex, n (%)			
Female	277 (100.0)	278 (100.0)	555 (100.0)
Smoking status, n (%)			
Current Smoker	67 (24.2)	65 (23.4)	132 (23.8)
Former Smoker	39 (14.1)	35 (12.6)	74 (13.3)
Never-Smoker	171 (61.7)	178 (64.0)	349 (62.9)
Race, n (%)			
White	276 (99.6)	275 (98.9)	551 (99.3)
American Indian or Alaska Native	1 (0.4)	3 (1.1)	4 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	10 (3.6)	13 (4.7)	23 (4.1)
Not Hispanic or Latino	267 (96.4)	265 (95.3)	532 (95.9)
Baseline height (cm)			
n	277	278	555
Mean (SD)	159.97 (6.252)	159.99 (6.131)	159.98 (6.186)
Median	160.00	160.00	160.00
Min, Max	144.0, 174.1	138.0, 180.0	138.0, 180.0
Baseline weight (kg)			
n	277	278	555
Mean (SD)	63.063 (8.8299)	63.328 (8.7580)	63.196 (8.7870)
Median	62.100	62.500	62.400
Min, Max	48.60, 90.30	48.40, 96.80	48.40, 96.80
Baseline BMI (CRF) (kg/m^2)[1]			
n	277	278	555
Mean (SD)	24.629 (3.0184)	24.737 (3.0661)	24.683 (3.0401)
Median	24.200	24.300	24.200
Min, Max	18.10, 35.40	18.10, 35.90	18.10, 35.90
Baseline BMI group (CRF), n (%)			
≥25 kg/m^2	115 (41.5)	122 (43.9)	237 (42.7)
<25 kg/m^2	162 (58.5)	156 (56.1)	318 (57.3)

Abbreviations: BMI, body mass index; CRF, case report form; Max, maximum; Min, minimum; SD, standard deviation.

[1] BMI was calculated as (weight [kg])/(height [m])^2.

Source: Table 14.1.4.1.1.

Table 24: Demographics – Transition period (safety analysis set - transition period)

	MB09-MB09 (N=244)	Prolia-MB09 (N=130)	Prolia-Prolia (N=123)	Total (N=497)
Age (years)				
n	244	130	123	497
Mean (SD)	65.5 (5.86)	66.1 (6.04)	65.7 (5.74)	65.7 (5.87)
Median	66.0	66.0	65.0	66.0
Min, Max	55, 80	55, 80	55, 80	55, 80
Age group, n (%)				
≥55 to <68 years	156 (63.9)	80 (61.5)	77 (62.6)	313 (63.0)
≥68 to ≤80 years	88 (36.1)	50 (38.5)	46 (37.4)	184 (37.0)
Sex, n (%)				
Female	244 (100.0)	130 (100.0)	123 (100.0)	497 (100.0)
Smoking status, n (%)				
Current Smoker	60 (24.6)	29 (22.3)	31 (25.2)	120 (24.1)
Former Smoker	34 (13.9)	20 (15.4)	9 (7.3)	63 (12.7)
Never-Smoker	150 (61.5)	81 (62.3)	83 (67.5)	314 (63.2)
Race, n (%)				
White	243 (99.6)	127 (97.7)	123 (100.0)	493 (99.2)
American Indian or Alaska Native	1 (0.4)	3 (2.3)	0	4 (0.8)
Ethnicity, n (%)				
Hispanic or Latino	8 (3.3)	7 (5.4)	5 (4.1)	20 (4.0)
Not Hispanic or Latino	236 (96.7)	123 (94.6)	118 (95.9)	477 (96.0)
Baseline height (cm)				
n	244	130	123	497
Mean (SD)	159.92 (6.240)	159.25 (5.686)	160.73 (6.426)	159.94 (6.158)
Median	160.00	159.95	161.00	160.00
Min, Max	144.0, 174.0	138.0, 174.0	144.0, 180.0	138.0, 180.0
Baseline weight (kg)				
n	244	130	123	497
Mean (SD)	63.00 (8.509)	63.14 (8.381)	63.03 (8.980)	63.04 (8.578)
Median	62.05	62.85	62.00	62.00
Min, Max	50.0, 90.3	50.1, 87.0	48.4, 96.8	48.4, 96.8
Baseline BMI (kg/m^2)[1]				
n	244	130	123	497
Mean (SD)	24.63 (2.929)	24.89 (2.957)	24.39 (3.069)	24.64 (2.971)
Median	24.20	24.60	24.10	24.20
Min, Max	18.1, 30.6	18.7, 30.1	18.1, 30.5	18.1, 30.6
Baseline BMI group, n (%)				
≥25 kg/m^2	102 (41.8)	58 (44.6)	51 (41.5)	211 (42.5)
<25 kg/m^2	142 (58.2)	72 (55.4)	72 (58.5)	286 (57.5)

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation.

[1] BMI was calculated as (weight [kg])/(height [m])^2.

Source: Table 14.1.4.1.2.

Baseline Disease Characteristics

Table 25: Baseline disease characteristics demographics – Main treatment period (safety analysis set)

	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Baseline BMD T-score at the lumbar spine (CRF) (SD), n (%)			
>−3.0	144 (52.0)	143 (51.4)	287 (51.7)
≤−3.0	133 (48.0)	135 (48.6)	268 (48.3)
Lumbar spine BMD (g/cm^2)			
n	277	277	554
Mean (SD)	0.766 (0.0878)	0.773 (0.0862)	0.770 (0.0870)
Median	0.755	0.762	0.758
Min, Max	0.54, 1.18	0.59, 1.15	0.54, 1.18
Total hip BMD (g/cm^2)			
n	277	278	555
Mean (SD)	0.731 (0.0973)	0.745 (0.0946)	0.738 (0.0961)
Median	0.718	0.743	0.730
Min, Max	0.49, 1.13	0.52, 1.04	0.49, 1.13
Femur neck BMD (g/cm^2)			
n	277	278	555
Mean (SD)	0.672 (0.1085)	0.685 (0.1084)	0.679 (0.1086)
Median	0.655	0.681	0.669
Min, Max	0.45, 1.13	0.45, 1.01	0.45, 1.13
Menopause duration (years)			
n	277	277	554
Mean (SD)	16.422 (7.0597)	16.991 (7.3539)	16.707 (7.2074)
Median	16.000	16.000	16.000
Min, Max	1.00, 34.00	1.77, 48.00	1.00, 48.00

Osteoporosis duration (years)			
n	277	278	555
Mean (SD)	2.656 (4.3900)	2.042 (3.8967)	2.348 (4.1579)
Median	0.280	0.290	0.290
Min, Max	0.00, 24.00	0.00, 30.00	0.00, 30.00
Prior use of bisphosphonates, n (%)[1]			
Yes	25 (9.0)	21 (7.6)	46 (8.3)
No	252 (91.0)	257 (92.4)	509 (91.7)
Fracture history, n (%)[2]			
Yes	108 (39.0)	102 (36.7)	210 (37.8)
No	169 (61.0)	176 (63.3)	345 (62.2)
History of vertebrae fractures, n (%)[3]			
Yes	37 (34.3)	31 (30.4)	68 (32.4)
No	71 (65.7)	71 (69.6)	142 (67.6)

Abbreviations: BMD, bone mineral density; CRF, case report form; IV, intravenous; Max, maximum; Min, minimum; SD, standard deviation.

[1] Prior use of bisphosphonates included oral bisphosphonate use prior to screening, IV bisphosphonate use within 5 years of screening as reported on the "Bisphosphonates" form and prior bisphosphonates (ie, those with the stop date prior to the first dose of study treatment in the Main Treatment Period) reported on the "Prior and Concomitant Medications" form.

[2] Fracture history included fractures reported on the "Medical and Disease History" forms.

[3] Percentages were calculated out of those who had a fracture.

Source: Table 14.1.4.1.1.

Table 26: Baseline disease characteristics demographics – Transition period (safety analysis set for transition period)

	MB09-MB09 (N=244)	Prolia-MB09 (N=130)	Prolia-Prolia (N=123)	Total (N=497)
Baseline BMD T-score at the lumbar spine (Clario) (SD), n (%)				
>−3.0	125 (51.2)	70 (53.8)	63 (51.2)	258 (51.9)
≤−3.0	119 (48.8)	60 (46.2)	60 (48.8)	239 (48.1)
Lumbar spine BMD (g/cm^2)				
n	244	130	122	496
Mean (SD)	0.76 (0.087)	0.77 (0.070)	0.77 (0.096)	0.77 (0.085)
Median	0.75	0.76	0.76	0.76
Min, Max	0.5, 1.2	0.6, 1.0	0.6, 1.1	0.5, 1.2
Total hip BMD (g/cm^2)				
n	244	130	123	497
Mean (SD)	0.73 (0.097)	0.75 (0.092)	0.73 (0.096)	0.74 (0.096)
Median	0.72	0.76	0.72	0.73
Min, Max	0.5, 1.1	0.5, 1.0	0.5, 1.0	0.5, 1.1
Femur neck BMD (g/cm^2)				
n	244	130	123	497
Mean (SD)	0.67 (0.109)	0.69 (0.107)	0.68 (0.108)	0.68 (0.108)
Median	0.66	0.69	0.67	0.67
Min, Max	0.4, 1.1	0.5, 1.0	0.5, 1.0	0.4, 1.1
Menopause duration (years)				
n	244	129	123	496
Mean (SD)	16.09 (6.943)	17.34 (7.360)	16.60 (6.774)	16.54 (7.018)
Median	16.00	17.00	16.00	16.00
Min, Max	1.0, 34.0	1.8, 38.0	2.0, 38.0	1.0, 38.0

Osteoporosis duration (years)				
n	244	130	123	497
Mean (SD)	2.77 (4.440)	1.99 (4.092)	2.18 (3.887)	2.42 (4.225)
Median	0.37	0.28	0.28	0.30
Min, Max	0.0, 24.0	0.0, 30.0	0.0, 21.0	0.0, 30.0
Prior use of bisphosphonates, n (%)[1]				
Yes	23 (9.4)	10 (7.7)	8 (6.5)	41 (8.2)
No	221 (90.6)	120 (92.3)	115 (93.5)	456 (91.8)
Fracture history, n (%)[2]				
Yes	94 (38.5)	53 (40.8)	41 (33.3)	188 (37.8)
No	150 (61.5)	77 (59.2)	82 (66.7)	309 (62.2)
History of vertebrae fractures, n (%)[3]				
Yes	28 (29.8)	15 (28.3)	15 (36.6)	58 (30.9)
No	66 (70.2)	38 (71.7)	26 (63.4)	130 (69.1)

Abbreviations: BMD, bone mineral density; IV, intravenous; Max, maximum; Min, minimum; SD, standard deviation.

1 Prior use of bisphosphonates included oral bisphosphonate use prior to screening, IV bisphosphonate use within 5 years of screening as reported on the "Bisphosphonates" form and prior bisphosphonates (ie, those with the stop date prior to the first dose of study treatment in the Main Treatment Period) reported on the "Prior and Concomitant Medications" form.

2 Fracture history included fractures reported on the "Medical and Disease History" forms.

3 Percentages were calculated out of those who had a fracture.

Source: Table 14.1.4.1.2.

Medical/Surgical History

Most prominent items listed for the medical history of study participants were by SOC "musculoskeletal and connective tissue disorders" (296 (53.3%) patients), "vascular disorders" (278 (50.1%) patients), "surgical and medical procedures" (265 (47.7%) patients); "metabolism and nutrition disorders" (224 (40.4%) patients), "endocrine disorders" (125 (22.5%) patients), and "neoplasms benign, malignant and unspecified (incl. cysts and polyps)" (111 (20.0%) patients).

Table 27: Medical history reported in >10% of total subjects – Main treatment period (safety analysis set)

Preferred Term	MB09 (N=277) n (%)	Prolia (N=278) n (%)	Total (N=555) n (%)
Subjects with any medical history	253 (91.3)	257 (92.4)	510 (91.9)
Medical history reported in >10% subjects			
Hypertension	118 (42.6)	119 (42.8)	237 (42.7)
Osteoarthritis	59 (21.3)	66 (23.7)	125 (22.5)
Spinal osteoarthritis	51 (18.4)	55 (19.8)	106 (19.1)
Hypercholesterolaemia	52 (18.8)	44 (15.8)	96 (17.3)
Hyperlipidaemia	31 (11.2)	38 (13.7)	69 (12.4)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.

Note 1: At each level of subject summarisation, a subject was counted once if the subject reported one or more findings.

Note 2: Medical histories were coded using MedDRA, Version 24.1.

Source: Table 14.1.6.1.

Table 28: Medical history reported in >10% of total subjects – Transition period (safety analysis set - transition period)

Preferred Term	MB09-MB09 (N=244) n (%)	Prolia-MB09 (N=130) n (%)	Prolia-Prolia (N=123) n (%)	Total (N=497) n (%)
Subjects with any medical history	223 (91.4)	120 (92.3)	112 (91.1)	455 (91.5)
Medical history reported in >10% subjects				
Hypertension	107 (43.9)	59 (45.4)	50 (40.7)	216 (43.5)
Osteoarthritis	51 (20.9)	33 (25.4)	24 (19.5)	108 (21.7)
Spinal osteoarthritis	41 (16.8)	31 (23.8)	19 (15.4)	91 (18.3)
Hypercholesterolaemia	46 (18.9)	23 (17.7)	16 (13.0)	85 (17.1)
Hyperlipidaemia	26 (10.7)	18 (13.8)	19 (15.4)	63 (12.7)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities.

Note 1: At each level of subject summarisation, a subject was counted once if the subject reported one or more findings.

Note 2: Medical histories were coded using MedDRA, Version 24.1.

Source: Table 14.1.6.2.

Prior Medication

Overall, 365 (65.8%) patients reported at least one prior medication. The most common classes of prior medications (reported in >10.0% of total subjects) included vitamin D and analogues (215 (38.7%) patients), mostly cholecalciferol (193 (34.8%) patients); other viral vaccines (167 (30.1%) patients), mostly tozinameran (136 (24.5%) patients); calcium combinations with vitamin D and/or other drugs (86 (15.5%) patients); and calcium (77 (13.9%) patients).

Concomitant Medication in the Main Treatment Period

Table 29: Concomitant medications in >10% of total subjects by ATC – Main treatment period (safety analysis set)

ATC Level 4 Preferred term	MB09 (N=277)	Prolia (N=278)	Total (N=555)
Number of subjects with at least one concomitant medication	229 (82.7)	238 (85.6)	467 (84.1)
Beta blocking agents, selective	75 (27.1)	70 (25.2)	145 (26.1)
Bisoprolol fumarate	32 (11.6)	34 (12.2)	66 (11.9)
HMG CoA reductase inhibitors	70 (25.3)	62 (22.3)	132 (23.8)
Rosuvastatin calcium	26 (9.4)	33 (11.9)	59 (10.6)
Thyroid hormones	42 (15.2)	41 (14.7)	83 (15.0)
Levothyroxine sodium	35 (12.6)	28 (10.1)	63 (11.4)
ACE inhibitors, plain	44 (15.9)	38 (13.7)	82 (14.8)
Ramipril	25 (9.0)	21 (7.6)	46 (8.3)
Anilides	30 (10.8)	36 (12.9)	66 (11.9)
Paracetamol	27 (9.7)	30 (10.8)	57 (10.3)
Dihydropyridine derivatives	36 (13.0)	24 (8.6)	60 (10.8)
Amlodipine	15 (5.4)	11 (4.0)	26 (4.7)
Platelet aggregation inhibitors excl. heparin	27 (9.7)	32 (11.5)	59 (10.6)
Acetylsalicylic acid	23 (8.3)	27 (9.7)	50 (9.0)

Abbreviations: ACE, angiotensin converting enzyme; ATC, Anatomical Therapeutic Classification; HMG CoA, β-hydroxy β-methylglutaryl coenzyme A.

Note 1: Concomitant medications were coded with the WHO Drug Version B-3 dictionary dated September, 2021.

Note 2: Subjects may have had more than one medication per ATC level 4 category and preferred term. At each level of subject summarization, a subject was counted once if the subject reported one or more medications.

Note 3: Medications with missing ATC level 4 terms were summarised using the highest level term that was available.

Source: Table 14.1.8.1.

Table 30: Concomitant medications in >10% of total subjects by ATC – Transition period (safety analysis set for transition period)

ATC Level 4 Preferred term	MB09-MB09 (N=244)	Prolia-MB09 (N=130)	Prolia-Prolia (N=123)	Total (N=497)
Number of subjects with at least one concomitant medication	190 (77.9)	112 (86.2)	97 (78.9)	399 (80.3)
HMG CoA reductase inhibitors	70 (28.7)	33 (25.4)	26 (21.1)	129 (26.0)
Rosuvastatin calcium	25 (10.2)	17 (13.1)	14 (11.4)	56 (11.3)
Beta blocking agents, selective	64 (26.2)	27 (20.8)	35 (28.5)	126 (25.4)
Bisoprolol fumarate	28 (11.5)	14 (10.8)	15 (12.2)	57 (11.5)
Thyroid hormones	35 (14.3)	22 (16.9)	14 (11.4)	71 (14.3)
Levothyroxine sodium	29 (11.9)	12 (9.2)	11 (8.9)	52 (10.5)
ACE inhibitors, plain	35 (14.3)	18 (13.8)	15 (12.2)	68 (13.7)
Ramipril	20 (8.2)	11 (8.5)	8 (6.5)	39 (7.8)
Dihydropyridine derivatives	32 (13.1)	12 (9.2)	12 (9.8)	56 (11.3)
Amlodipine	13 (5.3)	6 (4.6)	5 (4.1)	24 (4.8)
Platelet aggregation inhibitors excl. heparin	24 (9.8)	17 (13.1)	13 (10.6)	54 (10.9)
Acetylsalicylic acid	21 (8.6)	14 (10.8)	11 (8.9)	46 (9.3)

Abbreviations: ACE, angiotensin converting enzyme; ATC, Anatomical Therapeutic Classification; HMG CoA, β-hydroxy β-methylglutaryl coenzyme A.

Note 1: Concomitant medications were coded with the WHO Drug Version B-3 dictionary dated September, 2021.

Note 2: Subjects may have had more than one medication per ATC level 4 category and preferred term. At each level of subject summarization, a subject was counted once if the subject reported one or more medications.

Note 3: Medications with missing ATC level 4 terms were summarised using the highest level term that was available.

Source: Table 14.1.8.2.

Prohibited Concomitant Medication

Table 31: Prohibited concomitant medications – Main treatment period (safety analysis set)

ATC=Anatomical Therapeutic Classification.
Prohibited medications are defined in the protocol. Concomitant medications for the Main Treatment Period are those with start dates prior to the first dose of the Main Treatment Period and continuing after the first dose of the Main Treatment Period or with start dates between the first dose of the Main Treatment Period and the first dose of the Transition Period.
Only clinically significant prohibited medications are included but these are not considered as an intercurrent event.
Subjects may have more than one medication per ATC level 4 category and preferred term.
At each level of subject summarization, a subject is counted once if the subject reported one or more medications. Medications with missing ATC level 4 terms are summarized using the highest level term that is available.
Prohibited concomitant medications were coded with the WHO Drug Version B-3 dictionary dated September, 2021.
Source Data: Listing 16.2.4.3 and Report of prohibited medication

ATC Level 4 Preferred Term	MB09 (N=277) n(%)	Prolia (N=278) n(%)	Total (N=555) n(%)
Total number of prohibited medications	5	1	6
Number of subjects with at least one prohibited medication	4 (1.4)	1 (0.4)	5 (0.9)
PROTON PUMP INHIBITORS	2 (0.7)	0	2 (0.4)
Esomeprazole	1 (0.4)	0	1 (0.2)
Lansoprazole	1 (0.4)	0	1 (0.2)
GLUCOCORTICOIDS	0	1 (0.4)	1 (0.2)
Methylprednisolone	0	1 (0.4)	1 (0.2)
OTHER ANALGESICS AND ANTIPYRETICS	1 (0.4)	0	1 (0.2)
Gabapentin	1 (0.4)	0	1 (0.2)
OTHER ANTIDEPRESSANTS	1 (0.4)	0	1 (0.2)
Lamotrigine	1 (0.4)	0	1 (0.2)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	1 (0.4)	0	1 (0.2)
Clopidogrel	1 (0.4)	0	1 (0.2)

Note: Notes are listed on page 1.
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Table 32: Concomitant medications – Transition period safety analysis set for transition period

ATC Level 4 Preferred Term	MB09 => MB09 (N=244) n(%)	Prolia => MB09 (N=130) n(%)	Prolia => Prolia (N=123) n(%)	Total (N=497) n(%)
Total number of prohibited medications	4	1	0	5
Number of subjects with at least one prohibited medication	3 (1.2)	1 (0.8)	0	4 (0.8)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	2 (0.8)	0	0	2 (0.4)
CLOPIDOGREL	1 (0.4)	0	0	1 (0.2)
CLOPIDOGREL BESYLATE	1 (0.4)	0	0	1 (0.2)
PROTON PUMP INHIBITORS	2 (0.8)	0	0	2 (0.4)
ESOMEPRAZOLE	1 (0.4)	0	0	1 (0.2)
LANSOPRAZOLE	1 (0.4)	0	0	1 (0.2)
GLUCOCORTICOIDS	0	1 (0.8)	0	1 (0.2)
METHYLPREDNISOLONE	0	1 (0.8)	0	1 (0.2)

ATC=Anatomical Therapeutic Classification.
Prohibited medications are defined in the protocol. Concomitant medications for Transition Period are those with start dates prior to Day 1 of the Transition Period and continuing after Day 1 of the Transition Period or with start dates on or after Day 1 of the Transition Period. Only clinically significant prohibited medications are included but these are not considered as an intercurrent event.
Subjects may have more than one medication per ATC level 4 category and preferred term.
At each level of subject summarization, a subject is counted once if the subject reported one or more medications. Medications with missing ATC level 4 terms are summarized using the highest level term that is available.
Prohibited concomitant medications were coded with the WHO Drug Version B-3 dictionary dated September, 2021.
Source Data: Listing 16.2.4.3 and report of prohibited medication.

