25 April 2025
EMA/164535/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evfraxy

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006526/0000

Note

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

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Table of contents

List of abbreviations

AEX	Anion Exchange Chromatography
AC	Acceptance Criterion
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AGE	Advanced Glycation End products
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the serum concentration versus time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the serum concentration versus time curve from time zero to the last sampling time at which concentrations were at or above the limit of quantification
AUEC	Area under the effect curve
AUIC	Area under the % inhibition curve
BET	Bacterial endotoxin test
BMD	Bone mineral density
BMI	Body mass index
BP	Bubble Point
%CfB	Percent change from baseline
cfb	Change from baseline
CEX	Cation Exchange Chromatography
CFU	Colony Forming Unit
CHO	Chinese hamster ovary
CHMP	EMA Committee for Medical Products for Human Use
CI	Confidence interval
cIEF	capillary Iso-electric Focusing
CL/F	Apparent clearance
C_{max}	Maximum observed denosumab concentration
Cmin	Minimum concentration
COVID-19	Coronavirus disease 2019
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	Case report form
CRO	Contract research organisation
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal telopeptide of Type 1 collagen
CTXI	Type I collagen C-telopeptides
C_t	Last observed quantifiable serum denosumab concentration
CV	Coefficient of variation
DP	Drug Product
DS	Drug Substance
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCTD	electronic Common Technical Document
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
E_{max}	Maximal inhibitory effect
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EoS	End-of-study
EoSL	End of Shelf life
EU	European union
FAS	Full analysis set

FAS-TP	Full analysis set for Transition Period
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	General Process parameter
HC	Heavy Chain
HILIC-UHPLC-FL	Hydrophobic Interaction Chromatography-Ultra HPLC with Fluorescence
HMW	High Molecular Weight Species
HPLC	High Performance Liquid Chromatography
ICE	Intercurrent event
ICF	Informed consent form
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
Imax	Maximum % inhibition
IND	International New Drug
IRB	Institutional review board
IRT	Interactive response technology
IPC	In-process Control
IPM	In-Process Monitoring
ISR	Injection-site reaction
IWRS	Interactive web response system
k_{el}	Terminal elimination rate constant
LC	Light Chain
LMW	Low Molecular Weight Species
LS mean	Least squares mean
MAR	Missing at random
MCB	Master Cell Bank
Met253	Methionine in the 253 position
mFAS	Modified full analysis set
mFAS-TP	Modified full analysis set for Transition Period
MFI	Micro Flow Imaging
MI	Multiple imputation
MMRM	Mixed model for repeated measures
N/A	Not Applicable
NAb	Neutralizing antibody
NF-κB	Nuclear factor-kappa B
NHV	Normal healthy volunteer
NMT	Not More Than
NOR	Normal Operating Range
NR-CE-SDS	Non-reducing Capillary Electrophoresis Sodium Dodecyl Sulfate
NTU	nephelometric turbidity unit
P1NP	Procollagen type 1 N-terminal propeptide
PAR	Proven Acceptable Range
PCEs	Process Control Elements
PD	Pharmacodynamics
pDADMAC	Poly (diallyldimethylammonium chloride)
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PMO	Postmenopausal Women with Osteoporosis
PPI	Process performance indicator
PPP	Process performance parameter
PPQ	Process Performance Qualification
PPS	Per-protocol set
PT	Preferred term
PV	Process Validation
QA	Quality Attribute
QTPP	Quality Target Product Profile
R&D	Research and Development
RANKL	Receptor Activator of Nuclear Factor kappa-B Ligand

R-CE-SDS	Reducing Capillary Electrophoresis Sodium Dodecyl Sulfate
RMP	Reference Medicinal Product
RNS	Rigid Needle Shield
RP-HPLC	Reversed-phase HPLC
RP-HPLC-UV	RP-HPLC UV detector
SAE	Serious adverse event
SAF	Safety analysis set
SAF-TP	Safety analysis set for transition period
SAP	Statistical analysis plan
sAUEC	Standardised AUEC
SC	Subcutaneous
sCTX	Serum C-terminal telopeptide of Type 1 collagen
SD	Standard deviation
SE	Standard error
SEC	Size-exclusion chromatography
SE-HPLC	Size-exclusion-HPLC
SmPC	Summary of Product Characteristic
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time at which Cmax occurred
T_{min}	Time of occurrence of the minimum concentration
TPP	Target Product Profile
US	United States
USP	United States Pharmacopeia
Vd/F	Apparent volume of distribution
WCB	Working Cell Bank
WFI	Water for Injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biosimilar Collaborations Ireland Limited submitted on 28 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Evfraxy, 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:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Evfraxy significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Evfraxy significantly reduces the risk of vertebral fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Vevzuo 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: Prolia 60 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26 May 2010
- Marketing authorisation granted by:

  - Union
- Marketing authorisation number: EU/1/10/618

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

- Product name, strength, pharmaceutical form: Prolia (denosumab); 60 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26 May 2010
- Marketing authorisation granted by:

- Union

- Marketing authorisation number: EU/1/10/618

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: Prolia 60 mg solution for injection
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26-05-2010
- Marketing authorisation granted by:
  - Union

  Marketing authorisation number(s): EU/1/10/618
- Bioavailability study number(s): B1000-NHV-01-G-01 and B1000-PMO-03-G-02

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
26 March 2020	EMEA/H/SA/4398/1/2020/III	Juha Kolehmainen, Linda Trauffler
14 October 2021	EMA/SA/0000063174	Juha Kolehmainen, Ferran Torres
21 July 2022	EMA/SA/0000091701	Linda Trauffler, Juha Kolehmainen
21 March 2023	EMA/SA/0000164124	Sheila Killalea, Hrefna Gudmundsdottir

The Scientific advice pertained to quality and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Thalia Marie Blicher

The application was received by the EMA on	28 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 November 2024
The CHMP Co-Rapporteur's Critique was circulated to all PRAC and CHMP members on	18 November 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP agreed on a List of Outstanding Issues to be sent to the applicant on	27 March 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 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	9 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 Evfraxy on	25 April 2025

2. Scientific discussion

2.1. About the product

Evfraxy (also referred to as Bmab 1000) contains the active substance denosumab and is being developed as a proposed biosimilar product to Prolia.

The product was initially referred to as Denosumab BBL during the procedure. However, upon request by the applicant, the trade name was changed to Evfraxy during the decision-making phase after the adoption of the CHMP Opinion.

Denosumab is a fully human IgG2 monoclonal antibody with high affinity and specificity for the human RANKL. By binding to RANKL, denosumab inhibits RANKL from activating its only receptor RANK on the

surface of osteoclasts and their precursors. Prevention of RANKL-RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and attenuating bone rarefication.

The proposed indications for Evfraxy (Bmab 1000) are the same as those approved for Prolia:

- Treatment of osteoporosis in post-menopausal 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.

The applicant is claiming all approved indications of the reference product.

2.2. Type of application and aspects on development

Evfraxy and Vevzuo are proposed biosimilars to EU-Prolia and EU-Xgeva, respectively. The applicant has applied for two denosumab biosimilar MAs, the present Evfraxy (60 mg denosumab, biosimilar to Prolia) and the Vevzuo (120 mg denosumab, biosimilar to 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.

The clinical development programme comprises two trials:

- Study B1000-NHV-01-G-01: a single-dose bioequivalence study with a 36-week post-dose follow-up with the primary purpose was to establish PK similarity between Bmab 1000 and Prolia in normal healthy volunteers (NHVs).
- Study B1000-PMO-03-G-02: a confirmatory Phase 3 study comparing the efficacy, pharmacodynamics (PD), safety, immunogenicity, and PK of Bmab 1000 with Prolia in post-menopausal women with osteoporosis.

2.3. Quality aspects

2.3.1. Introduction

Evfraxy (Bmab 1000-P) finished product contains the active substance denosumab (Bmab 1000 AS). Bmab 1000 AS is a human lgG2 monoclonal antibody expressed in CHO cells which binds the cytokine RANKL (receptor activator of NFKB ligand), an essential factor for bone turnover. Inhibition of RANK-RANKL binding prevents osteoclast maturation, function, and survival and has the potential to reduce bone resorption, thereby offering new therapeutic options.

The Bmab 1000-P finished product is presented as solution for injection containing 60 mg of denosumab as active substance in 1mL Prefilled syringe (PFS) of solution (60 mg/mL). The Bmab 1000-P finished product (60 mg/mL in PFS) presentation is a proposed biosimilar to EU-approved Prolia (EMEA/H/C/001120). Prolia (60 mg/mL in PFS) solution for injection is administered via subcutaneous injection.

Bmab 1000-P other ingredients are: acetic acid glacial, Sodium acetate trihydrate, Sodium hydroxide, Sorbitol, Polysorbate 20 and water for injections

The product is available in a one single use pre-filled syringe made from type I glass with stainless steel needle (29 G×½-inch), with automatic needle guard and a rubber plunger stopper (fluoropolymer coated bromobutyl rubber).

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied. During active substance (AS) process characterisation and finished product formulation development, a multivariate approach using Design of Experiment (DoE) and univariate studies were used to evaluate the impact on individual operating parameters on identified Critical Quality Attributes (CQAs).

Evfraxy has been compared against denosumab from both EU authorised products Prolia (denosumab, 60 mg/ml PFS) and Xgeva (denosumab, 120mg/1.7 mL vial) during its development.

2.3.2. Active substance

2.3.2.1. General information

Biocon has developed Bmab 1000 AS as proposed similar biological medical product; where Bmab 1000-P (60mg/mL in PFS) and Bmab 1000-X (120mg/1.7mL in vial) are proposed biosimilars to EU-Approved and US-Licensed Prolia and Xgeva respectively.

Denosumab as active substance in Prolia , Xgeva and Bmab 1000 AS belongs to the pharmaco-therapeutic group of drugs for treatment of bone diseases. The IgG2 monoclonal antibody consists of 2 heavy chains, and 2 light chains of the kappa subclass. It contains 36 total cysteine residues, which are involved in both intra-chain and inter-chain disulfide bonds. Each heavy chain contains 448 amino acids (including C-terminal lysine) with 4 intra-chain disulphides and an N-linked glycan at the consensus glycosylation site at asparagine 298. Each light chain contains 215 amino acids with 2 intramolecular disulphides. Additional modifications such as oxidation of methionine residues, C-terminal lysine, proline amidation at the C-terminus, and deamidation sites were identified in Bmab 1000 AS.

Bmab 1000-P and Bmab 1000-X (denosumab 70 mb/mL in vial) are produced by recombinant DNA technology in a mammalian cell expression system and is purified by using a process that includes a series of chromatographic steps, viral inactivation and removal steps, and filtration steps. Structure and general properties are sufficiently described, including primary structure details. Like other complex glycoproteins, denosumab displays a certain amount of microheterogeneity in terms of different degrees of glycosylation and modifications of amino acids.

2.3.2.2. Manufacture, process controls and characterisation

All manufacturing and testing sites of Bmab 1000-P active substance are covered by valid GMP certificates.

- Manufacturing of Bmab 1000-P Active substance: Biocon Biologics Limited Block No. B1, B2, B3, B5, Q13 of Q1 and W20 & Unit S18, 1st Floor, Block B4, Special Economic Zone Plot No. 2, 3, 4 & 5, Phase IV Bommasandra - Jigani Link Road, Bommasandra, Bengaluru – 560099, India (IND)

Description of manufacturing process and process controls

The Bmab 1000-P active substance manufacturing process has been adequately described. Main steps are cell culture, fermentation, purification and formulation. The ranges of critical process parameters

and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

The Bmab 1000-P active substance (AS) manufacturing process is composed of upstream and downstream parts followed by formulation, filling, storage and transport of the formulated bulk AS. Bmab 1000-P is produced by recombinant DNA technology in a mammalian cell expression system (CHO cells) and is purified by using a process that includes a series of chromatographic steps, viral inactivation and removal steps, and filtration steps. Denosumab displays a certain amount of microheterogeneity in terms of different degrees of glycosylation and modifications of amino acids.

The cell culture upstream part of the manufacturing process starts with thawing of one WCB (Bmab 1000 AS expression in recombinant CHO cells), followed by propagation in shake flasks used to inoculate single-use seed bioreactor, followed by inoculation of batch fermentation process in a progressively scale-up.

The downstream process of Bmab 1000 AS commences with clarification of the cell culture harvest. The harvest cell culture fluid containing Bmab 1000 AS is clarified by subsequent filtration steps in series.

The clarified harvest is concentrated using chromatography (Protein-A), and is processed for virus deactivation (low pH incubation), filtration and removal of impurities by chromatography (ANEX, CEX). The eluate is filtered for viral clearance, followed by ultrafiltration/diafiltration and diafiltration (buffer exchange) to formulate the final bulk active substance.

Following the UF/DF filtration, the Bmab 1000 AS is formulated into first an intermediate AS and later formulated bulk drug substance (FBDS) to adjust target protein concentration. Finally, the FBDS is filtered and filled into single use bags for freezing and long-term storage.

Control of materials

A comprehensive overview of the used raw materials and reagents has been given. Some of the raw materials comply with relevant compendia (EP and/or USP/NF). Non-compendial materials are released using internal methods and standards. Acceptance criteria and analytical methods used for testing of non-compendial raw materials are provided. The chromatography resins and filters (material, pore size, manufacturer and specifications) are adequate. Qualitative composition of media used is stated.

The Chinese Hamster Ovary (CHO) derived cell line employed for the expression of high levels of Denosumab was established using a replication-defective retroviral technology, gene product expression (GPEx) technology.

Denosumab cell lines were developed by performing multiple rounds of transduction of the GPEx Chinese Hamster Ovary (GCHO) parental cell line with retro vectors made from the gene constructs developed to express denosumab antibody light chain (LC) and heavy chain (HC).

A peptide mapping was performed against Xgeva to confirm the amino acid sequence for light chain (LC) and heavy chain (HC) of monoclonal antibody expressed by cell lines. The coding DNA sequences (CDS) for optimal expression of the antibody LC and HC was designed. The identity of the plasmids encoding the LC and HC CDS of the denosumab monoclonal antibody were confirmed by DNA sequencing. These retroviral expression vectors were used for development of denosumab production cell lines. The cell bank system for Bmab 1000 AS comprises a two-tier system with Master Cell Bank (MCB) and Working Cell Bank (WCB). All cell banks were tested in accordance with ICH Q5A, Q5B and ICH Q5D and found to be free from adventitious agent. End of Production Cell Bank (EPCB) and Post-Production Cell Bank (PPCB) were further established. Bmab 1000 AS Limit of In Vitro Cell Age (LIVCA) was established.

The qualification protocol for the new WCB and analytical methods used (for cell characterisation and testing) was found acceptable. In general, adequate information on assay description and/or qualification/validation is provided.

Control of critical steps and intermediates

Overall, the analytical tools used for IPC process control and monitoring are suitable for intended purpose. A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the Bmab 1000 active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

IPCs are controlled through action limits or acceptance criteria at each stage of the manufacturing process to process control and consistent quality of AS.

The definition of criticality of parameters and IPCs is sufficient, based on risk management principles of ICH Q9 and Q11.

The analytical methods for IPCs are described and adequately validated.

Process validation

The Bmab 1000-P active substance manufacturing process has been validated adequately. Consistency in production has been shown on a sufficient number of process validation (PV) full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces Bmab 1000 active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The manufacturing process has been evaluated using a combination of conventional univariate studies and elements of QbD such as design of experiments (DOE).

Process characterisation:

A multivariate approach using Design of Experiment (DoE) and univariate studies were used to evaluate the effect of individual operating parameters and their interactions response on identified Critical Quality Attributes (CQAs), which is endorsed. Based on statistical analysis of the results obtained from the process characterisation experiments, the process parameters that were found to have significant impact on a CQAs were designed as a Critical Process Parameters (CPPs). In addition, linkage studies were performed, where low and high ranges obtained as outcome from the process characterisation studies were evaluated. During the linkage study, if the product quality was found to be within the desired acceptable range, then these parameters were categorised as non-critical and if found beyond the desired acceptable range then it was categorised as critical. The proven acceptance range (PAR) for process parameters were defined based on both the PC study and subsequent linkage study. Based on this data, the proven acceptable range was derived for identified process parameters.

Process characterisation studies have been performed at small scale models. The approach used for scale down model qualification was to keep the scale independent parameters identical to that used in the manufacturing process and change appropriately the scale dependent process parameters. Comparison of small scale models and commercial process is clearly presented in the dossier, as well as qualification of these models. Results confirm representativeness of small scale models to commercial process.

Based on process experience through process development, risk assessment (FMEA) and process characterisation studies, the process parameters are categorised as critical process parameters (CPPs) or non-critical process parameters (NCPPs) and their proven acceptable range (PAR) was defined.

All in-process and release methods used during the Process Validation (PV) studies were validated and all non-routine test methods were adequately qualified. The PV campaign demonstrated process parameters remain within the defined manufacturing operating range (MOR) or proven acceptable range (PAR) and sufficient control of potential extractables and leachables.

The continuous process validation (CPV) approach to ensure that the manufacturing process of Bmab 1000 AS remains validated during routine and product lifecycle is acceptable

Bmab 1000-P cell culture process is consistent, reproducible and validated. The results for PV batches using the finalised commercial process demonstrated process parameters and IPC are within predefined limits, including adequate control of endotoxin and bioburden during formulation.

Downstream process showed capability to clear impurities related to host, process and product.

Manufacturing process development

The primary objective of process development was to ensure similarity to the reference product. The formulation process development ensured that the product would be amenable for long-term storage and match the reference product's degradation profiles.

The manufacturing process for Bmab 1000-P AS was first developed using laboratory scale bioreactors and downstream unit operation systems. A stepwise approach for development of each unit operation of the manufacturing process was carried out.

This approach ensured that the manufacturing process consistently produced Bmab 1000-P product meeting the targeted quality profile. Bmab 1000 AS was targeted to have identical formulation components as that of reference product.

Characterisation

The Bmab 1000-P active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of denosumab active substance. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterisation of Bmab 1000-P indicates that this antibody has the ability to bind human RANKL with high affinity and to specifically bind to Fc Receptor as expected of an IgG2. In summary, the characterisation is considered appropriate for this type of molecule.

The analytical techniques to assess the structural, physicochemical and biological properties of Bmab 1000-P AS are qualified. Results of the physicochemical and functional characterisation of Bmab 1000 AS batches demonstrated batch consistency and comparability.

The finished product (Bmab 1000-P shares the same formulation as that of Bmab 1000 AS, hence the characterisation performed for the AS is also applicable for the FP.

2.3.2.3. Specification

The specification for the Bmab 1000-P AS is applicable for release and stability and comprises physicochemical parameters for control of appearance and solution parameters, quantity, identity, purity and impurities, functional characterisation and microbial contamination.

Justification of specification

The specification for denosumab DS has been established considering concepts outlined in ICH guidelines, pharmacopeia guidelines, and using data from Bmab 1000 AS batches as applicable. The proposed acceptance criteria (ranges, limits) for selected CQAs are appropriate and in line with available results, assay performance, and mentioned guidelines.

Analytical methods

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

All validation results were within acceptance criteria and therefore the methods are considered validated and suitable for the intended use, in line with the principles outlined in ICH Q2(R2) guideline. The principles of the analytical procedures for the non-compendial methods are acceptable. Acceptable description of compendial methods (colour, clarity, pH, osmolality) with references to the Ph. Eur. and validation summaries are provided.

Batch analysis

The batch analysis results are provided for AS batches manufactured at intended commercial scale.

All results comply with the DS specifications in place at the time of manufacture/time of the batch release. In addition, all available release data met the acceptance criteria of the proposed commercial specification.

Reference materials

Reference standards for Bmab 1000 (denosumab) have been qualified against Prolia or previously established reference standards.

Container Closure System

The Bmab1000 formulated AS is filtered (low bioburden specification) and stored in single-use, sterile, bag.

2.3.2.4. Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

Bmab 1000 AS process validation batches were further placed for 6 months under accelerated conditions (at 5 ± 3 ºC) under long-term conditions according to the ICH guidelines. All the physicochemical, functional, and microbiological quality parameters tested for stability batches are within the defined specification limits. Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The pharmaceutical development of Bmab 1000-P finished product (FP) utilised principles described in the ICH Q8 Pharmaceutical Development guideline and was based on scientific knowledge and prior experience with similar protein products, as well as risk assessments and development studies.

Description and Composition

The Bmab 1000-P FP is developed as a proposed biosimilar product to Prolia. The components of Bmab 1000-P FP are adequately reported. All excipients comply with Ph. Eur / USP-NF. The composition of Bmab 1000-P FP is the same as the composition of the reference medicinal product, EU-Approved Prolia. The Bmab 1000-P FP is a sterile, preservative free, clear to slightly opalescent, colourless to pale yellow solution in a single dose pre-filled syringe (PFS) for subcutaneous use. Each PFS is filled with a target fill volume of 1.02 mL of denosumab as an active ingredient at a concentration of 60 mg/mL.

The excipients used in Bmab 1000-P FP formulation (PFS) include acetic acid glacial, sodium acetate trihydrate, sodium hydroxide, sorbitol, polysorbate 20 and water for injections excipients in 60 mg/mL.

The primary packaging is a single use pre-filled syringe made from type I glass with stainless steel needle (29 G×½-inch), with a needle guard and a rubber plunger stopper (fluoropolymer coated bromobutyl rubber). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Formulation Development

The pharmaceutical development of Bmab 1000-P FP focused on developing a formulation similar to its reference product Prolia. Formulation robustness studies were conducted based on a design of experiments (DoE) to characterise the influence of critical formulation factors and confirm stability of the FP. Overall, the formulation development data is robust and support the adequacy of the chosen formulation.

Manufacturing Process Development

The comparability of clinical and commercial material was sufficiently demonstrated. The pharmaceutical development was acceptable, with sufficient data, justification and conclusions.

Bmab 1000-P finished product manufacturing process was developed at FP PFS filling line with a smaller batch size. Subsequently in order to meet the commercial supply, the manufacturing process for Bmab 1000-P FP was transferred and validated at another filling line. No major changes were introduced between these batches except for filling line. Due to change in filling line a detailed comparability assessment was performed between two filling lines The comparability assessment was conducted between FP manufactured at both filling lines as per ICH Q5E. The assessment of support comparability between the product manufactured at both filling lines The introduced processing changes in the FP B1 to B2 filling line were acceptable, given the AS manufacturing process did not change substantially between the batches executed at both filling lines. Process characterisation was performed at the intended manufacturing scale. Process characterisation identified critical process parameters (CPP). The established process parameters and controls are adequate to ensure process consistency (when operated within acceptable ranges) and product quality.

Container Closure System

The selection of the commercial primary container closure systems (CCS) is based on the results of physical, chemical, and functional tests. The chosen primary CCSs are compatible for Bmab 1000-P FP storage. The primary packaging is a glass syringe barrel. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Bmab 1000-P FP is filled aseptically into ready to use pre-sterilised 1mL USP Type 1 glass syringes fitted with a staked needle and stoppered using Flurotec coated bromobutyl plunger stoppers. The pre-filled syringe (PFS) is also presented with a needle guard to reduce the occurrence of needle-stick injuries post injection. A plunger rod is assembled onto the plunger stopper, which does not come in contact with the product and helps in extruding the product out from the syringe. The compatibility between the chosen primary CCS and Bmab 1000-P FP is demonstrated. The recommended storage temperature for the FP is 2-8°C.

Leachable screening study was performed for FP in contact with the primary container closure No volatile, semi-volatile or non-volatile compounds were found at or above the respective Analytical Evaluation Threshold (AET) level in FP stored in PFS. The results demonstrate that the risks to patient safety from leachables originating from the manufacturing process and PFS and Vial container closure systems is low.

The risk assessment on extractables and process components was endorsed. Main key parameters considered are exposure temperature, exposure duration, process fluid interaction, dilution ratio and pre-treatment. The risk for process materials and equipment is deemed low/negligible, hence, no leachable study is deemed necessary for process materials and equipment.

Bacterial Endotoxin test (BET), Sterility test and Seal Integrity tests are performed as a part of the batch release testing and during stability testing to confirm sterility of the final product and integrity of the CCS. All FP batches tested met the pre-defined acceptance limit for bacterial endotoxin BET and the compendial requirements of the sterility test. Bmab 1000-P FP is administered by subcutaneous injection, directly from PFS without requirement of diluents or reconstitution. Therefore, compatibility studies are not applicable. In addition, batch release testing and on-going stability studies support SC FP compatibility with respective primary container closure system (PFS).