Co-administration of Calcium and Vitamin D

Table 33: Vitamin D and calcium supplementation – Main treatment period safety analysis set

Supplement: Vitamin D

Visit	MB09 (N=277) n (%)	Prolia (N=278) n (%)	Total (N=555) n (%)
Baseline			
Number of subjects at this visit	277	278	555
Subjects reporting Vitamin D was taken?[1]	276 (99.6)	277 (99.6)	553 (99.6)
Day 11			
Number of subjects at this visit	276	278	554
Subjects reporting Vitamin D was taken?[1]	276 (100.0)	277 (99.6)	553 (99.8)
Month 1			
Number of subjects at this visit	275	277	552
Subjects reporting Vitamin D was taken?[1]	275 (100.0)	275 (99.3)	550 (99.6)
Month 3			
Number of subjects at this visit	273	276	549
Subjects reporting Vitamin D was taken?[1]	273 (100.0)	276 (100.0)	549 (100.0)
Month 6			
Number of subjects at this visit	271	271	542
Subjects reporting Vitamin D was taken?[1]	271 (100.0)	270 (99.6)	541 (99.8)
Month 9			
Number of subjects at this visit	259	264	523
Subjects reporting Vitamin D was taken?[1]	258 (99.6)	264 (100.0)	522 (99.8)
Month 12 EOT			
Number of subjects at this visit	256	262	518
Subjects reporting Vitamin D was taken?[1]	256 (100.0)	260 (99.2)	516 (99.6)

[1] Percentages are based on the number of subjects at the corresponding visit.
Source Data: Listings 16.2.5.2, 16.2.5.3

Table 14.1.10.1
Vitamin D and Calcium Supplementation – Main Treatment Period
Safety Analysis Set

Supplement: Calcium

Visit	MB09 (N=277) n (%)	Prolia (N=278) n (%)	Total (N=555) n (%)
Baseline			
Number of subjects at this visit	277	278	555
Subjects reporting Calcium was taken? [1]	277 (100.0)	278 (100.0)	555 (100.0)
Day 11			
Number of subjects at this visit	276	278	554
Subjects reporting Calcium was taken? [1]	276 (100.0)	278 (100.0)	554 (100.0)
Month 1			
Number of subjects at this visit	275	277	552
Subjects reporting Calcium was taken? [1]	275 (100.0)	276 (99.6)	551 (99.8)
Month 3			
Number of subjects at this visit	273	276	549
Subjects reporting Calcium was taken? [1]	272 (99.6)	276 (100.0)	548 (99.8)
Month 6			
Number of subjects at this visit	271	271	542
Subjects reporting Calcium was taken? [1]	271 (100.0)	269 (99.3)	540 (99.6)
Month 9			
Number of subjects at this visit	259	264	523
Subjects reporting Calcium was taken? [1]	258 (99.6)	263 (99.6)	521 (99.6)
Month 12 EOT			
Number of subjects at this visit	256	262	518
Subjects reporting Calcium was taken? [1]	256 (100.0)	259 (98.9)	515 (99.4)

[1] Percentages are based on the number of subjects at the corresponding visit.
Source Data: Listings 16.2.5.2, 16.2.5.3

Table 34: Intake of vitamin D and calcium supplementation – Transition period safety analysis set for transition period

Supplement: Vitamin D

Visit	Prolia => MB09 (N=130) n (%)	Prolia => Prolia (N=123) n (%)	Total (N=253) n (%)
Month 12 EOT			
Number of subjects with available data	130	122	252
Subjects reporting Vitamin D was taken?[1]	130 (100.0)	122 (100.0)	252 (100.0)
TP Day 11			
Number of subjects with available data	129	120	249
Subjects reporting Vitamin D was taken?[1]	129 (100.0)	120 (100.0)	249 (100.0)
TP Month 1			
Number of subjects with available data	129	118	247
Subjects reporting Vitamin D was taken?[1]	129 (100.0)	118 (100.0)	247 (100.0)
TP Month 3			
Number of subjects with available data	129	120	249
Subjects reporting Vitamin D was taken?[1]	129 (100.0)	120 (100.0)	249 (100.0)
TP Month 6 EOS			
Number of subjects with available data	127	119	246
Subjects reporting Vitamin D was taken?[1]	127 (100.0)	119 (100.0)	246 (100.0)

[1] Percentages are based on the number of subjects with available data at that visit.
Source Data: Listing 16.2.5.2, 16.2.5.3

Supplement: Calcium

Visit	Prolia => MB09 (N=130) n (%)	Prolia => Prolia (N=123) n (%)	Total (N=253) n (%)
Month 12 EOT			
Number of subjects with available data	129	121	250
Subjects reporting Calcium was taken? [1]	129 (100.0)	121 (100.0)	250 (100.0)
TP Day 11			
Number of subjects with available data	128	120	248
Subjects reporting Calcium was taken? [1]	128 (100.0)	120 (100.0)	248 (100.0)
TP Month 1			
Number of subjects with available data	128	118	246
Subjects reporting Calcium was taken? [1]	128 (100.0)	118 (100.0)	246 (100.0)
TP Month 3			
Number of subjects with available data	128	120	248
Subjects reporting Calcium was taken? [1]	128 (100.0)	120 (100.0)	248 (100.0)
TP Month 6 EOS			
Number of subjects with available data	126	119	245
Subjects reporting Calcium was taken? [1]	126 (100.0)	119 (100.0)	245 (100.0)

[1] Percentages are based on the number of subjects with available data at that visit.
Source Data: Listing 16.2.5.2, 16.2.5.3

Numbers analysed

Table 35: Numbers of subjects in each analysis set (all randomised analysis set)

	MB09 (N=281) n (%)	Prolia (N=277) n (%)	Total (N=558) n (%)
All Enrolled Analysis Set[1]			1383
All Randomised Analysis Set[2]	281	277	558 (40.3)
SAF[3]	277	278	555
FAS[3]	278 (98.9)	277 (100.0)	555 (99.5)
mFAS[4]	258 (91.8)	266 (96.0)	524 (93.9)
PKCS[5]	277 (100.0)	278 (100.0)	555 (100.0)
PKPS[6]	269 (97.1)	274 (98.6)	543 (97.8)

Abbreviations: FAS, Full Analysis Set; ICE, intercurrent event; ICF, informed consent form; mFAS, modified Full Analysis Set; PK, pharmacokinetics; PKCS, Pharmacokinetics Concentration Set; PKPS, Pharmacokinetics Parameter Set; SAF, Safety Analysis Set.

Note: Counts were presented according to treatment as randomised except for the SAF, PKCS, and PKPS where counts were presented according to the treatment received.

1 All subjects who signed an ICF. The original subject identification numbers for subjects rescreened were not included.

2 All randomised subjects. The N is used for percentage calculation of mFAS. The total in All Randomised Analysis Set is the percentage of All Enrolled Analysis Set.

3 All randomised subjects who received at least one dose of the study treatment. The SAF uses actual treatment and FAS uses planned treatment.

4 All (consenting) randomised eligible subjects who received at least one dose of study treatment, modified at observation level to exclude data after the first occurrence of those ICEs where a hypothetical strategy was taken (eg, missing a dose, errors or deviations in dosing, or receipt of any prohibited therapies or other osteoporosis medication).

5 All subjects in the SAF, excluding observations after relevant ICEs which impact PK (eg, missing a dose, errors or deviations in dosing, or receipt of other therapies which also contain denosumab).

6 All subjects who had at least 3 measurable concentrations in PKCS including on Day 11.

Source: Table 14.1.1.1.

Table 36: Numbers of subjects in each analysis set – Transition period (full analysis set for transition period)

	MB09-MB09 (N=245) n (%)	Prolia-MB09 (N=130) n (%)	Prolia-Prolia (N=122) n (%)	Total (N=497) n (%)
FAS-TP	245 (100)	130 (100)	122 (100)	497 (100)
mFAS-TP	233 (95.1)	127 (97.7)	121 (99.2)	481 (96.8)
SAF-TP	244 (100)	130 (100)	123 (100)	497 (100)
PKCS-TP	244 (100)	130 (100)	123 (100)	497 (100)
PKPS-TP	228 (93.4)	126 (96.9)	111 (90.2)	465 (93.6)

Abbreviations: FAS-TP, Full Analysis Set for Transition Period; mFAS-TP, modified Full Analysis Set for Transition Period; PKCS-TP, Pharmacokinetic Concentration Set for Transition Period; PKPS-TP, Pharmacokinetic Parameter Set for Transition Period; SAF-TP, Safety Analysis Set for Transition Period.

Note: Counts were presented according to treatment as randomised except for the SAF-TP, PKCS-TP, and PKPS-TP where counts were presented according to the treatment received. Subject RS001106 was not dosed per the randomisation schedule. This was handled as an intercurrent event.

Source: Table 14.1.1.2.

Major Protocol Deviations

Table 37: Major protocol deviations – Main treatment period (full analysis set)

Deviation type	MB09 (N=278) n (%)	Prolia (N=277) n (%)	Total (N=555) n (%)
Subjects with at least one major protocol deviation	20 (7.2)	11 (4.0)	31 (5.6)
Exclusion criteria	14 (5.0)	7 (2.5)	21 (3.8)
Inclusion criteria	6 (2.2)	5 (1.8)	11 (2.0)

Note: A major deviation was defined as leading to exclusion of the entire subject from the modified Full Analysis Set.

Source: Table 14.1.3.1.

Table 38: Major protocol deviations – Transition period (full analysis set for transition period)

Deviation type	MB09-MB09 (N=245) n (%)	Prolia-MB09 (N=130) n (%)	Prolia-Prolia (N=122) n (%)	Total (N=497) n (%)
Subjects with at least one major protocol deviation	12 (4.9)	3 (2.3)	1 (0.8)	16 (3.2)
Exclusion criteria	11 (4.5)	3 (2.3)	0	14 (2.8)
Inclusion criteria	1 (0.4)	0	1 (0.8)	2 (0.4)

Note: A major deviation was defined as leading to exclusion of the entire subject from the modified Full Analysis Set- Transition Period. There were no major protocol deviations related to eligibility in the Transition Period.

Source: Table 14.1.3.2.

Table 39: Distribution of ICEs and assessment delays in the main treatment period (full analysis set)

	MB09 (N=278) n (%)	Prolia (N=277) n (%)	Total (N=555) n (%)
ICE1: Discontinuation of study treatment due to any reason (ie, Month 6 dose not taken)	21 (7.6)	14 (5.1)	35 (6.3)
ICE2a: Errors or deviations in dosing on Day 1	1 (0.4)	0	1 (0.2)
ICE2b: Errors or deviations in dosing at Month 6	2 (0.7)	2 (0.7)	4 (0.7)
ICE3: Administration of prohibited therapies or other osteoporosis medication	4 (1.4)	1 (0.4)	5 (0.9)
BMD assessment delay:			
Month 6 assessment >181+28 days after the first dose	10 (3.6)	4 (1.4)	14 (2.5)
Month 12 assessment >365+28 days after the first dose	1 (0.4)	1 (0.4)	2 (0.4)

Abbreviations: ADA, antidrug antibody; BMD, bone mineral density; ICE, intercurrent event.

Note: This table presents the number of subjects who had the ICE or an assessment delay. Other ICEs (formation of ADAs and changes in the use of vitamin D and calcium supplementation) were not considered here as a treatment policy strategy was used for these ICEs in all estimands. No deaths occurred during the Main Treatment Period of the study.

Source: Table 14.1.12.2.

Outcomes and estimation

Primary Efficacy Endpoint - Difference in means in %CfB in lumbar spine BMD after 52 weeks

Table 40: Main estimation of primary estimated 1a by MMRM: Difference in means in %CfB in lumbar spine BMD at Month 12 (modified full analysis set)

Analysis of %CfB in Lumbar Spine BMD at Month 12	MB09 (N=258)	Prolia (N=266)
n	233	250
LS mean %CfB[1]	5.47	5.27
LS mean %CfB[2]	5.86	5.66
LS mean difference (MB09 − Prolia)[3]	0.20	
95% CI[4]	−0.51, 0.91	

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; LS, least square; MMRM, mixed model for repeated measures; SC, subcutaneous.

Note: MMRM model included terms for visit by treatment; baseline BMD (g/cm^2) at the lumbar spine (as a covariate); and classification variables for age, BMI, and prior use of bisphosphonates. Subject was included as a random effect.

1 Using equal weights for the strata.

2 Using weights for the strata as per representation in data (using SAS OM option).

3 Estimate of primary estimand 1a: Difference in means (MB09 − Prolia) in composite endpoint of %CfB in lumbar spine BMD after 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received two denosumab doses without any errors or deviations in dosing and without the receipt of any prohibited therapies or other osteoporosis medications.

4 Therapeutic equivalence was demonstrated if 95% CI at Month 12 was entirely within the predefined margins of [−1.45%, 1.45%].

Source: Table 14.2.1.2.1.

Secondary Efficacy Endpoints

Table 41: Summary of estimation of estimand 2a: Difference in means in %CfB in lumbar spine BMD at Month 6 (modified full analysis set)

	LS Mean[1]		LS Mean Difference (MB09 – Prolia)	
MMRM analysis of %CfB in Lumbar Spine BMD at Month 6	**MB09 (N=258)**	**Prolia (N=266)**	**Estimate[2]**	**95% CI**
(a) Main analysis (without imputation)	n=246	n=258		
	4.03	3.96	0.07	(−0.55, 0.69)
(b) Sensitivity analysis (MI)	4.04	3.94	0.10	(−0.52, 0.72)

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; CI, confidence interval; LS, least square; MI, multiple imputation; MMRM, mixed model for repeated measures; SC, subcutaneous.

1 Using weights for the strata as per representation in data (using SAS OM option).

2 Estimate of estimand 2a: Difference in means (MB09 − Prolia) in composite endpoint of %CfB in lumbar spine BMD after 6 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received denosumab without any errors or deviations in dosing and without the receipt of any prohibited therapies or other osteoporosis medications.

Source: (a) Table 14.2.1.2.1; (b) Table 14.2.1.3.1.

Table 42: Estimation of secondary estimands 3a and 3b: Difference in means in %CfB in hip BMD at Months 6 and 12

	n		LS Mean[1]		LS Mean Difference (MB09 – Prolia)	
Analysis of %CfB in Hip BMD	**MB09**	**Prolia**	**MB09**	**Prolia**	**Estimate[2,3]**	**95% CI**
(a) Estimand 3a (MMRM on mFAS)	(N=258)	(N=266)				
Month 6	241	257	2.29	2.46	-0.17	(−0.61, 0.27)
Month 12	232	252	3.37	3.28	0.10	(−0.39, 0.59)
(b) Estimand 3b (ANCOVA on FAS)	(N=278)	(N=277)				
Month 6	262	270	2.28	2.49	−0.21	(−0.65, 0.22)
Month 12	254	260	3.31	3.27	0.03	(−0.45, 0.51)

Abbreviations: %CfB, percentage change from baseline; ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval; FAS, Full Analysis Set; LS, least square; mFAS, modified Full Analysis Set; MMRM, mixed model for repeated measures; SC, subcutaneous.

1 Using weights for the strata as per representation in data (using SAS OM option).

2 Estimate of secondary estimand 3a: Difference in means (MB09-Prolia) in composite endpoint of %CfB in hip BMD after 6 and 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without the receipt of any prohibited therapies or other osteoporosis medications.

3 Estimate for secondary estimand 3b: Difference in means (MB09-Prolia) in composite endpoint of %CfB in hip BMD after 6 and 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing, and whether any prohibited therapies or other osteoporosis medications were taken.

Source: (a) Table 14.2.3.1.1; (b) Table 14.2.3.2.1.

Table 43: Estimation of secondary estimands 4a and 4: Difference in means in %CfB in femur neck BMD at Months 6 and 12

Analysis of %CfB in Femur Neck BMD	n		LS Mean[1]		LS Mean Difference (MB09 – Prolia)	
	MB09	Prolia	MB09	Prolia	Estimate[2,3]	95% CI
(a) Estimand 4a (MMRM on mFAS)	(N=258)	(N=266)				
Month 6	241	257	2.18	1.93	0.25	(−0.35, 0.86)
Month 12	232	252	2.75	2.39	0.36	(−0.28, 1.00)
(b) Estimand 4b (ANCOVA in FAS)	(N=278)	(N=277)				
Month 6	262	270	2.18	1.92	0.26	(−0.32, 0.84)
Month 12	254	260	2.70	2.38	0.32	(−0.31, 0.95)

Abbreviations: %CfB, percentage change from baseline; ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval; FAS, Full Analysis Set; LS, least squares; mFAS, modified Full Analysis Set; MMRM, mixed model for repeated measures; SC, subcutaneous.

1 Using weights for the strata as per representation in data (using SAS OM option).

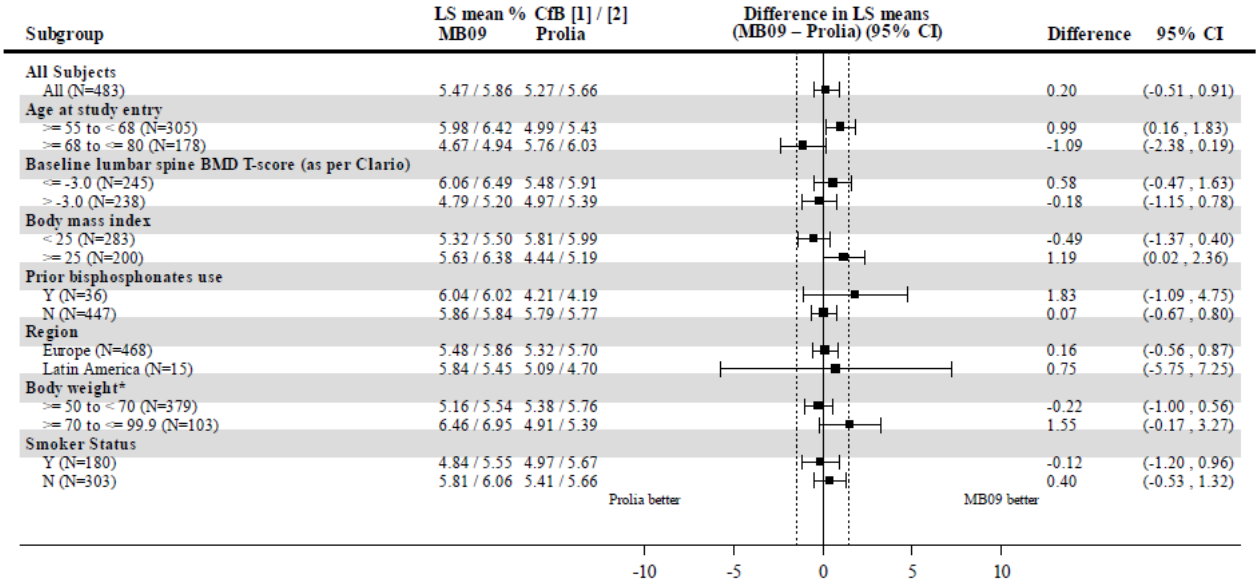
2 Estimate of secondary estimand 4a: Difference in means (MB09−Prolia) in composite endpoint of %CfB in femur neck BMD after 6 and 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without the receipt of any prohibited therapies or other osteoporosis medications.