2.3.3.2. Manufacture of the product and process controls

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate, and re-processing is not considered.

Manufacturers

All manufacturing and testing sites are covered by valid GMP certificates.

For batch certification of finished product (QP release) in the EU is responsible manufacturing site is Biosimilar Collaborations Ireland Limited (BCIL) Block B, The Crescent Building, Santry, Demesne, Dublin, D09 C6X8, Ireland.

Batch Formula

With respect to Bmab 1000-P, AS is diluted to 60 mg/mL FP. The quality standards for each component of the FP are provided. Batch sizes and number of units are appropriately covered for each FP presentation by process validation.

Description of Manufacturing Process and Process Controls

Overall the process is sufficiently described. The Bmab 1000-P FP manufacturing process comprises preparation and filtration of formulation/dilution buffer, AS thawing, dilution of AS with formulation buffer, mixing of formulated bulk solution, pre-filtration (offline) for bioburden reduction, sterile filtration (online), aseptic filling, stoppering, visual inspection, assembly of plunger rod and needle safety device, labelling, packing, and storage at 2-8°C.

Critical process parameters and their control strategy are adequate, with confirmed process step durations and hold times during process validation and media fills.

Controls of Critical Steps and Intermediates

Critical in-process controls with are presented for FP manufacturing steps. Respective action limits and acceptance criteria are acceptable. Analytical methods are adequately described and validated.

Process Validation and/or Evaluation

The Bmab 1000-P FP manufacturing process is validated using several FP batches at commercial scale at the intended commercial production site.

The process validation covered thawing and mixing of frozen formulated DS, pooling and mixing of formulated AS, preparation of formulation/dilution buffer, dilution of pooled DS with formulation/dilution buffer, pre-filtration of formulated AS (offline filtration), sterile filtration of formulated AS (online filtration), aseptic filling, stoppering, visual inspection, storage, labelling, plunger rod and needle guard assembly, and storage manufacturing steps.

Overall, process parameters were adequately controlled within the pre-defined ranges during PV studies. All PV FP batches are successfully validated, meeting the release results of the proposed commercial specification acceptance criteria and FP quality attributes, demonstrating consistency and reproducibility.

Routine monitoring is performed as part of the Continued Process Verification (CPV), to ensure product quality and process control. The CPV protocol is acceptable.

Validation studies including hold times, media fills, filter validation, shipping validation, sterilisation process validation, and plunger stopper movement are performed. Hold times during the manufacturing processes are appropriately validated. Comparative assessment of product quality attributes for source AS batches and released PV FP batches showed no significant change in product quality attributes which demonstrates reliable FP manufacturing within the recommended (cumulative) hold times. Bmab 1000-P FP PFS shipment is validated, without compromising syringe functionality, FP quality, and container closure integrity.

Control of Excipients

The excipients used are of Ph. Eur quality and controlled in line with the current version of the respective Ph. Eur monographs. Excipients are tested with compendial methods and no validation of the methods are required. No novel excipients nor excipients originated from human or animal source are used.

2.3.3.3. Product specification

A Comprehensive panel of specification are set for Bmab 1000-P FP, in accordance with ICH Q6B principles and. Specification tests cover all relevant characteristics of Bmab 1000-P FP including: appearance identity, product purity and impurities adventitious agents sterility, and container closure integrity (CCI), product potency, quantity and excipient concentration.

Analytical Procedures and Validation of Analytical Procedures

Analytical procedures utilised in the specification determination of Bmab 1000-P FP are described based on Ph. Eur/USP monographs.

The Microbial Safety Testing methods are suitable for routine release and stability testing of FP samples.

Based on results obtained, the Syringe Functionality Tests are considered verified methods for routine analysis and stability testing of Bmab 1000-P FP.

In-house analytical methods for determination of quantity (identity, purity/impurity and potency/biological activity are suitable and validated method according to ICH Q2 (R1) principles.

Biological methods for potency are validated at the proposed as EU QC release site for biological testing.

Batch Analysis

Batch analytical data is provided for all FP batches. All batches met the acceptance criteria of release in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process.

Characterisation of Impurities

To detect the presence of elemental impurities, batches of Bmab 1000-P were analysed based on ICH Q3D Class 1, Class 2A and Class 3 elements and safety assessment based on their Permitted Daily Exposure (PDE). The used methods for detection were qualified. Test results were clearly below PDE limits, concluding a negligible risk of exposure s to patient.

The risk assessment regarding nitrosamine impurities conducted in accordance with principles from ICH Q9 and M7 evaluated all potential sources of nitrosamine formation or contamination during manufacture. No significant risk derived from AS, excipients, manufacturing process, equipment, utilities, and packaging is identified.

The risk assessment regarding nitrosamine impurities conducted in accordance with principles from ICH Q9 and M7 evaluated all potential sources of nitrosamine formation or contamination during manufacture. No significant risk derived from AS, excipients, manufacturing process, equipment, utilities, and packaging is identified.

Justification of Specifications

Overall, a sufficient panel of quality attributes is proposed for release and shelf-life/stability specifications of Bmab 1000-P FP. Acceptance criteria were set based on manufacturing experience and knowledge of process capability and consistency, experience with the analytical procedures and knowledge of the method capabilities and dataset consisting of analytical test results. Overall, the proposed limits for selected CQAs are appropriate and in line with available results, assay performance and guidelines.

The purity and impurity specifications for Bmab 1000 have different acceptance ranges/limits for release and stability assessments, which is acceptable. The specification limit for endotoxin is considered acceptable and provides adequate safety margin. The acceptance range for potency/biological activity is the same for AS and FP release and shelf-life specifications, which is acceptable.

Device functionality testing is included, performed at both release and upon stability using the same specifications. The proposed acceptance criteria for device functionality testing (break loose force, glide force and needle guard activation force) are acceptable.

Similarly, the proposed acceptance criteria for the general test, safety tests and identification test are adequate for release and shelf-life/stability.

Container Closure System

The primary CCS for Bmab 1000-P FP PFS (60 mg) is composed of a 1mL USP Type 1 glass syringe fitted with a staked needle and stoppered with a Flurotec coated bromobutyl plunger stoppers. The PFS is configured with a plunger rod and needle safety guard that do not come in contact with the product.

The conformity of the device part with the relevant general safety and performance requirements (GSPR) set out in Annex I Regulation (EU) 2017/745 was evaluated and approved by notified body.

The selection of the primary packaging components was based on results of physical, chemical, and functional testing. Incoming material testing is performed according to validated compendial or non-compendial methods. The compatibility and suitability of the CCS is confirmed during pharmaceutical development.

2.3.3.4. Stability of the product

Stability studies on Bmab 1000-FP PFS are conducted in line with ICH Q1A (R2) and ICH Q5C guidelines. Photostability studies on Bmab 1000-P FP are conducted in accordance with ICH Q1B guideline. Based on the provided stability data, the proposed shelf-life of 36 months for Bmab 1000-P PFS is acceptable when stored at 5ºC±3ºC and protected from the light.

Long-term (5°C ± 3°C) stability data and accelerated stability data conditions of commercial scale batches of Bmab 1000-P is available. In-use stability studies confirmed that Bmab 1000-P FP is stable at 25 ± 2°C (60% ± 5% RH) for a period of 30 days when removed from the refrigerator (2-8°C), similarly to RMP Prolia. Forced degradation studies showed comparability to EU/US RMP Prolia under various stress conditions (i.e. temperature, pH, chemical oxidation, photo exposure, and mechanical stress). Results confirmed no significant changes, with all sample batches within the stability acceptance criteria.

The post-approval stability protocol for ongoing stability of commercial scale process validation batches under long-term and accelerated conditions (for 6 months) is adequate, using the intended commercial primary CCS.

2.3.3.5. Adventitious agents

TSE compliance:

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) is demonstrated. The active drug substance is produced in a serum-free culture medium. The MCB is free from TSE-risk substances.

Virus safety:

The virus safety of Bmab 1000 is sufficiently demonstrated based on the routine screening during fermentation (i.e. adventitious viruses, viral particles) and effectiveness of manufacturing steps to clear enveloped and non-enveloped viruses (i.e. purification, Anion exchange chromatography and filtration steps).

2.3.3.6. GMO

Not applicable

2.3.3.7. Biosimilarity

Evfraxy (Bmab 1000-P FS) has been developed as biosimilar biological product to Prolia PFS (60 mg/mL).

An RMP US-licensed and EU-approved Prolia and Xgeva (EU/US) are compared. Bmab 1000-P has the same active substance, formulation, dosage form, and product strengths as the reference product Prolia.

A comprehensive 3-way, side-by side comparability study has been conducted to compare the biosimilar Bmab 1000 with the EU reference product, the biosimilar Bmab 1000 with the US reference product, and the EU reference product with the US reference products (Prolia PFS and Xgeva vial presentations. The presented data of US reference products is considered supportive information and it serves to bridge the data for the comparative clinical studies (PK/PD, efficacy) that have been conducted with the US product Prolia. The approach for pooling the Bmab 1000 FP ((Bmab 1000-P and Bmab 1000-X) presentations is agreed by the Scientific advice EMA/CHMP/SAWP/135989/2020 and the comparability exercise follows the general principles outlined in "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012).

A comprehensive physicochemical and biological characterisation and comparison between Bmab 1000 FP (Bmab 1000-X vial and Bmab 1000-P PFS) presentations and EU- Approved and US-Licensed Prolia/Xgeva reference medicinal product have been conducted. Both FP presentations i.e., PFS and vial (60mg/mL in PFS and 120mg/1.7mL in vial) of Bmab 1000 and Prolia/Xgeva were pooled for similarity exercise. The approach for pooling the Bmab 1000 FP presentations is agreed by the Scientific advice EMA/CHMP/SAWP/135989/2020 and the comparability exercise follows the general principles outlined in "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012). The evaluation of general properties, primary structure, secondary, tertiary and higher order structure, post-translational modifications, product purity, and biological activity is addressed with orthogonal and state-of-the art analytical methods. Appropriate validated analytical methods are utilised to ensure an understanding of Prolia and Xgeva (EU/US) product profile and Bmab 1000 (Bmab 1000-P and Bmab 1000-X).

Overall, biosimilarity of the quality attributes is demonstrated with minor observed differences not impacting on the clinical performance of Bmab 1000 FP. In addition, the results support the comparability of EU-sourced with EU-authorised RMP Therefore, the provided comparability results support the biosimilarity claim.

Proposed Formulation and Packaging Configuration

The same excipient formulation composition as that of Prolia is used for Bmab 1000 formulation As part of the analytical similarity assessment (also termed comparative analytical assessment, CAA) quality attributes are identified that characterise the reference product in terms of its physicochemical and functional properties. Those attributes were ranked according to their risk to potentially affect efficacy, immunogenicity, safety, and/or PK/PD. Quality attributes were categorised as very high, high, moderate, low, or very low risk parameters. This approach follows the principles of the ICH Q9 guideline, and the criticality risk ranking (CRR) for the selected CQA is found acceptable.

Comparability studies between the different FP presentations

Studies have been conducted between EU-approved reference products Prolia and Xgeva, US-licenced Prolia and Xgeva and biosimilar products Bmab 1000.

An acceptable number of reference product batches for setting acceptance criteria for similarity evaluation has been used. A comprehensive panel of orthogonal standard and state-of-the-art methods has been applied for biosimilarity evaluation to address primary structure, product-related substances and impurities, higher order structure, general properties, biological activity, degradation studies and the targeted similarity assessment with the necessary level of depth.

The critical quality attributes that were assessed concluded high comparability, aside from the expected differences and demonstrated that the different FP presentations can be combined.

Comparability studies between the biosimilar and reference products

EU reference product lots US lots and biosimilar lots are included in the study. To capture lot-to-lot variability, the reference product lots with different expiry dates were used. The comparability analytical assessment include a comprehensive array of physico-chemical methods to demonstrate structural and product heterogeneity similarities in the product as well as *in vitro* functional bioassays that were designed to demonstrate the mechanism of action (MoA) of denosumab. Primary structure assessment confirms that the primary structure of Bmab 1000-P and Bmab 1000-X is identical to that of US-licensed and EU-approved Prolia and Xgeva.

Assessment of Secondary structure confirms that secondary structure demonstrates a high level of similarity of Bmab 1000-P and Bmab 1000-X to US-licensed and EU-approved Prolia and Xgeva.

Higher order structure assessment confirms a high level of similarity between Bmab 1000-P and Bmab 1000-X to US-licensed and EU-approved Prolia and Xgeva.

The glycan profiles of Bmab 1000-P and Bmab 1000-X are highly similar to EU-Approved and US-licensed Prolia and Xgeva. The level of oxidation, acidic variants (Deamidation) and C-terminal lysine variants are marginally lower in Bmab 1000, whereas the e level of proline amidation is higher in Bmab 1000 compared to reference products. However, these differences are located in the Fc region without impact on the MoA. The observed differences in oxidation and post translational modifications have no impact in potency and biding, as demonstrated by the functional assays between Bmab 1000 and the reference products. Further, the clinical performance in phase 1 and phase 3 study outcomes confirm the similarity of Bmab 1000 to the US-Licensed Prolia, confirming that minor differences in variants/impurities are not significant to preclude biosimilarity.

Molecular weight of monomer and dimer, is highly similar between biosimilar and reference products.

Size heterogeneity assessed using CE-SDS (NR, R), confirmed high similarity of the biosimilar with EU and US reference products with regard to % total fragments. Differences in acidic and basic variants (measured by icIEF) are observed. Lower levels of acidic variants were justified by lower levels of deamidation in non-CDR regions, while higher levels of basic variants were attributed to proline amidation on both heavy chains. These differences are acceptable and not expected to impact on safety, efficacy or immunogenicity as supported by extensive characterisation of enriched and native charge variants. The disulphide variants are identical between Bmab 1000 and the reference products. All functional assays include measurement of mechanism of action involving Fab, demonstrating a high level of similarity of Bmab 1000 to the reference products. Similarly, the performed binding kinetics assay for FcγRIIIa-V158 (involved for ADCC activity), FcγRIIIa-F158 (involved for ADCC activity), FcRn (impact the antibody half-life) and other Fc receptors FcγRIIa and FcγRIIb support a high level of similarity despite the observed marginal lower binding to FcγRIIIa. Used technology confirmed denosumab does not bind to FcγRI and FcγRIIIb, being an IgG2. The binding to C1q is assessed as highly similar to the reference products. Absence of ADCC and CDC activity for Bmab1000-P, Bmab 1000-X and Prolia and Xgeva is confirmed using cell-based assays.

The comparative forced degradation study show a comparable behaviour of Bmab 1000FP to EU-Approved and US-Licensed Prolia and Xgeva.

Overall Conclusion

The comprehensive comparative analytical similarity and comparative forced degradation stability programme demonstrates that Bmab 1000 is acceptable as proposed biosimilar to EU-Approved and US-Licensed Prolia and Xgeva.

Based on the presented data, the biosimilarity is considered appropriate. Further, the Table 1 below includes a summary of the biosimilarity assessment including a critical evaluation of biosimilarity.

Table 1: Biosimilarity assessment comparison between Bmab 1000-X vial, Bmab 1000-P PFS and EU/US sourced RMP Prolia/Xgeva

Molecular parameter	Attribute			Key Findings Similarity Bmab1000 vs EU RMP
General test	Protein content			highly similar
Primary structure	Intact mass			identical
	Reduced mass			identical
	Amino acid sequence			identical
High Order Structure	Disulfide bridges			Identical
	Free cysteine			Highly similar
	Disulfide variants			Minor differences observed , This difference is not expected to have any impact on safety, efficacy or immunogenicity.
	Secondary structure			Highly similar
	Extinction coefficient			Highly similar
	Tertiary structure			Highly similar
	Structural integrity			Highly similar
	Structural integrity			Highly similar
	Thermal stability			Highly similar
Post translational modifications	Charge variants	Acidic		Lower level. No impact on safety, efficacy and immunogenicity.
		Basic		Lower level. No impact on safety, efficacy and immunogenicity.
	Oxidation			Highly similar
	Hydrophobic variants			Lower level. These differences in levels are not expected to have any impact on safety, efficacy or immunogenicity.
	Deamidation of asparagine and glutamine in CDR			Not-detected
	Deamidation in non-CDR			Highly similar
	Aspartic acid isomerisation			Not-detected
	N-terminal pyroglutamate content			Not-detected
	C-terminal lysine			Highly similar
	C-terminal proline amidation			Common posttranslational modification. Hence difference in this has no impact on safety, efficacy or immunogenicity.
	Glycosilation	Released N-glycan analysis	Afucosylated	Lower but has no impact on safety, efficacy or immunogenicity due to lack of F c function.
			Galactosylated	Highly similar
			Total Sialylated	Highly similar
			Mannosylated	Similar
Product purity		Aggregates/HMWP		Comparable at comparable age hence considered highly similar
		Aggregates/HMWP (molecular weight of monomer)		Highly similar
		Aggregates/HMWP (sedimentation coefficient)		Highly similar
		Fragments/LMWP		Highly similar

Molecular parameter	Attribute	Key Findings Similarity Bmab1000 vs EU RMP
Biological activity (Fab region)	RANKL binding	Highly similar
	mRANKL binding	Highly similar
	Relative potency	Highly similar
	Relative potency	Highly similar
Biological activity (Fc region)	FcRn binding	Highly similar
	FcγRIIa binding	Highly similar
	FcγRIIa binding	Highly similar
	FcγRIIb binding	Highly similar
	FcγRIIIa F158 binding	Similar, marginal difference. No impact on safety, efficacy and immunogenicity due to lack of Fc function
	FcγRIIIa V158 binding	Similar
	C1q binding	Highly similar

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process.

The manufacturing of Bmab 1000 Active substance and finished product are well-controlled and validated manufacturing processes.

Bmab 1000-P is developed as a proposed biosimilar product to EU-approved Prolia. The presented analytical data demonstrate analytical similarity of the proposed Bmab 1000-P biosimilar and the EU reference products Prolia. A broad panel of validated orthogonal standard and state-of-the-art methods was applied. The biosimilarity evaluation sufficiently covered primary structure, product-related substances and impurities, higher order structure, general properties, biological activity, degradation studies and the targeted similarity assessment.

The analytical similarity exercise demonstrated overall biosimilarity of Bmab 1000 to the EU-approved Prolia (RMP). A 3-way, side-by side comparability study was conducted to compare the biosimilarity with the EU reference product, the biosimilar with the US reference product, and the EU reference product with the EU and US-sourced reference products. The presented data of US reference products is considered supportive information and it serves to bridge the data for the comparative clinical studies that have been conducted with the US product. Acceptable number of reference product batches for setting acceptance criteria for similarity evaluation is used.

Bmab 1000 (Bmab 1000-P PFS, Bmab 1000-X vial), US-licensed and EU-approved Prolia/Xgeva have the same amino acid sequence, formulation, dosage form, and product strengths as reference product Prolia/Xgeva.

All biological activities relevant to the primary mechanism of action, including RANKL binding, inhibition of NF-κB activation, and inhibition of RANKL-induced osteoclast differentiation are similar. Minor differences in glycosylation, oxidation, acidic/basic variants, isoform levels and impurities compared to

the RMP (Prolia and Xgeva (EU/US) are not expected to clinically impact on PK, efficacy, safety, and immunogenicity as corroborated in functional assay and clinical study outcomes.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

The observed analytical differences with the RMP are discussed and considered acceptable. Therefore, the biological and physiochemical comparability data support the claim of biosimilarity for (Bmab 1000-P, PFS and reference product Prolia (EU/US-sourced, PFS).

2.3.6. Recommendations for future quality development

Not applicable

2.4. Non-clinical aspects

2.4.1. Introduction

Activation of Nuclear Factor κB (NF-κB) plays a central role in orchestrating the formation and function of osteoclasts, making it a key target for therapies aimed at modulating bone resorption such as denosumab.

Denosumab is a full-length human monoclonal antibody of the IgG2 subclass that binds with high affinity to nuclear factor kappa-B ligand (RANKL), which prevents RANKL from activating its only receptor (RANK) on the surface of osteoclasts and their precursors, independent of the bone surface. Prevention of RANKL/RANK interaction inhibits osteoclast differentiation activity and survival, thereby decreasing bone resorption in cortical and trabecular bone.

The active substance of Bmab 1000 DP (Bmab 1000-P and Bmab 1000-X) and US-Licensed and EU-Approved reference products Prolia and Xgeva is denosumab.

Based on the mechanism of action (MOA), the pharmacology of Bmab1000 (Bmab 1000-P and Bmab 1000-X) was evaluated *in vitro* side by side with US-licensed and EU-approved reference products Prolia and Xgeva to demonstrate functional similarity. A comprehensive battery of *in vitro* pharmacodynamical characterisation studies was performed to compare the key biological activities.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The assays assessed the primary pharmacodynamics of Bmab 1000 (denosumab) that directly impact clinical effects.

All methods used in the functional similarity exercise were qualified or validated and suitable for the intended purpose. Respective descriptions of analytical methods/procedures as well as method development/qualification reports are provided.

The number of batches used for comparative analytical assessment was provided for each method. Information on batches used for ADCC and CDC testing is missing. This is acceptable as both functional assays gave a negative response so that comparability for these assays is not required.

The formulations of Bmab1000 DP that were used in the pharmacology studies are representative of Bmab1000 clinical formulations and identical/highly similar with RMP Prolia and Xgeva formulations.

In summary, results obtained across the various comparative assays demonstrate that Bmab1000 and RMPs Prolia and Xgeva are highly similar in terms of primary pharmacodynamics. Consequently, the applicant has sufficiently demonstrated biological/functional similarity between Bmab1000 and US-licensed and EU-approved reference product Prolia and Xgeva.

No additional *in vivo* pharmacology, secondary PD, safety pharmacology or pharmacodynamic drug interactions studies were performed. This is in line with EMA guidelines for biosimilar development.

No issues were identified on the biological and functional similarity assessment. The pharmacology package was considered to sufficiently demonstrate the similarity of Bmab1000 and Prolia and Xgeva (EU and US).

2.4.2.2. Secondary pharmacodynamic studies

Comparative secondary pharmacodynamics studies with Bmab1000 and Prolia and Xgeva were not conducted. During the analytical similarity exercise no uncertainties are identified that need to be addressed by secondary pharmacodynamics testing.

2.4.2.3. Safety pharmacology programme

Safety pharmacology studies comparing Bmab1000 and Prolia and Xgeva were not conducted. The approach is considered acceptable.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding safety pharmacology are not required for non-clinical testing of biosimilars.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies comparing Bmab1000 and Prolia and Xgeva were conducted. Given the results of the analytical similarity exercise, pharmacodynamic drug interactions for Bmab1000 are expected to be similar to those of Prolia and Xgeva.

2.4.3. Pharmacokinetics

No non-clinical pharmacokinetic (PK) studies comparing Bmab1000 (Bmab 1000-P and Bmab 1000-X) and Prolia and Xgeva were conducted.

Data from the analytical similarity assessment appear to demonstrate biosimilarity between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and the reference medicinal products Prolia and Xgeva and no further non-clinical PK studies are deemed necessary.

The absence of PK studies is acceptable and in agreement with the stepwise approach mentioned in EMA "Guideline on similar biological medicinal products CHMP/437/04 Rev 1" and EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1".

In addition, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals", no standard absorption, distribution, metabolism, and excretion studies are warranted for biopharmaceuticals.

Labelling of Bmab1000 (Bmab 1000-P and Bmab 1000-X) is based on the product labelling for Prolia and Xgeva.

2.4.4. Toxicology

No comparative toxicology studies have been conducted with Bmab1000 (Bmab 1000-P and Bmab 1000 X) and reference medicinal products Prolia and Xgeva.

Bmab1000 (Bmab 1000-P and Bmab 1000-X) has the same formulation, dosage form, presentation, and product strength as the reference medicinal products Prolia and Xgeva.

In addition, data from the analytical similarity assessment in Module 3 appear to demonstrate biosimilarity between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and the reference medicinal products Prolia and Xgeva.

From the provided similarity exercise no uncertainties arise which could be addressed in non-clinical *in vivo* toxicology studies. Observed differences in the analytical similarity exercise are small and non-clinical *in vivo* studies are not considered sensitive enough to further evaluate these differences. Consequently, no further non-clinical toxicology studies are deemed necessary.

The absence of toxicology studies is acceptable and in agreement with the stepwise approach mentioned in EMA "Guideline on similar biological medicinal products CHMP/437/04 Rev 1" and EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1".

In addition, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals", genotoxicity and carcinogenicity studies are not warranted for biopharmaceuticals.

2.4.4.1. Single dose toxicity

Comparative single-dose toxicity studies with Bmab1000 (Bmab 1000-P and Bmab 1000-X) and Prolia and Xgeva were not conducted, which is acceptable.

2.4.4.2. Repeat dose toxicity

Comparative repeat-dose toxicity studies with Bmab1000 (Bmab 1000-P and Bmab 1000-X) and Prolia and Xgeva were not conducted, which is acceptable.

2.4.4.3. Genotoxicity

No genotoxicity studies have been conducted. The waiving of such studies is in line with relevant guidelines.

In general, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals" routine genotoxicity studies are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

2.4.4.4. Carcinogenicity

Carcinogenicity studies comparing Bmab1000 (Bmab 1000-P and Bmab 1000-X) and Prolia and Xgeva were not conducted. The waiving of carcinogenicity studies is in line with relevant guidelines.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding carcinogenicity are not required for non-clinical testing of biosimilars.

Furthermore, according to "ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals" standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.

2.4.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies comparing Bmab1000 (Bmab 1000-P and Bmab 1000 X) and Prolia and Xgeva were not conducted. This approach is acceptable.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies regarding reproduction toxicology are not required for non-clinical testing of biosimilars.

2.4.4.6. Toxicokinetic data

Not applicable.

2.4.4.7. Local tolerance

Local tolerance studies comparing Bmab1000 (Bmab 1000-P and Bmab 1000-X) and Prolia and Xgeva were not conducted. The waiving of these studies is acceptable and in line with relevant guidelines.

According to EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1" studies on local tolerance are usually not required for non-clinical testing of biosimilars.

Bmab1000 (Bmab 1000-P and Bmab 1000-X) has the same formulation, dosage form, presentation, and product strengths as the reference medicinal products Prolia and Xgeva. In addition, sufficient experience with the excipients (glacial acetic acid, sodium acetate trihydrate, sodium hydroxide, sorbitol, and polysorbate 20) is available.

2.4.4.8. Other toxicity studies

Not applicable.

2.4.5. Ecotoxicity/environmental risk assessment

Bmab1000 (Bmab 1000-P and Bmab 1000-X) is a proposed biosimilar to the reference medicinal product Prolia and Xgeva. The approval of Bmab1000 (Bmab 1000-P and Bmab 1000-X) is not expected to cause increase in environmental exposure and any additional hazards to the environment. 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 to 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 corr 2)', denosumab is exempted from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.4.6. Discussion on non-clinical aspects

Bmab 1000-P has been developed as a biosimilar to the reference product Prolia. Bmab 1000-P has the same amino acid sequence, formulation, dosage form, and product strengths as reference product Prolia.

The biological activity (functional) studies of Bmab1000 (Bmab 1000-P and Bmab 1000-X) are part of the comparative analytical assessment presented in the quality section above.

The results of *in vitro* pharmacodynamic studies demonstrated similar functional/biological effects and binding properties between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva, which also provides support for the claimed therapeutic indications of Bmab1000. The analytical methods used in the functional similarity exercise were qualified/validated and suitable for the intended purpose.

Comparative *in vivo* pharmacology, secondary PD, safety pharmacology, and PD drug interaction studies as well as *in vivo* pharmacokinetics (PK) and toxicology (or toxikinetic) studies were not conducted. The absence of these studies is considered justified because (i) animal models are not considered sensitive enough to determine pharmacological differences and (ii) comparability exercise revealed no uncertainties, which could be addressed in non-clinical *in vivo* pharmacokinetics and toxicology studies.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Bmab1000 (denosumab) is not expected to pose a risk to the environment.

2.4.7. Conclusion on non-clinical aspects

In general, the provided non-clinical part for Bmab 1000-P is of good quality, and relevant aspects of Bmab1000 *in vitro* functional activity compared to reference product Prolia (EU/US) are appropriately addressed.

No issues were identified on the biological/functional similarity assessment. The pharmacology package was considered to sufficiently demonstrate the similarity of Bmab 1000-P and reference product Prolia (EU/US).

The non-clinical biosimilar comparability exercise was solely based on functional and biological *in vitro* pharmacodynamic assays. All functional and biological assays showed sufficient similarity between the biosimilar and its reference product, and where minor divergences were observed these are not considered clinically relevant. According to current guidance, the *in vitro* assays is considered paramount for the non-clinical biosimilar comparability exercise since they are generally more specific and sensitive in detecting differences between the biosimilar and the reference product. Hence, further procedure specific pharmacology, pharmacokinetic and toxicology studies are not considered necessary.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 2: Clinical studies with PK, PD and immunogenicity assessment

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK and PD parameters
B1000-NHV-01-G-01	Randomised, double-blind, two–arm, single-dose, parallel-group study to compare the PK, PD, safety, and tolerability of Bmab 1000 and Prolia	Healthy volunteers, 70.4% male Randomised: 189 Completed: 185	60 mg single SC dose	PK Primary: Cmax, AUC0-t, AUC0-inf Secondary: partial AUCs, tmax, kel, t1/2, Vd/F, CL/F PD Secondary: Emax and AUEC of the sCTX (0-36 weeks)
B1000-PMO-03-G-02	Randomised, double-blind, multicentre, parallel-arm Phase 3 study to compare the efficacy, PD, safety, and immunogenicity between Bmab 1000 and Prolia	Post-menopausal women with osteoporosis Randomised: 479 Completed: 426	60 mg, 3 SC doses	PK Secondary: serum concentrations of denosumab (0-52 weeks) PD Co-primary: AUEC of sCTX (0-26 weeks) Secondary: Cmin, Imax, TImax and AUIC of sCTX (0-26 weeks), serum

				concentrations of P1NP (0-52 weeks)

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

Denosumab drug concentration was measured by a sandwich electrochemiluminescence (ECL) assay using mouse anti-idiotypic denosumab monoclonal antibody as capture and a different sulfo-tag labelled mouse anti-idiotypic denosumab monoclonal antibody as a detection reagent.

The method was equivalent for the detection of Bmab 1000 and reference products Prolia using a single set of calibrators and quality controls (QCs) made from Bmab 1000 and US-Licensed Prolia.

This method was used to analyse normal healthy subject serum samples from Study B1000-NHV-01-G-01 and diseased (PMO matrix) serum samples from Study B1000-PMO-03-G-02.

Calibrators were prepared in neat human serum with Bmab 1000, and QCs (ULOQ QC, HQC, MQC, LQC, and LLOQ QC) were prepared in neat human serum using Bmab 1000 and US-Licensed Prolia. All samples, including those from the clinical study underwent a minimum required dilution in assay buffer before loading on the antibody-coated wells of a 96-well plate. The plate was washed after incubation with the samples, calibrators, and QCs. The sulfo-tagged mouse anti-idiotypic denosumab monoclonal antibody (detection reagent) was added to quantitate the bound Prolia and Bmab 1000. After a second incubation and the addition of read buffer containing tripropylamine, the plate was read. The Relative light units (RLUs) measured are directly proportional to the level of denosumab present in the sample. The serum concentrations of Bmab 1000 and Prolia in samples were then back calculated from a 5-Parametric Logarithmic calibration curve. A single calibration curve was prepared by spiking Bmab 1000 in serum and was employed to quantitate both products (Prolia and Bmab 1000).

The bioanalytical method for determination of denosumab serum concentrations used in the clinical studies has been validated according to EMA guideline EMA/CHMP/ICH/172948/2019.

Pivotal PK biosimilarity Phase 1 Study B1000-NHV-01-G-01

This was a randomised, double-blind, two-arm, single-dose, parallel-group study in healthy adult volunteers. The study consisted of up to 4 weeks of screening period, 10 days of in-clinic stay, and 36 weeks of outpatient follow up period after dosing on Day (D) 1. The total duration of study participation for a participant was up to 40 weeks.

Participants who signed the informed consent form underwent a screening evaluation prior to study D1. All eligible participants entered the study following successful screening and were randomised on a 1:1 basis to receive either Bmab 1000 or Prolia on D1. Participants were stratified based on site, on ethnicity (Japanese versus non-Japanese), body weight (55 to <60 kg for Japanese only, 60-80 kg and 81-95 kg) and on gender. This study was the first time Bmab 1000 was administered; therefore, for safety reasons, sentinel dosing was used such that 2 cohorts of 2 participants (1 Bmab 1000, 1 Prolia) were dosed at least 24 hours apart and, providing no safety concerns arose as determined by the PI, remaining participants could be dosed starting at least 24 hours later. After dosing on D1, participants

were accommodated at the study centre for 10 days as part of the in-clinic stay period and all required assessments were performed. Participants left the study centre after completion of all required assessments on D10 and followed up on outpatient basis till the End of Study (EOS) visit at Week 36, where blood samples were collected at scheduled timepoints for PK, PD, immunogenicity and safety laboratory assessments, or early termination (ET). The participants were also observed for AEs in this 36-week period.

PK sampling was performed on the following time points and days in the study: day of first denosumab administration: D1 - pre-dose (up to 60 mins prior to drug administration), and, at 4 h and 12 h post drug administration. Then on D2 (24 h), D3, D4, D6, D8, D10, D13, D15, D18, D29, D43, D57, D71, D85, D113, D141, D155, D169, D197, D225, and D253.

The protocol V1.0 and amended versions V2.1, V4.0, and V5.0 were provided, versions V2.0 and V3.0 were not implemented.

The main protocol changes were the following:

- The protocol was modified to allow the inclusion of female participants.
- The number of participants to be included was updated following recommendations from the FDA. 190 participants were planned to be included (increased from 166).
- Participants were no longer to be replaced in case of withdrawal.
- BMI requirements were modified for Japanese participants in the inclusion and exclusion criteria.
- The method of stratification was updated for weight ranges of Japanese subjects.

PK data analysis

All statistical and PK analyses were conducted according to the methods described in the Statistical Analysis Plan, which was finalised before the database lock.

Table 3: PK parameters in study B1000-NHV-01-G-01

Parameters (unit)	Definition
C_{max} (ng/mL)	Maximum observed serum denosumab concentration
t_{max} (h)	Time to reach maximum observed serum denosumab concentration
C_t (ng/mL)	Last observed quantifiable serum denosumab concentration
t_t (h)	Time to reach last observed quantifiable serum denosumab concentration
$AUC_{0\text{-}t}$ (ng/mL.h)	Area under the serum denosumab concentration-time curve from time zero to the last quantifiable serum denosumab concentration
$AUC_{18\text{-}85days}$ (ng/mL.h)	Area under the serum denosumab concentration-time curve from Day 18 to Day 85
$AUC_{113\text{-}253days}$ (ng/mL.h)	Area under the serum denosumab concentration-time curve from Day 113 to Day 253
$AUC_{0\text{-}inf}$ (ng/mL.h)	Area under the serum denosumab concentration-time curve from time zero to infinity, calculated as follows: $AUC_{0\text{-}inf} = AUC_{0-t} + \frac{C_t}{k_{el}}$, where C_t is the last observed quantifiable concentration
AUC_{ext} (%)	Percentage of AUC_{inf} due to extrapolation from t_t (time of last measurable concentration) to infinity, calculated as follows: $AUC_{ext} = \left(1 - \frac{AUC_{0-t}}{AUC_{0-inf}}\right) * 100$
$t_{1/2}$ (h)	Terminal elimination half-life, calculated as follows: $t_{1/2} = Ln(2)/k_{el}$
k_{el} (/h)	First order terminal elimination rate constant
CL/F (mL/h)	Apparent total body clearance, calculated as follows: $CL/F = Dose / AUC_{0\text{-}inf}$
Vd/F (mL)	Apparent volume of distribution, calculated as follows: $Vd/F = CL/F / k_{el}$

Any missing sample will be considered on case-by-case during BDRM.

In addition, the following protein-adjusted PK parameters will be derived, where protein content P is the investigational product content in protein (P=58.5 mg/mL for US-Licensed Prolia, and 60.4 mg/mL for Bmab 1000):

Parameters (unit)	Definition
C_{max}/P [(ng/mL)/(mg/mL)]	Protein-adjusted maximum observed serum denosumab concentration
$AUC_{0\text{-}t}$/P [(ng/mL.h)/(mg/mL)]	Protein-adjusted area under the serum denosumab concentration-time curve from time zero to the last quantifiable serum denosumab concentration
$AUC_{0\text{-}inf}$/P [(ng/mL.h)/(mg/mL)]	Protein-adjusted area under the serum denosumab concentration-time curve from time zero to infinity

Before concentration data were communicated by the bioanalytical laboratory, relevant cases including use of prohibited concomitant medication, technical sampling issues, missing samples were discussed to exclude a subject from the PK set.

In the following cases (exceptions), the decision to exclude a subject from the statistical analysis (i.e. subject kept in the PK set but flagged and only listed; concentrations and parameters not used for statistical analysis) could be done after concentration data are communicated by the bioanalytical laboratory:

- Any subject with lack of any measurable concentrations or only very low serum concentrations for reference formulation (i.e. its AUC is less than 5% of reference formulation geometric mean AUC, calculated without inclusion of data from the outlying participant),
- Any subject with pre-dose concentrations > 5% of Cmax.

All BLQ values will be substituted according to the rules described in the following table and by type of analysis:

Substitution value if BLQ occurs:		
Type of analysis	Predose or before first quantifiable concentration	After first quantifiable concentration
PK non-compartmental analysis	0	Missing
Descriptive statistics	0	Missing
Plotting of individual data	0	Missing
Listing of individual data	BLQ	BLQ

Treatments

Table 4: IMPs in study B1000-NHV-01-G-01

Study Treatment Name	Bmab 1000	Prolia
Active ingredients	Bmab 1000 (r-DNA origin)	Denosumab
Excipients	4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2	4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2
Dosage formulation:	Pre-filled syringe (PFS)	PFS
Unit dose strength(s)/Dosage level(s):	60 mg/mL	60 mg/mL
Route of Administration	Subcutaneous (s.c)	Subcutaneous (s.c)
Dosing instructions:	A single 60 mg dose of Bmab 1000 administered by s.c injection into the abdomen	A single 60 mg dose of Prolia® administered by s.c injection into the abdomen
Packaging and Labelling	Study Treatment was provided in single PFS. Each PFS was labelled as required per US or French requirements, as applicable.	
Manufacturer	Biocon Biologics Limited	Amgen Inc.

NIMP: Daily calcium (at least 1000 mg) and vitamin D (at least 400 IU) was administered during the treatment period.

Study population

Key inclusion criteria

- Gender: Male or female.
- Age: Male participants: 28-55 years, inclusive at screening; Female participants: 28-45 years, inclusive at screening.
- Weight: For non-Japanese participants 60.0-95.0 kg, inclusive at screening. For Japanese participants 55.0-95.0 kg, inclusive at screening.
- Body mass index (BMI) between 18.0 and 30.0 kg/m2, inclusive, at screening
- The subject did not show clinically relevant deviations as judged by the Investigator in haematology and for biochemistry tests of blood and urine (albumin-adjusted serum calcium

had to be within the normal range), vital sign measurements, and 12-lead electrocardiogram (ECG) results.

- Adequate method of contraception for female participants of childbearing potential and fertile male participants.

Exclusion criteria

1. Evidence of clinically relevant pathology: Like a history of and/or current clinically significant gastrointestinal, renal, hepatic, cardiovascular, haematological, pulmonary, neurologic, metabolic, psychiatric disorder, drug or alcohol abuse, or allergic disease excluding mild asymptomatic seasonal allergies. Had a history of malignancy (including lymphoma, leukaemia, and skin cancer).

2. Unable to follow protocol instructions or not likely to complete the study in the opinion of the Investigator or their designee.

3. Use of tobacco or nicotine containing products (including but not limited to, cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum).
Participant who smokes >5 cigarettes (or >3 cigars or >3 pipe full) or equivalent (>10 puffs of an e cigarette was considered equivalent to 1 combustible cigarette) for e cigarettes per day; and did not have the ability and willingness to refrain from smoking/tobacco/nicotine product use during confinement in the clinical research centre.

4. History of relevant drug and/or food allergies (including hypersensitivity to any recombinant protein drug or any of the constituents of denosumab, or latex allergy or hereditary problems of fructose intolerance).

5. Known history of previous exposure to denosumab.

6. Had previously been exposed to a monoclonal antibody or fusion protein (other than denosumab) within 270 days (or 5 half-lives whichever was the longest) prior to randomisation and/or there was confirmed evidence or clinical suspicion of immunogenicity from previous exposure to a monoclonal antibody or fusion protein.

7. Had previously been exposed to an immunosuppressive agent or biological agent (any other than a monoclonal antibody or fusion protein) within 120 days (or 5 half-lives whichever is the longest) prior to randomisation, except Coronavirus Disease 2019 (COVID-19) vaccine.

8. Prior diagnosis of bone disease, or any condition that affected bone metabolism such as, but not limited to: osteoporosis, osteogenesis imperfecta, hyperparathyroidism, hyperthyroidism, hypothyroidism, osteomalacia, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, current flare-up of osteoarthritis and/or gout, active malignancy, renal disease (defined as glomerular filtration rate [GFR] < 60 mL/min), Paget's disease of the bone, recent bone fracture (within 6 months), malabsorption syndrome.

9. Any use of the following bone modifying medications, with no limitation on time since administration: e.g., intravenous bisphosphonates, strontium, fluoride (if administered in treatment of osteoporosis), romosozumab, teriparatide or any parathyroid hormone analogues, calcitonin, and cinacalcet.

10. Use of systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for ≥10 days) within past 3 months before screening. Topical and nasal corticosteroids were allowed.

11. Other bone active drugs including but not limited to anticoagulants, anticonvulsives systemic ketoconazole, adrenocorticotropic hormone, lithium, proton pump inhibitors, supplemental vitamin D

[>1000 IU/day], anabolic steroids, calcitriol, diuretics, over the counter medications, herbal supplements: within the last 3 months before screening.

12. Any past or concurrent medical conditions potentially increasing the participant's risks. Examples of these included medical history with evidence of clinically relevant pathology (e.g., malignancies, demyelinating disorders).

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

14. Treatment with non-topical medications (including over the counter medication, and herbal remedies such as St. John's Wort extract) within 7 days prior to study drug administration, with the exception of topical medications, multivitamins, vitamin C, food supplements and a limited amount of paracetamol / acetaminophen, which could be used throughout the study, at the discretion of the PI.

15. Personal/family history of prolonged QT interval syndrome or family history of sudden death.

16. Having received live vaccines during the past 4 weeks prior to study drug administration or had the intention to receive live vaccination during the study. For non- live vaccination, a window of 2 weeks before and after dosing had to be respected.

17. Osteonecrosis of the jaw (ONJ) or risk factors for ONJ such as invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery in the past 6 months), poor oral hygiene, periodontal, and/or pre-existing dental disease, recent tooth extraction (within 6 months of prior to study drug administration).

18. Current hypocalcaemia (albumin-adjusted serum calcium below the lower limit of normal range of the analytical laboratory).

19. Allergy to vitamin D or calcium supplements, or intolerant to long-term calcium or vitamin D supplementation, or malabsorption of calcium or vitamin D supplements.

20. Participation in a drug study within 60 days or 5 half-lives of the previous drug (if known), whichever was longer, prior to drug administration.

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

22. History of drug addiction (including soft drugs like cannabis products).

23. History of alcoholism within 1 year before Day 1. Consumption of more than 50 g of ethanol per day (12.5 cL glass of 10° [10%] wine = 12 g; 4 cL of aperitif, 42° [42%] whiskey = 17 g; 25 cL glass of 3° [3%] beer = 7.5 g; 25 cL glass of 6° [6%] beer = 15 g).

24. Positive urine drug screen (opiates, methadone, cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants) or positive alcohol breath test.

25. Positive screen on hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or anti-human immunodeficiency virus (HIV) type 1/2 antibodies.

26. Post-menopausal women or women with bilateral ovariectomy.

27. Breast-feeding women.

Objectives and endpoints

Primary PK objective

- To demonstrate PK bioequivalence of Bmab 1000 versus Prolia.

Secondary objectives

- To assess PK similarity of Bmab 1000 versus Prolia based on secondary PK parameters;
- To assess PD similarity of Bmab 1000 versus Prolia based on the serum concentration of C-terminal telopeptide of Type 1 collagen (sCTX);
- To assess safety and tolerability of Bmab 1000 as compared to Prolia;
- To assess immunogenicity between Bmab 1000 and Prolia.

Primary PK endpoint

Maximum observed serum denosumab concentration (Cmax), area under the serum concentration versus time curve from time zero to the last sampling time at which concentrations were at or above the limit of quantification (AUC0-t) and AUC from time zero to the infinity (AUC0-inf).

Secondary endpoints

PK: Area under the concentration-time curve from 18 to 85 days (AUC18-85 days) and from 113 to 253 days (AUC113-253 days), time at which the Cmax occurred (tmax), terminal elimination rate constant (kel), terminal half-life (t1/2), apparent volume of distribution (Vd/F) and apparent clearance (CL/F)

PD: Area under the effect curve (AUEC) of serum concentration of C-terminal telopeptide of Type 1 collagen (sCTX) (0-36 weeks) and maximal inhibitory effect (Emax) of sCTX

Safety: Adverse events (AEs), vital signs, physical examination, 12-lead electrocardiogram (ECG); safety laboratory (including biochemistry, haematology, urinalysis)

Immunogenicity: Incidence and titre of anti-drug antibodies (ADA)

Randomisation

Participants were randomised to either Bmab 1000 or Prolia in a 1:1 ratio.

Participants were stratified based on site, on ethnicity (Japanese versus non-Japanese), body weight (55 to <60 kg for Japanese only, 60-80 kg and 81-95 kg) and on gender.

Sample size and statistical methods

The sample size was determined as the number of participants needed in the study to establish PK bioequivalence with sufficient power. PK bioequivalence was established if the 90% confidence intervals (CI) for the geometric least squares means (LSM) ratios of AUC0-t, AUC0-inf and Cmax for the comparison of the Bmab 1000 with the reference product fell within the prespecified limits of 80.00% and 125.00%. The inter-participant coefficient of variation (CV) for denosumab PK parameters Cmax and AUC was found to range between 32% and 40% in literature. Based on the current study duration (i.e., 9 months) and reported literature information, interparticipant CV% of 40% was considered as the basis for calculating the sample size. Based on CV% assumption of 40%, and the assumption of bioequivalence (as defined above) a sample size of 176 healthy participants (88 per arm) was needed to establish bioequivalence with a power of 90% with an expected difference of not more than 5% (treatment ratios of 0.95 – 1.05) between treatments with 5% level of significance. It was anticipated that about 7% of participants would not complete the study or PK sample would not be

available for analysis. Hence, 190 participants (95 per arm) were required to ensure study completion and availability of PK primary endpoints by 176 participants.

The following analysis sets were defined:

Screened set: all the participants having signed their informed consent.

Randomised set: all the participants randomised in the study.

Safety set: all the randomised participants who received one full or partial administration of the IMP, including those who did not complete the study.

Pharmacodynamic set: all participants in the safety set without any event and/or major protocol deviation affecting PD evaluation. The inclusion of the subjects with incomplete PD profile(s) was discussed before the database lock (DBL).

Pharmacokinetic set: all participants in the safety set without any event and/or major protocol deviation affecting PK evaluation and with adequately characterised PK profile(s). The inclusion of the subjects with incomplete PK profile(s) was discussed before the DBL.

For the evaluation of the bioequivalence, an analysis of variance (ANCOVA) was performed using log-transformed data for Cmax, AUC0-t and AUC0-inf of denosumab with treatment as fixed effect and ethnicity, age, weight, and site as covariates. Geometric mean ratios (GMRs) of Cmax, AUC0-t and AUC0-inf and the corresponding 90% CIs were determined, comparing Test (Bmab 1000) versus Reference (Prolia) treatments. The bioequivalence was concluded if the 90% CI lies within the bioequivalence range of (80.00%-125.00%).