3 Estimate for secondary estimand 4b: Difference in means (MB09−Prolia) in composite endpoint of %CfB in femur neck BMD after 6 and 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing, and whether any prohibited therapies or other osteoporosis medications were taken.

Source: (a) Table 14.2.4.1.1; (b) Table 14.2.4.2.1.

Subgroup analyses

Figure 6-1 Forest Plot of Difference in Means in %CfB in Lumbar Spine BMD at Month 12 (Primary Estimand 1a) in Predefined Subgroups (Modified Full Analysis Set)



Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; LS, least square; MMRM, mixed model for repeated measures; SC, subcutaneous.

Note 1: N is the number of subjects with data available for analysis at 12 months.

Note 2: The MMRM model included terms for visit by treatment, baseline BMD at the lumbar spine (as a covariate), and classification variables for: age, BMI, and prior use of bisphosphonates. Subject was included as a random effect.

Note 3: There were two subjects whose weight at baseline decreased to below 50 kg but had weight >50 kg at screening; these subjects were not included in the respective subgroup analysis.

Note 4: Dashed lines at −1.45 and 1.45 are reference lines for the equivalence margins at Month 12.

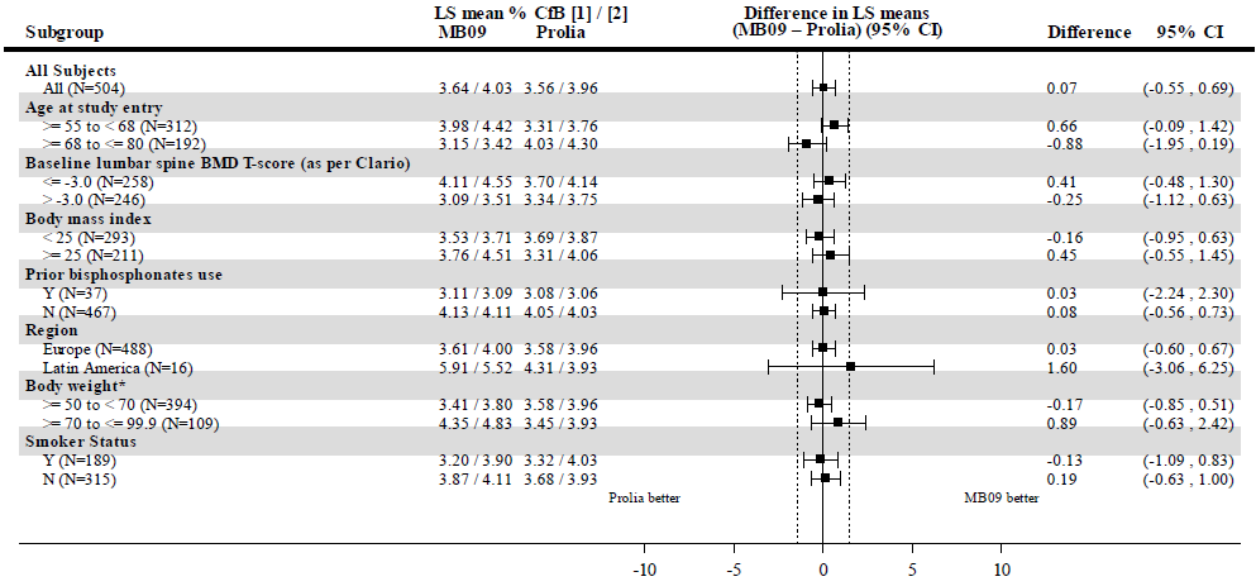
[1] Using equal weights for the strata.

[2] Using weights for the strata as per representation in data (using SAS OM option).

[3] Subgroups applied to estimand 1a: Difference in means (MB09 − Prolia) in composite endpoint of %CfB in lumbar spine BMD (g/cm^2) after 12 months (where %CfB of zero was taken for anyone who died) in postmenopausal women with osteoporosis treated with SC denosumab injections every 6 months assuming that all women received two denosumab doses without any errors or deviations in dosing and without the receipt of any prohibited therapies or other osteoporosis medications.

Source: Figure 14.2.1.1.

Figure 6-2 Forest Plot of Difference in Means in %CfB in Lumbar Spine BMD at Month 6 (Primary Estimand 2a) in Predefined Subgroups (Modified Full Analysis Set)



Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; LS, least square; MMRM, mixed model for repeated measures.

Note 1: N is the number of subjects with data available for analysis at 6 months.

Note 2: The MMRM model included terms for visit by treatment, baseline BMD (g/cm^2) at the lumbar spine (as a covariate), and classification variables for: age, BMI, and prior use of bisphosphonates. Subject was included as a random effect.

Note 3: There were two subjects whose weight at baseline decreased to below 50 kg but had weight >50 kg at screening; these subjects were not included in the respective subgroup analysis.

Note 4: Dashed lines at −1.45 and 1.45 are reference lines.

[1] Using equal weights for the strata.

[2] Using weights for the strata as per representation in data (using SAS OM option).

Source: Figure 14.2.2.1.

Ancillary analyses

N/A

2.5.5.3. 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 44: Summary of efficacy for trial MB09-C-01-19

Title: A Randomised, Double-Blind, Parallel, Multicentre, Multinational Study to Compare the Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Immunogenicity of MB09 (Proposed Denosumab Biosimilar) Versus Prolia® (EU-sourced) in Postmenopausal Women with Osteoporosis (SIMBA Study)			
Study identifier	Study code: MB09-C-01-19 EudraCT: 2021-003609-24		
Design	Randomised, double-blind, parallel, multi-centre, fixed-dose response		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 6 months
Hypothesis	Equivalence		
Treatments groups	MB09-MB09		MB09 60 mg/mL, one 60 mg dose on Day 1, Month 6 and at Month 12, 281 subjects randomised
	Prolia-MB09		Prolia 60 mg/mL, one 60 mg dose on Day 1 and at Month 6 MB09 60 mg/mL, one 60 mg dose at Month 12 140 subjects randomised
	Prolia-Prolia		Prolia 60 mg/mL, one 60 mg dose on Day 1, Month 6 and at Month 12, 137 subjects randomised
Endpoints and definitions	Primary endpoint	%CfB in lumbar spine BMD-m12	Percentage of change from baseline in lumbar spine bone mineral density (BMD) after 52 weeks
	Secondary endpoints	%CfB in lumbar spine BMD-m6	Percentage of change from baseline in lumbar spine BMD after 6 months
		%CfB in hip BMD-m6	Percentage of change from baseline in hip BMD after 6 months
		%CfB in femur neck BMD-m6	Percentage of change from baseline in femur neck BMD after 6 months
		%CfB in hip BMD-m12	Percentage of change from baseline in hip BMD after 12 months
		%CfB in femur neck BMD-m12	Percentage of change from baseline in femur neck BMD after 12 months
Final Database lock	26 June 2024		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Modified Full Analysis Set, Month 12 or Month 6** *The modified FAS (mFAS) consisted of the subset of subjects in FAS (all consenting randomised subjects who received at least one dose of study treatment) who met all eligibility criteria. The mFAS term defined a set at the data point level which included a data record at each timepoint for all eligible subjects in the FAS but excluded data observed after the first occurrence of those intercurrent events where a hypothetical strategy was taken (e.g., missing a dose, errors or deviations in dosing, or receipt of any prohibited therapies or other osteoporosis medication)*		
Descriptive statistics and estimate variability	**Treatment group**	**MB09**	**Prolia**
	Number of subjects	233	250
	%CfB in lumbar spine BMD-m12 LS mean	5.47	5.27
	Variability statistic	NA	NA
	%CfB in lumbar spine BMD-m6 LS mean	4.03 (N=246)	3.96 (N=258)
	Variability statistic	NA	NA
	%CfB in hip BMD-m6 LS means	2.29 (N=241)	2.46 (N=257)
	Variability statistic	NA	NA
	%CfB in femur neck BMD-m6 LS means	2.18 (N=241)	1.93 (N=257)
	Variability statistic	NA	NA
	%CfB in hip BMD-m12 LS means	3.37 (N=232)	3.28 (N=252)
	Variability statistic	NA	NA
	%CfB in femur neck BMD-m12 LS means	2.75 (N=232)	2.39 (N=252)
	Variability statistic	NA	NA

Effect estimate per comparison	Primary endpoint: %CfB in lumbar spine BMD-m12	Comparison groups	MB09 - Prolia
		LS mean difference	0.20
		95% CI	-0.51, 0.91
		P-value	NA
	Secondary endpoint: %CfB in lumbar spine BMD-m6	Comparison groups	MB09 - Prolia
		LS mean difference	0.07
		95% CI	-0.55, 0.69
		P-value	NA
	Secondary endpoint: %CfB in hip BMD-m6	Comparison groups	MB09 - Prolia
		LS mean difference	-0.17
		95% CI	-0.61, 0.27
		P-value	NA
	Secondary endpoint: %CfB in femur neck BMD-m6	Comparison groups	MB09 - Prolia
		LS mean difference	0.25
		95% CI	-0.35, 0.86
		P-value	NA
	Secondary endpoint: %CfB in hip BMD-m12	Comparison groups	MB09 - Prolia
		LS mean difference	0.10
		95% CI	-0.39, 0.59
		P-value	NA
	Secondary endpoint: %CfB in femur neck BMD-m12 LS means	Comparison groups	MB09 - Prolia
		LS mean difference	0.36
		95% CI	-0.28, 1.00
		P-value	NA

<table>
<tr><td>Notes</td><td colspan="3">Therapeutic equivalence was demonstrated in all endpoints since the 95% CIs fell entirely within the predefined margins of [-1.45%, 1.45%].

For the primary efficacy analysis, a mixed model for repeated measures (MMRM) was fitted to the composite %CfB lumbar spine BMD at Month 6 and Month 12 on the mFAS.

A total of 61 subjects (10.9%) discontinued the study after receiving one or two doses during the Main Treatment Period: 36 subjects (12.8%) in the MB09 group and 25 subjects (9.0%) in the Prolia group. Reasons for discontinuation from the study during the Main Treatment Period were balanced between MB09 and Prolia groups, and included the following categories: other (39 subjects [7.0%], including 30 subjects who withdrew consent, 7 subjects who discontinued the study per investigator’s decision, and 2 subjects randomised in error), subject dosed in error and did not meet the eligibility criteria (12 subjects [2.2%]), adverse events (4 subjects [0.7%]), lost to follow-up (3 subjects [0.5%]), protocol violation (2 subjects [0.4%]), and unrelated medical conditions (1 subject [0.2%]).

A total of 497 subjects (89.1%) entered the Transition Period to receive the third dose of the study treatment: 245 subjects in the MB09-MB09 arm; 130 subjects in the Prolia-MB09 arm; and 122 subjects in the Prolia-Prolia arm. Of the 497 subjects, 12 subjects (2.4%) discontinued the study: 6 subjects (2.4%) in the MB09-MB09 arm, 3 subjects (2.3%) in the Prolia-MB09 arm, and 3 subjects (2.5%) in the Prolia-Prolia arm. Reasons for discontinuation from the study were balanced between the treatment arms and included the following categories: other (10 subjects [2.0%], including 9 subjects who withdrew consent and 1 subject who left the country and could not return for study visits), death (1 subject [0.2%]), and burden of study procedures (1 subject [0.2%]).</td></tr>
<tr><td>Analysis description</td><td colspan="3">Other: Sensitivity analysis for primary endpoint</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">mFAS (see above description), Month 12

Multiple imputation (MI) data set produced under missing at random (MAR) was applied to the mFAS; “sensitivity using tipping point” assessed the robustness of results in both of the one-sided hypotheses by adding penalties in both directions to all missing data.</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>MB09</td><td>Prolia</td></tr>
<tr><td>Number of subjects</td><td>258</td><td>266</td></tr>
<tr><td>%CfB in lumbar spine BMD-m12 (MI)

LS mean</td><td>5.83</td><td>5.63</td></tr>
<tr><td>Variability statistic</td><td>NA</td><td>NA</td></tr>
<tr><td rowspan="4">Effect estimate per comparison</td><td rowspan="4">%CfB in lumbar spine BMD-m12 (MI)</td><td>Comparison groups</td><td>MB09 - Prolia</td></tr>
<tr><td>LS mean difference</td><td>0.20</td></tr>
<tr><td>95% CI</td><td>-0.51, 0.90</td></tr>
<tr><td>P-value</td><td>NA</td></tr>
<tr><td>Notes</td><td colspan="3">Therapeutic equivalence was demonstrated since 95% CI fell entirely within the predefined margins of [-1.45%, 1.45%].

Tipping Point Sensitivity analysis (MI+ANCOVA) also showed therapeutic equivalence (data not shown).</td></tr>
</table>

Analysis description	**Other: Supportive analysis for primary endpoint (difference in LS means after MI using treatment-failure penalty)** (pre-specified)		
Analysis population and time point description	FAS (see definition above), Month 12		
Descriptive statistics and estimate variability	**Treatment group**	**MB09**	**Prolia**
	Number of subjects	278	277
	%CfB lumbar spine BMD-m12 (MI + treatment-failure) LS mean	5.40	5.38
	Variability statistic	NA	NA
Effect estimate per comparison	%CfB lumbar spine BMD-m12(MI + treatment-failure)	Comparison groups	MB09 - Prolia
		LS mean difference	0.03
		95% CI	-0.69, 0.74
		P-value	NA
Notes	Therapeutic equivalence was demonstrated since 95% CI fell entirely within the predefined margins of [-1.45%, 1.45%]. A MI with treatment-failure penalty + ANCOVA was used for this analysis.		

Note: Subgroup analysis of the primary endpoint by age at study entry, baseline lumbar spine BMD T-score, body mass index, prior bisphosphonate use, region, body weight, or smoking status showed that the LS mean differences in %CfB in lumbar spine BMD between MB09 and Prolia at Month 12 were small and consistent with the overall estimate, with the lower limit of 95% CI above -1.45 for most subgroups (data not shown).

%CfB: percentage change from baseline, ANCOVA: analysis of covariance, BMD: bone mineral density, CI: confidence interval, FAS: full analysis set, LS: least squares, m6: month 6, m12: month 12, MAR: missing at random, mFAS: modified full analysis set, MI: multiple imputation, MMRM: mixed model for repeated measures, NA: not applicable.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data was generated in one Phase III study (Study MB09-C-01-19) in postmenopausal women with osteoporosis (PMO). Study MB09-C-01-1 was a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety, and immunogenicity of MB09 vs. EU-Prolia in women with PMO.

MB09-C-01-19 study design

The study consists of two periods; the Main Treatment period (Day 1 to Month 12) during which patients received 2 injections of either MB09 or Prolia at 6-month intervals (Day 1 and Month 6); and a Transition/Safety Follow-Up Period (Month 12 to Month 18) during which patients received an additional dose). Patients who received MB09 in the Main study period, received either an additional dose of MB09 or

Prolia in the Transition period; and patients who received EU-Prolia in the Main study period, received one additional dose of EU-Prolia in the Transition period. The duration of the Main Treatment Period of 12 months is considered appropriate for the evaluation of efficacy based on the percent change from baseline in lumbar spine BMD at Week 52 (primary efficacy endpoint).

The duration of the Transition period is another 6 months, and allows assessment of switching from Prolia to MB09, but also provides additional PK, PD, efficacy and safety data for those patients who continue on the same treatment as initially assigned. The overall study design is deemed acceptable.

Study population: Female patients with postmenopausal osteoporosis (PMO) are considered the most sensitive population with respect to the approved indications.

Inclusion & Exclusion Criteria

Subjects were to have absolute BMD consistent with T-score ≤-2.5 and ≥-4 at the lumbar spine or total hip as measured by DXA during the Screening Period with at least two intact, nonfractured vertebrae in the L1 to L4 region (vertebrae were to be assessed by central reading of lateral spine X-ray during the Screening Period) and at least one hip joint evaluable by DXA. Inclusion of postmenopausal women with a T-score of ≤-2.5 is in line with the state of art definition and WHO criteria of osteoporosis. The exclusion of patients with T-score ≥-4.0 is also endorsed to reduce inter-subject variability of PMO patients. Lower and upper body weight limits (≥50 kg and ≤99.9 kg) have been set as discussed during scientific advice procedure "EMEA/H/SA/4356/1/2019/II": it was suggested to enhance the homogeneity of the study population furthermore by setting the lower and upper weight limits in the inclusion criteria and/or stratify the study according to body weight. Thus, setting of weight limits is endorsed.

In addition, it is known that baseline BMD relates to age and the 10-year probability of major osteoporotic fractures starts to increase more rapidly after the age of about 65 years. In this regard, the set age range of and age limits ≥55 and ≤80 years may introduce heterogeneity in disease severity and, therefore, stratification for age was recommended. This was followed, which is endorsed.

Medication used prior to the study may have long-term effects on bone metabolism (e.g., bisphosphonates, fluoride, or strontium). Inclusion of patients with prior bisphosphonate use, whether parenteral or oral, is expected to cause heterogeneity in the study population as the inhibition of bone turnover lasts for several years after cessation of bisphosphonates. However, prior bisphosphonates therapy (Yes vs. No) was used as stratification variable in the randomisation and was adjusted for in the statistical analyses.

Overall, the inclusion and exclusion criteria are considered acceptable.

Trial intervention

During the Main Treatment Period, patients received 60 mg of either MB09 or EU-Prolia on Day 1 and at Month 6 as s.c. injections in the upper arm, upper thigh, or abdomen. A third dose of either 60 mg MB09 or EU-Prolia was administered at the beginning of the Transition/Safety Follow-up Period at Month 12. This is in line with 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. [Prolia SmPC, 2023].

The reference medicinal product Prolia is a medicinal product authorised in the EEA. This is endorsed.

Concomitant Therapies

Prohibited concomitant medication and accepted washout periods have been described in the study protocol and were part of the exclusion criteria of study MB09-C-01-19. Any concomitant medication deemed necessary for the welfare of the subject during the study could be given at the discretion of the investigator. Listed prohibited concomitant medications are considered appropriate and, therefore, acceptable.

All subjects received daily supplementation of at least 1000 mg elemental calcium, which is in line with recommendations in Prolia SmPC.

Study assessment

Dual-energy X-ray absorptiometry (DXA)

For the assessment of BMD in the lumbar spine (vertebrae L1 to L4), DXA scans have been performed at Screening, at Day 182 ± 10 Days (Month 6), and Day 365 ± 10 Days (Month 12, EOT) during the Main Treatment Period. No scan was scheduled during Transition/Safety Follow-Up Period.

The densitometric response to denosumab is individually variable, with a consequent low signal/noise ratio for BMD. In good responders to denosumab, some change in BMD can be seen already at 6 months, though BMD continues to increase in many patients up to 2 years. On the other hand, in poor responders, no change is seen, or the increase in BMD starts only after 1 year (Laroche, M., Baradat, C., Ruyssen-Witrand, A. et al. Rheumatol Int (2018) 38: 461. https://doi.org/10.1007/s00296-018-3929-0). Differences in therapeutic response to the biosimilar vs. originator cannot be reliably assessed at 6 months after the onset of treatment. Therefore, the follow-up after the onset of treatment of one year for evaluation of the primary endpoint, %CFB LS BMD, and the secondary BMD endpoints, %CFB in hip and femur neck BMD is acceptable, as a minimum evaluation timespan. However, an additional timepoint at EOS (M18) would have been appreciated to follow the development of BMD increase further.