Participant flow, important protocol deviations and numbers analysed

Table 5: Summary of subject disposition

Status / Reason	**US-Licensed Prolia**	**Bmab 1000-P**	**Overall**
Screened			387
Screen-failed			196
Randomised	95	94	189
Dosed Fully administered Partially administered	95 95 0	94 94 0	189 189 0
Completed study	93	92	185
Discontinued Withdrawn by participant Other[1]	2 1 1	2 0 2	4 1 3

Screened: having signed their informed consent.

1 Other reasons for withdrawal were lack of compliance with the protocol, loss to follow-up, and personal relocation (leading to consent withdrawal).

There was no protocol deviation related to inclusion or exclusion criteria. Two participants in the Bmab 1000 group presented a major protocol deviation, missing visits in both cases.

Five (5) randomised participants were excluded from the PK set and the PD set prior to data base lock (DBL) in a blinded-data review meeting (BDRM).

- Four (4) participants who did not complete the study: 2 in the Prolia group and 2 in the Bmab 1000 group.
- One participant in the Bmab 1000 group missed all visits from Day 13 to Day 43 for personal reasons, which constituted a major deviation, deemed to have an impact on PK and PD variables, and which led to the decision to exclude this participant from the PK set and the PD set.

Baseline Data

Table 6: Summary of demographic characteristics (randomised set)

Parameter (Unit)	Statistics / Category	US-Licensed Prolia (N=95)	Bmab 1000 (N=94)	Overall (N=189)
Site	France n (%)	43 (45.3)	45 (47.9)	88 (46.6)
	United-States n (%)	52 (54.7)	49 (52.1)	101 (53.4)
Age (years)	Mean ± SD	38.0 ± 6.7	38.9 ± 7.5	38.4 ± 7.1
	Min ; Max	28; 54	28; 55	28; 55
Sex	Female n (%)	29 (30.5)	27 (28.7)	56 (29.6)
	Male n (%)	66 (69.5)	67 (71.3)	133 (70.4)
Race	American Indian or Alaska Native n (%)	0	2 (2.1)	2 (1.1)
	Asian n (%)	24 (25.3)	18 (19.1)	42 (22.2)
	Black or African American n (%)	31 (32.6)	33 (35.1)	64 (33.9)
	White n (%)	40 (42.1)	41 (43.6)	81 (42.9)
Ethnicity	Hispanic or Latino n (%)	5 (5.3)	5 (5.3)	10 (5.3)
	Not Hispanic or Latino n (%)	90 (94.7)	89 (94.7)	179 (94.7)
Japanese Origin	Japanese n (%)	21 (22.1)	17 (18.1)	38 (20.1)
	Non-Japanese n (%)	74 (77.9)	77 (81.9)	151 (79.9)
Height (cm)	Mean ± SD	172.4 ± 8.2	173.0 ± 8.9	172.7 ± 8.6
	Min ; Max	155; 191	146; 194	146; 194
Weight at baseline (kg)	Mean ± SD	74.21 ± 9.96	75.31 ± 9.68	74.76 ± 9.81
	Min ; Max	55.6; 94.2	57.0; 93.3	55.6; 94.2
Weight at baseline	55 to <60 kg (for Japanese only) n (%)	8 (8.4)	6 (6.4)	14 (7.4)
	60-80 kg n (%)	59 (62.1)	59 (62.8)	118 (62.4)
	81-95 kg n (%)	28 (29.5)	29 (30.9)	57 (30.2)
BMI at baseline (kg/m^2)	Mean ± SD	24.95 ± 2.70	25.15 ± 2.54	25.05 ± 2.62
	Min ; Max	19.6; 29.4	20.4; 30.0	19.6; 30.0

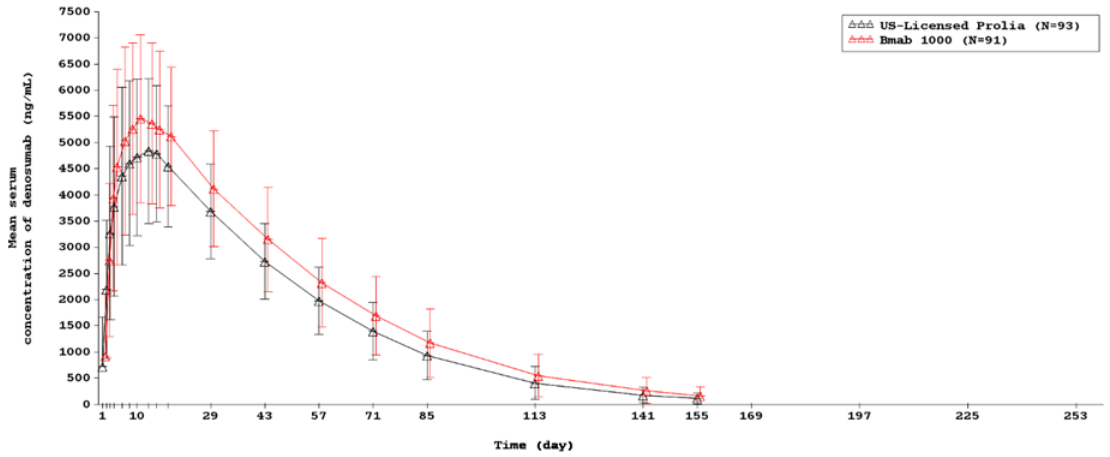
Baseline is defined as the last available measurement prior to the IMP administration.
Source: Table 14.1.3.1

PK outcomes

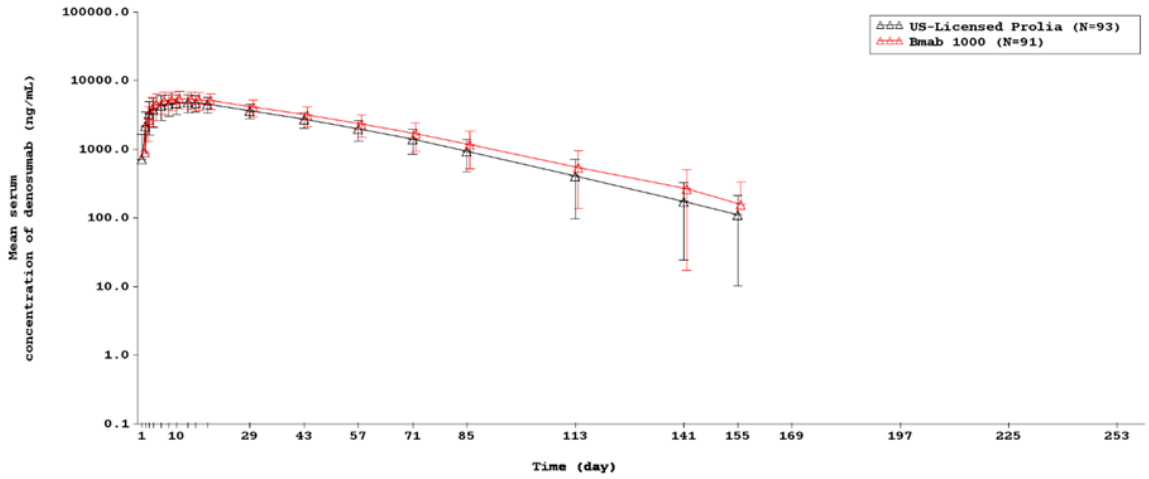
Denosumab serum concentration time profiles

Figure 1: Arithmetic mean (±SD) serum denosumab concentration versus time curves following single SC dose administration of Bmab 1000-P and Prolia (linear and semi-logarithmic scale)

Linear Scale



Semi-logarithmic scale



Denosumab PK parameters

Table 7: Summary of pharmacokinetic parameters by treatment group (PK Set)

Parameter	Prolia (N=93)	Bmab 1000-P (N=91)
C_{max} (ng/mL)	5050.9 (30.2)	5633.1 (31.0)
t_{max} (day)	11.99 (3.0 – 42.0)	9.00 (3.0 – 28.1)
C_t (ng/mL)	19.039 (160.5)	18.467 (179.8)
t_t (day)	154.0 (84.0 – 197.0)	154.1 (84.1 – 252.2)
$AUC_{0\text{-}t}$ (h*ng/mL)	5949517.1 (32.2)	6872387.7 (36.9)
$AUC_{18\text{-}85days}$ (h*ng/mL)	3648455.2 (30.0)	4162355.1 (34.8)
$AUC_{113\text{-}253days}$ (h*ng/mL)	120902.9 (197.6)	169443.9 (210.2)
$AUC_{0\text{-}inf}$ (h*ng/mL)	5975333.9 (32.0)	6903269.4 (36.6)
AUC_{ext} (%)	0.19641 (200.7)	0.16870 (243.9)
$t_{1/2}$ (day)	17.8 (24.9)	18.2 (22.6)
k_{el} (h)	0.0016222 (24.9)	0.0015858 (22.6)
CL/F (mL/h)	10.041 (32.0)	8.692 (36.6)
Vd/F (mL)	6189.8 (26.8)	5481.1 (28.7)
Geometric mean (Geometric CV%) are displayed for all parameters except for t_{max} and t_t described by median (min-max).		

Statistics on primary PK endpoints

Table 8: Statistical analysis of primary PK parameters between US-licensed Prolia and Bmab 1000-P (PK Set)

Parameter (Unit)	Test[1] Bmab 1000-P (n=91)	Reference[1] US-Licensed Prolia (n=93)	Test / Reference[2]	CV%
C_{max} (ng/mL)	5552.82	4983.42	111.43 [103.96; 119.43]	28.9
$AUC_{0\text{-}t}$ (h*ng/mL)	6827143.10	5933144.30	115.07 [106.45; 124.39]	32.6
$AUC_{0\text{-}inf}$ (h*ng/mL)	6853233.60	5955005.60	115.08 [106.53; 124.33]	32.3
[1]Geometric LS mean.				

[2]Point estimate [90% confidence interval] for the Test / Reference geometric LS mean ratio derived from ANCOVA using log-transformed data with treatment as fixed effect and ethnicity, age, weight, and site as covariates.

Table 9: Statistical comparison of primary PK protein-adjusted parameters between Prolia and Bmab 1000-P (PK Set)

Parameter (Unit)	Test[1] Bmab 1000-P (n=91)	Reference[1] Prolia (n=93)	Test / Reference[2]	CV%
C_{max} / P [(ng/mL)/(mg/mL)]	91.934167	85.186697	107.92 [100.69; 115.67]	28.9
AUC_{0-t} / P [(h*ng/mL)/(mg/mL)]	113032.17	101421.27	111.45 [103.10; 120.47]	32.6
AUC_{0-inf} / P [(h*ng/mL)/(mg/mL)]	113464.13	101794.97	111.46 [103.18; 120.42]	32.3

[1]Geometric LS mean.

[2]Point estimate [90% confidence interval] for the Test / Reference geometric LS mean ratio derived from ANCOVA using log-transformed data with treatment as fixed effect and ethnicity, age, weight, and site as covariates.

Upon request, a sensitivity analysis for all PK parameters with BLQ values after the first quantifiable concentration set to zero has been provided.

Table 10: PK Parameters from original and sensitivity analysis with BLQ values after the first quantifiable concentration set to zero

PK Parameters	Geometric mean value (Original analysis)		Geometric mean value (Sensitivity analysis)	
	Prolia®	Bmab1000	Prolia®	Bmab1000
AUC0-t (h*ng/mL)	5949517.1	6872387.7	5949517.5	6872096
AUC18-85days (h*ng/mL)	3648455.2	4162355.1	3648435	4162318.3
AUC113-253days (h*ng/mL	120902.9	169443.9	69871.1	84666.1
AUC0-inf (h*ng/mL)	5975333.9	6903269.4	5975334.2	6902976.5

Table 11: Statistical analysis from original and sensitivity analysis with BLQ values after the first quantifiable concentration set to zero

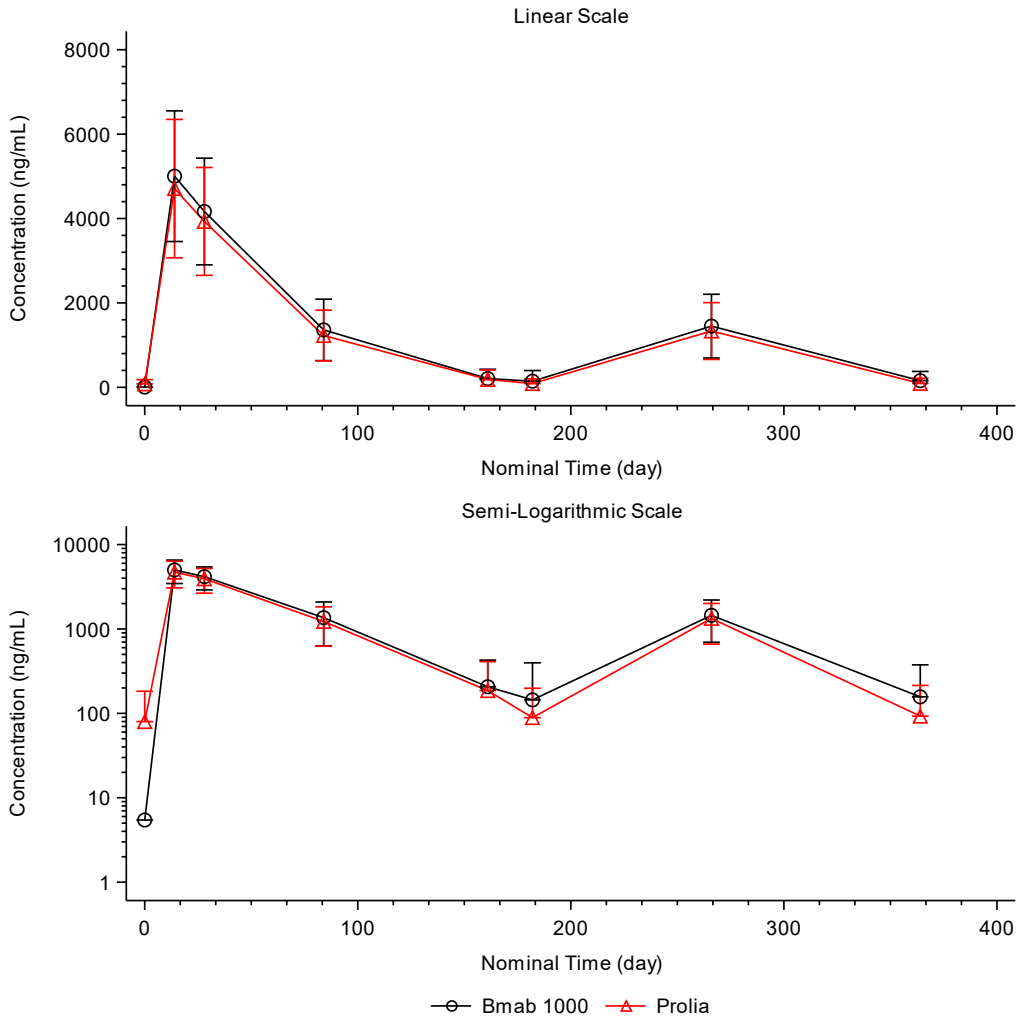
Parameter (Unit)	Point estimate [90% confidence interval]	
	Original Analysis	Sensitivity Analysis
Cmax (ng/mL)	111.43 [103.96; 119.43]	111.43 [103.96; 119.43]
AUC0-t (h*ng/mL)	115.07 [106.45; 124.39]	115.06 [106.44; 124.38]
AUC0-inf (h*ng/mL)	115.08 [106.53; 124.33]	115.08 [106.52; 124.32]

PK analysis in Phase 3 Study B1000-PMO-03-G-02

Secondary PK endpoints were denosumab concentrations at Weeks 2, 4, 12, 23, 26, 38, and 52.

A total of 472 (98.5%) patients were included in the mFAS and analysed for PK.

Figure 2: Mean (±SD) serum concentrations of denosumab, study B1000-PMO-03-G-02



Supportive PK results from the transition period (switch from Prolia to Bmab 1000)

At Week 56 (Day 393), mean denosumab concentrations were 4190 ng/mL, 4209 ng/mL, and 4242 ng/mL in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively. At Week 64 (Day 449), mean denosumab concentrations were 1426 ng/mL, 1356 ng/mL, and 1426 ng/mL in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively. The denosumab concentrations at Week 78 (Day 547) were similar to the trough concentrations observed at Week 26 (Day 183) and Week 52 (Day 365) and were similar for all the 3 treatment groups in Part 2. The mean Week 78 (Day 547) denosumab concentrations were 89.1 ng/mL, 69.9 ng/mL, and 61.6 ng/mL in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively.

2.5.2.2. Pharmacodynamics

Mechanism of action

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Primary and Secondary pharmacology

Bioanalytical methods

CTX-1 (β-CrossLaps) and **P1NP** were quantified on the Roche Cobas 8000 E602 analyser at an accredited laboratory. The standardised method of an electrochemiluminescence immunoassay (ECLIA) is intended for use on Roche Cobas E602 immunoassay analysers. This assay employed the Sandwich principle.

The results were determined via a calibration curve which was instrument-specifically generated by a 2-point calibration and a master curve provided via the reagent barcode, which resulted in a reportable range between 10-5000 pg/mL for CTX-1 (β-CrossLaps) and 5.0 - 1000.0 ng/mL. for P1NP.

A validation study was performed. Acceptability of results throughout the entire validation period was based on the concept of Total Allowable Error (TaE) which uses generally accepted medical targets for accuracy, imprecision, bias and are published in the literature.

PD analysis in study B1000-PMO-03-G-02

Serum sCTX and P1NP were measured throughout the study. PD samples (sCTX and P1NP) were scheduled for collection on Week 0 (Day 1), Week 0 (Day 3 ± 1 day); Week 2 (Day 15 ± 2 days), Week 4 (Day 29 ± 5 days), Week 12 (Day 85 ± 5 days), Week 20 (Day 141 ± 5 days), Week 23 (Day 162 ± 7 days), Week 26 (Day 183 ± 7 days), Week 38 (Day 267 ± 7 days), Week 52 (Day 365 ± 7 days), and Week 78 (Day 547 ± 7 days).

PD parameters were analysed using noncompartmental methods and actual sampling times. In cases where an actual sampling time was not recorded, the nominal time was used.

The main PD endpoint was a co-primary endpoint to establish PD equivalence in terms of AUEC of the bone resorption marker sCTX calculated from baseline to Week 26. The comparability of sCTX levels between Bmab 1000-P and Prolia was assessed by fitting an ANCOVA to log-transformed AUEC (mFAS) to give the ratio of geometric means with 95% CI. Comparability between Bmab 1000-P and Prolia was concluded if the 95% CI around the GLSM ratios for AUEC were entirely contained within 80.00% - 125.00%.

Main Estimation of estimand 1b-EMA (Co-primary PD): Comparability of sCTX levels between Bmab 1000 and Prolia will be assessed by fitting an ANCOVA to log-transformed AUEC (mFAS) to give the ratio of geometric means with 95% CI. Logged pre-dose sCTX concentrations will be fitted as a covariate since baseline-adjustment is not included in the AUEC calculation, baseline eGFR will be included as a covariate since renal function is known to affect sCTX levels, and treatment group and all stratification factors will be fitted as fixed effects. Comparability between Bmab 1000 and Prolia will be

concluded if the 95% CI around the geometric mean ratios for AUEC lie entirely within 80.00%-125.00%.

Upon request the applicant provided additional clarification on handling of intercurrent events: Intercurrent events have been addressed by the primary estimand by excluding observations from the analysis after the occurrence of ICE3 (dosing deviation) or ICE5 (medications affecting bones). Additionally, observations have been excluded in case the sample was not taken in the fasted state, in case the subject had strenuous physical activity within 2 days prior to sample collection or in case baseline data were taken post-dose. For the primary analysis of the co-primary PD endpoint AUEC was calculated using interpolation and/or extrapolation if the predefined rule was satisfied and otherwise, the resulting AUEC was missing.

Table 12: Secondary PD parameters estimated for sCTX using absolute sCTX concentrations in the mFAS

C_{min}	The minimum concentration (which represents the maximum PD effect) [Time Frame: Baseline up to Week 26 Visit within the first dosing interval]
T_{min}	Time of occurrence of the minimum concentration [Time Frame: Baseline up to Week 26 Visit within the first dosing interval]
AUEC	AUEC will be calculated provided the rule to impute the C_{182imp} is met. The area under the effect curve from first dose to 182 days post-dose (26 weeks), calculated using absolute sCTX data (without baseline-adjustment) and including C_{182imp}. The calculation will use the linear trapezoidal rule which sums the area of each trapezoid as the average of two consecutive concentrations multiplied by the difference between their respective actual timepoints. Inclusion of C_{182imp} ensures an extrapolated area if $T_{last} < 182$, otherwise if $T_{last} > 182$, the calculation results in a partial area, and if $T_{last} = 182$, it equates to $AUEC_{last}$.
sAUEC	Standardized AUEC. AUEC divided by 182 and baseline sCTX.

Table 13: Secondary PD parameters estimated for sCTX using %inhibition sCTX values

I_{max}	The maximum % inhibition [Time Frame: Baseline up to Week 26 Visit within the first dosing interval]
TI_{max}	The time of occurrence of maximum % inhibition [Time Frame: Baseline up to Week 26 Visit within the first dosing interval]
AUIC	AUIC will be calculated provided the rule to impute the I_{182imp} is met. The area under the % inhibition curve from first dose to 182 days post-dose (26 weeks), calculated using %inhibition and including I_{182imp} using the linear trapezoidal rule to calculate the area above zero without extrapolating below zero and including any negative areas [Time Frame: Baseline up to Week 26 Visit within the first dosing interval].

Serum sCTX and P1NP concentrations were listed and summarised using descriptive statistics (n, mean, SD, CV%, median, minimum, and maximum) by treatment and visit. Mean sCTX and P1NP concentration versus scheduled time profiles by treatment were presented in figures on both linear and semi-logarithmic scales.

The mFAS was identical to FAS and comprised 472 patients (237 patients receiving Bmab 1000 and 235 patients receiving Prolia). AUEC and AUIC PD parameters were not included in the primary and sensitivity analysis for 35 patients (13 patients receiving Bmab 1000 and 22 patients receiving Prolia). One patient in the Bmab 1000 group withdrew on Day 65 and no PD samples or concentrations were recorded. Therefore, a total of 436 patients provided AUEC and AUIC parameters (223 patients receiving Bmab 1000 and 213 patients receiving Prolia).

Table 14: Main estimation of estimand 1b-EMA (Co-Primary PD) by ANCOVA: Ratio of geometric means of sCTX AUEC (mFAS)

Parameter (unit)	Bmab 1000-P (N=237)		Prolia (N=235)		Ratio of Geometric LS Means (%)	95% CI of the Ratio (%)
	n	Geometric LS Mean	n	Geometric LS Mean		
AUEC (day*pg/mL)	223	11954.89	213	11481.40	104.12	(97.74, 110.93)

Abbreviations: ANCOVA, analysis of covariance; AUEC, area under sCTX curve; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; LS, least squares; N, total number of patients; n, number of patients at each level of summarisation.
Notes: Values were excluded from calculation of AUEC if any of the following criteria applied: patient did not fast as instructed prior to sample collection; patient performed physical activity within 2 days prior to sample collection; patient consumed prohibited medication; dosing deviation; death; pre-dose sample was collected post-dose; or pre-dose sample was collected in a non-fasted state.

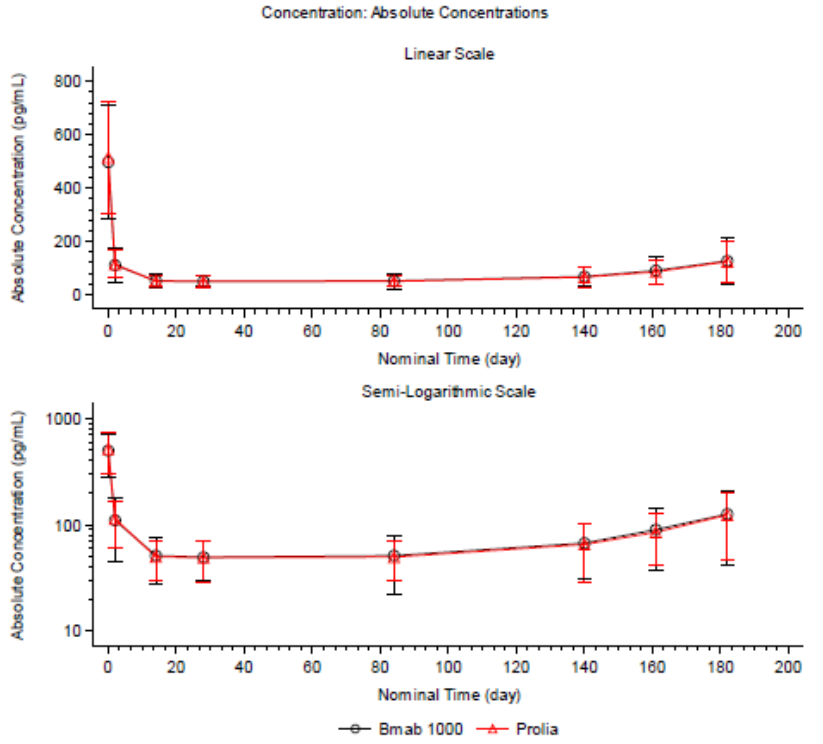
An ANCOVA model was fitted to logged AUEC including baseline covariates eGFR and logged sCTX, treatment group and stratification factors [geographical region (US, Europe), prior use of bisphosphonate treatment (Yes, No), and age of the patient (<65, ≥65)] as fixed effects.

Comparability between Bmab 1000-P and Prolia was concluded if the 95% CI lie entirely within 80.00% to 125.00%.

All secondary PD endpoints (C_{min}, T_{min}, AUEC, sAUEC, I_{max}, TI_{max}, and AUIC) were comparable between treatments.

As an alternative approach to handling missing data, a MMRM supplementary analysis was performed which included all subjects in mFAS (N=472) and adjusts LSmeans at each timepoint using all partial data.

Figure 3: Mean (±SD) serum concentrations of sCTX modified full analysis set



All values below the limit of quantification (10 pg/mL) were treated as ½ LLOQ for calculation of summary statistics.

Note: Values were excluded from calculation of summary statistics if any of the following criteria applied: sample collected outside the specified window; subject did not fast as instructed prior to sample collection; subject performed physical activity within 2 days prior to sample collection; subject consumed prohibited medication; dosing deviation; death; predose sample was collected postdose; or predose sample was collected in a non-fasted state.

Source: Table 14.3.8.1.2

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Table 15: Summary of serum concentrations of sCTX after second dose, Modified Full Analysis Set

Concentration: Absolute Concentrations (pg/mL)

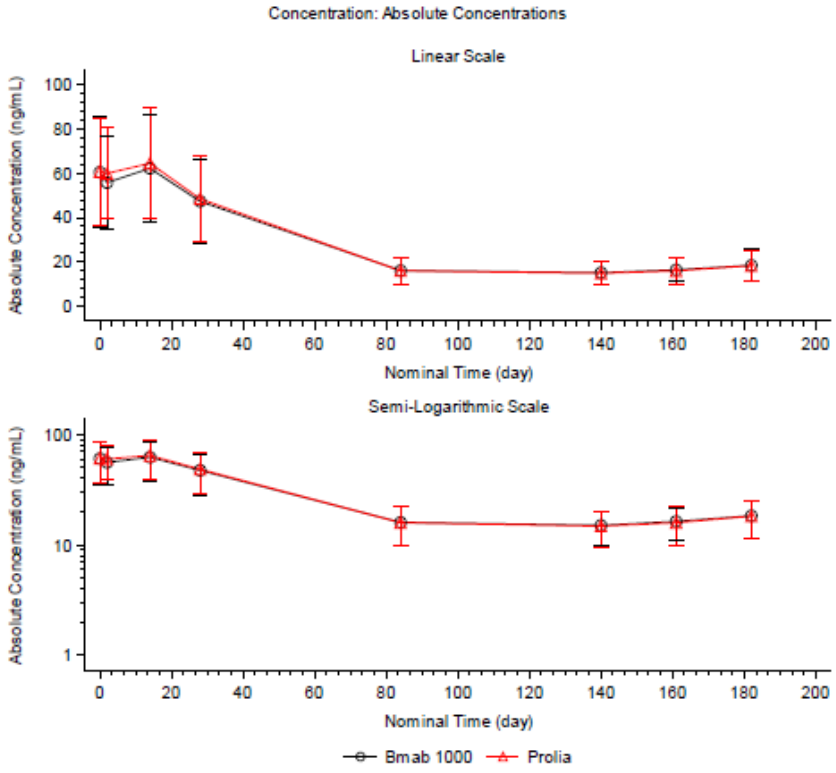
		Treatment	
Study Week (Day)	Summary Statistic	Bmab 1000 (N=237)	Prolia (N=235)
Week 38 (Day 267)	n	178	177
	Mean	57.0	58.4
	SD	18.2	27.5
	CV%	31.9	47.1
	Median	55.5	56.0
	Minimum	21.0	5.00
	Maximum	129	317
Week 52 (Day 365)	n	170	172
	Mean	148	148
	SD	91.3	101
	CV%	61.5	68.4
	Median	126	123
	Minimum	40.0	34.0
	Maximum	499	712

BLQ = Below the limit of quantification (10 pg/mL); CV = coefficient of variation; ET = Early termination; NA = not applicable; SD = standard deviation.
For the calculation of summary statistics, BLQ values were treated as ½ LLOQ and negative % inhibition values were treated as 0.
Note: Values were excluded from calculation of summary statistics if any of the following criteria applied: sample collected outside the specified window; subject did not fast as instructed prior to sample collection; subject performed physical activity within 2 days prior to sample collection; subject consumed prohibited medication; dosing deviation; death; predose sample was collected postdose; or predose sample was collected in a non-fasted state.
Source: Listing 16.2.16.2

sCTX during transition period (switch from Prolia to Bmab 1000)

Following the third administration of Bmab 1000 or Prolia on Week 52 (Day 365), the sCTX concentrations on Week 78 (Day 547) were similar to the concentrations observed on Week 26 (Day 183) and Week 52 (Day 365). The concentrations on Week 78 (Day 547) were similar for the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, showing no effect of transition from Prolia to Bmab 1000 on the sCTX concentrations. The mean Week 78 (Day 547) sCTX concentrations were 152 pg/mL, 166 pg/mL, and 153 pg/mL for the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively.

Figure 4: Mean (±SD) serum concentrations of P1NP, modified full analysis set



All values below the limit of quantification (5 ng/mL) were treated as ½ LLOQ for calculation of summary statistics.
Note: Values were excluded from calculation of summary statistics if any of the following criteria applied: sample collected outside the specified window; subject did not fast as instructed prior to sample collection; subject performed physical activity within 2 days prior to sample collection; subject consumed prohibited medication; dosing deviation; death; predose sample was collected postdose; or predose sample was collected in a non-fasted state.
Source: Table 14.3.8.1.3
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P1NP during transition period (switch from Prolia to Bmab 1000)

Following the third administration of Bmab 1000 or Prolia on Week 52 (Day 365), the P1NP concentrations on Week 78 (Day 547) were similar to the concentrations observed on Week 26 (Day 183) and Week 52 (Day 365). The concentrations on Week 78 (Day 547) were similar for the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, showing no effect of transition from Prolia to Bmab 1000 on the P1NP concentrations. The mean Week 78 (Day 547) P1NP concentrations were 19.8 ng/mL, 20.3 ng/mL, and 19.2 ng/mL for the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively.

Erratum to CSR Week 78

After finalisation of the Final Week 78 CSR (dated 29 Aug 2024), during a random check an error was identified on 3 Dec 2024 where in the local daylight-saving clock changes did not accurately account for the PK (denosumab) and PD (sCTX and P1NP) analysis (i.e: actual times (days) calculated relative to the date/time of dosing used throughout the PK and PD analyses, including the estimation of AUEC PD parameters used to assess the co-primary objective in Part 1 (estimand 1b).

The following listing and analyses were affected:

- PK: Listing on Individual Serum Concentrations of denosumab; Descriptive Statistics on Serum Concentrations of denosumab by Timepoint
- PD: Listing on Individual Serum Concentrations of sCTX and P1NP; Descriptive Statistics on Serum Concentrations of xCTX and P1NP by Timepoint; Individual sCTX AUEC and AUIC Parameter Calculation; Inferential Statistical Analyses on sCTX AUEC (Co-primary PD endpoint)

The applicant provided an impact assessment and re-ran all analyses affected with correct actual times.

The impact of the daylight-saving errors on the individual concentration data, individual PD parameter data and all inferential analyses pertaining to sCTX data was negligible.

PD analysis in study B1000-NHV-01-G-01

PD sampling was done on D1 - pre-dose (up to 60 mins prior to drug administration), then on D2 (24 h), D3, D4, D6, D10, D13, D29, D57, D85, D113, D141, D197, and D253. A fasting period of at least 8 hours was required before obtaining PD samples.

The pharmacodynamic analysis was performed on the Pharmacodynamic set.

Pharmacodynamic set: all participants in the safety set without any event and/or major protocol deviation affecting PD evaluation. The inclusion of the subjects with incomplete PD profile(s) was discussed before the database lock (DBL).

Actual sampling times were used for deriving PD parameters. All BLQ values were replaced by 'LLOQ/2' for descriptive statistics, plots and PD parameters calculation. However, all BLQ concentrations and missing data were labelled as such in the sCTX concentration data listings.

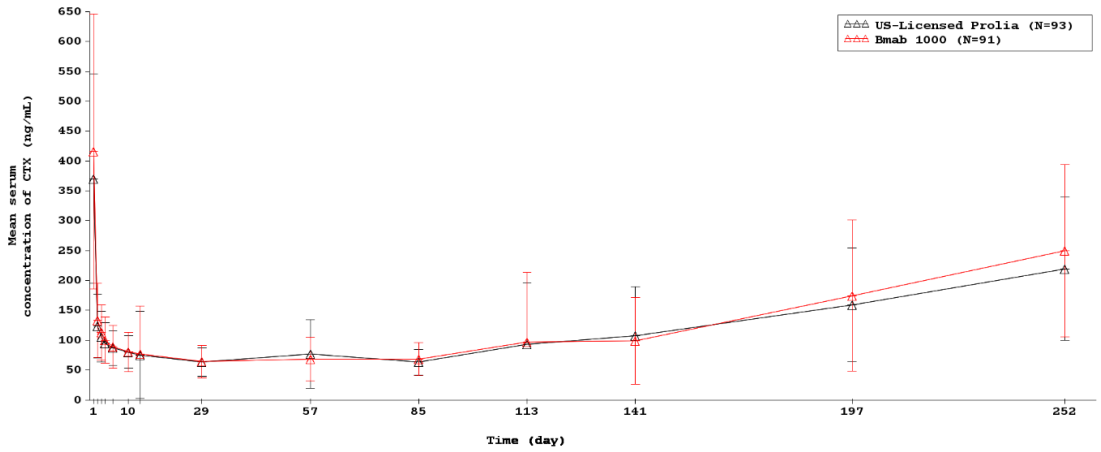
Table 16: PD parameters in study B1000-NHV-01-G-01

Parameters (unit)	Definition
$AUEC_{0\text{-}253days}$ (pg/mL.h)	Area under the effect curve of sCTX concentrations were calculated from time zero (pre-dose measurement on Day 1) to Day 253 using the linear trapezoidal summation based on actual elapsed time: $AUEC_{0\text{-}253days} = \sum_{i=a}^{b-1}\{0.5 \times (t_{i+1} - t_i) \times (Y_i + Y_{i+1})\}$ where Y_i is the sCTX concentration at Day i, t_i is the actual elapsed time at Day i, a is the baseline timepoint, and b is the last available timepoint up to Day 253 or early termination. If the actual time was missing, the nominal time could be substituted in order to calculate the AUEC. In case of sCTX concentration missing or excluded, the AUEC calculation was done with the timepoint before and the timepoint after.
E_{max} (pg/mL)	Maximal inhibitory effect of sCTX

An ANCOVA was performed to assess biosimilarity of Bmab 1000 and Prolia using log-transformed data for AUEC and Emax with treatment as fixed effect and ethnicity, age, weight and site as covariates. GMRs of AUEC and Emax and the corresponding 95% CIs were constructed, comparing Test (Bmab 1000) versus Reference (Prolia) treatments. As AUEC and Emax were secondary endpoints, the CIs of their GMRs were not required to fulfil any equivalence limits and were not used to conclude on bioequivalence.

Figure 5: Arithmetic mean (± SD) sCTX concentrations over time profiles following single SC dose administration of Prolia and Bmab 1000-P (linear and Log-linear scales) from study B1000-NHV-01-G-01

Linear-scale



Log-linear-scale

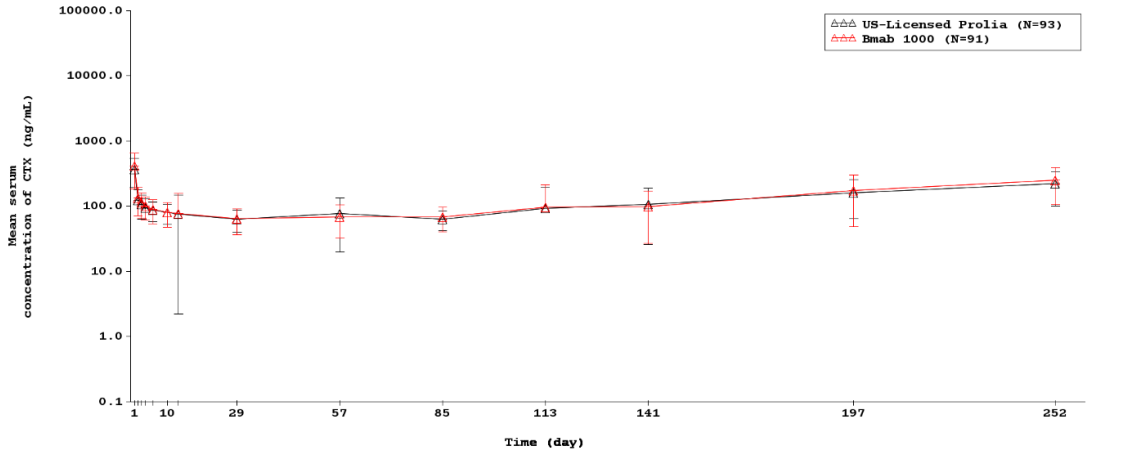


Table 17: Statistical analysis of PD parameters - AUEC0-253 days and Emax (PD Set of study B1000-NHV-01-G-01)

Parameter (Unit)	Test[1] Bmab 1000-P	n	Reference[1] US-Licensed Prolia	n	Test / Reference[2]	CV%
$AUEC_{0\text{-}253\ days}$ (h*pg/mL)	672332.11	91	642813.41	93	104.59 [94.38; 115.91]	36.3
E_{max} (pg/mL)	51.00	91	49.31	93	103.43 [91.56; 116.84]	43.6

[1]Geometric LS mean.

[2]Point estimate [95% confidence interval] for the Test / Reference geometric Ls mean ratio derived from ANCOVA using log-transformed data with treatment as fixed effect and ethnicity, age, weight, and site as covariates.

Immunogenicity

Bioanalytical methods

Bioanalytical assays for detection, confirmation, and titration of anti-Bmab 1000 and anti-Prolia antibodies in human serum

The anti-denosumab (binding) antibodies (ADA) in human serum were detected using a bridging ECLIA method. In this method, samples underwent acid dissociation to release any anti-denosumab antibodies complexed with free drug. Samples were then neutralised and incubated with a Master Mix which contains Biotinylated Bmab 1000 and s/Tag labelled Bmab 1000 to allow anti-denosumab antibodies to bind to Biotinylated Bmab 1000, and s/Tag labelled BmAb 1000, thus forming the bridging complexes. After incubation, the antibody complex bridge was added to a pre-blocked streptavidin-coated plate. The Biotinylated BmAb 1000 in the complex binds to the streptavidin-coated wells. Read buffer containing tripropylamine was added, and the s/Tag labelled Bmab 1000 produces a chemiluminescent signal when an electrical voltage is applied. This signal is directly proportional to the level of anti-denosumab antibodies present in the sample.

A single assay comprising Biotinylated Bmab 1000 as the capture and s/Tag labelled Bmab 1000 as a detection reagent in the ECL (electrochemiluminescence) assay was used for the determination of anti-denosumab (binding) antibodies. The method was validated as per FDA guidelines titled "Immunogenicity Testing of Therapeutic Protein Products Developing and Validating Assays for Anti-Drug Antibody Detection".

To achieve a good drug tolerance in a method and thereby to minimise the risk of false negative results, samples were treated with acid that resulted in a drug tolerance of detecting 100 ng/mL ADA in the presence of 50 µg/mL circulating drug across both the products (Bmab 1000 and Prolia).

Detection of neutralizing antibody against Bmab 1000 and Prolia

The method validated for the detection of neutralizing antibodies against Bmab 1000, and Prolia was sandwich indirect ECLIA format.

A ligand binding assay was used to detect neutralizing anti-denosumab antibodies in human serum. To minimise the effect of free drug interference, the drug was removed from samples by the addition of excess Biotin-RANKL depletion solution and Streptavidin MagneSphere Paramagnetic particles forming a free drug-Biotin-RANKL-Streptavidin -bead complex. The complex was removed from the sample solution by immobilizing the Streptavidin MagneSphere Paramagnetic particles on 96 well magnetic stands, and the supernatant was collected. Then, the samples underwent acid dissociation to release anti-denosumab antibodies complexed with free drug (Prolia/Bmab 1000). Samples were then

neutralised and incubated onto a plate coated with denosumab (Prolia/Bmab 1000). After incubation, Biotin-RANKL was added as a primary detection solution. After incubation with Biotin-RANKL, streptavidin-sulfotag was added as secondary detection solution. After required incubation and the addition of read buffer containing tripropylamine, the plate was read. The RLUs measured are inversely proportional to the level of neutralizing anti-denosumab antibody present in the sample.

ADA analysis from studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02

In the phase 1 **study B1000-NHV-01-G-01**, blood samples were collected at D1 - pre-dose (up to 60 mins prior to drug administration), then on D10, D29, D57, D85, D169, and D253.

Table 18: Incidence of final ADA, study B1000-NHV-01-G-01

Visit	Time Point	Category	US-Licensed Prolia (N=95) n (%)	Bmab 1000-P (N=94) n (%)
D1	H00:00 (Pre-dose)	Negative	94 (98.9)	94 (100)
		Positive	1(1.1)	0
D10	H216:00	Negative	65 (68.4)	54 (57.4)
		Positive	30 (31.6)	40 (42.6)
D29	H672:00	Negative	15 (15.8)	16 (17.2)
		Positive	80 (84.2)	77 (82.8)
D57	H1344:00	Negative	6 (6.5)	1 (1.1)
		Positive	87 (93.5)	91 (98.9)
D85	H2016:00	Negative	5 (5.4)	1 (1.1)
		Positive	88 (94.6)	91 (98.9)
D169	H4032:00	Negative	39 (42.4)	29 (31.5)
		Positive	53 (57.6)	63 (68.5)
EOS/ET	H6048:00	Negative	91 (97.8)	87 (94.6)
		Positive	2 (2.2)	5 (5.4)

In the phase 3 **study B1000-PMO-03-G-02**, blood samples were collected at D1 (pre-dose), D15, D29, D85, D183 (pre-dose), D267, and D365 (pre-dose). Blood samples were further planned to be collected during the transition period on D393, D449, and D547. In case of positive results in the ADA evaluation, the ADA titre was evaluated, and an evaluation of neutralizing antibody (NAb) reactivity was conducted.

Table 19: Incidence of anti-drug antibody by timepoint - Double-blind active-controlled period, safety analysis set

Subject Status	Bmab 1000 (N=238) n (%)	Prolia (N=240) n (%)	Total (N=478) n (%)
Overall ADA			
ADA positive [1]	215 (90.3)	205 (85.4)	420 (87.9)
ADA negative [1]	22 (9.2)	28 (11.7)	50 (10.5)
Overall NAb			
NAb positive [1]	7 (2.9)	5 (2.1)	12 (2.5)
NAb negative [1]	208 (87.4)	200 (83.3)	408 (85.4)
Treatment-emergent ADA [2]	213 (89.5)	203 (84.6)	416 (87.0)
Baseline			
Baseline ADA positive [3]	2 (0.8)	3 (1.3)	5 (1.0)
Baseline NAb positive [5]	0	0	0
Baseline NAb negative [5]	2 (100)	3 (100)	5 (100)
Baseline ADA negative [4]	236 (99.2)	236 (98.3)	472 (98.7)
Baseline ADA assessment missing	0	0	0
Week 2			
ADA positive [1]	57 (23.9)	33 (13.8)	90 (18.8)
NAb positive [7]	2 (0.8)	2 (0.8)	4 (0.8)
NAb negative [8]	55 (23.1)	31 (12.9)	86 (18.0)
ADA negative [6]	175 (73.5)	197 (82.1)	372 (77.8)
Week 4			
ADA positive [1]	111 (46.6)	90 (37.5)	201 (42.1)
NAb positive [7]	1 (0.4)	0	1 (0.2)
NAb negative [8]	110 (46.2)	90 (37.5)	200 (41.8)
ADA negative [6]	124 (52.1)	141 (58.8)	265 (55.4)
Week 12			
ADA positive [1]	163 (68.5)	150 (62.5)	313 (65.5)
NAb positive [7]	3 (1.3)	0	3 (0.6)
NAb negative [8]	160 (67.2)	150 (62.5)	310 (64.9)
ADA negative [6]	69 (29.0)	77 (32.1)	146 (30.5)
Week 26			
ADA positive [1]	70 (29.4)	62 (25.8)	132 (27.6)
NAb positive [7]	0	0	0
NAb negative [8]	70 (29.4)	62 (25.8)	132 (27.6)
ADA negative [6]	153 (64.3)	154 (64.2)	307 (64.2)
Week 38			
ADA positive [1]	136 (57.1)	111 (46.3)	247 (51.7)
NAb positive [7]	1 (0.4)	2 (0.8)	3 (0.6)
NAb negative [8]	135 (56.7)	109 (45.4)	244 (51.0)
ADA negative [6]	87 (36.6)	104 (43.3)	191 (40.0)
Week 52			
ADA positive [1]	70 (29.4)	64 (26.7)	134 (28.0)
NAb positive [7]	0	1 (0.4)	1 (0.2)
NAb negative [8]	70 (29.4)	63 (26.3)	133 (27.8)
ADA negative [6]	148 (62.2)	148 (61.7)	296 (61.9)

ADA= Anti-Drug Antibody; NAb=Neutralising Antibody.
Subjects with baseline and at least one post-baseline immunogenicity assessment within the Double-blind Active-controlled Period are presented in the table.
Blood samples at visits day 1, week 26 and week 52 were collected before study drug administration.
[1] Overall ADA Positive: subjects with at least ADA positive sample at any time after initiation of treatment during double-blind period, irrespective of baseline result. Overall ADA Negative: subjects with only ADA negative samples at any time after initiation of treatment during double-blind period, irrespective of baseline result. Overall NAb Positive (for ADA positive subjects): subjects with at least one ADA positive sample with neutralising antibodies detected post-baseline during double-blind period. Overall NAb Negative (for ADA positive subjects): subjects with only ADA positive samples with no neutralising antibodies at any time after initiation of treatment during double-blind period.
Subjects 3001106, 3001132, 3001194, 3002113, 3008108, 3016109, 3022110, 3023128 only have baseline ADA results so these subjects do not have overall ADA status.
[2] Treatment-emergent ADA is defined for a subject with at least one post-baseline positive result having a negative or non-evaluable baseline result.
[3] Subjects with baseline ADA positive sample.
[4] Subjects with ADA negative or no evaluable ADA assessment at baseline.
[5] Percentage is calculated based on the number of subjects with positive ADA results at baseline.
[6] A subject with ADA negative sample, irrespective of baseline ADA result.
[7] For ADA positive subjects and NAb positive subjects, with at least one ADA positive sample with neutralizing antibodies detected post-baseline during double-blind period.
[8] For ADA positive subjects and NAb negative subjects, with only ADA positive samples with no neutralizing antibodies detected at any time after initiation of treatment during double-blind period.