The applicant states that the efficacy analysis was to be based on the adjusted total spine BMD results (if corrections were applied). "Adjusted results" referred to the corrections done retrospectively to the prior lumbar spine BMD results based on imaging at subsequent timepoints as there may have been changes to the vertebrae over time, one or more vertebrae may have become unevaluable due to fracture or degenerative changes, a vertebra may have been excluded due to the anatomy being missed in the scan or an artifact, or due to reasons pertaining to longitudinal drift, cross-calibration, and machine equivalence (scanner upgrades). To assess the changes from baseline to follow-up timepoints, it was necessary to compare the exact same vertebrae from timepoint to timepoint; thus, efficacy analysis was based on the adjusted results, if corrections were applied as follows: To evaluate the calibration stability of each DXA scanner during the study, measurements of a quality control (QC) phantom were collected by the investigative sites. For each scanner, a baseline calibration reference point was established based on the spine phantom QC data collected and the date of the first subject scan on that particular scanner. Furthermore, the QC phantom was to be measured each day, and a study subject was scanned but not less than three days per week for each scanner. Scanners with a CV% outside of normal specifications underwent additional evaluation using cumulative sum (CUSUM) tabular control charts to determine breakpoints in scanner performance. Upon identification of statistically (p-value less than 0.05 for a t-test of mean phantom BMD before and after the break point) and clinically (difference in BMD across the breakpoint greater than 0.5%) significant breakpoints longitudinal correction factors were developed from the QC data and were applied to the subject data collected on the respective DXA scanner. Software upgrades were permitted if the evaluation indicated that there was no impact of the upgrade on BMD results or if the impact could be adequately managed (i.e., original analysis protocols were still available after the software update). Also,

DXA scanner hardware upgrades had to be approved in advance by the central reader in collaboration with the CRO and required phantom cross-calibration. If the mean BMD of a scanner differed by more than 1% from the reference scanner, a cross-calibration correction factor was developed and applied to the subject BMD results from that scanner.

The approach for correction/adjustment of BMD data was discussed in sufficient detail and seems plausible. Therefore, this approach is overall acceptable.

Radiography

An X-ray of the lateral spine was performed at Screening and as required for confirmation of suspected new vertebral fractures throughout the study. Radiographs were assessed by quantitative grading at a central imaging centre. Any new fractures confirmed by the central imaging vendor were recorded as an AE. The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and/or radiology report, surgical report, or discharge summary were included in the subject's individual source documents and were submitted to the central imaging vendor for confirmation of fracture. Description of radiography measurements are acceptable.

Randomisation & Blinding

Enrolled subjects were randomly assigned in a 2:1:1 ratio to one of the 3 arms of the study (Arm 1 - MB09-MB09, administered as SC injection (60 mg/mL) on Day 1 and at Month 6, Arm 2, Prolia-MB09, administered as one SC injection of EU-Prolia on Day 1 and at Month 6, Arm 3 EU-Prolia administered on Day 1 and at Month 6. Permuted block randomisation with block size of 4 was used. The randomisation was stratified by baseline BMD T-score at the lumbar spine (≤-3.0 and >3.0), body mass index (BMI; <25 kg/m2 and ≥25 kg/m2), age at study entry (≥55 to <68 years and ≥68 to ≤80 years), and prior bisphosphonate medication use at study entry (prior use of bisphosphonates and no prior bisphosphonate use), which is considered adequate.

The use of the stratification variables body mass index, age and bisphosphonate medication had been recommended during a scientific advice procedure. In addition, BMD T-score at the lumbar spine was employed as stratification variable, which is considered reasonable. Neither centre nor geographic region is listed as stratification factor, although stratification by geographic region was recommend in a scientific advice procedure. It is unclear, whether stratification was performed on site, which would imply stratification by centre. Anyhow, as there were only few patients from Latin America (15 patients among the 484 patients eligible for the primary analysis of estimand 1a) and all other patients from Europe, this issue is not further pursued.

The study is described as conducted in a double-blind manner. The study was subject- and investigator blinded. However, the study drug was administered by unblinded study site personnel as the study drugs were not identical in visual appearance. The unblinded study site personnel were not involved in any clinical or safety evaluations that were part of the blinded protocol or had other subject contact. Subjects were blinded by using a blindfold, screen, or similar method during the dosing procedure so that the injection syringe was not visible to them. The process of blinding was adequately described and is considered acceptable.

With the initial submission, the applicant stated that the study remained double-blinded until the end of all follow-up procedures and was not to be broken until all final clinical data have been entered into the database, the database was locked and released for final analysis. However, to enable reporting of the Main Treatment Period results, partial unblinding took place after database lock for data up to the end of Month 12 for all subjects (interim database lock date: 19/01/2024). The decision to maintain the blinding of individual subject treatment assignment in the CSR by presenting only cumulative summary results and blinded SAE

narratives was not agreed to and severely hindered the safety assessment. For the final analysis the database was locked on 26 Jun 2024 followed by unblinding of individual subject treatment assignment. The final CSR (Document Version 2.0, dated 30 August 2024) includes the unblinded results of the complete study up to Week 78, i.e., the Main Treatment Period and the Transition/Safety Follow-up Period.

Objectives, endpoints and estimands

Primary objective and endpoint

To demonstrate equivalent efficacy of MB09 vs. EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12, the applicant chose to evaluate **%CFB in lumbar spine BMD** after 52 weeks as single primary efficacy endpoint. Evaluation of this primary efficacy endpoint is acceptable.

The primary estimand 1a is based on hypothetical strategies for the intercurrent events discontinuation of study drug, errors or deviations in dosing and administration of prohibited medications and is thus considered a sensitive approach to detect any differences attributable to the pharmacological action. On the other hand, the supportive estimand 1b applies the treatment policy strategy to these three intercurrent events, reflecting clinical practice. Both, the primary and the supportive estimand, apply the treatment policy strategy to the formation of antidrug antibodies and to the adjustments to calcium and vitamin D. Death was to be handled by the composite strategy but there were not any deaths observed during the main treatment period. The defined estimands are considered adequate.

However, as also discussed in CHMP Scientific Advice procedure EMEA/H/SA/4356/1/2019/II, it would have been preferable to include both mean percent change in lumbar BMD and sCTX 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 sCTX are large and dynamic. Thus, sCTX 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 MB09-C-01-19 would have been more appropriate.

Of note, the area under the inhibition curve from time zero to Month 6 (AUIC0-6months) of percent change from baseline in serum CTX was included as a key secondary PD endpoint. The fact that this parameter has not been defined as a co-primary endpoint for study MB09-C-01-19 by the applicant will be addressed in this assessment by treating the respective results on sCTX as co-primary.

For AUIC0-6months, no estimand was defined. However, the estimand defined for the area under the absolute sCTX values (AUEC0-6months) based on a hypothetical strategy for errors in dosing and administration of prohibited therapy is understood to be equally applicable to AUIC0-6months and was considered its primary estimand for the assessment.

The proposed margin of 1.45 for %CFB in lumbar spine BMD after 52 weeks was derived from a meta-analysis of three historical studies and is narrower than suggested in received Clarification Letter (EMEA/H/SA/4356/1/2019/II), where a margin below 2% was recommended. This is endorsed.

The proposed acceptance range of 80-125% for the PD endpoint AUIC0-6months is based on margins used for conventional bioequivalence analyses without further justification. The acceptance range of 80–125% is not appropriate per se, but as the provided results are considered clear enough to support equivalence, this

issue is not further pursued. Further discussion will be required nevertheless should the confidence interval for the additionally requested analysis of %CfB sCTX lie away from the currently available results.

The secondary efficacy endpoints (%CFB in lumbar spine BMD after 6 months, hip BMD after 6 and 12 months and femur neck BMD after 6 and 12 months) are considered clinically relevant and adequate to support the primary efficacy endpoint. Secondary efficacy endpoints are considered acceptable.

Statistical methods for estimation and sensitivity analysis

The mFAS used for the primary analysis excluded subjects, which were later found to not have fulfilled the eligibility criteria at the time of enrolment. This is acceptable as it approximates the preferable situation, where eligibility criteria were evaluated more strictly at study initiation.

The primary analysis of estimand 1a uses an MMRM on the mFAS, which is considered suitable for targeting a hypothetical strategy for discontinuation of study drug, errors or deviations in dosing and administration of prohibited medications as defined for estimand 1a.

Estimand 1b, based on the treatment policy strategy for all listed intercurrent events, was analysed using an ANCOVA in combination with multiple imputation including a 'treatment failure offset', which is also considered appropriate.

The tipping point analyses performed both for estimand 1a and estimand 1b are considered useful to evaluate the robustness of the results.

The key secondary BMD endpoints were analysed in a similar way as the primary BMD endpoint but using only available data when targeting the treatment policy strategy, which is considered sufficient for secondary analyses.

Sample size appears adequate. The sample size calculation can be followed. A 15% dropout can be considered a reasonable assumption from the planning perspective.

The changes from the protocol-specified analyses are not considered concerning as they were decided before the database lock for Month 12.

Efficacy data and additional analyses

Results

The original version (1.0) of the study protocol for study MB09-C01-19 was amended after study initiation (study initiation date: 16/03/2022, amended protocol version 2.0 dated 07/11/2022). Implemented changes allowed, e.g., subjects that had been discontinued from the study drug due to "dosing despite not meeting the eligibility criteria" to continue in the study if they had osteoporosis and no safety concerns per principal investigator's discretion. "Subject dosed in error and did not meet eligibility criteria" was reason for discontinuation from treatment prior to Month 12 for 13 (2.3% of randomised) patients (MB09 vs. EU-Prolia: 7 (2.5%) vs. 6 (2.2) patients). In addition, there were 31 (5.6%) patients who did not meet the eligibility criteria but were allowed to stay in the study (MB09 vs. EU-Prolia: 20 vs. 11 patients).

The remaining amendments are considered minor and are not assumed to have had an impact on the results. All amendments happened prior to study unblinding.

Participant flow and numbers analysed

Numbers of patients randomised and treated were comparable between treatment groups. Only slightly fewer patients received two doses of study drug (MB09 vs. EU-Prolia: 257 (91.5% of randomised patients) vs. 263 (94.9%) patients). This holds also true for the number of patients that completed Month 6 BMD assessment (264 (94.0%) vs. 270 (97.5%)) and Month 12 BMD assessment (255 (90.7%) vs. 260 93.9%) patients). Moreover, differences between treatment groups are small and do not give reason for concern.

Discontinuations from study during Main Treatment Period were higher in the MB09 than in the EU-Prolia group (36 (12.8%) vs. 25 (9.0%) patients). Main cause was "withdrawal prior to Month 12 (not returning for Month 12 visit) which was also more frequently reported in the MB09 group (24 (8.5%) vs. 15 (5.4%) patients). Discontinuations from study during Transition Period were balanced between MB09-MB09, Prolia-Prolia and Prolia-MB09 groups (6 (2.4%), 3 (2.3%) and 3 (2.5%) patients). Main cause was "withdrawal of consent" which was slightly less frequently reported in the MB09-MB09 group (4 (1.6%), 3 (2.3%) and 3 (2.5%) patients). However, disbalances are considered minor and do not give reason for concern.

Protocol deviations

Regarding major protocol deviations, slightly more patients of the MB09 than of the EU-Prolia group had at least one major protocol deviation (20 (7.2%) vs. 11 (4.0%) patients) during the Main Treatment Period. During the Transition Period, a higher proportion of patients of the MB09-MB09 group had at least one major protocol deviation compared to the Prolia-Prolia and the Prolia-MB09 group (12 (4.9%), 1 (0.8%) and 3 (2.3%) patients, respectively). Per definition, major deviations led to exclusion of the patient from the mFAS, i.e. were related to deviations concerning the eligibility criteria. Differences in numbers are considered acceptable. Furthermore, discrepancies between the IRT (interactive response technology, used to administer the randomisation schedule) and the eCRF/ is a company providing medical imaging services) regarding stratification by baseline lumbar spine BMD T-score, baseline BMI, and prior bisphosphonate medication use at study entry have been reported. Number of patients with stratification discrepancies was low and comparable between treatment groups.

In addition, the frequency of intercurrent events was low and overall comparable between treatment groups during the Main Treatment Period. Most prevalent ICE was 'Discontinuation of study treatment due to any reason (i.e., Month 6 dose not taken) with 21 (7.6%) patients of the MB09 group and 14 (5.1%) patients of the Prolia group. Delays in BMD assessment at Month 6 were slightly higher for the MB09 treatment arm (10 (3.6%) patients) versus the Prolia arm (4 (1.4%) patients) and occurred in low frequency. This is acceptable.

Demographic Data

Overall, the demographics data were well balanced between the MB09 and EU-Prolia group for the Safety Analysis Set of the Main Treatment Period. The mean age for MB09 vs. EU-Prolia was 65.8 vs. 65.9 years. Also, number of participants in the respective age subgroups (≥55 to <68 years and ≥68 to ≤80 years) was evenly distributed between treatment groups. Most patients were "White" (MB09 vs. EU-Prolia: 276 (99.6%) vs. 275 (98.9%) patients), the majority was "Non-Hispanic or Non-Latino". In addition, baseline height, weight, BMI and smoking status were comparable for the patients of both groups. This is also true for demographic data as presented for the mFAS. Overall, demographic data remained well balanced for the Transition Period, with exception of former smokers that were slightly less frequent in the Prolia-Prolia group (MB09-MB09, Prolia-Prolia and Prolia-MB09: 34 (13.9%), 20 (15.4%), and 9 (7.3%) patients). In summary, the demographics indicate that a very balanced population of female patients with a diagnosis of osteoporosis was analysed.

Baseline disease characteristics

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

Medical History

Medical history was overall balanced between treatment groups. However, the frequency of spinal osteoarthritis was lower in the MB09-MB09 and Prolia-Prolia group versus Prolia-MB09 group of the Transition Phase (41 (16.8%) and 19 (15.4%) versus 31 (23.8%) patients). Also, the frequency of osteoarthritis was lower in the MB09-MB09 and Prolia-Prolia group versus Prolia-MB09 group (51 (20.9%) and 24 (19.5%) versus 33 (25.4%)). However, no impact of (spinal) osteoarthritis on the results/endpoints of the Transition Period is expected as these degenerative diseases are primarily a sign of wear and tear of joints and tendons.

Therefore, the rather low number of patients with a medical history of "musculoskeletal and connective tissue disorders" does not indicate a lacking osteoporotic status of the study population.

Furthermore, the minimum of osteoporosis duration was reported as 0.00 years for both treatment groups. This was due to subjects who provided only partial dates of the respective diagnosis (month and/or year). The applicant explained in sufficient detail and there no deemed uncertainties.

Prior Medication

Most common prior medications by drug class were vitamin D and analogues, COVID-19 vaccines and calcium preparations. This is plausible. Bisphosphonates have been used by 38 (6.8%) patients prior to study begin. Remaining medications prior to study begin have been used by at most 1.1% of study participants (total numbers). Therefore, the influence on the biosimilarity exercise is considered negligible even if numbers were maximally imbalanced.

(Prohibited) Concomitant Medication in the Main Treatment Period

Overall use of prohibited concomitant medication in the Main Treatment Period was low, as presented by the applicant. Number of patients with at least one prohibited medication was higher for the MB09 group vs. EU-Prolia group (4 (1.4%) vs. 1 (0.4%) patients) during the Main Treatment Period. During the Transition Period, respective number of patients was slightly higher in the MB09-09 group vs. the Prolia-MB09 group (3 (1.2%) vs. 1 (0.8%) patients). No prohibited medication was reported for the Prolia-Prolia group. In addition to reported prohibited medication, 1 (0.2%) patient received bisphosphonate treatment (ibandronic acid) as a concomitant medication. In contrast to what has been presented in the list of prohibited concomitant medications, proton pump inhibitors have been used by 36 (6.5%) patients. Also, medications from the heparin group have been used (20 (3.6%) patients) that were mentioned in the exclusion criteria. However, given that the total numbers for both treatment groups are rather low, no serious concern is raised.

Co-administration of Calcium and Vitamin D

With few exceptions, all patients received daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D from randomisation until the End of Study visit (Transition Period Month 6). This is in line with recommendations of the Prolia SmPC [Prolia SmPC, 2023]. Number of patients that discontinued co-administration calcium and/or vitamin D were comparable between treatment groups. This is acceptable.

Primary Efficacy Endpoint

For the primary efficacy analysis, the applicant assessed the difference in means in %CFB in lumbar spine BMD (L1 to L4) after 52 weeks by DXA assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications using an MMRM on mFAS (Estimand 1a). The LS mean %CFB in lumbar spine BMD at Week 52 using weights for the strata as per representation in data, was 5.86% for the MB09 treatment group and 5.66% for the EU-Prolia treatment group. The estimated difference between the MB09 and the EU-Prolia group was 0.20% (95% CI: -0.51, 0.91). Thus, the 95% CI was contained within the predefined margin of [-1.45, 1.45], supporting the claim of biosimilarity.

The supplementary analysis of %CFB in lumbar spine BMD, which assessed the treatment effect irrespective of discontinuation of treatment for any reason, errors or deviations in dosing, and whether any prohibited therapies or other osteoporosis medications were taken, gave similar results (estimated difference of 0.03 with 95% CI: -0.69, 0.74).

Subgroup analyses have been performed for %CFB in lumbar spine BMD at Month 12. The presented subgroup analyses gave results consistent with those of the primary analysis. Subgroup analysis by age at study entry, baseline lumbar spine BMD T-score, BMI, prior bisphosphonate use, region, body weight, or smoking status did not demonstrate relevant differences and generally showed that the LS mean differences in %CfB in lumbar spine BMD between MB09 and Prolia at Month 12 were limited. Also, subgroup analyses for AUIC of % change from baseline in s-CTX after the first dose have been provided. Similar to subgroup analyses as presented for %CFB in lumbar spine BMD at Month 12, no relevant differences have been demonstrated. The ratios of geometric means between MB09 and Prolia were shown to be comparable.

As expected, the sensitivity analysis for the primary estimand 1a using multiple imputation before applying the MMRM as defined for the primary analysis gave very similar results as the primary analysis with an estimated difference between the MB09 and the EU-Prolia group of 0.10% (95% CI: -0.52, 0.72). Thus, the results of the sensitivity analysis using MMRM supported the main analysis.

In the tipping point analysis for the primary BMD endpoint, the missing MB09 population would have to have at least -4.5 to -6% less lumbar spine BMD improvement from baseline than the non-missing average population in order to result in non-equivalence. This scenario is considered unlikely given that the primary analysis resulted in an LS mean of 5.85 %CFB in lumbar spine BMD for MB09 and of 5.66 %CFB in the Prolia arm. Thus, the provided tipping point analysis indicates robustness of the primary analysis.

Secondary Efficacy Endpoints

Differences in means (MB09 minus EU-Prolia) of %CFB in lumbar spine BMD after 6 months; hip BMD after 6 and 12 months; femur neck BMD after 6 and 12 months have been assessed as secondary efficacy endpoints.

The LS mean %CFB in lumbar spine BMD at Month 6 was 4.00% for the MB09 treatment group and 3.96% for the EU-Prolia treatment group assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications using weights for the strata as per representation in data (Estimand 2a, MMRM on mFAS). The difference between the MB09 and the EU-Prolia group was 0.07% (95% CI: -0.55, 0.69).

The LS mean %CFB in hip BMD at Month 6 was 2.29% for the MB09 treatment group and 2.46% for the EU-Prolia treatment group assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications (Estimand 3a, MMRM on mFAS). The difference between the MB09 and the EU-Prolia group was -0.17%

(95% CI: -0.61, 0.27). The LS mean %CFB in hip BMD at Month 12 was 3.37% for the MB09 treatment group and 3.28% for the EU-Prolia treatment group. The difference between the MB09 and the EU-Prolia group was 0.10% (95% CI: -0.39, 0.59).

The LS mean %CFB in femur neck BMD at Month 6 was 2.18% for the MB09 treatment group and 1.93% for the EU-Prolia treatment group assuming that all women received scheduled denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications (Estimand 4a, MMRM on mFAS). The difference between the MB09 and the EU-Prolia group was 0.25% (95% CI: -0.35, 0.86). The LS mean %CFB in femur neck BMD at Month 12 was 2.75% for the MB09 treatment group and 2.39% for the EU-Prolia treatment group. The difference between the MB09 and the EU-Prolia group was 0.36% (95% CI: -0.28, 1.00).

For all the parameters (lumbar spine BMD after 6 months; hip BMD after 6 and 12 months; femur neck BMD after 6 and 12 months), the supplementary analyses estimating the treatment effect irrespective of discontinuation of treatment for any reason, errors or deviations in dosing or any prohibited therapies or other osteoporosis medication (estimands 2b-4b), gave similar results to the analyses described above. Generally, the results for the secondary BMD endpoints support the claim of biosimilarity.