Source Data: Listing 16.2.17

ADA analysis during transition period (switch from Prolia to Bmab 1000)

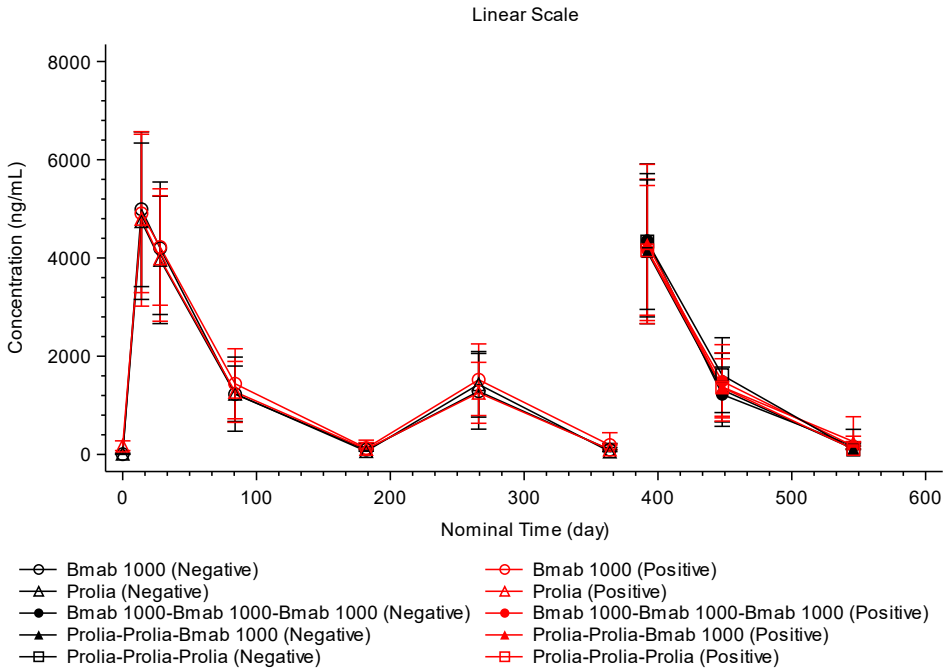
The proportion of patients with ADA-positive result was similar between the Prolia-Bmab 1000 and Prolia-Prolia treatment groups (87 [83.7%] and 90 [86.5%] patients, respectively). At Week 52, 1% patients in the Prolia-Bmab 1000 treatment group and no patient in the Prolia-Prolia treatment group was NAb-positive. Overall, the incidence of NAb-positive did not increase in patients who transitioned from Prolia to Bmab 1000 (1.0% patients); however, it increased for patients in the Prolia-Prolia treatment group (5.8% patients) and remained numerically low.

Investigation of PK by ADA status

Denosumab serum concentrations over time for ADA-positive subjects in groups of titres (quartiles) versus the ADA-negative subjects for Bmab 1000 and Prolia treatment group of study B1000-NHV-01-G-01 and study B1000-PMO-03-G-02 have been analysed upon request.

For this, the ADA titres have been classified into low, moderate and high based on quartile distribution of subject titre values [low (<=Q1, for first 25%), medium (Q1-Q3, between 25 – 75%), high (>Q3, for last 25%) on visits where immunogenicity sample was collected concurrently with the PK sample.

Figure 6: Posthoc mean (±SD) serum concentrations of denosumab by concurrent ADA status (modified full analysis set) from study B1000-PMO-03-G-02



Investigation of efficacy by ADA status

Table 20: Posthoc summary of %CfB in lumbar spine BMD by visit and concurrent ADA status and titre quartile group from study B1000-PMO-03-G-02, modified FAS

			Bmab 1000 (N=237)		Prolia (N=235)		Total (N=472)	
			Lumbar Spine		Lumbar Spine		Lumbar Spine	
Visit	ADA Status	ADA Titer	BMD (g/cm^2)	% CfB	BMD (g/cm^2)	% CfB	BMD (g/cm^2)	% CfB
Baseline [1]								
n			237		235		472	
Mean (SD)			0.766 (0.059)		0.762 (0.064)		0.764 (0.062)	
Median			0.768		0.763		0.765	
Min, Max			0.623, 1.000		0.620, 0.980		0.620, 1.000	
Mean 95% CI			(0.758, 0.773)		(0.753, 0.770)		(0.758, 0.769)	
Week 26	Negative							
n			149	149	151	151	300	300
Mean (SD)			0.790 (0.063)	3.853 (3.748)	0.793 (0.073)	3.461 (3.356)	0.791 (0.068)	3.656 (3.556)
Median			0.793	3.561	0.790	3.387	0.791	3.504
Min, Max			0.629, 0.988	-5.889, 13.220	0.634, 1.020	-7.364, 15.087	0.629, 1.020	-7.364, 15.087
Mean 95% CI			(0.780, 0.800)	(3.246, 4.460)	(0.781, 0.805)	(2.922, 4.001)	(0.784, 0.799)	(3.252, 4.060)
Week 26	Positive							
n			68	68	62	62	130	130
Mean (SD)			0.793 (0.054)	3.401 (3.563)	0.791 (0.066)	3.830 (3.054)	0.792 (0.060)	3.605 (3.324)
Median			0.802	3.658	0.807	3.330	0.805	3.512
Min, Max			0.658, 0.896	-5.805, 13.361	0.649, 0.905	-3.081, 10.403	0.649, 0.905	-5.805, 13.361
Mean 95% CI			(0.780, 0.806)	(2.539, 4.264)	(0.774, 0.808)	(3.054, 4.605)	(0.782, 0.803)	(3.029, 4.182)
Week 26	Positive	Low						
n			20	20	27	27	47	47
Mean (SD)			0.801 (0.051)	2.251 (2.586)	0.785 (0.074)	3.358 (2.797)	0.792 (0.065)	2.887 (2.737)
Median			0.818	2.687	0.799	3.158	0.806	3.090
Min, Max			0.713, 0.877	-5.805, 5.656	0.663, 0.905	-3.081, 8.283	0.663, 0.905	-5.805, 8.283
Mean 95% CI			(0.778, 0.825)	(1.040, 3.461)	(0.755, 0.814)	(2.252, 4.465)	(0.773, 0.811)	(2.083, 3.690)
Week 26	Positive	Moderate						
n			30	30	20	20	50	50
Mean (SD)			0.782 (0.051)	3.691 (3.874)	0.781 (0.067)	3.372 (3.000)	0.782 (0.057)	3.564 (3.521)
Median			0.784	3.658	0.798	3.101	0.784	3.397
Min, Max			0.660, 0.885	-4.545, 13.361	0.649, 0.881	-2.019, 9.451	0.649, 0.885	-4.545, 13.361
Mean 95% CI			(0.763, 0.801)	(2.245, 5.138)	(0.750, 0.813)	(1.968, 4.776)	(0.765, 0.798)	(2.563, 4.564)
Week 26	Positive	High						
n			18	18	15	15	33	33
Mean (SD)			0.803 (0.062)	4.197 (3.818)	0.816 (0.041)	5.287 (3.299)	0.809 (0.053)	4.692 (3.579)
Median			0.815	5.222	0.818	5.767	0.818	5.309
Min, Max			0.658, 0.896	-4.204, 9.002	0.743, 0.880	-0.668, 10.403	0.658, 0.896	-4.204, 10.403
Mean 95% CI			(0.772, 0.834)	(2.298, 6.095)	(0.793, 0.839)	(3.460, 7.114)	(0.790, 0.828)	(3.423, 5.961)

ADA= Anti-Drug Antibody; BMD=Bone Mineral Density; % CfB=Percentage Change from Baseline.
Includes subjects with at least one post-baseline evaluable ADA assessment in the Double-blind treatment period.
Baseline is defined as the last non-missing assessment prior to the first study drug administration.
Early Termination visits for discontinued subjects and unscheduled visits collected were reallocated to the respective planned study visit as per study day (the one nearer to the planned visit day within 30 days window was allocated).
[1] At baseline, combined data are presented since only 5 subjects were ADA-positive.
ADA status and titer groups are based on ADA data collected at the concurrent timepoint. Titer groups (low, moderate and high) are defined based on lower (Q1) and upper (Q3) quartiles in the ADA positive subjects where Low = ADA Titer = Q1 ; Moderate = Q1 < ADA Titer = Q3 ; High = ADA Titer > Q3
Source Data: Listing 16.2.6.1, 16.2.17

2.5.3. Discussion on clinical pharmacology

Two clinical studies were completed for Bmab 1000 from which PK, PD and immunogenicity data were obtained: A Phase 1 study in healthy volunteers and a Phase 3 study in postmenopausal women with osteoporosis. In both studies an approved 60 mg dose was administered via SC route.

Bioanalytical assays

A single PK assay was utilised for both products and bioanalytical similarity between Bmab 1000 and US-licensed Prolia was confirmed during method validation. A quantitative sandwich ECLIA method was used for the quantification of Bmab 1000 and originator US-Prolia concentrations in healthy human serum (clinical study B1000-NHV-01-G-01) and in serum samples from postmenopausal women with osteoporosis (clinical study B1000-PMO-03-G-02). The method was validated according to EMA guideline EMA/CHMP/ICH/172948/2019. During validation, antibody interference was determined for both drugs by the use of a rabbit anti-Bmab1000/Prolia polyclonal antibody. It cannot be completely ruled out that the assay might underestimate denosumab concentrations in the presence of anti-drug

antibodies. However, as a comparable number of samples was potentially affected in both treatment groups and results from the PK assay in the phase 1 study do not indicate a relevant difference in presence of ADAs (see also assessment below), the potential impact of ADA interference on PK biosimilarity assessment is deemed to be low. Upon request the applicant clarified that approximately 1/3 of the PK samples of the phase 1 study and approximately 40% of the samples from the phase 3 study were covered by long-term stability data at the time of the present assessment.

The fully automated module Roche Cobas measuring multiple analytes simultaneously was used for quantitative immunoassay analysis of sCTX and P1NP by electrochemiluminescence (ECL) technology. The validation data is based on Total Allowable Error (TaE) concept. This procedure might be acceptable as Cobas system is widely used and thoroughly validated as an instrument platform. Overall, the bioassay is considered to be fit for its intended purpose. Bioanalytical reports for analysis of sCTX (and P1NP) in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02 have been provided upon request. Presented results for study B1000-NHV-01-G-01 and study B1000-PMO-03-G-02 on analysis of sCTX and P1NP do not raise a concern.

For investigation of anti-denosumab antibodies a 3-tiered approach comprising a screening assay followed by a confirmatory assay and the analysis of ADA titre and neutralizing capacity was utilised, which agrees with the Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010). Antigenic equivalence of both drugs was demonstrated during validation and thus, the applied single assay approach (biosimilar used as antigen) is supported. For the screening, confirmation, and titration of anti-denosumab antibodies in human serum an ECLIA assay was developed and validated. A full validation was conducted for the method used for both clinical trials. Relevant assay parameters as cut-point, sensitivity, drug tolerance, selectivity, precision, robustness and stability were assessed. Assay sensitivity was established for concentrations < 1 ng/mL of a polyclonal rabbit anti-denosumab antibody used as positive control. Drug tolerance was sufficient for reliable ADA analysis in the presence of denosumab.

A non-cell-based sandwich indirect ECLIA method has been developed and validated for determination of neutralising anti-drug antibodies. As none of the 2 products applied in the clinical trials exhibits FC effector functions, this may be appropriate. Overall, the method was validated for relevant parameters including cut-point, sensitivity, drug tolerance, selectivity, precision, robustness and stability.

During analysis of study samples from the phase I clinical study Bmab1000-NHV-01-G-01, 710 out of 1307 (54.3%) samples were found to be positive for anti-denosumab antibodies, with a false positive rate (FPR) of 11.2%. NAb was not evaluated for this study. In the phase III clinical study B1000-PMO-03-G-02, 1127 out of 3185 (35.4%) samples were found to be positive for anti-denosumab antibodies, with an FPR of 19.1%. This rate was calculated form a sCF constructed without the removal of a biological outlier identified during inhibition cut point calculations. The current sCF of 1.10 is considered acceptable as the corrected sCF of 1.11 result in negligible difference as the corrected FPR of 16.4% is lower, resulting in a diminishing in the likelihood of a false negative outcome. Twelve (12) of the 1127 (1.06%) samples were NAb positive. The high FPR of ADA detection in both studies indicates low specificity of the screening assay, increasing the number of runs necessary in the confirmatory assay.

PK biosimilarity assessment

Denosumab PK was investigated for Bmab 1000 compared to US-licenced Prolia in both submitted clinical trials. Analytical similarity of EU- and US-licenced Prolia was demonstrated (see Quality section above).

The **pivotal PK study B1000-NHV-01-G-01** was a randomised, double-blind, two-arm, single-dose, parallel-group study in healthy adult volunteers. General design aspects were discussed in CHMP

Scientific Advice (EMEA/H/SA/4398/1/2020/III) as well as 3 follow-up advices and are considered acceptable.

A single dose of Bmab 1000 or US-licenced Prolia was administered subcutaneously in the abdomen at day 1. The route of administration is agreed as it is in line with the recommendations of the Prolia SmPC and sensitive to detect any potential PK differences during the absorption phase. The selected dose was 60 mg, which is the therapeutic dose of Prolia and was previously discussed during CHMP Scientific Advice. As stated in Prolia SmPC, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater. Thus, denosumab is eliminated through a non-target-mediated, linear pathway at higher concentrations and a target-mediated non-linear pathway at lower concentrations. The 60 mg therapeutic dose for denosumab falls close to the plateau of the dose-response relationship. According to EMA guideline on similar biological medicinal products containing monoclonal antibodies, PK should be demonstrated where each mechanism of clearance predominates in cases were the reference mAb is eliminated both by target-mediated and nontarget-mediated mechanisms. Thus, partial AUCs reflecting the different elimination pathways (nontarget-mediated vs target-mediated) were recommend as secondary PK endpoints and considered by the applicant (AUC18-85days and AUC113-253days).

The included healthy population was restricted in age (male participants: 28-55 years; female participants: 28-45 years), weight (non-Japanese participants 60.0-95.0 kg; Japanese participants 55.0-95.0 kg) and BMI (18-30 kg/m2). This is acceptable for the purpose of PK biosimilarity testing, where a homogenous population is intended in order to detect potential product differences in PK characteristics. Male and female subjects were eligible. The upper age limit of 45 years for females is supported to reduce the risk of including women with post-menopausal osteoporosis. The exclusion of any prior use of bone active drugs is supported in order to reduce unwanted heterogeneity.

The primary PK endpoints (Cmax, AUC0-t and AUC0-inf) are in line with EMA guideline (EMA/CHMP/BMWP/403543/2010) and acceptable. Criteria of EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) were applied for bioequivalence assessment - bioequivalence was concluded if the 90% CI lies within the range of 80.00%-125.00%. Additional endpoints were discussed previously at CHMP scientific advice, and proposals were followed (inclusion of partial AUCs, calculation of the parameters volume of distribution and systemic clearance, AUEC of sCTX as PD endpoint, immunogenicity assessment included).

Subjects were randomly assigned to 1 of the 2 study arms (1:1) to receive either Bmab 1000 or US-licenced Prolia. Randomisation was stratified based on site, on ethnicity (Japanese versus non-Japanese), body weight (55 to <60 kg for Japanese only, 60-80 kg and 81-95 kg) and on gender. Stratification factors were considered as covariates in the ANCOVA model for main PK analysis, which is supported.

Protocol changes were non-critical. SAP was finalised prior to data base lock and only based on latest protocol version (V5.0). All BLQ values occurring after first quantifiable concentration were planned to be handled as missing in the non-compartmental analysis. This is potentially problematic as it may overestimate denosumab serum concentration. An additional sensitivity analyses for all PK parameters with BLQ values after the first quantifiable concentration set to zero has been provided upon request. The different handling of BLQ values did not affect geometric mean Cmax. For AUC0-inf and AUC0-t marginal changes were observed for geometric mean compared to original analysis. The statistical analyses from sensitivity analyses show that primary PK parameters were still within the acceptance range of 80.00 to 125.00%. With regard to AUC113-253days, sensitivity analysis resulted in lower geometric mean values for both, biosimilar and originator, as compared to main analysis. With the main analysis, AUC113-253days was approximately 40% higher for Bmab 1000 as compared to Prolia,

while for the sensitivity analysis the difference was approximately 20%. Thus, sensitivity analysis does not raise an additional concern with regard to PK biosimilarity assessment for Bmab 1000 and Prolia.

The decision on subject inclusion in PD and PK analysis set had to be made during blind data review meeting prior to data base lock. Five (5) randomised subjects were excluded from the PK set due to early discontinuation and missed visits which is deemed appropriate. Demographics and baseline characteristics were similar between the treatment groups in the PK analysis set.

The PK profile of denosumab was well characterised by the utilised sampling scheme, AUCext (%) was well below 1%. Arithmetic Mean (±SD) serum denosumab concentration versus time curves following single SC dose administration of Bmab 1000 and Prolia indicate similar course of denosumab concentrations over time of both products with somewhat higher mean exposure seen after Bmab 1000 treatment as compared to Prolia. For the PK parameters Cmax, AUC0-t, AUC0-inf, and partial AUC18-85days mean values were higher for the Bmab 1000 compared to Prolia group. With regard to partial AUC113-253 dissimilarity was observed between Prolia and Bmab 1000, with Bmab 1000 values being approximately 40% higher compared to Prolia. As AUC113-253 constitutes less than 3% of the AUC0-t, the impact on exposure is considered negligible. Overall, it is assumed that exposure after bmab 1000 administration is slightly higher as compared to Prolia which might potentially be attributed to differences in bioavailability after SC use or to differences in elimination.

The 90% CIs for test to reference ratios of Cmax, AUC0-t and AUC0-inf were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among the 2 study drugs (Cmax: 111.43 [103.96; 119.43]; AUC0-t: 115.07 [106.45; 124.39]; AUC0-inf: 115.08 [106.53; 124.33]). For the primary endpoint PK parameters, inter-individual variability was moderate, with CV% ranging between 28.9% and 32.6%. However, 2 issues were observed: 1) The upper bound of the 90% CI for AUC0-t and AUC0-inf was very close to 125.00%, i.e. acceptance criteria were just met. 2) For all 3 parameters, the lower limit of 90%CI was slightly above 100% and the 90%CI consequently did not include 100%. As protein content was slightly higher in bmab-1000 (batch BM21004054: 60.4mg/ml) as compared to Prolia (batch 1135692: 58.5 mg/ml), a supportive analysis of protein-adjusted PK parameters was also conducted. Statistical comparison of primary PK protein-adjusted parameters showed that test/reference ratio was closer to 100% for all 3 parameters, however, the lower limit of 90%CI was still above 100% (Cmax / P: 107.92 [100.69; 115.67]; AUC0-t / P: 111.45 [103.10; 120.47]; AUC0-inf / P: 111.46 [103.18; 120.42]).

Overall, the pre-defined PK criteria on bioequivalence were barely met. PK analysis and exclusion of patients was pre-planned and transparently documented, which is acknowledged. Furthermore, the somewhat higher denosumab mean concentrations determined for Bmab 1000 as compared to Prolia are unlikely be caused by population differences in baseline characteristics in this highly standardised study.

Study B1000-PMO-03-G-02 was a randomised, double-blind, multicentre, parallel-arm, Phase 3 study in post-menopausal women with osteoporosis. For further discussion on study design see section 3.10. For the phase 3 study, the applicant provided concentration time profiles and summarizing statistics of denosumab serum concentrations on D1 (pre-dose), D15, D29, D85, D162, D183 (pre-dose), D267, and D365 (pre-dose). Denosumab concentration time profiles indicate comparable PK characteristics of both products in the patient population. Pre-dose values were determined, although previous use of denosumab was an exclusion criterion. The applicant initiated additional investigation in order to find a reason for denosumab pre-dose concentrations seen in 6 subjects in study B1000-PMO-03-G-02, however, no explanation was revealed. As concentrations were <5% of Cmax, pre-dose values are not considered to have a relevant impact on biosimilarity assumption.

Analyses by timepoint show that mean exposure was slightly higher for Bmab 1000 as compared to Prolia throughout the study. This is in line with results seen in the pivotal PK study. Difference was

strongest for trough values: 26 weeks after first dose a mean concentration of 54.4 ng/ml was found for Bmab 1000 vs 40.3 ng/ml for Prolia; 26 weeks after second administration a mean concentration of 70.2 ng/ml was found for bmab 1000 vs 38.6 ng/ml for Prolia. However, it has to be considered that variability at these late timepoints was high (CV% up to 231.0%). No further analyses on PK parameters were foreseen in this study. Summary statistics of other PK parameters as well as geometric mean ratios of AUCinf and Cmax would have been of interest. However, blood sampling was sparse in this study and, thus, further analysis is not regarded helpful here.

Supportive PK data from the transition period were provided. Denosumab concentration were comparable between subjects receiving Prolia-bmab (switch to biosimilar) and subjects receiving Prolia-Prolia. Results do not raise an additional concern.

Overall, the PK characterisation in the Phase 3 study is regarded acceptable and PK profiles from the osteoporosis patients support PK similarity of the biosimilar and originator.

PD biosimilarity assessment

Bmab 1000 was developed as a biosimilar product to Prolia. The mechanism of action is identical to the reference product. The monoclonal antibody denosumab targets and binds to human receptor activator of nuclear factor kappa-B ligand (RANKL), thus preventing interaction of RANKL with receptor activator of nuclear factor kappa-B (RANK). Block of this interaction leads to reduced osteoclast number and function. Thus, bone resorption is decreased. The mode of action has been adequately described by the applicant.

Relevant PD endpoints of denosumab were compared for Bmab 1000 and Prolia in both, the phase 1 and the phase 3 study, which is in line with EMA scientific advice. The chosen biomarkers s-CTX and P1NP are acceptable bone turnover markers. They are used for the monitoring of e.g. bisphosphonate treatment effect in osteoporosis. Even though they are not validated surrogate markers for the fracture risk, which is a relevant efficacy measure, they are dynamic markers with higher sensitivity and correlates with bone turnover rate and bone remodelling.

In the **phase 3 study B1000-PMO-03-G-02**, serum sCTX and P1NP were measured throughout the study. AUEC of sCTX over the initial 26 weeks was assessed as co-primary PD endpoint. The biomarker s-CTX is a dynamic marker of bone metabolism with large effect size. CTX is not validated to correlate with a clinically important outcome, however, both co-primary endpoints complement each other and provide evidence for similarity in terms of efficacy. PD parameters were analysed using noncompartmental methods and actual sampling times, which is endorsed. Handling of BLQ (set to ½ LLOQ) and missing values (set to missing) for calculation of PD parameters and summary statistics is acceptable. For co-primary analysis, an ANCOVA model was applied, with logged pre-dose sCTX concentrations and baseline eGFR fitted as covariate as well as treatment group and all stratification factors (region, age, and prior use of bisphosphonates) fitted as fixed effects. Justification for covariates was provided and is deemed reasonable. The applied acceptance range of 80.00-125.00% is based on margins used for conventional bioequivalence analyses as there is limited historical s-CTX data in women with postmenopausal osteoporosis. This acceptance range can be accepted and would support PD similarity of Bmab 1000 and Prolia, given that the CI of the point estimate also contains value 1 and confidence interval does not lie towards the extremes of the acceptance range - borderline cases would require further discussion.

The geometric LS means for the Phase 3 co-primary PD endpoint, s-CTX AUEC over the initial 26 weeks in mFAS population, were 11954.89 and 11481.40 for bmab 1000 and Prolia group, respectively. The geometric LS mean ratio was 104.12% with the 95% CI [97.74, 110.93] being entirely contained within the pre-defined equivalence limits of 80.00% to 125.00%. Results indicate PD similarity of bmab 1000 and Prolia, however, the underlying analysis set currently requires clarification. According to SAP,

analysis of the co-primary PD endpoint was planned in the mFAS. In this study mFAS was identical to FAS. However, sCTX data for 35 patients of the mFAS were not included in the primary analysis. Upon request, the applicant provided an additional explanation saying that AUEC was pre-planned to be calculated only provided that 2 out of 3 last sample timepoints were available and thus, concentration at day 182 could be imputed. Additional analyses considering subjects with partial data (without evaluable AUEC by SAP definition), support the robustness of sCTX AUEC results from phase 3 study B1000-PMO-03-G-02.

Investigation of secondary PD endpoints for sCTX (Cmin, Imax, TImax and AUIC (0-26 weeks)) is supported. Analysis of serum sCTX and P1NP concentrations by timepoint was planned, which is deemed supportive for assessment of PD similarity of both products. The planned investigation over 1 year is supported, however, PD information obtained after a second dose of both products will be rather sparse.