GCP aspects

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier. GCP inspection of site Health Center 4 (117 K. Barona Street, Riga 1012) has been triggered by the State Agency of Medicines, Lativa for study MB09-C-01-19 on 11.-13. October 2023. The respective certificate has been provided by the applicant.

2.5.7. Conclusions on the clinical efficacy

In study MB09-C-01-19, the efficacy analysis was based on the primary efficacy endpoint %CFB in lumbar spine BMD after 52 weeks. The primary efficacy analysis revealed that the difference between the MB09 and the EU-Prolia group was 0.20% (95% CI: -0.51, 0.91). Thus, the 95% CI was contained within the predefined margin of [-1.45, 1.45], supporting the claim of biosimilarity. Furthermore, $AUIC_{0\text{-}6months}$ for %CFB of sCTX has been addressed to as co-primary endpoint. Results showed that point estimate of geometric means and corresponding 95% CI of the ratio (MB09/EU-Prolia) was contained within the pre-defined [80.00%, 125.00%] interval, supporting the claim of biosimilarity.

This was further supported by secondary endpoints (%CFB in lumbar spine BMD after 6 months, hip BMD after 6 and 12 months, femur neck BMD after 6 and 12 months).

In summary, the provided efficacy results of study MB09-C-01-09 support the biosimilarity between MB09 and EU-Prolia.

2.5.8. Clinical safety

The clinical safety of MB09 has been assessed in two clinical studies, a clinical Phase I PK study in healthy male subjects (MB09-A-01-19) and a clinical Phase III efficacy and safety study in female patients with postmenopausal osteoporosis (PMO) (MB09-C-01-19). In the Phase I study a subtherapeutic dose (35mg) was used, while in the Phase III study a therapeutic dose (60mg) was used. Due to the heterogeneity of the study population and differences in the treatment regimens including the dose, the duration of exposure, a pooled safety analysis of two studies was not performed.

Table 45: Overview of the studies contributing to the safety evaluation of MB09

Study code	Objective(s) of the Study	Study design and type of control	Test products; Dosage regimen; Route of administration	No. subjects enrolled	Healthy subjects or diagnosis of patients	Duration of treatment
MB09-A-01-19	To assess the bioequivalence of MB09 vs EU-sourced Xgeva® and of EU- vs US-sourced Xgeva® Comparative assessment of other PK parameters, PD, safety and immunogenicity	Randomised, double blind, parallel arm, comparator	MB09 EU-sourced Xgeva® US-sourced Xgeva® Single dose 35 mg SC administration	N=257 enrolled* (n=85 in the MB09 arm, 86 in the EU-Xgeva® arm, 86 in the US-Xgeva® arm)	Healthy male volunteers	Single dose
MB09-C-01-19	To demonstrate equivalent efficacy of MB09 to EU-sourced Prolia® in post-menopausal women with osteoporosis. Comparative assessment of secondary efficacy parameters, PK, PD, safety and immunogenicity	Randomised, double-blind, parallel arm, multiple dose	MB09 EU-sourced Prolia® 60 mg every 6 months SC administration	N=558 randomised** Main Treatment Period: (n=281 in the MB09 arm, 277 in the Prolia® arm) Transition Period***: n=245 in the MB09-MB09 arm, 130 in the Prolia®-MB09 arm, 122 in the Prolia®-Prolia® arm	Postmenopausal women with osteoporosis	Two single doses administered in a period of 12 months (Day 1, Month 6) in the Main Treatment Period Third dose administered at 12 months in the Transition Period

Note: In both studies the safety populations include all subjects exposed to MB09 or the reference product that have at least one post-dose safety assessment.
Abbreviations: EU: European Union; PD, pharmacodynamics; PK, pharmacokinetic(s); SC, subcutaneous; US: United States; vs, *versus*.
* Of 257 enrolled subjects, 255 (99,2%) received the study treatment and 254 (98.8%) completed the study. Three subjects were discontinued (1 subject in EU-Xgeva arm and 2 subjects in US-Xgeva arm).
** Of 558 randomised subjects, 555 (99.5%) received the first dose of study treatment and of these 520 subjects (93.2%) received both the first and second dose of study treatment. The reasons for not receiving the second dose of study treatment (n=35) were similarly distributed in the two treatment groups and included other (a total of 18 subjects [3.2%], from them, 15 withdrawn of consent and 3 was for Principal Investigator decision), subject dosed in error and did not meet the eligibility criteria (13 subjects [2.3%]), adverse events (3 subjects [0.5%]), and lost to follow up (1 subject [0.2%]).
*** A total of 497 subjects entered the Transition Period to receive the third dose of the study treatment: 245 subjects in the MB09-MB09 arm; 130 subjects in the Prolia-MB09 arm; and 122 subjects in the Prolia-Prolia arm. Of the 497 subjects, 12 subjects discontinued the study: 6 subjects in the MB09-MB09 arm, 3 subjects in the Prolia-MB09 arm, and 3 subjects in the Prolia-Prolia arm. Reasons for discontinuation from the study were balanced between the treatment arms and included the following categories: other (10 subjects, including 9 subjects who withdrew consent and 1 subject who left the country and could not return for study visits), death (1 subject), and burden of study procedures (1 subject). A total of 485 of 497 subjects completed the study.

Following the posology of the originator Prolia, during the treatment period patients were supplemented with calcium (at least 1000 mg/day) and vitamin D (at least 400 IU/day if screening levels of 25-hydroxy (25-OH) vitamin D were more than 20 ng/mL or at least 800 IU daily if screening levels of 25-OH vitamin D were 12 to 20 ng/mL). In both the Phase I and Phase III trial, calcium levels were regularly monitored, and serum vitamin D levels were assessed in regular intervals.

The safety analyses for the Screening, Main, and Overall study periods were carried out using the safety analysis set (SAF), which was defined as all subjects who received at least 1 dose of IP.

Safety data collection

In both studies safety and tolerability endpoints included monitoring and recording of AEs (including SAE), clinical laboratory test results (haematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and targeted physical examination findings.

In addition, based on the safety information of Prolia, in study MB09-C-01-19 adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction monitoring, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) were monitored and recorded.

Adverse event definitions (applicable to both studies)

'Adverse event – AE' is defined as 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.

'Treatment-emergent adverse event – TEAE' was defined as any event not present before exposure to study drug or any event already present that worsened in either intensity (severity) or frequency after exposure to study drug.

'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.

Definitions of AESI (applicable to Phase IIIIII study only):

- **Injection site reaction**: Injection site reactions were to be observed after study drug administration and were assessed based on CTCAE version 5.0. All AEs related to injection site reaction including erythema, itching, haemorrhage, pain, and swelling were to be reported.
- **(Drug-related) hypersensitivity/allergic reaction**: All AEs related to hypersensitivity/allergic reactions including anaphylaxis after study drug administration were to be reported. Symptoms included but not limited to hypotension, dyspnoea, throat tightness, facial and upper airway oedema,

pruritus, and urticaria were to be reported. Diagnosis of anaphylaxis was to be based on the anaphylaxis criteria of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.

- **Infection**: All AEs related to infections included but not limited to urinary tract infection, upper respiratory tract infections, skin infections including but not limited to erysipelas and cellulitis, abdomen infection and ear infection were to be reported.
- **Hypocalcaemia**: All AEs related to hypocalcaemia included but not limited to paraesthesia or muscle stiffness, twitching, spasms and muscle cramps, QT interval prolongation, tetany, seizures and altered mental status were to be reported.
- **Osteonecrosis of the jaw**: All AEs related to ONJ included but not limited to jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, and gingival erosion were to be reported.
- **Atypical femoral fracture**: All AEs related to atypical femoral fracture included but not limited to new or unusual thigh, hip, or groin pain were to be reported.
- **Dermatologic reactions**: All AEs related to dermatologic reactions included but not limited to dermatitis, eczema, and rashes were to be reported.

2.5.8.1. Patient exposure

Study MB09-A-01-19:

A total of 255 healthy male volunteers received a single s.c. injection of 35 mg of study drug (85 subjects in MB09, EUXgeva, and USXgeva study arm, respectively). The Safety Set (SAF) consisted of all subjects who received investigational product (IP). The duration of the study, excluding screening, was approximately 36 weeks. All subjects (100%) in the MB09 and EU-Xgeva arm who were treated completed the study. In the US-Xgeva arm, 84/85 treated subjects completed the study. One subject who was treated discontinued from the study due to adverse event. All treated subjects were included in the safety assessments (85 per study arm).

Table 46: Summary of subject disposition (all subjects)

	MB09 (N=85) n (%)	EU-sourced Xgeva (N=86) n (%)	US-sourced Xgeva (N=86) n (%)	Overall (N=257) n (%)
Total Number of Subjects				
Enrolled	85 (100.0)	86 (100.0)	86 (100.0)	257 (100.0)
Treated	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)
Completed	85 (100.0)	85 (98.8)	84 (97.7)	254 (98.8)
Discontinued	0	1 (1.2)	2 (2.3)	3 (1.2)
Reason for Discontinuation from Study				
Adverse Event	0	0	1 (1.2)	1 (0.4)
Lost to Follow-Up	0	0	1 (1.2)	1 (0.4)
Withdrawal y Subject	0	1 (1.2)	0	1 (0.4)
Analysis Populations				
Safety Population[1]	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)
PK Population[2]	85 (100.0)	85 (98.8)	85 (98.8)	255 (99.2)

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test)
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference)
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference)
Percentages are based on the number of subjects that entered the trial.
Subject with screening number 00166 was enrolled and randomised to US-sourced Xgeva but discontinued before drug intake due to adverse event.
Subject with screening number 00237 was enrolled and randomised to EU-sourced Xgeva but withdrew before drug intake.
Subject with screening number 00488 was enrolled and randomised to US-sourced Xgeva, completed treatment but was lost during follow-up.
[1] Safety population includes all subjects who received the study treatment.
[2] Pharmacokinetic (PK) population includes subjects who received the study treatment, who did not have major protocol deviations, and had sufficient data to calculate primary PK endpoints.
Source: End-of-Text Table 14.1.1.

Study MB09-C-01-19:

Female patients with postmenopausal osteoporosis initially received two s.c. injections of 60 mg of either MB09 or EU-Prolia at 6-month intervals during the Main study period (on Day 1 and at Month 6). A total of 278 patients received at least one dose of study treatment in the MB09 arm, and 277 patients received at least one dose of study treatment in the EU-Prolia arm.

A total of 277 subjects received the first dose and 256 subjects (92.4%) received both doses (Day 1 and Month 6) of MB09. A total of 278 subjects (100%) received the first dose and 264 subjects (95.0%) received both doses (Day 1 and Month 6) of Prolia. All dosed subjects, including those who only received the first dose, were allowed to perform Month 12 visit assessments for safety and efficacy reasons. The duration of study participation in the main period was 12 months per subject.

From Month 12, subjects who were to continue in the study entered the second treatment period of the study, the Transition/Safety Follow-Up Period, where the third dose of study treatment was administered. Patients who received MB09 in the Main study period, received either an additional dose of MB09 or Prolia in the Transition period; and patients who received EU-Prolia in the Main study period, received one additional dose of EU-Prolia in the Transition period. The duration of the Transition period is another 6 months, for a total of 18 months follow-up.

In total, 555 subjects completed the main study period and are included in the safety analysis (277 MB09 vs 278 EU-Prolia). A total of 497 subjects (89.1%) entered the Transition Period and received the third dose of the study treatment.

Table 47: Subject disposition – Main treatment period (all enrolled analysis sets)

	MB09 (N=281) n (%)	Prolia (N=277) n (%)	Total (N=1424) n (%)
Total number of subjects			
Screen failures			866 (60.8)
Randomised	281 (100)	277 (100)	558 (39.2)
Treated[1,2]	278 (98.9)	277 (100)	555 (99.5)
Received study treatment on Day 1 and at Month 6[2]	257 (91.5)	263 (94.9)	520 (93.2)
Received 3 doses of study treatment[2]	245 (87.2)	252 (91.0)	497 (89.1)
Discontinued from treatment prior to Month 12[2]	21 (7.5)	14 (5.1)	35 (6.3)
	MB09 (N=281) n (%)	**Prolia (N=277) n (%)**	**Total (N=1424) n (%)**
Primary reasons for discontinuation from treatment prior to Month 12[2]			
Adverse event			3 (0.5)
Lost to follow-up			1 (0.2)
Subject dosed in error and did not meet eligibility criteria	7 (2.5)	6 (2.2)	13 (2.3)
Other[5]	11 (3.9)	7 (2.5)	18 (3.2)
Withdrawal of consent			15
Investigator's decision			3
Primary reasons for discontinuation from study during the Main Treatment Period[2]			
Adverse event			4 (0.7)
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)
Subject dosed in error and did not meet eligibility criteria	6 (2.1)	7 (2.5)	13 (2.3)
Protocol violation			1 (0.2)
Unrelated medical conditions			1 (0.2)
Other[5]	23 (8.2)	16 (5.8)	39 (7.0)
Withdrawal of consent			30
Investigator's decision			7
Randomised in error			2

Abbreviation: BMD, bone mineral density.

Note: Screen failures included 41 subjects who initially failed screening but were later successfully rescreened.

1 All randomised subjects who received at least one dose of study treatment.

2 Numbers are shown according to the planned treatment arm, and percentages are based on the number of subjects randomised.

3 Includes subjects with at least one of lumbar spine, hip, or femur neck BMD assessment collected by Clario.

4 Status of subjects in the Transition Period at the time of the data cut.

5 "Other" category was collected manually in a blinded manner from eCRF because it was a free text field and it was not possible to automatise the data extraction.

Source: Adapted from Table 14.1.2.1.

2.5.8.2. Adverse events

Table 48: Overall summary of treatment-emergent adverse events (safety population)

Study MB09-A-01-19

	MB09 (N=85) n (%) [E]	EU-sourced Xgeva (N=85) n (%) [E]	US-sourced Xgeva (N=85) n (%) [E]	Overall (N=255) n (%) [E]
Any TEAE	18 (21.2) [29]	28 (32.9) [40]	17 (20.0) [23]	63 (24.7) [92]
Any Grade 1 TEAE	4 (4.7) [5]	5 (5.9) [6]	3 (3.5) [3]	12 (4.7) [14]
Any Grade 2 TEAE	10 (11.8) [11]	14 (16.5) [17]	11 (12.9) [16]	35 (13.7) [44]
Any Grade 3 or Higher TEAE	9 (10.6) [13]	13 (15.3) [17]	4 (4.7) [4]	26 (10.2) [34]

System Organ Class Preferred Term	MB09 (N=85) n (%) [E]	EU-sourced Xgeva (N=85) n (%) [E]	US-sourced Xgeva (N=85) n (%) [E]	Overall (N=255) n (%) [E]
Investigations	7 (8.2) [10]	12 (14.1) [16]	3 (3.5) [3]	22 (8.6) [29]
Blood creatine phosphokinase increased	6 (7.1) [9]	9 (10.6) [11]	2 (2.4) [2]	17 (6.7) [22]
Blood triglycerides increased	1 (1.2) [1]	3 (3.5) [4]	1 (1.2) [1]	5 (2.0) [6]
Aspartate aminotransferase increased	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Infections and infestations	6 (7.1) [6]	6 (7.1) [6]	6 (7.1) [9]	18 (7.1) [21]
Nasopharyngitis	3 (3.5) [3]	2 (2.4) [2]	2 (2.4) [3]	7 (2.7) [8]
Urinary tract infection	0 [0]	1 (1.2) [1]	3 (3.5) [4]	4 (1.6) [5]
COVID-19	1 (1.2) [1]	1 (1.2) [1]	0 [0]	2 (0.8) [2]
Boston exanthema	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Giardiasis	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Otitis media	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Pharyngotonsillitis	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Sinusitis	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Tooth abscess	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Nervous system disorders	3 (3.5) [4]	3 (3.5) [3]	2 (2.4) [2]	8 (3.1) [9]
Headache	2 (2.4) [3]	1 (1.2) [1]	1 (1.2) [1]	4 (1.6) [5]
Syncope	0 [0]	2 (2.4) [2]	1 (1.2) [1]	3 (1.2) [3]
Presyncope	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Injury, poisoning and procedural complications	1 (1.2) [2]	3 (3.5) [3]	2 (2.4) [2]	6 (2.4) [7]
Joint injury	1 (1.2) [2]	1 (1.2) [1]	0 [0]	2 (0.8) [3]
Arthropod bite	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Hand fracture	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Thermal burn	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Tooth fracture	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Musculoskeletal and connective tissue disorders	1 (1.2) [1]	3 (3.5) [5]	1 (1.2) [1]	5 (2.0) [7]
Back pain	0 [0]	2 (2.4) [3]	0 [0]	2 (0.8) [3]
Arthralgia	0 [0]	1 (1.2) [2]	0 [0]	1 (0.4) [2]
Bone pain	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Pain in extremity	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]

System Organ Class Preferred Term	MB09 (N=85) n (%) [E]	EU-sourced Xgeva (N=85) n (%) [E]	US-sourced Xgeva (N=85) n (%) [E]	Overall (N=255) n (%) [E]
Gastrointestinal disorders	1 (1.2) [1]	0 [0]	1 (1.2) [3]	2 (0.8) [4]
Abdominal pain	0 [0]	0 [0]	1 (1.2) [2]	1 (0.4) [2]
Diarrhoea	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Vomiting	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.4) [2]	0 [0]	1 [1.2] 1	3 (1.2) [3]
Fibroma	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Lipoma	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Osteoma	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Psychiatric disorders	1 (1.2) [2]	1 (1.2) [1]	0 [0]	2 (0.8) [3]
Adjustment disorder	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Depression	1 (1.2) [2]	0 [0]	0 [0]	1 (0.4) [2]
Respiratory, thoracic and mediastinal disorders	0 [0]	1 (1.2) [1]	1 (1.2) [1]	2 (0.8) [2]
Pharyngeal inflammation	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Sinus pain	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Skin and subcutaneous tissue disorders	0 [0]	1 (1.2) [1]	1 (1.2) [1]	2 (0.8) [2]
Rash maculo-papular	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Rash papular	0 [0]	0 [0]	1 (1.2) [1]	1 (0.4) [1]
Blood and lymphatic system disorders	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Lymphadenitis	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
General disorders and administration site conditions	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Peripheral swelling	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Metabolism and nutrition disorders	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Hyperkalaemia	1 (1.2) [1]	0 [0]	0 [0]	1 (0.4) [1]
Renal and urinary disorders	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]
Micturition urgency	0 [0]	1 (1.2) [1]	0 [0]	1 (0.4) [1]

Common Adverse events

Overall, the most commonly reported TEAEs were blood creatine phosphokinase increased (17 [6.7%] subjects), nasopharyngitis (7 [2.7%] subjects) and blood triglycerides increased (5 [2%] subjects). The most commonly reported TEAEs in each study arm were as follows,

• MB09 arm: blood creatine phosphokinase increased (6 [7.1%] subjects) and nasopharyngitis (3 [3.5%] subjects).

• EU-Xgeva arm: blood creatine phosphokinase increased (9 [10.6%] subjects) and blood triglycerides increased (3 [3.5%] subjects).

• US-Xgeva arm: urinary tract infection (3 [3.5%] subjects).

Study MB09-C-01-19

Table 49: Deaths and overall summary of treatment-emergent adverse events - Main treatment period (safety analysis set)

Number of Subjects With	MB09 (N=277) n (%) [E]	Prolia (N=278) n (%) [E]	Total (N=555) n (%) [E]
Any TEAEs	161 (58.1) [442]	150 (54.0) [397]	311 (56.0) [839]
Any study treatment-related TEAEs	41 (14.8) [57]	24 (8.6) [36]	65 (11.7) [93]
Any serious TEAEs	19 (6.9) [21]	13 (4.7) [16]	32 (5.8) [37]
Any study treatment-related serious TEAEs	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Any AESIs	80 (28.9) [119]	75 (27.0) [113]	155 (27.9) [232]
Any serious AESIs	4 (1.4) [4]	0	4 (0.7) [4]
Any TEAEs leading to treatment discontinuation	4 (1.4) [4]	0	4 (0.7) [4]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Note 1: [E] represents the number of AEs at each level of summarisation. n represents the number of subjects at each level of summarisation.

Note 2: For Main Treatment Period, TEAE was an event observed after first administration of study treatment on Day 1 until Month 12 and no more than 6 months after the last administration of study treatment in case of early treatment discontinuation unless the TEAE was considered as related to the study treatment by investigator.

Note 3: The following AEs were considered as AESI: injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction, atypical femoral fracture.

Note 4: Adverse events that were missing the relationship to study treatment were considered as treatment-related AEs.

Note 5: Adverse events were coded using MedDRA, Version 24.1.

In the main period, a total of 839 TEAEs were reported in 311 subjects (56.0%): 161 subjects (58.1%; 442 events) in the MB09 group and 150 subjects (54.0%; 397 events) in the EU-Prolia group with the proportion of patients experiencing any TEAEs, as well as the total number of TEAEs between the treatment groups being similar.

The TEAEs in most subjects were Grade 1 (90 subjects [16.2%]; 356 events) or Grade 2 (188 subjects [33.9%]; 445 events) in severity. Grade 3 TEAEs were reported in 33 subjects (5.9%; 38 events). No Grade 4 or Grade 5 TEAEs were reported during the Main Treatment Period.

Transition Period

In these two arms, a total of 114 TEAEs were reported in 72 subjects (28.5%): 36 subjects (27.7%; 51 events) in the Prolia-MB09 arm and 36 subjects (29.3%; 63 events) in the Prolia-Prolia arm. Majority of the TEAEs were Grade 1 (19 subjects [7.5%]; 41 events) or Grade 2 (51 subjects [20.2%]; 71 events) in severity. There was no greater tendency for more TEAEs or more severe TEAEs in the transitioning arm (Prolia-MB09) and specifically, 9 subjects (6.9%) in this arm had Grade 1 and 27 subjects (20.8%) had

Grade 2 TEAEs that started during the Transition Period. Two Grade 3 TEAEs were reported in 2 subjects (1.6%) in the Prolia-Prolia arm following the third dose of Prolia in the Transition Period. No Grade 4 or Grade 5 TEAEs were reported during the Transition Period in the Prolia-MB09 and Prolia-Prolia arms.

Table 50: Overall summary of treatment-emergent adverse events – Transition period (safety analysis set for transition period)

Number of Subjects With	Prolia-MB09 (N=130) n (%) [E]	Prolia-Prolia (N=123) n (%) [E]	Total (N=253) n (%) [E]
Any TEAEs	36 (27.7) [51]	36 (29.3) [63]	72 (28.5) [114]
Any study treatment-related TEAEs	3 (2.3) [4]	5 (4.1) [8]	8 (3.2) [12]
Any serious TEAEs	0	2 (1.6) [3]	2 (0.8) [3]
Any AESIs	17 (13.1) [21]	21 (17.1) [24]	38 (15.0) [45]

Abbreviations: AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Note 1: [E] represents the number of AEs at each level of summarisation. n represents the number of subjects at each level of summarisation.

Note 2: For Transition Period, TEAE was an event observed after the third dose of study treatment at Month 12 until Month 18.

Note 3: The following AEs were considered as AESI: injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction, atypical femoral fracture.

Note 4: Adverse events that were missing the relationship to study treatment were considered as treatment-related AEs.

Note 5: Adverse events were coded using MedDRA, Version 24.1.

Table 51: Deaths overall summary of treatment-emergent adverse events – Main treatment period and throughout the study (safety analysis set)

	Main Treatment Period		Throughout the Study		
Number of Subjects With	MB09 (N=277) n (%) [E]	Prolia (N=278) n (%) [E]	MB09-MB09 (N=277) n (%) [E]	Prolia-MB09 (N=140) n (%) [E]	Prolia-Prolia (N=138) n (%) [E]
Any TEAEs	161 (58.1) [442]	150 (54.0) [397]	180 (65.0) [567]	87 (62.1) [267]	75 (54.3) [244]
Any study treatment-related TEAEs	41 (14.8) [57]	24 (8.6) [36]	45 (16.2) [73]	11 (7.9) [19]	17 (12.3) [29]
Any serious TEAEs	19 (6.9) [21]	13 (4.7) [16]	21 (7.6) [25]	11 (7.9) [13]	4 (2.9) [6]
Any study treatment-related serious TEAEs	1 (0.4) [1]	1 (0.4) [1]	1 (0.4) [1]	0	1 (0.7) [1]
Any AESIs	80 (28.9) [119]	75 (27.0) [113]	96 (34.7) [172]	47 (33.6) [84]	43 (31.2) [74]
Any serious AESIs	4 (1.4) [4]	0	5 (1.8) [6]	0	0
Any TEAEs leading to treatment discontinuation	4 (1.4) [4]	0	4 (1.4) [4]	0	0
Any TEAEs leading to death	0	0	1 (0.4) [1]	0	0
Any deaths	0	0	1 (0.4) [1]	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Note 1: In the Transition Period, all arms contain subjects who did not progress to the third dose but had MB09 or Prolia in the Main Period.

Note 2: [E] represents the number of AEs at each level of summarisation. n represents the number of subjects at each level of summarisation.

Note 3: For Main Treatment Period, TEAE was an event observed after first administration of study treatment on Day 1 until Month 12 and no more than 6 months after the last administration of study treatment in case of early treatment discontinuation unless the TEAE was considered as related to the study treatment by investigator. Throughout the study, TEAE was an event observed after first administration of study treatment on Day 1 until Month 18.

Note 4: The following AEs were considered as AESI: injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction, atypical femoral fracture.

Note 5: Adverse events that were missing the relationship to study treatment were considered as treatment-related AEs.

Note 6: Adverse events were coded using MedDRA, Version 24.1.

Adverse drug reactions

Study MB09-A-01-19

During the study, 4 TEAEs reported in 3 (1.2%) subjects were considered as possibly related to the study treatment by the investigator. The study treatment-related TEAEs included Grade 1 headache (MB09 arm), 2 episodes of Grade 1 arthralgia (EU-Xgeva arm), and Grade 2 rash papular (US-Xgeva arm). The TEAE of rash papular resolved after treatment with cetirizine (Zyrtec), fusidic acid (Fucidin), and calcium. Other study treatment-related TEAEs resolved without treatment.

Study MB09-C-01-19

Overall, TEAEs in 65 subjects (11.7%; 94 events) were considered related to study treatment by the investigator: 41 subjects (14.8%; 58 events) in the MB09 group and 24 subjects (8.6%; 36 events) in the Prolia group and the most commonly reported (in ≥1.0% subjects) included the following TEAEs or related TEAEs:

• Blood PTH increased (14 subjects [2.5%]). Other study treatment-related TEAEs included blood calcium decreased (5 subjects [0.9%]), hypocalcaemia (3 subjects [0.5%]), and adjusted calcium decreased (2 subjects [0.4%]).

• Urinary tract infection (6 subjects [1.1%]); other study treatment-related TEAE included cystitis (2 subjects [0.4%]). Most study treatment-related TEAEs were Grade 1 or 2 in severity. Grade 3 TEAEs considered related to the study treatment included osteonecrosis of jaw and migraine, each of which was reported in 1 subject (0.2%).

Overall, in the **Transition Period**, TEAEs in 8 subjects (3.2%; 12 events) were considered related to study treatment by the investigator: 3 subjects (2.3%; 4 events) in the Prolia-MB09 arm and 5 subjects (4.1%; 8 events) in the Prolia-Prolia arm and included the following TEAEs:

• Prolia-MB09 arm: upper respiratory tract infection and asymptomatic bacteriuria, each in 1 subject [0.8%], and dizziness and pruritus in 1 subject (0.8%).

• Prolia-Prolia arm: bronchitis and cataract in 1 subject (0.8%), myalgia, spinal pain, and asthenia in 1 subject (0.8%), and headache, alopecia, and injection site mass, each in 1 subject (0.8%).

2.5.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Study MB09-A-01-19

In MB09 arm, 2 SAEs were reported in 2 (2.4%) subjects. One subject was reported with osteoma and one subject was reported with depression, but none were considered related to the IP. No SAEs were reported in EU- or US-Xgeva arms.

Study MB09-C-01-19

Serious TEAEs were reported in 32 subjects (5.8%; 37 events): 19 subjects (6.9%; 21 events) in the MB09 group and 13 subjects (4.7%; 16 events) in the Prolia group.

Serious TEAEs were most frequently (>0.5% of total subjects) reported in the SOCs of musculoskeletal and connective tissue disorders (7 subjects [1.3%]), mostly fractures (hip fracture, ankle fracture, and ulna fracture in 2 [0.4%], 1 [0.2%], and 1 [0.2%] subjects, respectively) followed by gastrointestinal disorders (5 subjects [0.9%]) and hepatobiliary disorders (4 subjects [0.7%]). Except for the fracture PTs (4 subjects) and cholelithiasis (2 subjects [0.4%]), all other serious TEAEs were reported in 1 subject.

Table 52: Serious treatment-emergent adverse events – Main treatment period

System Organ Class Preferred Term	MB09 (N=277) n (%) [E]	Prolia (N=278) n (%) [E]	Total (N=555) n (%) [E]
Total number of serious TEAEs	21	16	37
Number of subjects with at least one serious TEAE	19 (6.9)	13 (4.7)	32 (5.8)
Musculoskeletal and connective tissue disorders	3 (1.1) [3]	4 (1.4) [4]	7 (1.3) [7]
Hip fracture	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Osteonecrosis of jaw	1 (0.4) [1]	0	1 (0.2) [1]
Ulna fracture	1 (0.4) [1]	0	1 (0.2) [1]

System Organ Class Preferred Term	MB09 (N=277) n (%) [E]	Prolia (N=278) n (%) [E]	Total (N=555) n (%) [E]
Ankle fracture	0	1 (0.4) [1]	1 (0.2) [1]
Intervertebral disc disorder	0	1 (0.4) [1]	1 (0.2) [1]
Spinal osteoarthritis	0	1 (0.4) [1]	1 (0.2) [1]
Gastrointestinal disorders	3 (1.1) [3]	2 (0.7) [2]	5 (0.9) [5]
Gastritis	1 (0.4) [1]	0	1 (0.2) [1]
Ileus paralytic	1 (0.4) [1]	0	1 (0.2) [1]
Large intestine polyp	1 (0.4) [1]	0	1 (0.2) [1]
Gastric polyps	0	1 (0.4) [1]	1 (0.2) [1]
Pancreatitis acute	0	1 (0.4) [1]	1 (0.2) [1]
Hepatobiliary disorders	1 (0.4) [1]	3 (1.1) [3]	4 (0.7) [4]
Cholelithiasis	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Hepatic steatosis	0	1 (0.4) [1]	1 (0.2) [1]
Steatohepatitis	0	1 (0.4) [1]	1 (0.2) [1]
Cardiac disorders	2 (0.7) [2]	1 (0.4) [1]	3 (0.5) [3]
Atrial fibrillation	1 (0.4) [1]	0	1 (0.2) [1]
Supraventricular tachycardia	1 (0.4) [1]	0	1 (0.2) [1]
Bundle branch block left	0	1 (0.4) [1]	1 (0.2) [1]
Infections and infestations	2 (0.7) [2]	1 (0.4) [1]	3 (0.5) [3]
Pneumonia	1 (0.4) [1]	0	1 (0.2) [1]
Pulmonary tuberculosis	1 (0.4) [1]	0	1 (0.2) [1]
Post-acute COVID-19 syndrome	0	1 (0.4) [1]	1 (0.2) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.1) [3]	0	3 (0.5) [3]
Adenocarcinoma metastatic	1 (0.4) [1]	0	1 (0.2) [1]
Pituitary tumour benign	1 (0.4) [1]	0	1 (0.2) [1]
Renal cancer metastatic	1 (0.4) [1]	0	1 (0.2) [1]
Nervous system disorders	1 (0.4) [1]	2 (0.7) [2]	3 (0.5) [3]
Transient ischaemic attack	1 (0.4) [1]	0	1 (0.2) [1]
Lumbosacral radiculopathy	0	1 (0.4) [1]	1 (0.2) [1]
Migraine	0	1 (0.4) [1]	1 (0.2) [1]
Endocrine disorders	0	2 (0.7) [2]	2 (0.4) [2]
Goitre	0	1 (0.4) [1]	1 (0.2) [1]
Toxic goitre	0	1 (0.4) [1]	1 (0.2) [1]
Blood and lymphatic system disorders	1 (0.4) [1]	0	1 (0.2) [1]
Anaemia	1 (0.4) [1]	0	1 (0.2) [1]
General disorders and administration site conditions	1 (0.4) [1]	0	1 (0.2) [1]
Nodule	1 (0.4) [1]	0	1 (0.2) [1]
Injury, poisoning and procedural complications	0	1 (0.4) [1]	1 (0.2) [1]
Thermal burn	0	1 (0.4) [1]	1 (0.2) [1]

System Organ Class Preferred Term	MB09 (N=277) n (%) [E]	Prolia (N=278) n (%) [E]	Total (N=555) n (%) [E]
Renal and urinary disorders	1 (0.4) [2]	0	1 (0.2) [2]
Ureteric obstruction	1 (0.4) [1]	0	1 (0.2) [1]
Ureterolithiasis	1 (0.4) [1]	0	1 (0.2) [1]
Reproductive system and breast disorders	1 (0.4) [1]	0	1 (0.2) [1]
Uterine haemorrhage	1 (0.4) [1]	0	1 (0.2) [1]
Skin and subcutaneous tissue disorders	1 (0.4) [1]	0	1 (0.2) [1]
Psoriasis	1 (0.4) [1]	0	1 (0.2) [1]

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note 1: Adverse events were coded using MedDRA, Version 24.1.

Note 2: [E] represents the number of AEs at each level of summarisation. n represents the number of subjects at each level of summarisation. In SOC and PT summarisation, a subject was counted once if the subject reported one or more events.

Note 3: For the Main Treatment Period, TEAE was an event observed after the first administration of study treatment on Day 1 until Month 12 and no more than 6 months after the last administration of study treatment in case of early treatment discontinuation unless the TEAE was considered as related to the treatment by investigator.

Transition Period

In the Transition Period, serious TEAEs were reported in 2 subjects (1.6%; 3 events) in the Prolia-Prolia arm and included Grade 3 cardiac disorder in 1 subject and Grade 2 diverticulitis and thrombophlebitis in subject. None of the serious TEAEs were considered related to the study treatment.

Table 53: Serious treatment-emergent adverse events – Transition period (safety analysis set for transition period)

System Organ Class Preferred Term	Prolia-MB09 (N=130) n (%) [E]	Prolia-Prolia (N=123) n (%) [E]	Total (N=253) n (%) [E]
Total number of serious TEAEs	0	3	3
Number of subjects with at least one serious TEAE	0	2 (1.6)	2 (0.8)
Cardiac disorders	0	1 (0.8) [1]	1 (0.4) [1]
Cardiac disorder	0	1 (0.8) [1]	1 (0.4) [1]
Infections and infestations	0	1 (0.8) [1]	1 (0.4) [1]
Diverticulitis	0	1 (0.8) [1]	1 (0.4) [1]
Vascular disorders	0	1 (0.8) [1]	1 (0.4) [1]
Thrombophlebitis	0	1 (0.8) [1]	1 (0.4) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note 1: Adverse events were coded using MedDRA, Version 24.1.

Note 2: [E] represents the number of AEs at each level of summarisation. n represents the number of subjects at each level of summarisation. In SOC and PT summarisation, a subject was counted once if the subject reported one or more events.

Note 3: For Transition Period, TEAE was an event observed after the third dose of study treatment at Month 12 until Month 18.

Deaths

There were no deaths during Study MB09-A-01-19. No deaths were reported during the Main Treatment Period of Study MB09-C-01-19. One subject (Subject PL005128) in the MB09-MB09 arm experienced a TEAE of pneumonia that led to the subject's death in the **Transition Period.** The TEAEs of pneumonia haemophilus (Grade 4) and pneumonia (Grade 5) were considered unrelated to the study treatment.

Other significant events

Study MB09-A-01-19: During the study pregnancy was reported in 1 subject's partner, which was considered as significant AE (Xgeva group). Following a full term pregnancy, the subject's partner gave birth to a healthy child.

Study MB09-C-01-19: No other significant events were reported.

ADRs of special interest

Study MB09-C-01-19

Treatment-emergent AESIs were reported in a total of 155 subjects (27.9%; 232 events): 80 subjects (28.9%; 119 events) in the MB09 group and 75 subjects (27.0%; 113 events) in the Prolia group.

Injection site reactions were reported in 3 subjects (0.5%), all in the MB09 group, and included: injection site erythema in 2 subjects (0.4%) and injection site hypersensitivity in 1 subject (0.2%). All injection site reactions were nonserious and Grade 1 in severity.

For the transition period treatment-emergent AESIs were reported in a total of 38 subjects (15.0%; 45 events): 17 subjects (13.1%; 21 events) in the Prolia-MB09 arm and 21 subjects (17.1%; 24 events) in the Prolia-Prolia arm. None of the treatment-emergent AESIs were serious in nature.

Table 54: Injection site reactions – Throughout the study (safety analysis set)

Preferred Term	MB09-MB09 (N=277) n (%)	Prolia-MB09 (N=140) n (%)	Prolia-Prolia (N=138) n (%)
Injection site erythema	2 (0.7)	0	0
Injection site hypersensitivity	1 (0.4)	0	0
Injection site mass	0	0	1 (0.7)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Note 1: Adverse events were coded using MedDRA, Version 24.1.

Note 2: n represents the number of subjects at each level of summarisation. A subject was counted once if the subject reported one or more events.

Note 3: TEAE was an event observed after the first administration of study treatment on Day 1 until Month 18.

Drug-related hypersensitivity, allergic, and dermatologic reactions:

In this study, AESIs of hypersensitivity, allergic, and dermatologic reactions were reported in 14 subjects (2.5%): 10 subjects (3.6%) in the MB09 group and 4 subjects (1.4%) in the Prolia group. All reactions were Grade 1 or 2 in severity, except Grade 3 serious event of psoriasis reported in 1 of 3 subjects with psoriasis in the MB09 group.

In this study, AESIs of hypersensitivity, allergic, and dermatologic reactions were reported in 4 subjects (1.6%) in **the Transition Period**: pruritus and rash, each in 1 subject (0.8%) in the Prolia-MB09 arm and rash papulosquamous and rosacea, each in 1 subject (0.8%) in the Prolia-Prolia arm. All reactions were Grade 1 or 2 in severity. The treatment-emergent AESI of pruritus was considered related to the study treatment; all others were unrelated.

Table 55: Hypersensitivity, allergic, and dermatologic reactions as treatment-emergent AESIs – Throughout the study (safety analysis set)

System Organ Class Preferred Term	MB09-MB09 (N=277) n (%)	Prolia-MB09 (N=140) n (%)	Prolia-Prolia (N=138) n (%)
Skin and subcutaneous tissue disorders	11 (4.0)	4 (2.9)	3 (2.2)
Psoriasis	3 (1.1)	0	0
Dermatitis allergic	3 (1.1)	0	0
Rash pruritic	2 (0.7)	0	0
Dermatitis atopic	1 (0.4)	0	0
Onycholysis	1 (0.4)	0	0
Rash	1 (0.4)	1 (0.7)	
Urticaria	1 (0.4)	0	1 (0.7)
Alopecia	0	0	1 (0.7)
Eczema	0	1 (0.7)	0
System Organ Class Preferred Term	**MB09-MB09 (N=277) n (%)**	**Prolia-MB09 (N=140) n (%)**	**Prolia-Prolia (N=138) n (%)**
Pruritus	0	1 (0.7)	0
Rash papulosquamous	0	0	1 (0.7)
Rosacea	0	0	1 (0.7)
Seborrhoeic dermatitis	0	1 (0.7)	0

Abbreviations: AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Note 1: Adverse events were coded using MedDRA, Version 24.1.

Note 2: n represents the number of subjects at each level of summarisation. A subject was counted once if the subject reported one or more events.

Note 3: TEAE is an event observed after first administration of study treatment on Day 1 until Month 18.