Secondary PD endpoints were highly comparable for both products. Mean Imax of approximately 90% was observed at week 4 for both products. Furthermore, mean serum concentration-time profile of sCTX were similar for both products until week 26. Values obtained after the second dose were not contained in the concentration-time profiles but summarizing statistics for timepoints week 38 and week 52 were provided. Mean concentrations of sCTX on week 52 were 148 pg/mL for both treatment groups and comparable with week 26 values. For marker P1NP, mean serum concentration-time profile were also similar for both products until week 26. P1NP inhibition started after week 2 with maximum reached at week 12 for both products. Week 53 concertation was almost identical for both products and comparable to week 26 values (bmab 1000 18.6 ng/ml and Prolia 18.3 ng/mL).

Additionally, PD data from the transition period were assessed as supportive data. No change in the sCTX and P1NP concentration was observed in Week 78 (Day 547) following transition from Prolia to Bmab 1000 compared to patients who continued to receive Prolia at Week 52. Overall, secondary PD results support statement on PD similarity of both products.

During the procedure, the applicant also provided an Erratum on B1000-PMO-03-G-02 CSR that has been created on 17 Dec 2024. This erratum describes errors that were randomly found and occurred with regard to consideration of local daylight-saving clock changes. Actual times (days) calculated relative to the date/time of dosing used throughout the PK and PD analyses were partly wrong. The applicant provided an impact assessment and re-ran all analyses affected with correct actual times. Overall, it can be agreed with the applicant that the impact of the daylight-saving errors on the individual concentration data, individual PD parameter data and all inferential analyses pertaining to sCTX data was negligible. The overall assessment on biosimilarity is not changed.

In the **phase 1 study B1000-NHV-01-G-01**, AUEC0-253 days and Emax of s-CTX were calculated as PD parameters, descriptive statistics were provided. Summary descriptive statistics of s-CTX concentrations over time by treatment group were also generated, which is endorsed. An ANCOVA model was planned to assess biosimilarity of bmab 1000 and Prolia using log-transformed data for AUEC and Emax with all stratification factors (ethnicity, age, weight and site) as covariates. GMRs of AUEC and Emax and the corresponding 95% CIs were constructed, without predefined acceptance limits. Overall, the planned PD analysis is considered reasonable.

The s-CTX curves over time of both products are overall comparable. After maximum inhibitory effect (Emax) is reached within the 1st month after treatment administration, a progressive recovery is seen until day 252 for both products. Based on presented mean curves, recovery after Bmab 1000 administration appears to be slightly faster as compared to Prolia. It is noted that the study duration was too short to appropriately characterise the PD profile, as s-CTX values have not yet returned to baseline at the last sampling time point. On study day 29, arithmetic mean s-CTX levels were highly comparable for both products (bmab 1000 64.0 ± 27.3 ng/ml vs Prolia 63.4 ± 24.2 ng/ml). Overall,

there were only slight differences in mean s-CTX levels at the different time-points. Analysis of PD parameters showed that the point estimates (95% CIs) of Test/Reference GLSMs ratio derived for Emax and AUEC0-253days were 103.43 [91.56; 116.84] and 104.59 [94.38; 115.91], respectively. This supports PD similarity between Bmab 1000 and Prolia, as the 95% CIs of GLSMs ratio for PD parameters (AUEC0-253 days and Emax) were entirely contained within the standard bioequivalence range of 80.00-125.00%. Overall, PD results from the phase 1 study in healthy volunteers support the claim on biosimilarity between bmab 1000 and US-licenced Prolia.

Immunogenicity

ADA results up to week 52 were presented for the **phase 3 study B1000-PMO-03-G-02** in the osteoporosis patient population. Overall, ADA incidence rate was high, with 87.9% of subjects with at least one post-baseline evaluable ADA+ value. At baseline only 5 (1%) subjects were ADA+. ADA positivity rate increased until week 12 after the first dose, where highest positivity rate was seen (65.5%). ADA positivity rate decreased with decreasing denosumab serum concentrations, with a positivity rate of 27.6% at trough prior to second dose and comparable positivity rate prior to third dosing after 1 year (28.0% at week 52). ADA incidence rate was overall comparable between both treatment groups, with slightly higher rates seen for Bmab 1000, however, difference was <10% between treatment groups at each timepoint investigated. Median ADA titres were overall low, with highest values seen 3 months after dosing in both treatment groups (3 months after first dose (week 12): Bmab 1000 184 vs Prolia 175; 3 months after second dose (week 38): bmab 1000 235 vs Prolia 209). Median ADA titres were slightly higher for Bmab compared to Prolia at each timepoint investigated after first dose. Overall, nAB incidence was low, with 12 subjects tested positive for neutralising antibodies at any timepoint after treatment (7 in bmab 1000 group and 5 in Prolia group). However, sensitivity and drug tolerance of the applied assay was low, thus, nAB incidence may be underestimated.

During the transition period (switch from Prolia to Bmab 1000), there was no meaningful difference between treatment groups with regard to ADAs and nABs. Data are considered supportive and do not raise an additional concern.

In **phase 1 study B1000-NHV-01-G-01**, ADA sampling was planned in parallel to PK/PD assessment and up to day 253, which is endorsed. Only 1 healthy subject in the Prolia group was ADA+ at baseline. After treatment, high ADA+ incidence rate was determined; All subjects had at least one post-baseline evaluable ADA+ value. ADA positivity occurred early, with more than 80% ADA+ 1 months after dosing. ADA positivity rate remained high until day 85 and decreased afterwards. At EOS visit, 7 subjects were still ADA+. ADA+ incidence rate was comparable between both treatment groups at each time point investigated. In the course of the study, ADA titres increased until D57 (median titre for Bmab 1000 454 vs 425 for Prolia), remained higher until D85 (median titre for Bmab 1000 457 vs 362 for Prolia), and decreased by the EOS visit (median titre for Bmab 1000 103 vs 81.3 for Prolia). ADA titres were overall comparable in both treatment groups, slightly higher median values were seen in the Bmab 1000 group at each timepoint investigated after treatment.

Impact of ADA on PK

Upon request, the applicant provided additional analyses for the phase 1 study B1000-NHV-01-G-01 and the phase 3 study B1000-PMO-03-G-02 in order to assess the impact of ADA on denosumab PK. ADA titres were classified into low, moderate and high based on quartile distribution of subject titre values [low (<=Q1, for first 25%), medium (Q1-Q3, between 25 – 75%), high (>Q3, for last 25%). This approach is considered reasonable.

In study B1000-NHV-01-G-01, neither for Bmab 1000 group nor for Prolia group, there was a clear trend for lower denosumab concentrations in ADA positives compared to ADA negatives. Furthermore, no such trend was seen with higher titres compared to lower titres.

Similarly, for study B1000-PMO-03-G-02, data did not indicate a trend for lower denosumab concentrations with higher ADA titres. Interestingly, denosumab serum concentrations tended to be higher in >Q3 quartile compared to the lower quartile group. 95% CI of mean denosumab concentrations were presented and were rather broad with the small number of subjects per group, however, overall overlapping between analysis groups.

Overall, there was no apparent impact of ADAs on denosumab PK after both, Bmab 1000 and Prolia use.

Impact of ADA on efficacy

A post-hoc analysis investigating the potential impact of ADA by groups of titres on efficacy in study B1000-PMO-03-G-02 was presented upon request. ADA titres were classified into low, moderate and high based on quartile distribution of subject titre values [low (<=Q1, for first 25%), medium (Q1-Q3, between 25 – 75%), high (>Q3, for last 25%), which is acceptable. There was no apparent effect of ADA titre level on efficacy, no clear trend was seen with a tendency for higher %CfB in the lumbar spine BMD with higher ADA titre.

Overall, there was no apparent impact of ADAs on denosumab efficacy after both, Bmab 1000 and Prolia use.

In both clinical trials, significantly higher ADA incidence rates were found in both treatment groups as compared to historical data from the originator. The applicant identified the highly sensitive assay used as the main reasons for this observation, which may be agreed as assays have evolved since the initial MA of the originator. As results were comparable between products, the high ADA incidence does not raise a concern with regard to biosimilarity assessment. The incidence of NAb was low but may be underestimated by the applied assay, however, the presence of ADA (irrespective of titre level) did not have a clinical impact on the efficacy parameter investigated.

2.5.4. Conclusions on clinical pharmacology

In both clinical trials of the presented data package, PK, PD and immunogenicity parameters were investigated. US-licenced Prolia was used as comparator and is regarded as representative of the EU reference medicinal product as analytical similarity has been demonstrated.

In the pivotal PK phase 1 clinical trial B1000-NHV-01-G-01, the 90% CIs for test to reference ratios of Cmax, AUC0-t and AUC0-inf were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among the biosimilar and originator. For the upper bound of the 90% CI for AUC0-t and AUC0-inf acceptance criteria were barely met. Slightly higher denosumab serum concentrations for the biosimilar compared to originator were also represented by secondary PK parameters investigated and found in the phase 3 study in patients.

The co-primary PD endpoint of the phase 3 patient study, s-CTX AUEC over the initial 26 weeks, was well within the pre-defined acceptance range for the comparison biosimilar vs originator. All additional investigations on PD, including secondary endpoints on s-CTX and P1NP in the phase 3 study and analysis of s-CTX in the phase 1 study, support the assumption on PD biosimilarity between biosimilar and originator.

High ADA incidence rates were determined in both, patient and healthy population, by the use of a highly sensitive assay. As ADA incidence was comparable in both products, the high rates are not of

concern per se. No apparent correlation of ADA development with pharmacokinetics or clinical response has been observed.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

Not applicable.

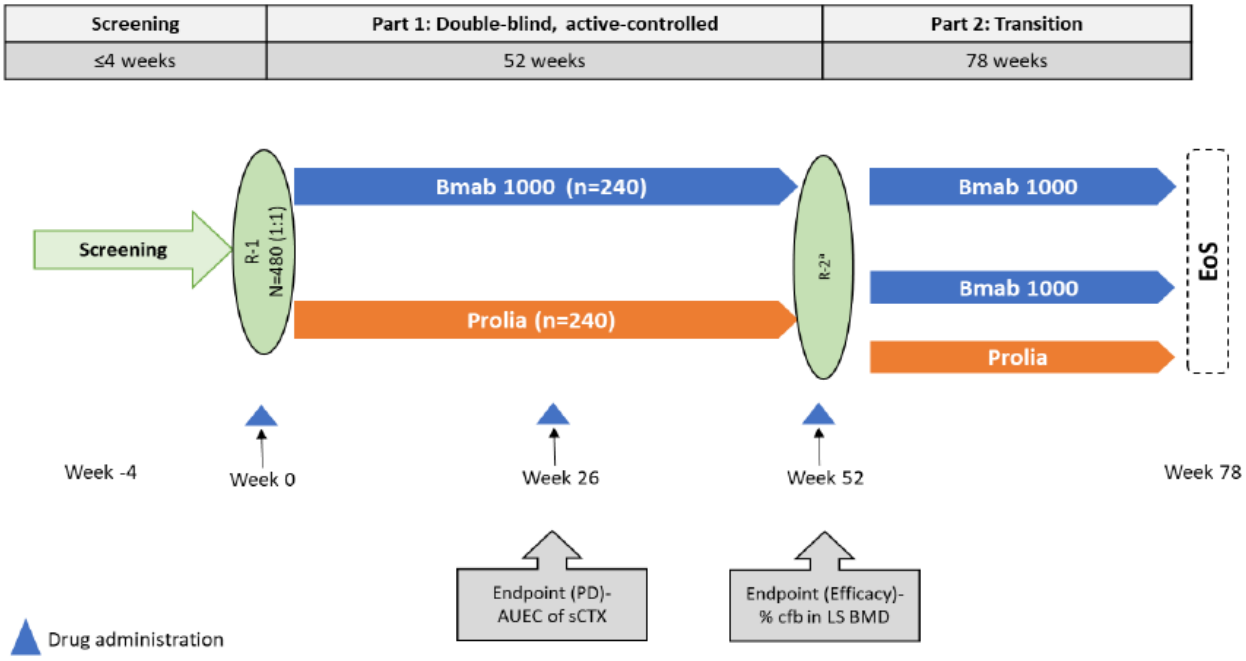
2.5.5.2. Main study(ies)

B1000-PMO-03-G-02: DEVOTE: DEnosumab biosimilar Versus Prolia for post-menopausal Osteoporosis: A randomized, double-blind, multicenter, two-arm phase 3 study comparing efficacy, safety, and immunogenicity

Methods

The Phase 3 pivotal study (BM1000-PMO-03-G-02) was a multicentre, randomised, double-blind, parallel-group study with 2 treatment groups designed to demonstrate the equivalent efficacy and PD between Bmab 1000-P and Prolia in postmenopausal women with osteoporosis. This study consisted of two parts. Part 1 was a double-blind active controlled period up to Week 52 pre-dose, and Part 2 was the transition/switching period up to Week 78 (End of the Study).

Figure 7: Study schema



Abbreviations: AUEC, area under the effect curve; BMD, bone mineral density; cfb, change from baseline; EoS, end-of-study; LS, lumbar spine; PD, pharmacodynamic; sCTX, serum C-terminal telopeptide of Type 1 collagen; R-1, first randomisation (randomisation for Part 1; Double-Blind Active-Controlled Period); R-2, re-randomisation (re-randomisation for Part 2; Transition Period).

a. Prior to dosing at Week 52, patients in the Prolia arm were re-randomised in 1:1 ratio to receive Bmab 1000 or Prolia. To maintain the blinding, patients in the Bmab 1000 arm also underwent re-randomisation procedure; however, they continued to receive Bmab 1000.

Study Participants

Main inclusion criteria

- Postmenopausal women, aged ≥55 and <80 years at screening. Postmenopausal is defined as 12 months of spontaneous amenorrhea with serum FSH levels ≥40 mIU/mL at screening or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
- Evidence of osteoporosis as assessed by lumbar spine (L1-L4) absolute BMD corresponding to a T-score classification ≤−2.5 and ≥−4.0. Bone mineral density measurements should be performed by DXA using Hologic or Lunar densitometers at screening visit. All DXA scans will be assessed by a central imaging centre for this purpose.
- At least 3 vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA at screening.
- Patients with body weight ≥50 to <90 kg at screening.

Main exclusion criteria

- Patients with T-score of <−4.0 at the lumbar spine, total hip, or femoral neck.
- Known history of previous exposure to denosumab (Prolia®, Xgeva®, or any biosimilar denosumab).
- For prior or ongoing use of any osteoporosis treatment (other than calcium and vitamin D supplements), following points to be considered for the washout periods prior to the screening visit:

a. Oral bisphosphonate

i. Ineligible if used for 3 or more years cumulatively

ii. If used for <3 years, a gap of at least 1 year since the last dose is required at the screening visit

b. Dose received any time for the following: intravenous bisphosphonate, strontium, fluoride (for osteoporosis), drugs being investigated for osteoporosis, teriparatide or any parathyroid hormone analogs, tibolone, oral or transdermal oestrogen, selective oestrogen receptor modulators, calcitonin, and cinacalcet

- Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days) within past 3 months before screening. Topical and nasal corticosteroids are allowed.
- Other bone active drugs including but not limited to anticoagulants, antiplatelet (with the exception of acetylsalicylic acid), anticonvulsants (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, and anabolic steroids within the last 3 months before screening. Direct oral anticoagulants will be allowed. Receipt of PPI for >1 year cumulatively will be allowed only after 3 months of washout prior to the screening. Patients receiving PPI for ≤1 year cumulatively are not allowed if they plan to continue the use of PPI during the study such that the cumulative use of PPI will be >1 year.

Treatments

Patients were randomly assigned to receive Bmab 1000 (proposed biosimilar, test drug) or Prolia (reference drug) using a 1:1 allocation ratio at the baseline/randomisation visit (Week 0/Day 1). Bmab 1000 (60 mg) or Prolia (60 mg) was administered SC, preferably in the abdomen using a PFS of 60 mg/mL solution for injection on Day 1, and at Week 26. The study drug was required to be administered by the site-qualified and trained clinical staff member(s) (eg, nurse/physician). Whenever possible, the same injection site was used for the study drug administration. Part 1 of the study was completed after a follow-up of 26 weeks after the 2nd dose.

Prior to dosing at Week 52 (Part 2), patients in the Prolia arm were randomly assigned again in a ratio of 1:1 to receive either Bmab 1000 or Prolia at Week 52. All patients who were initially randomly assigned to the Bmab 1000 on Week 0 (Day 1) should continue their treatment.

Part 1 of the study has been completed and includes the efficacy, PD, PK, immunogenicity, and safety analysis up to Week 52. The clinical phase of Part 2 of the study has been completed with the last patient last visit on 12 June 2024, and the data analysis is currently ongoing.

With submission of responses, the applicant provided the final study report and all analyses up to Week 78.

Calcium and vitamin D supplementation

All patients received daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D (via any route of administration) from randomisation and received the supplementation until the EoS visit (Week 78). Calcium and vitamin D were co-administered to prevent low serum calcium level while taking study drugs.

If a patient developed hypercalcaemia during the study, the calcium and/or vitamin D supplementation was to be interrupted or reduced per the investigator's discretion until the serum calcium concentration has returned to the normal range or as per the investigator's discretion.

Concomitant medication

Any concomitant medication deemed necessary for the welfare of the participant during the study could be given at the discretion of the investigator. However, it was the responsibility of the investigator to ensure that details regarding the medication were recorded in full in the eCRF.

Prohibited concomitant medications

- Denosumab other than study treatment or any other monoclonal antibodies (eg, romosozumab), protein, or fusion protein
- Treatments for osteoporosis (such as oral/intravenous bisphosphonates, fluoride, strontium, teriparatide or any parathyroid hormone analogs, tibolone, oral or transdermal oestrogen, selective oestrogen receptor modulators, calcitonin, or calcitriol)
- Other bone active drugs including but not limited to anticoagulants, antiplatelet (with the exception of acetylsalicylic acid), anticonvulsants (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, and anabolic steroids. Direct oral anticoagulants will be allowed. Receipt of PPIs in patients who have received for ≤1 year continuously are not allowed if patients plan to continue the use of PPI during the study such that the continuous use of PPI will be >1 year.

- Systemic glucocorticosteroids (≥ 5 mg prednisone equivalent per day for ≥ 10 days). Topical and nasal corticosteroids will be allowed
- Use of any biologic drugs (with the exception of insulin and insulin analogue and GLP-1 receptor agonists)
- Live virus vaccine
- Any other investigational drugs

Objectives

Primary objectives

Efficacy

- To demonstrate equivalent efficacy between Bmab 1000 and Prolia based on percentage change from baseline at Week 52 in lumbar spine BMD

Pharmacodynamics

- To demonstrate pharmacodynamics equivalence between Bmab 1000 and Prolia based on AUEC of the bone resorption marker sCTX from baseline to week 26

Secondary objectives

Efficacy

- The secondary efficacy objective was to compare other efficacy parameters (BMD of lumbar spine, total hip and femoral neck; fracture incidence) between Bmab 1000 and Prolia.

Pharmacodynamics

- To compare bone turnover between Bmab 1000 and Prolia based on serum Cterminal telopeptide of Type 1 collagen (sCTX) and procollagen Type 1 Nterminal propeptide (P1NP)
- To assess denosumab serum concentrations following Bmab 1000 and Prolia administration

Safety

- To compare safety and tolerability of 2 administrations of Bmab 1000 and Prolia 6 months apart

Immunogenicity

- To compare immunogenicity between Bmab 1000 and Prolia

Outcomes/endpoints

Primary endpoints

Efficacy

- %CfB at Week 52 in the lumbar spine BMD by DXA (Time frame: Baseline and Week 52)

Pharmacodynamics

- AUEC of sCTX from baseline to 26 weeks (Time frame: Baseline to Week 26)

Secondary endpoints

Efficacy

- Percentage change from baseline at Week 26 in lumbar spine BMD by DXA [Time Frame: Baseline and Week 26].
- Percentage change from baseline at Weeks 26 and 52 in total hip BMD by DXA [Time Frame: Baseline, Week 26, and Week 52]
- Percentage change from baseline at Weeks 26 and 52 in femoral neck BMD by DXA [Time Frame: Baseline, Week 26, and Week 52]
- Incidence of fracture up to Week 52 [Time Frame: Baseline up to Week 52]

Pharmacodynamics

- Minimum Concentration (Cmin) of sCTX [Time Frame: Baseline up to Week 26]
- Serum concentrations of P1NP [Time Frame: Baseline up to Week 52]
- PD parameters of sCTX: maximum % inhibition (Imax), time of occurrence of maximum % inhibition (TImax), area under the % inhibition curve (AUIC) [Time Frame: Baseline up to Week 26]
- Denosumab concentrations at Weeks 2, 4, 12, 26, 38, and 52 [Time Frame: Baseline up to Week 52]

Safety

- Incidence of treatment-emergent adverse event (TEAEs) up to 6 months after the second dose [Time Frame: Baseline up to Week 52]
- Incidence of clinically significant changes in vital sign, physical examinations, laboratory safety tests, and electrocardiogram (ECGs) up to 6 months after the second dose [Time Frame: Baseline up to Week 52]

Immunogenicity

- Incidence and titre of antidrug antibody (ADA), incidence of neutralizing antibodies (Nab) up to Week 52 [Time Frame: Baseline up to Week 52]

Table 21: Estimands for the co-primary endpoints with rationale for strategies to address intercurrent events

	Estimand 1a EMA (Co-primary: Efficacy)	Estimand 1a – US (FDA Efficacy)	Estimand 1b-EMA (Co-primary: PD)
Estimand description	Difference in means (Bmab 1000 – Prolia) in % change from baseline in lumbar spine BMD by DXA after 52 weeks in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements.	Difference in means (Bmab 1000 – Prolia) in composite endpoint of % change from baseline in lumbar spine BMD by DXA after 52 weeks (where % change from baseline of zero is taken for anyone who dies) in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any other osteoporosis medications are taken.	Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women[a] with osteoporosis treated with a SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements.
Treatment Conditions of Interest	Two doses of Bmab 1000 versus Prolia (without receipt of any other medications affecting bones except for vitamin D and calcium supplements)	Two doses of Bmab 1000 versus Prolia (irrespective of any other medications)	One dose of Bmab 1000 versus Prolia (without receipt of any other medications affecting bones except for vitamin D and calcium supplements)
Target population	Postmenopausal women with osteoporosis		
Endpoint	Percentage change from baseline at Week 52 in lumbar spine BMD by DXA	Composite endpoint of percentage change from baseline at Week 52 in lumbar spine BMD by DXA (and taking a value of zero for someone who dies)	AUEC calculated using absolute sCTX data (without baseline-adjustment) and actual sampling times using the linear trapezoidal rule to Week 26. Samples should be collected after 8 hours of fasting and no intense physical activity in 48-hour period prior to PD sample collection.
Population Level Summary	Difference between treatments in population mean % change from baseline BMD at Week 52 (Bmab 1000 / Prolia)		Ratio of geometric means (Bmab 1000/Prolia)
ICEs and Strategies to Handle ICEs			
ICE1 (Discontinue - related)	Hypothetical	Treatment policy	Not applicable (endpoint is measured before the second dose)
ICE2 (Discontinue - unrelated)	Hypothetical	Treatment policy	Not applicable (endpoint is measured before the second dose)
ICE3 (Dosing deviation)	Hypothetical	Treatment policy	Hypothetical
ICE4 (Death)	Hypothetical	Composite	Hypothetical

ICE5 (Medications affecting bones)	Hypothetical	Treatment policy	Hypothetical
ICE6 (Supplements)	Treatment policy	Treatment policy	Treatment policy
ICE7 (ADAs)	Treatment policy	Treatment policy	Treatment policy
Rationale of Strategies to Handle ICEs	Estimand 1a EMA (Co-primary) utilizes a mostly hypothetical approach and so is sensitive to pick up differences between treatments which will enable to demonstrate equivalence. The hypothetical strategy requires statistical modeling to estimate the difference that might exist in the scenario that those ICEs do not occur.	Estimand 1a-US FDA (Efficacy) utilizes a treatment policy strategy which targets the comparative effectiveness close to a real-world setting.	Estimand 1b (Co-primary: PD) utilizes a mostly hypothetical approach and so is sensitive to pick up differences between treatments.
	It is anticipated that the occurrence of each ICE will be balanced between groups since the biosimilar treatment, Bmab 1000, should have similar properties to Prolia. It should be noted that Prolia has a good safety profile, and it is anticipated that <1% of subjects will have tolerability issues or death during the year after the first dose. Note: The formation of ADAs against Prolia in the first year of treatment is not particularly common (<1%) and thus this ICE has not been specifically mentioned in the estimand description and will be ignored in estimation approaches		

Abbreviations: DXA, dual-energy X-ray absorptiometry; EMA, European Medicines Agency; FDA, Food and Drug Administration; PD, pharmacodynamic; sCTX, serum C-terminal telopeptide of Type 1 collagen.
Note: The screening BMD assessment will be taken as the baseline BMD assessment.

a. Women should not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered vitamin D and calcium supplements.