Infections:

In the current study, AESIs under the SOC of infections and infestations were reported in 135 subjects (24.3%): 65 subjects (23.5%) in the MB09 group and 70 subjects (25.2%) in the Prolia group. Common AESIs in this class (reported in ≥1% subject) included (MB09 versus Prolia) upper respiratory tract infection (7.2% in both the groups), COVID-19 (4.7% versus 5.4%), nasopharyngitis (3.6% versus 7.2%), and urinary tract infection (3.2% in both the groups). Most of these AESIs were nonserious and Grade 1 or 2 in severity. Grade 3 pulmonary tuberculosis in 1 subject (0.2%) and Grade 2 pneumonia in 1 (0.2%) of 3 subjects reporting pneumonia in the MB09 group were serious.

In the **Transition Period**, most treatment-emergent AESIs were reported in the SOC of infections and infestations (35 subjects [13.8%]). Treatment-emergent AESIs in the SOC of infections and infestations reported in >1 subject in total included (Prolia-MB09 versus Prolia-Prolia, respectively) upper respiratory tract infection (3.8% versus 1.6%), COVID-19 (2.3% versus 2.4%), nasopharyngitis (1.5% versus 1.6%),

bronchitis (0.8% versus 1.6%), Helicobacter infection (0.8% versus 0.8%), urinary tract infection (0.8% versus 1.6%), and pharyngitis (0 versus 1.6%). The treatment-emergent AESIs of upper respiratory tract infection and asymptomatic bacteriuria, each in 1 subject (0.8%) in the Prolia-MB09 arm and bronchitis in 1 subject (0.8%) in the Prolia-Prolia arm were considered by the investigator to be related to the study treatment.

Hypocalcaemia:

In the current study, hypocalcaemia (3 subjects [0.5%]: 1 subject [0.4%] in the MB09 group and 2 subjects [0.7%] in the Prolia group) and related PTs of adjusted calcium decreased (2 subjects [0.4%], both in the MB09 group) and blood calcium decreased (1 subject [0.2%] in the Prolia group) were reported as AESIs. All events of hypocalcaemia were nonserious, and most of them were Grade 1 in severity except for the Grade 2 event of blood calcium decreased in 1 subject in the Prolia group.

Osteonecrosis of jaw: Osteonecrosis of jaw was reported as an AESI in 1 subject (0.2%) in the MB09 group, it was a Grade 3 serious treatment-emergent AESI.

Atypical femoral fractures: No cases of atypical femoral fracture were reported.

Other PTs that were considered to be AESIs based on the investigator criteria included the following: gingivitis (3 subjects [0.5%]), periodontitis (3 subjects [0.5%]), pulpitis dental (2 subjects [0.4%]), pain in jaw (1 subject [0.2%]), hyperparathyroidism (1 subject [0.2%]), cough (1 subject [0.2%]), arthropod bite (1 subject [0.2%]), and allergy to arthropod bite (1 subject [0.2%]). Most of these AESIs were nonserious and Grade 1 or 2 in severity.

Fracture-Related Adverse Events

Fractures were reported in a total of 16 subjects (2.9%): 10 subjects (3.6%) in the MB09 group and 6 subjects (2.2%) in the Prolia group. Except for the thoracic vertebral fracture in 1 patient in the MB09 group that was probably a compression fracture as reported by the investigator, all other fracture events were reported to be due to trauma, as confirmed by the investigators. In the transition Period 2 fractures (lumbar vertebral fracture [MB09-MB09 arm] and thoracic vertebral fracture [Prolia-Prolia arm]) whose kinetics were unknown to the investigator were reported.

Table 56: Fracture treatment-emergent adverse events – Main treatment period (safety analysis set)

Preferred Term Grade	MB09 (N=277) n (%)	Prolia (N=278) n (%)	Total (N=555) n (%)
Number of subjects with at least one nontraumatic fracture TEAE	10 (3.6)	6 (2.2)	16 (2.9)
Forearm fracture	2 (0.7)	0	2 (0.4)
Grade 1	1 (0.4)	0	1 (0.2)
Grade 2	1 (0.4)	0	1 (0.2)

Preferred Term Grade	MB09 (N=277) n (%)	Prolia (N=278) n (%)	Total (N=555) n (%)
Hip fracture	1 (0.4)	1 (0.4)	2 (0.4)
Grade 3	1 (0.4)	1 (0.4)	2 (0.4)
Pelvic fracture	1 (0.4)	0	1 (0.2)
Grade 2	1 (0.4)	0	1 (0.2)
Rib fracture	1 (0.4)	0	1 (0.2)
Grade 1	1 (0.4)	0	1 (0.2)
Spinal compression fracture	1 (0.4)	1 (0.4)	2 (0.4)
Grade 2	1 (0.4)	1 (0.4)	2 (0.4)
Thoracic vertebral fracture	1 (0.4)	0	1 (0.2)
Grade 1	1 (0.4)	0	1 (0.2)
Ulna fracture	1 (0.4)	0	1 (0.2)
Grade 3	1 (0.4)	0	1 (0.2)
Upper limb fracture	1 (0.4)	0	1 (0.2)
Grade 2	1 (0.4)	0	1 (0.2)
Wrist fracture	1 (0.4)	1 (0.4)	2 (0.4)
Grade 2	1 (0.4)	1 (0.4)	2 (0.4)
Ankle fracture	0	1 (0.4)	1 (0.2)
Grade 3	0	1 (0.4)	1 (0.2)
Humerus fracture	0	1 (0.4)	1 (0.2)
Grade 2	0	1 (0.4)	1 (0.2)
Radius fracture	0	1 (0.4)	1 (0.2)
Grade 2	0	1 (0.4)	1 (0.2)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

Note 1: n represents the number of subjects at each level of summarisation. In PT summarisation, a subject was counted once if the subject reported one or more events.

Note 2: Adverse events were coded using MedDRA, Version 24.1.

Note 3: All new fractures are included in this table.

Note 4: The severity of AEs was rated using CTCAE, Version 5.0.

Table 57: Fracture treatment-emergent adverse events – Transition period (safety analysis set for transition period)

Preferred Term Grade	Prolia-MB09 (N=130) n (%)	Prolia-Prolia (N=123) n (%)	Total (N=253) n (%)
Number of subjects with at least one nontraumatic fracture TEAE	2 (1.5)	2 (1.6)	4 (1.6)
Fracture TEAE term			
Radius fracture	1 (0.8)	0	1 (0.4)
Spinal fracture	1 (0.8)	0	1 (0.4)
Foot fracture	0	1 (0.8)	1 (0.4)
Thoracic vertebral fracture	0	1 (0.8)	1 (0.4)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Note 1: n represents the number of subjects at each level of summarisation.
Note 2: Adverse events were coded using MedDRA, Version 24.1.
Note 3: All new fractures are included in this table.

Serious ADR

No serious AEs were considered related to the treatment in Study MB09-A-01-19.

In the Phase III study MB09-C-01-19 grade 3 serious TEAEs of osteonecrosis of jaw (confirmed by biopsy) and migraine, each reported in 1 subject (0.2%), were considered related, and all other serious TEAEs were considered unrelated to study treatment by the applicant.

2.5.8.4. Laboratory findings

Study MB09-A-01-19

Some of the clinical chemistry abnormal laboratory values of creatine kinase, triglycerides, potassium, bilirubin, and AST were considered as clinically significant by the investigator. All clinically significant values were reported as AEs. Treatment-emergent AEs of clinically significant laboratory values included blood creatine phosphokinase increased (22 TEAEs reported in 17 [6.7%] subjects), blood triglycerides increased (6 TEAEs reported in 5 [2%] subjects), aspartate aminotransferase increased (1 TEAE reported in 1 [0.4%] subject), and hyperkalaemia (1 TEAE reported in 1 [0.4%] subject). All TEAEs were either Grade 3 or Grade 4 and resolved without any treatment. No TEAEs were considered as related to the study treatment by the investigator.

Table 58: Treatment-emergent AEs of clinically significant laboratory values

PT	MB09 (N=85) n (%) [E]	EU-sourced Xgeva (N=85) n (%) [E]	US-sourced Xgeva (N=85) n (%) [E]	Overall (N=255) n (%) [E]
Blood creatine phosphokinase increased	6 (7.1%) [9]	9 (10.6%) [11]	2 (2.4%) [2]	17 (6.7%) [22]
Blood triglycerides increased	1 (1.2%) [1]	3 (3.5%) [4]	1 (1.2%) [1]	5 (2.0%) [6]
Aspartate aminotransferase increased	0 [0]	1 (1.2%) [1]	0 [0]	1 (0.4%) [1]
Hyperkalaemia	1 (1.2%) [1]	0 [0]	0 [0]	1 (0.4%) [1]

Note:
MB09: MB09 vial containing 70 mg/mL (Study Arm 1, test)
EU-sourced Xgeva: EU-sourced Xgeva vial containing 70 mg/mL (Study Arm 2, reference)
US-sourced Xgeva: US-sourced Xgeva vial containing 70 mg/mL (Study Arm 3, reference)
A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study treatment or any event already present that worsens in intensity of frequency after exposure.
At each level of subject summarisation, a subject is counted once if the subject reported one or more events. n represents the number of subjects at each level of summarisation.
Percentages are based on the number of subjects in the Safety Population within each treatment and overall. [E] represents the number of events at each level of summarisation.
Adverse events were coded using MedDRA Version 25.1.
Adverse events were graded for severity (intensity) according to the CTCAE, Version 5.0 — November 2017 (DHHS 2017).

Study MB09-C-01-19

Treatment-emergent AEs related to changes in clinical chemistry parameters were reported in few subjects under the SOC of investigations and metabolism and nutrition disorders. Of these, the TEAEs of blood PTH increased (14 subjects [2.5%]), blood calcium decreased (5 subjects [0.9%]), hypocalcaemia (3 subjects [0.5%]), adjusted calcium decreased (2 subjects [0.4%]), alanine aminotransferase (ALT) increased (1 subject [0.2%]), aspartate aminotransferase (AST) increased (1 subject [0.2%]), gamma-glutamyl transferase increased (1 subject [0.2%]), blood albumin decreased (1 subject [0.2%]), and hyperuricaemia (1 subject [0.2%]) were considered related to the study treatment. Treatment Period are summarised by worst postbaseline CTCAE in Table 14.3.2.2.1. Most subjects had Grade 0 (84.9%) or Grade 1 (13.7%) albumin-adjusted total serum calcium. Grade 2 albumin-adjusted total serum calcium was reported in 6 subjects (1.1%) and Grade 3 in 1 subject (0.2%) (considered as not clinically significant per the investigator criteria). In the transition period shifts were noted for most clinical laboratory parameters but were not considered to be of potential clinical concern. Treatment-emergent AEs related to changes in clinical laboratory parameters, vital signs, and ECGs were reported in few subjects. Of these, the TEAE of asymptomatic bacteriuria reported in 1 subject in the Prolia-MB09 arm was considered related to the study treatment.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable

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.

Study MB09-A-01-19

Immunogenicity endpoints

- Incidence of anti-drug antibodies (ADAs) at Day 0, 11, 43, 99, 169, 225, and 253
- Incidence of neutralising antibodies (NAbs) at Day 0, 11, 43, 99, 169, 225, and 253

There were in total 3 subjects who were anti-drug antibody positive at baseline, one in each of the treatment arms. Anti-drug antibody assay was positive in 1 subject at Day 169 in MB09 arm. In EU-sourced Xgeva arm ADA assay results were positive in 1 subject at Days 11, 99, 169, 225, and 253 (EOS) and in 2 (2.4%) subjects at Day 43. In US-sourced Xgeva arm ADA assay results were positive in 1 (1.2%) subject at Day 11. None of the ADAs detected had neutralising capacity.

Study MB09-C-01-19

Immunogenicity endpoints

- Incidence of anti-drug antibodies (ADAs) at Day 0, 11, 43, 99, 169, 225, and 253
- Incidence of neutralising antibodies (NAbs) at Day 0, 11, 43, 99, 169, 225, and 253

A total of 3 subjects (0.5%) were positive for ADA at baseline (predose). After initiation of treatment, a total of 6 subjects (1.1%) were found to be TI-ADA positive; none of the subjects who were positive for ADA at baseline (predose) were boosted throughout the Main Treatment Period. The ADA titres in the subjects ranged from <50 to 1350ng/mL. All ADAs were transient and none had neutralising capacity. In the **Transition Period**, only 1 subject (0.2%) was TI-ADA positive. This subject in the MB09-MB09 arm was detected to be ADA positive at Month 1 of the Transition Period, with ADA titres <50. At the time of EOS, no subjects were ADA positive.

As the number of subjects with positive TI-ADA was very low, no meaningful assessment could be performed to evaluate the impact of ADAs on efficacy. The %CfB in lumbar spine BMD at Months 6 and 12 remained similar to the overall results. The number of subjects experiencing treatment-induced immunogenicity was very low (n=6). As a result, no meaningful impact assessment could be performed and subjects experiencing treatment-induced immunogenicity had a negligible impact on the overall study conclusions.

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

Not applicable

2.5.8.8. Discontinuation due to adverse events

Study MB09-A-01-19

One subject in the US-Xgeva arm discontinued the study due to AE (body temperature increased, not related, resolved, no treatment required).

Study MB09-C-01-19

Treatment-emergent AEs leading to discontinuation of study treatment were reported in a total of 4 subjects (0.7%). Two subjects discontinued the study treatment due to Grade 2 gingivitis after receiving the first dose of the study treatment. One subject discontinued the study treatment due to Grade 3 serious TEAE of osteonecrosis of jaw. One subject discontinued the study treatment due to Grade 3 serious TEAE of renal cancer metastatic. No TEAEs led to treatment discontinuation in the **Transition Period.**

2.5.8.9. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

Safety data collection/exposure

The clinical safety of MB09 has been assessed in two clinical studies, a clinical Phase I PK study in healthy male subjects (MB09-A-01-19) and a clinical Phase III efficacy and safety study in female patients with postmenopausal osteoporosis (PMO) (MB09-C-01-19). In the Phase I study a subtherapeutic dose (35mg) was investigated, while in the Phase III study a therapeutic dose (60mg) was investigated. Due to the heterogeneity of the study population and differences in the treatment regimens including the dose and the duration of exposure, a pooled safety analysis of two studies was not performed, which is supported.

In the Phase I study, a total of 255 healthy subjects received a single dose (35 mg) of study drug (85 subjects in MB09, EU-Xgeva, and US-Xgeva study arm, respectively). Only one subjects (US-Xgeva arm) did not complete the study. All treated subjects were included in the safety assessments. The total duration of Study MB09-A-01-19, excluding the screening period, was approximately 36 weeks.

The Phase III consists of two periods: the Main Treatment period during which patients received 2 injections of either MB09 or EU-Prolia at 6-month intervals (Day 1 and Month 6); and a Transition/Safety Follow-Up Period during which patients received an additional dose. Patients who received MB09 in the Main study period, received either an additional dose of MB09 or EU-Prolia in the Transition period; and patients who received EU-Prolia in the Main study period, received one additional dose of EU-Prolia in the Transition period. The duration of the Transition period is another 6 months, for a total of 18 months follow-up. A total of 555 patients received at least one dose (60mg) of study drug (278 and 277 patients in MB09 and EU-Prolia arm, respectively). A total of 520 patients received both doses during the Main treatment period [256 subjects (92.4%) and 264 subjects (95.0%) in the MB09 and EU-Prolia arm, respectively]. The reasons for not administering Dose 2 due to adverse events was only described in total numbers (and not separately presented by the treatment group), therefore no definitive assessment can be made. However, based on the overall low frequency of 35 patients who did not receive the second dose and the individual reasons for not having received it, no issues have been identified presently. All 555 subjects completed the Main study period and are included in the safety analysis. A total of 497 subjects (89.1%) entered the Transition Period and

received a third dose of the study treatment. At the time of the data cut-off for the interim CSR, 352 subjects (63.1%) were translated to the Transition Period, 139 subjects (24.9%) had completed the study. A total of 497 subjects (89.1%) entered the Transition Period to receive the third dose of the study treatment: 245 subjects in the MB09-MB09 arm; 130 subjects in the Prolia-MB09 arm; and 122 subjects in the Prolia-Prolia arm. Of the 497 subjects, 12 subjects (2.4%) discontinued the study: 6 subjects (2.4%) in the MB09-MB09 arm, 3 subjects (2.3%) in the Prolia-MB09 arm, and 3 subjects (2.5%) in the Prolia-Prolia arm. Reasons for discontinuation from the study were balanced between the treatment arms. The size of the safety database and duration of collection of safety data is considered adequate for the purpose of biosimilarity assessment.

In both studies, the panel of AEs monitored, the frequency and duration of safety monitoring are considered adequate to detect potential differences between the products. Based on the known risks of denosumab, adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction monitoring, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) were monitored in the Phase III study.

Results

Adverse events

Study MB09-A-01-19: Overall 63 subjects (24.7%) experienced a total of 92 TEAEs. The proportion of subjects who experienced AEs was similar between the MB09 and US-Xgeva arms and higher in the EU-Xgeva arm (MB09: 21.2% of subjects with 29 AEs; EU-Xgeva 32.9% of subjects with 40 AEs; US-Xgeva 20.0% of subjects with 23 AEs in MB09). The most frequent AEs were increase in blood creatinine phosphatase increased [17 subjects (6.7%) in total], nasopharyngitis [7 subjects (2.7%) in total), blood triglycerides increased [5 subjects (2%) in total], urinary tract infection [4 subjects (1.6%) in total] and headache [4 subjects (1.6%) in total]. AEs were overall well balanced between the treatment groups. In the MB09 arm, blood creatinine phosphatase increased was reported with a higher incidence compared to the US-Xgeva arm (7.1% vs, 2.4%), but with a lower incidence compared to EU-Xgeva arm (10.6%.). None of these were considered related to the study treatment. The safety findings from study MB09-A-01-19 were overall in line with the known safety profile of Xgeva.

The majority of the reported TEAEs were of Grade 2 (11.8%) and Grade 3 (7.5%). None of these TEAEs were considered related to the study treatment. All TEAEs grade 1-3 are well balanced between the MB09 and EU Xgeva treatment group.

Four TEAEs reported in 3 (1.2%) subjects were considered as possibly related to the study treatment. The study treatment-related TEAEs included Grade 1 headache (MB09 arm), 2 episodes of Grade 1 arthralgia (EU-Xgeva arm), and Grade 2 rash papular (US-Xgeva arm). All the TEAEs resolved. These are known adverse events of denosumab. Due to the low frequencies and that the ADRs are well balanced between the treatment groups no concerns have been identified.

Study MB09-C-01-19: In the main period, a total of 839 TEAEs were reported in 311 subjects (56.0%): 161 subjects (58.1%; 442 events) in the MB09 group and 150 subjects (54.0%; 397 events) in the EU-Prolia group with the proportion of patients experiencing any TEAEs, as well as the total number of TEAEs between the treatment groups being similar. The overall incidence of TEAEs in the **transition period** in the Prolia-MB09 and Prolia-Prolia arms was similar (36 subjects [27.7%] and 36 subjects [29.3%], respectively). The safety findings from study MB09-C-01-19 were overall in line with the known safety profile of Prolia.

Overall, TEAEs in 65 subjects (11.7%; 94 events) were considered related to the study treatment by the investigator. A higher proportion of TEAEs related to study treatment was reported in the MB09 group

compared to the EU-Prolia group (14.8% vs 8.6%) in the MB09 and EU-Prolia group, respectively]. The most commonly reported treatment related TEAE (≥1.0% of subjects) were blood PTH increased (14 subjects [2.5%]) and urinary tract infection (6 subjects [1.1%]). These are known adverse events of denosumab. Most study treatment-related TEAEs were Grade 1 or 2 in severity. Grade 3 TEAEs considered related to the study treatment included osteonecrosis of jaw and migraine, each of which was reported in 1 subject (0.2%). In the **transition period**, overall, TEAEs in 8 subjects (3.2%; 12 events) were considered related to the study treatment by the investigator: 3 subjects (2.3%; 4 events) in the Prolia-MB09 arm and 5 subjects (4.1%; 8 events) in the Prolia-Prolia arm. All TEAEs related to the study treatment were either Grade 1 (4 subjects [1.6%]; 7 events) or Grade 2 (4 subjects [1.6%]; 5 events) in severity.

Serious adverse events/deaths

Study MB09-A-01-19: SAEs were reported in 2 (2.4%) subjects in MB09 arm (osteoma and depression reported in one subject, respectively), but none were considered to be related to the IP. No SAEs were reported in EU- or US-Xgeva arms. No concerns arise from the assessment of SAEs in this study.

Study MB09-C01-19: SAEs were reported in a total of 32 subjects (5.8%) with a slightly higher incidence in the MB09 group compared to the EU-Prolia group (6.9% vs. 4.7%). SAEs were most frequently (>0.5% of total subjects) reported in the SOCs of Musculoskeletal and connective tissue disorders (7 subjects [1.3%]), mostly fractures (hip fracture, ankle fracture, and ulna fracture in 2 [0.4%], 1 [0.2%], and 1 [0.2%] subjects, respectively) followed by gastrointestinal disorders (5 subjects [0.9%]) and hepatobiliary disorders (4 subjects [0.7%]). Except for the fracture PTs (4 subjects) and cholelithiasis (2 subjects [0.4%]), all other serious TEAEs were reported in 1 subject. In the Phase III study MB09-C-01-19 grade 3 serious TEAEs of osteonecrosis of jaw (confirmed by biopsy) and migraine, each reported in 1 subject (0.2%), were considered related, and all other serious TEAEs were considered unrelated to study treatment by the applicant. In the **Transition Period**, serious TEAEs were reported in 2 subjects (1.6%; 3 events) in the Prolia-Prolia arm and included Grade 3 cardiac disorder in 1 subject and Grade 2 diverticulitis and thrombophlebitis in 1 subject. None of the serious TEAEs were considered related to the study treatment.

There were no deaths during Study MB09-A-01-19 nor during the Main Treatment Period of Study MB09-C-01-19. One subject (Subject PL005128) in the MB09-MB09 arm experienced a TEAE of pneumonia that led to the subject's death in the **Transition Period.** The TEAEs of pneumonia haemophilus (Grade 4) and pneumonia (Grade 5) were considered unrelated to the study treatment.

Adverse events of special interest

In Study MB09-C-01-19 treatment-emergent AESIs were reported in a total of 155 patients (27.9%; 232 events): 80 subjects (28.9%; 119 events) in the MB09 group and 75 subjects (27.0%; 113 events) in the EU-Prolia group. For the **transition period** treatment-emergent AESIs were reported in a total of 38 subjects (15.0%; 45 events): 17 subjects (13.1%; 21 events) in the Prolia-MB09 arm and 21 subjects (17.1%; 24 events) in the Prolia-Prolia arm

Throughout the study, injection site reactions were reported in 4 subjects and included: injection site erythema in 2 subjects and injection site hypersensitivity in 1 subject in the MB09-MB09 arm in the Main Treatment Period and injection site mass in 1 subject in the Prolia-Prolia arm in the Transition Period. All injection site reactions were nonserious and Grade 1 in severity. Throughout the study, AESIs of hypersensitivity, allergic, and dermatologic reactions were reported in 4.0% subjects in the MB09-MB09 arm and 2.2% subjects in the Prolia-Prolia arm. All reactions were Grade 1 or 2 in severity, except Grade 3 serious event of psoriasis reported in 1 of 3 subjects with psoriasis in the MB09-MB09 arm. The treatment-emergent AESI of urticaria in 1 subject and rash pruritic in another subject in the MB09-MB09 arm were

considered related to the study treatment; all others in the MB09-MB09 and Prolia-Prolia arms were unrelated. Throughout the study, most treatment-emergent AESIs were reported in the SOC of infections and infestations (29.6% subjects in the MB09-MB09 arm and 29.0% subjects in the Prolia-Prolia arm). Few AESIs related to infections were reported in the SOC of gastrointestinal disorders and all infections as treatment-emergent AESIs. Most of these AESIs were nonserious and Grade 1 or 2 in severity. Grade 3 pulmonary tuberculosis in 1 subject and Grade 2 pneumonia in 1 subject in the MB09-MB09 arm were serious. Additionally, serious AESIs included a Grade 4 TEAE of pneumonia haemophilus that later worsened in severity leading to the subject's death (Grade 5 TEAE of pneumonia) in the MB09-MB09 arm. Throughout the study, hypocalcaemia (1 subject in the MB09-MB09 arm and 1 subject in the Prolia-Prolia arm) and related PTs of adjusted calcium decreased (2 subjects in the MB09-MB09 arm) and blood calcium decreased (1 subject in the Prolia-Prolia arm) were reported as AESIs, all in the Main Treatment Period. Osteonecrosis of jaw was reported as an AESI in 1 subject (0.2%) in the MB09-MB09 arm in the main treatment period, it was a Grade 3 serious treatment-emergent AESI. No cases of atypical femoral fracture were reported. Fractures were reported in a total of 22 subjects: 12 subjects (4.3%) in the MB09-MB09 arm, 6 subjects (4.3%) in the Prolia-MB09 arm, and 4 subjects (2.9%) in the Prolia-Prolia arm. All fractures were traumatic except for the thoracic vertebral fracture in the Main Treatment Period (MB09-MB09 arm) that was probably a compression fracture as reported by the investigator and 2 fractures (lumbar vertebral fracture [MB09-MB09 arm] and thoracic vertebral fracture [Prolia-Prolia arm]) in the Transition Period whose kinetics were unknown to the investigator.

Discontinuation due to adverse events

Study MB09-A-01-19: one subject in the US-Xgeva arm discontinued the study due to AE (body temperature increased, not related, resolved, no treatment required). No concerns arise from this study.

Study MB09-C-01-19: Treatment-emergent AEs leading to discontinuation of study treatment were reported in a total of 4 subjects in the MB09 treatment group (0.7%). Two subjects discontinued the study treatment due to Grade 2 gingivitis after receiving the first dose of the study treatment. One subject discontinued the study treatment due to Grade 3 serious TEAE of osteonecrosis of jaw. One subject discontinued the study treatment due to Grade 3 serious TEAE of renal cancer metastatic. No TEAEs led to treatment discontinuation in the Transition Period.

Laboratory findings

According to the applicant 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.

2.5.10. Conclusions on the clinical safety

Based on the provided data of two clinical studies, one in healthy male volunteers and one in female PMO patients, no unexpected safety concerns were detected across the clinical studies. The observed safety findings correspond to the known safety profile of the reference product Prolia/Xgeva and were well balanced between treatment groups. Also, the rate of fractures as TEAE, Grade ≥3 or serious event were balanced between both treatment groups of study 002 in postmenopausal women with osteoporosis at high risk of fracture.

Overall, the collected safety data appears indicative of comparable safety between the biosimilar candidate MB09 and the RMP Prolia/Xgeva, supporting the claim for biosimilarity.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 59: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcaemia several months after the last dose inpatients with giant cell tumour of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumour of bone • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 60: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. Additional risk minimisation measures • Patient reminder cards	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire - Osteonecrosis of the Jaw • Potential events of ONJ, reported in ongoing clinical trials, are adjudicated by a panel of external medical experts. • Potential events of ONJ reported in the post marketing setting are medically reviewed internally to determine if the ONJ events meet the AAOMS ONJ case definition. Additional pharmacovigilance activities: • None
Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip, or groin pain is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for reporting new or unusual pain in your thigh, hip, or groin is discussed. • PIL Section 4, where signs of thigh bone fracture are discussed. Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Denosumab core questionnaire – Post marketing reports of potential atypical fracture. • Potential cases of AFF from clinical trial setting are adjudicated by an independent committee that is blinded to treatment. • Potential cases of AFF from post marketing setting are medically reviewed internally based on diagnosis of the radiographic findings and without requiring the

		radiographs to be sent to mAbxience. Additional pharmacovigilance activities: • None
Hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons	Routine risk minimisation measures: • SmPC sections 4.4 where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Denbrayce is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Denbrayce treatment is discussed. • PIL Section 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Potential Risks		
Cardiovascular events	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimisation measures: • SmPC Section 4.4, where recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis is discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 Additional risk minimisation measures • None	Routine pharmacovigilance beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None

Delay in diagnosis of primary malignancy in giant cell tumour of bone	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Missing Information		
Patients with prior intravenous bisphosphonate treatment	Routine risk minimisation measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • None

Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xgeva. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Denbrayce (denosumab) is included in the additional monitoring list as it is a biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

MB09 was developed as a biosimilar product to the reference products Prolia and Xgeva (INN: denosumab). This MAA under the Centralised Procedure is an application for the proposed biosimilar MB09 to Xgeva according to Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The application has been submitted in accordance with Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product. Prolia and Xgeva were originally approved in the European Union on 13/07/2011 (marketing authorisation holder: Amgen Europe B.V.).

The reference product Xgeva has two presentations approved (XGEVA 120 mg/1.7 mL solution (70 mg/mL) for injection in a vial for s.c. use; and XGEVA 120 mg/1.0 mL solution (120 mg/mL) for injection in pre-filled syringe for s.c. use).

The applicant proposes one presentation of the biosimilar MB09 under the name **Denbrayce**: 120 mg/1.7 mL solution (70 mg/mL) for injection in a single-use vial.

The proposed indications are the same as approved for the reference product Xgeva that 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 Xgeva.

Quality aspects

In general, a very comprehensive and sound biosimilarity assessment has been conducted. Since both, EU-sourced reference product and US-sourced comparator product, have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product, based on 3 pairwise analytical comparisons has been established. MB09 has been developed as vial and as pre-filled syringe presentation similar to the reference product presentations. Comparability between the two presentations was demonstrated, supporting pooling of data for the biosimilarity evaluation.

A broad panel of orthogonal state-of-the-art methods has been applied for biosimilarity evaluation to address general properties, primary structure, secondary, tertiary and higher order structure, post-translational modifications, product purity, and biological activity. Degradation profiles have been analysed in comparative stability studies. All individual test results of the analytical similarity exercise are provided and based on the provided information, it is concluded that the analytical methods are suitable for the intended purpose.

Clinical aspects

The clinical development programme for MB09 included one completed Phase I clinical study in healthy male subjects (study MB09-A-01-19) and one completed Phase III study in postmenopausal women with osteoporosis (MB09-C-01-19).

Study **MB09-A-01-19** was a randomised, double-blind, 3-arm, single-dose, parallel bioequivalence Phase I study to compare the PK, PD, safety, and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-/US-Xgeva in healthy male volunteers.

A total of 257 subjects were enrolled and randomised in a 1:1:1 ratio to receive a single dose of 35 mg of either MB09, EU-Xgeva or US-Xgeva via s.c. injection. A total of 255 (99.2%) subjects was treated (before study treatment administration 1 subject in the EU-Xgeva arm withdrew, while another subject in the US-Xgeva arm was discontinued due to an adverse event) on Day 1. The study population was followed for 253 days for PK, PD, safety and immunogenicity assessment. Randomisation was stratified based on the subject's body weight (60 to <80 kg and 80 to 95 kg).

Study **MB09-C-01-19** was a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, PK, PD, safety and immunogenicity of MB 09 vs. Prolia in postmenopausal women with osteoporosis.

Patients received either MB09 or EU-Prolia 60 mg administered s.c. at Day 1 and at Month 6 during the Main Treatment Period. A third dose of either 60 mg MB09 or EU-Prolia was administered at the beginning of the Transition/Safety Follow-up Period at Month 12.

A total of 558 patients were randomised 2:1:1 to receive either MB09 in the Main Treatment Period and the Transition Period, Prolia in the Main Treatment Period and MB09 in the Transition Period, or Prolia in the Main Treatment Period and the Transition Period. Randomisation schedule was stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use). A total of 555 patients received one dose and 520 patients received two doses of study treatment. A total of 497 subjects received the third dose (Month 12) of the study treatment.

The safety profiles of MB09 and the reference products were assessed in the phase I study, as well as in the Phase III study.

3.2. Results supporting biosimilarity

Quality

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

Clinical Aspects

PK:

The pivotal demonstration of equivalence in PK of MB09 and EU-Xgeva was achieved in study **MB09-A-01-19** healthy male subjects. Overall, denosumab serum concentration vs. time profiles were comparable between the treatment arms. There was no relevant difference in the time to attain maximum serum concentrations of denosumab (Tmax) between all 3 treatment groups. In addition, remaining PK parameters (AUC0-99, t1/2, CL/F, Vz/L) were similar between treatment groups and support the PK similarity of the test and reference products.

The 90% CIs for the ratios of geometric means (MB09/EU-Xgeva) for Cmax, AUC0-inf and AUC0-last were entirely contained within the [80.00%, 125.00%] equivalence range. The ratios of geometric means [90% CI] (MB09/EU-Xgeva) for Cmax, AUC0-last and AUC0-inf were 105.15% [98.04%, 112.78%], 105.95% [98.63%, 113.82%], and 105.95% [98.58%, 113.87%], respectively. The results are supporting equivalence of MB09 to EU-Xgeva,

Biosimilarity in PK of MB09 and EU-Prolia was additionally shown in postmenopausal women with osteoporosis in study **MB09-C-01-19**.

PK parameters Cmax, AUC0-6months, Ctrough at Month 6, Ctrough at Month 12 were overall comparable for the Main Treatment Period as well as for the Transition Period.

PD:

Biosimilarity in PD of MB09 and EU-/US-Xgeva was assessed in healthy male subjects in study **MB09-A-01-19**. Comparative testing was performed for the PD endpoints AUEC0-253 based on absolute sCTX values and AUIC0-253 based on %CFB of sCTX. Furthermore, summary statistics of AUEC0-last, AUIC0-last, Cmin, Tmin, Imax and TImax have been presented. With the exception of AUEC0-253, for which the results were found to be not interpretable, PD parameters were comparable between treatment groups.

Biosimilarity in PD of MB09 and EU-Prolia was primarily assessed in postmenopausal women with osteoporosis in study **MB09-C-01-19**. Evaluated PD parameters were absolute sCTX concentration vs. nominal time profiles, percentage of change from baseline (%CfB) of sCTX vs. nominal time profiles, AUEC0-6 months, AUIC0-6 months (co-primary endpoint), Imax and TImax for the Main Treatment Period. Overall, parameters were comparable between treatment groups. The estimated ratio of geometric means ratio (MB09/EU-Prolia) for AUIC0-181days for %CFB sCTX values was 99.81% (95% CI: 97.07%, 102.62%). The 95% CIs presented are sufficiently narrow and close enough to 1 to support the claim of biosimilarity.

Also, during the Transition Period, levels of sCTX were overall comparable across treatment groups.

Efficacy:

The primary efficacy analysis resulted in an estimated difference in %CfB in lumbar spine BMD after 52 weeks between the MB09 and the EU-Prolia group of 0.20% (95% CI: -0.51, 0.91). Thus, the 95% CI was contained within the predefined similarity range of [-1.45, 1.45], supporting the claim of biosimilarity. Furthermore, the 95% CI for the ratio of geometric means (MB09/EU-Prolia) for AUIC0-181days based on %CfB of sCTX was contained within the pre-defined [80.00%, 125.00%] interval, supporting the claim of biosimilarity.

This was further supported by secondary endpoints (Difference in means (MB09 minus EU-Prolia) of %CfB in lumbar spine BMD after 6 months, hip BMD after 6 and 12 months, femur neck BMD after 6 and 12 months).

Immunogenicity

Overall, the observed low immunogenicity with both treatments is in line with the low historical rate of ADAs for Prolia (<1%). Due to the low numbers reported, it can be concluded that there is no impact of ADAs on the PK of MB09. The results of the immunogenicity assessment are considered supportive of biosimilarity.

Clinical Safety

In the Phase I study MB09-A-01-19, the safety profile in healthy men was comparable between MB09 and EU-Xgeva. Overall, 92 TEAEs were reported in this study from 21.2% of subjects (29 AEs) and 32.9% of subjects (40 AEs) of subjects in the MB09 and EU-Xgeva treatment groups, respectively. TEAEs considered to be related to study drug were reported in 1 subject and 2 subjects in the MB09 and EU-Xgeva groups, respectively. There were no deaths and only one AE leading to study discontinuation.

In the main treatment period of the Phase III study MB09-C-01-19, a total of 839 TEAEs were reported in 311 subjects (56.0%): 161 subjects (58.1%; 442 events) in the MB09 group and 150 subjects (54.0%; 397 events) in the EU-Prolia group with the proportion of patients experiencing any TEAEs, as well as the total number of TEAEs between the treatment groups being similar. The overall incidence of TEAEs in the **transition period** in the Prolia-MB09 and Prolia-Prolia arms was similar (36 subjects [27.7%] and 36 subjects [29.3%], respectively). The safety findings from study MB09-C-01-19 were overall in line with the known safety profile of Prolia.

3.3. Uncertainties and limitations about biosimilarity

Quality

No uncertainties about biosimilarity remain.

Clinical Aspects

In the Phase I study, the review of individual denosumab concentrations revealed fluctuations in concentrations around expected Tmax (double peaking) and at later time points (albeit to a lesser extent) in a small number of participants. This phenomenon was observed with both the biosimilar candidate and the reference product. The fact that some of these fluctuations were observed around the expected Tmax introduces uncertainty on the capture of Cmax (one of two co-primary endpoints) and thereby on the exact equivalence testing results, though biosimilarity can be concluded.

3.4. Discussion on biosimilarity

Quality

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

Clinical Aspects

PK similarity between the investigated product and the reference product has been demonstrated in healthy volunteers based on the standard criteria used for biosimilars, i.e. the 90% CIs around the geometric LS mean ratios for Cmax and AUC0-6months (used as co-primary endpoints) were entirely included within the predefined acceptance limits (80.00%, 125.00%). The review of individual denosumab concentrations revealed fluctuations in concentrations around expected Tmax (double peaking) and at later time points (albeit to a lesser extent) in a small number of participants. This phenomenon was observed with both the biosimilar candidate and the reference product. The fact that some of these fluctuations were observed around the expected Tmax introduces uncertainty regarding the exact data for Cmax (one of two co-primary endpoints) in equivalence testing.

Phenomena of huge short-term PK fluctuations were discussed by Reijers et al. (Clin Pharmacokinet, 2017). This paper shows that the plasma concentration–time course of selected monoclonal antibodies can show considerable fluctuations with no straightforward explanations based on physiology or assay variability.

Although the reasons for these fluctuations are currently not understood, the frequency and magnitude of concentration fluctuations observed in this application were sufficiently low/small to not raise concerns about the overall similarity conclusion for Cmax. The other co-primary endpoint AUC, which is less affected by these fluctuations compared to Cmax, was also within the usual equivalence margins and overall biosimilarity in PK is demonstrated.

Further PK data collected in women with PMO support similarity.

PD similarity between the investigated product and the reference product has been demonstrated in women with PMO based on the evaluations of the bone turnover parameter sCTX.

Furthermore, similarity between the investigated product and the reference product regarding efficacy was demonstrated in women with PMO using percent change from baseline in lumbar spine BMD after 52 weeks as a primary endpoint, and hip BMD (after 6 and 12 months) and femur neck BMD (after 6 and 12 months) as secondary endpoints.

Incidences of adverse events were overall comparable between the two treatments and the safety risks identified in the Phase I study are overall consistent with the known safety profile of the reference product.

The discrepancies between the treatment arms regarding the higher proportion of TEAEs related to study treatment reported in the MB09 group compared to the Prolia group in the Phase III study is of no concern, as the total numbers are low and the adverse events are the most common events listed in the SmPC of the reference product.

Overall, the submitted data supports the similarity of the biosimilar candidate to the reference product Prolia/Xgeva. The uncertainties regarding the individual denosumab concentration levels, apart from being observed with low frequency and of magnitude, were not associated with relevant difference in efficacy and safety outcomes in PMO patients in a Phase III study. Biosimilarity of MB09 to Prolia/Xgeva is considered demonstrated.

3.5. Extrapolation of safety and efficacy

MB09 was developed as a biosimilar to Prolia and Xgeva. The active substance of MB09 and both originators, denosumab, is a human monoclonal antibody of the IgG2 subtype that inhibits the interaction of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) with RANK on the surface of osteoclasts. This inhibition prevents the development (genesis, maturation, activation and survival) of osteoclasts, the cells responsible for bone resorption that play a critical role in bone modelling and remodelling during growth. 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 post-menopausal women with osteoporosis. These are regarded sensitive populations in terms of evaluating biosimilarity of MB09 and the reference product.

Consequently, as biosimilarity has been demonstrated in a full analytical similarity exercise and extended functional characterisation, and since Phase I and III clinical data demonstrate i) PK similarity and ii) similarity in an indication representative for both efficacy and safety (i.e. in post-menopausal women with osteoporosis), extrapolation to all EU-approved indications for Prolia/Xgeva is acceptable.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

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