Sample size

The initial sample size calculation is based on the co-primary endpoint, percent change from baseline in lumbar spine BMD by DXA at Week 52.

Equivalence will be established if the 95% CI of the difference (T-R) in mean percent change in lumbar spine BMD from baseline at Week 52 is within equivalence margin of (±1.45%). Equivalence margin is derived from meta-analysis of previous similar studies (Bone et al., 2008, Cummings et al., 2009, McClung et al., 2006) which 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%). Assuming that the treatments are equally effective and that the common SD for percent change from baseline in lumbar spine BMD at Week 52 is 4.5, a sample size of 204 subjects per treatment group (total 408 subjects) ensures a power of minimum 80% with two one-sided test at 2.5% level of significance. Considering a dropout of 15%, the total sample size required is 480 subjects (240 per treatment group).

Since sCTX is a co-primary endpoint with BMD, 95% CI will be applied. In addition, standard equivalence limits of 80.00%-125.00% will be applied. Thus, if Bmab 1000 achieves a true inhibition level in the region of 85% (as expected), giving rise to sCTX levels around 15% of baseline, meeting these limits would equate to 80%-125% of 15% (ie, 12% to 18.75%), which would give confidence that Bmab 1000 preserves much of the Prolia inhibition rate and, on average, achieves 81.25% to 88% inhibition over a 6-month period. The current sample size has high power for the co-primary sCTX AUEC endpoint; 204 evaluable subjects/group with a margin of 80%-125% and between-subject CV of 45% would give >95% power to demonstrate similarity for the co-primary endpoint (using 95% CI equivalent to 2 one-sided tests at 2.5% level).

Randomisation and blinding (masking)

Randomisation

An interactive web response system (IWRS) will be used for the randomisation. The responsible Biostatistician will generate the randomisation schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential participant randomisation numbers to treatment codes.

In Part 1 (Double-blind Active-controlled Period), eligible subjects will be randomly assigned (1:1) to receive either Bmab 1000 or Prolia. All subjects who complete Part 1 will undergo the re-randomisation process prior to the study treatment administration at Week 52. Prior to dosing at Week 52, subjects in the Prolia arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia at Week 52.

All subjects who were initially randomly assigned to the Bmab 1000 at Day 1 will continue their treatment of Bmab during the transition period.

Blinding

This study was double-blind until the end of all follow-up procedures. The randomisation codes were not revealed to study subjects, investigators, and study centre personnel, except for delegated unblinded staff who handled the study treatment, and predefined unblinded sponsor and CRO personnel, until all final clinical data have been entered into the database and the database was locked and released for analysis.

Bmab 1000 was supplied as prefilled syringe (PFS) without needle safety guard, whereas Prolia was supplied as PFS with needle safety guard. Thus, blinding from the primary packaging was not feasible, but blinding was maintained at the secondary packaging level with similar packaging for both the products. Therefore, 2 different teams, ie, blinded and unblinded teams, were assigned to maintain the blinding and handle the study treatment administration. The designated, unblinded site staff administered the study medication injections in such a manner that the subject remained blinded (eg, blindfold, screen, or similar method during the dosing procedure so that the injection syringe will not be visible to the subject). Blinded staff/any other person was not involved in any activities about the receipt, handling, or administration of study medication.

Analyses of Double-blind Active-controlled Period (Part 1) included data after all subjects have received the Week 52 assessments (prior to the third administration of study treatment) or have terminated the study before Week 52. At Week 52, the investigators, subjects and other members of staff involved with the study remained blinded.

Randomisation data, including any documentation identifying the treatment allocation, was kept strictly confidential.

Statistical methods

Analysis sets

The **full analysis set (FAS)** was planned to consist of all randomised patients who meet the eligibility criteria and receive at least one dose of study treatment. Patients from the FAS were planned to be analysed under the treatment as randomised and were planned to be used for supportive analyses for efficacy endpoints.

The term **modified full analysis set 1 (mFAS1)** was planned to be used to define the analysis data set which includes a data record at each time point for all patients in the FAS but to exclude data

observed after the first occurrence of those intercurrent events where a hypothetical strategy is taken for estimand 1a and estimand 1b (e.g., missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS1 were planned to be analysed under the treatment as randomised and used as the primary analysis data set for efficacy, PD and PK. For PD, data points within 8 hours of food-intake or 48-hours of intense physical activity were planned not to be used.

The term **modified full analysis set 2 (mFAS2)** was planned to be used to define the analysis data set which includes a data record at each time point for all patients in the FAS but excludes data observed after treatment discontinuation for unrelated reasons. Data in the mFAS2 was planned to be analysed under the treatment as randomised and used as the analysis dataset for supportive efficacy.

The **safety analysis set (SAF)** was planned to consist of all randomised patients who received at least one administration of study treatment. The SAF was planned to be used for all safety and immunogenicity analyses. In the SAF, patients were planned to be analysed per the actual treatment received.

Analysis of primary endpoint

For the primary efficacy analysis, estimand 1a-EMA, an MMRM was planned to be fitted to the % change from baseline in lumbar spine BMD at Week 26 and Week 52 on the mFAS1. The MMRM was planned to include terms for randomisation strata, visit by treatment, and baseline BMD included as a continuous covariate. The repeated measures on subjects were planned to be modelled with an unstructured covariance structure. The estimated mean difference in % change from baseline in lumbar spine BMD was planned to be presented with 95% CI at each time point. The estimated mean difference in % change from baseline in lumbar spine BMD at Week 52 was planned to be presented with 95% CI and equivalence concluded if this falls within predefined equivalence margins of [−1.45%, 1.45%]. The main analysis method was planned to be on the mFAS1 and therefore was planned to not use data after any dosing errors, treatment discontinuation or receipt of any other medications affecting bone health (except for supplements).

The key secondary estimand (estimand 1a-US FDA) was based on the FAS. To estimate the composite primary endpoint (for patients who died, the %CfB was taken as 0), an ANCOVA model fitted to the composite %CfB in the lumbar spine BMD until Week 52 was used. This estimation was done on the FAS multiply imputed data sets for visit by treatment, with stratification variables (region, age, and prior use of bisphosphonates) included as classification factors, baseline BMD included as a continuous covariate and treatment. For the estimand 1a-US FDA, the estimated mean difference in % change from baseline in lumbar spine BMD at Week 52 was planned to be presented with 90% CI.

The primary efficacy endpoint % change from baseline at Week 52 in the lumbar spine BMD by DXA and the primary PD endpoint Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks were planned to be considered as co-primary, hence no multiplicity adjustment was necessary.

Analysis of secondary endpoints

An MMRM as per the main estimation of estimand 1a-EMA (co-primary efficacy) (see Section 7.6.3.2) was planned to be used to estimate the mean percent change from baseline and difference between treatments for the mFAS in:

- Lumbar spine BMD after 26 weeks
- Hip BMD after 26 and 52 weeks
- Femoral neck BMD after 26 and 52 weeks

Similarly, ANCOVA on composite endpoint of percent change from baseline for FAS as per main estimation of estimand 1a-US FDA (efficacy) was planned to be performed but without the penalty being applied.

Sensitivity analysis

Two sensitivity approaches were planned to be performed for the primary estimand 1a-EMA: MI under MAR approach was planned to be applied to the mFAS and data at Week 52 was planned to be analysed using same ANCOVA model as estimand 1a-FDA.

As second sensitivity analysis, a penalty a penalty was planned to be added to the imputed % change from baseline values on mFAS and same analysis as estimand 1a-FDA was planned to be performed.

No sensitivity analyses were planned for estimand 1a-US FDA.

Interim analysis

No interim analysis was planned.

Planned subgroup analysis

Subgroup analyses were planned to be conducted for the primary estimand 1a-US FDA and 1a-EMA on FAS and mFAS respectively and the below subgroups were planned to be examined. Other exploratory subgroups that may have implications on the treatment effect may be examined as well. Difference in means (Bmab 1000 - Prolia) were planned to be estimated using the same analysis model as described in the subsection above for the main analyses.

- Geographical region (US, Europe)
- Prior use of bisphosphonate treatment (Yes, No)
- Age group at randomisation (< 65, ≥ 65 years)
- BMD lumbar spine T-score (≤ -3, >-3)
- Body weight (≥ 50 to < 70 kg, ≥ 70 to < 99.9 kg)

Forest plots of difference in means were planned to be produced. The number and percentage of subjects in each subgroup level, difference in means and corresponding 95% CI were planned to be provided. The analyses were planned to be conducted if number of subjects in the subgroup category would be more than 10% of the analysis set.

Results

Participant flow

A total number of 1219 subjects were screened for eligibility, of whom 479 subjects were randomised into one of the two treatment groups. 740 patients were excluded from the study because of Screen failures. No data with regard to numbers of re-screened subjects was provided in the initial submission. With submission of responses, the applicant provided information regarding the number of re-screened subjects (see Table 22). Re-screened and randomised patients were distributed equally between treatment groups.

Figure 5-1 Patient Disposition - Double-Blind Active-Controlled Period (Part 1)

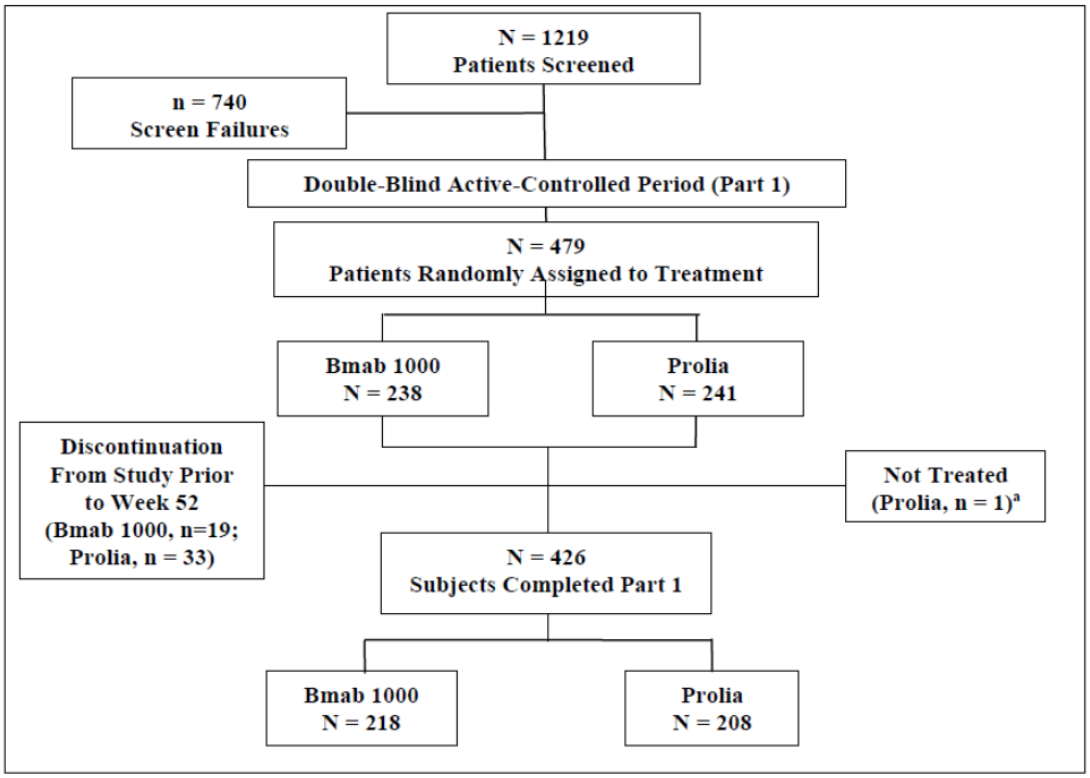


Table 22: Disposition of re-screened patients

Treatment arm	Count of Treatment arm
Number of the patient re-screened	40
Number of patient re-screen failures	11
Number of patients re-screened and randomised	29
Bmab 1000	15
Prolia	14

Table 5-1 Patient Disposition - Double-Blind Active-Controlled Period (All Randomized Analysis Set)

	Bmab 1000 (N=238) n (%)	Prolia (N=241) n (%)	Total (N=479) n (%)
Randomized	238 (100)	241 (100)	479 (100)
Not treated[a]	0	1 (0.4)	1 (0.2)
Received study drug on Day 1[a]	238 (100)	240 (99.6)	478 (99.8)
Received study drug on Week 26[a]	222 (93.3)	213 (88.4)	435 (90.8)
Completed double-blind period[a]	218 (91.6)	208 (86.3)	426 (88.9)
Discontinued from treatment prior to Week 26[a]	16 (6.7)	27 (11.2)	43 (9.0)
Discontinued from treatment prior to Week 52[a]	20 (8.4)	32 (13.3)	52 (10.9)
Discontinued from study prior to Week 52[a]	19 (8.0)	33 (13.7)	52 (10.9)
Primary reasons for discontinuation from treatment prior to Week 52[a, b]			
AE	4 (1.7)	4 (1.7)	8 (1.7)
Calcium/vitamin D non-compliance or inability to tolerate	0	1 (0.4)	1 (0.2)
Investigator decision	1 (0.4)	1 (0.4)	2 (0.4)
Other[a]	15 (6.3)	26 (10.8)	41 (8.6)
Primary reasons for discontinuation from study prior to Week 52[b]			
Withdrawal of consent	13 (5.5)	19 (7.9)	32 (6.7)
Significant protocol violation (non-compliance)	1 (0.4)	3 (1.2)	4 (0.8)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Investigator decision	0	2 (0.8)	2 (0.4)
AE	3 (1.3)	4 (1.7)	7 (1.5)
Other	1 (0.4)	4 (1.7)	5 (1.0)
Doses received by patients who discontinued from study prior to Week 52[c]			
n	19	33	52
0 Dose	0	1 (3.0)	1 (1.9)
1 Dose	16 (84.2)	27 (81.8)	43 (82.7)
2 Doses	3 (15.8)	5 (15.2)	8 (15.4)

Discrepancies in patient numbers have been clarified by the applicant with submission of responses. There was one patient who was randomised, but not treated. Furthermore, reasons for discontinuations were not collected in all eCRF forms leading to discrepancies in numbers in different tables.

Recruitment

First patient first visit: 24 May 2022

Last patient last visit of the Double-Blind Active-Controlled Period: 19 December 2023

Date of Data Cut-off (Part 1): 30 January 2024

Last patient last visit of the Transition Period: 12 June 2024

Date of Data Cut-off (Part 2): 05 July 2024

Conduct of the study

Two amendments to the study protocol were implemented: the first one prior to study start and the second amendment appr. three months after first patient first visit. The amendments are not considered to have an impact on the study integrity.

Table 5-3 Significant Protocol Deviations – Double-Blind Active-Controlled Period (All Randomized Analysis Set)

Category for Protocol Deviation Protocol Deviation Coded Term	Bmab 1000 (N=238) n (%)	Prolia (N=241) n (%)	Total (N=479) n (%)
Number of patients with at least 1 significant protocol deviation	47 (19.7)	49 (20.3)	96 (20.0)
Protocol deviation	39 (16.4)	40 (16.6)	79 (16.5)
Concomitant or prohibited medication	12 (5.0)	6 (2.5)	18 (3.8)
Missing endpoint assessments	2 (0.8)	8 (3.3)	10 (2.1)
Other protocol deviation	1 (0.4)	1 (0.4)	2 (0.4)
Selection criteria not met	1 (0.4)	5 (2.1)	6 (1.3)
Study procedures/assessments	6 (2.5)	2 (0.8)	8 (1.7)
Study treatment admin/dispense	1 (0.4)	0	1 (0.2)
Study treatment compliance	2 (0.8)	0	2 (0.4)
Visit scheduling	21 (8.8)	24 (10.0)	45 (9.4)
ICH/GCP deviation	13 (5.5)	10 (4.1)	23 (4.8)
Data privacy	0	1 (0.4)	1 (0.2)
ICF process/timing	9 (3.8)	7 (2.9)	16 (3.3)
Investigator oversight	4 (1.7)	2 (0.8)	6 (1.3)

Table 5-6 Distribution of Intercurrent Events During Double-Blind Active-Controlled Period (FAS)

	Bmab 1000 (N=237) n (%)	Prolia (N=235) n (%)	Total (N=472) n (%)
ICE1: Discontinue – related	0	2 (0.9)	2 (0.4)
ICE2: Discontinue – unrelated	19 (8.0)	25 (10.6)	44 (9.3)
ICE3: Dosing deviation	15 (6.3)	22 (9.4)	37 (7.8)
ICE4: Death	0	1 (0.4)	1 (0.2)
ICE5: Medications affecting bones	10 (4.2)	7 (3.0)	17 (3.6)
ICE6: Supplements	51 (21.5)	52 (22.1)	103 (21.8)

Abbreviations: ADA, anti-drug antibody; BMD, bone mineral density; CfB, change from baseline; FAS, full analysis set; ICE, intercurrent event; mFAS, modified full analysis set; N, total number of patients; n, number of patients at each level of summarization.

Notes: This table presents patients who fulfilled the criteria of the defined ICEs. For ICEs ICE1 to ICE3, not all patients presented had BMD observations removed as per the hypothetical strategy in the mFAS analysis.

Discrepancies between patient numbers in different tables were clarified with submissions of responses regarding concomitant or prohibited medications as well as for patients discontinuing from treatment.

Baseline data

Table 5-4 Demographics and Baseline Characteristics (All Randomized Analysis Set)

	Bmab 1000 (N=238)	Prolia (N=241)	Total (N=479)
Age (years)			
n	238	241	479
Mean (SD)	66.7 (5.55)	66.5 (5.77)	66.6 (5.66)
Median (Min, Max)	67.0 (55, 78)	67.0 (55, 79)	67.0 (55, 79)
Age group (years), n (%)[a]			
≥ 55 to < 65	84 (35.3)	88 (36.5)	172 (35.9)
≥ 65 to < 80	154 (64.7)	153 (63.5)	307 (64.1)
Geographical region, n (%)[a]			
US	3 (1.3)	3 (1.2)	6 (1.3)
Europe	235 (98.7)	238 (98.8)	473 (98.7)
Race, n (%)			
White	237 (99.6)	241 (100)	478 (99.8)
Japanese	1 (0.4)	0	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	2 (0.8)	0	2 (0.4)
Not Hispanic or Latino	236 (99.2)	241 (100)	477 (99.6)
Baseline height (cm)			
n	238	240	478
Mean (SD)	159.30 (5.551)	159.03 (5.816)	159.16 (5.682)
Median (Min, Max)	159.00 (142.0, 172.0)	159.00 (145.4, 174.5)	159.00 (142.0, 174.5)
Baseline weight (kg)			
n	238	240	478
Mean (SD)	63.36 (8.944)	63.42 (9.280)	63.39 (9.105)
Median (Min, Max)	62.20 (48.1, 88.9)	61.80 (50.0, 89.7)	62.00 (48.1, 89.7)
Baseline BMI (kg/m^2)[b]			
n	238	240	478
Mean (SD)	24.96 (3.224)	25.11 (3.664)	25.04 (3.449)
Median (Min, Max)	24.53 (17.8, 34.1)	24.49 (19.0, 39.7)	24.53 (17.8, 39.7)
Baseline systolic BP (mmHg)			
n	238	240	478
Mean (SD)	130.24 (12.530)	130.77 (13.538)	130.51 (13.035)
Median (Min, Max)	131.00 (100.0, 167.0)	131.50 (88.0, 168.0)	131.00 (88.0, 168.0)
Baseline diastolic BP (mmHg)			
n	238	240	478
Mean (SD)	78.29 (8.365)	79.04 (8.089)	78.67 (8.228)
Median (Min, Max)	78.00 (60.0, 110.0)	79.00 (57.0, 102.0)	79.00 (57.0, 110.0)

Abbreviations: BMI, body mass index; BP, blood pressure; Max, maximum; Min, minimum; N, total number of patients; n, number of patients at each level of summarization; SD, standard deviation.

a. Stratification factors.

b. BMI was calculated as weight (kg) divided by squared height (m).

Source: Table 14.1.4.1

Data concerning the smoking status/history of patients at baseline are missing. With submission of responses, the applicant clarified that information concerning baseline smoking status/history was not collected and thus, cannot be provided. As indicated by the applicant, negative effects of smoking on BMD are reported in the scientific literature. Thus, due to the missing data, a heterogeneity in the current patient population cannot be excluded and confirmation of an equal distribution would have been reassuring. But it is agreed with the applicant that the randomisation per se should account for baseline imbalance.

Table 5-5 Baseline Disease Characteristics (All Randomized Analysis Set)

	Bmab 1000 (N=238)	Prolia (N=241)	Total (N=479)
Years since menopause (years)			
n	238	241	479
Mean (SD)	17.7 (7.75)	17.0 (7.14)	17.3 (7.45)
Median (Min, Max)	18.0 (0.0, 58.0)	17.0 (2.0, 53.0)	17.0 (0.0, 58.0)
Baseline lumbar spine BMD (g/cm^2)[a]			
n	238	241	479
Mean (SD)	0.765 (0.0599)	0.761 (0.0656)	0.763 (0.0628)
Median (Min, Max)	0.765 (0.623, 1.000)	0.761 (0.611, 0.980)	0.763 (0.611, 1.000)
Baseline lumbar spine BMD T-score (SD)			
n	238	241	479
Mean (SD)	-3.056 (0.3824)	-3.071 (0.3815)	-3.064 (0.3816)
Median (Min, Max)	-2.980 (-3.92, -2.52)	-3.010 (-3.96, -2.50)	-3.000 (-3.96, -2.50)
Baseline lumbar spine BMD T-score (SD), n (%)			
≤-3	117 (49.2)	125 (51.9)	242 (50.5)
>-3	121 (50.8)	116 (48.1)	237 (49.5)
Baseline total hip BMD (g/cm^2)[a]			
n	238	241	479
Mean (SD)	0.754 (0.0924)	0.762 (0.0963)	0.758 (0.0944)
Median (Min, Max)	0.750 (0.547, 1.079)	0.755 (0.500, 1.082)	0.752 (0.500, 1.082)

	Bmab 1000 (N=238)	Prolia (N=241)	Total (N=479)
Baseline femoral neck BMD (g/cm²)[a]			
n	238	241	479
Mean (SD)	0.684 (0.0986)	0.693 (0.1087)	0.689 (0.1038)
Median (Min, Max)	0.692 (0.431, 0.981)	0.680 (0.458, 1.055)	0.688 (0.431, 1.055)
Baseline CTXI (pg/mL)			
n	237	240	477
Mean (SD)	496.975 (213.6050)	511.354 (208.9418)	504.210 (211.1722)
Median (Min, Max)	472.000 (35.00, 1115.00)	497.500 (28.00, 1283.00)	486.000 (28.00, 1283.00)
Baseline P1NP (µg/L)			
n	237	239	476
Mean (SD)	60.499 (25.0035)	60.828 (24.7148)	60.664 (24.8333)
Median (Min, Max)	58.100 (13.20, 154.10)	58.600 (9.40, 165.90)	58.200 (9.40, 165.90)
Prior use of bisphosphonates, n (%)[b]			
Yes	15 (6.3)	17 (7.1)	32 (6.7)
No	223 (93.7)	224 (92.9)	447 (93.3)
Vitamin D at baseline (nmol/L)			
n	238	240	478
Mean (SD)	95.092 (28.0361)	92.729 (28.7821)	93.906 (28.4080)
Median (Min, Max)	91.000 (48.00, 275.00)	88.000 (45.00, 290.00)	90.000 (45.00, 290.00)
Lateral spine X-ray performed, n(%)			
Yes	238 (100)	241 (100)	479 (100)
Fracture detected, n (%)[c]			
Yes	49 (20.6)	48 (19.9)	97 (20.3)
No	189 (79.4)	193 (80.1)	382 (79.7)
Type of fracture, n (%)[d,e]			
Vertebrae	49 (100)	48 (100)	97 (100)
Vertebrae Genant grade at baseline, n (%)[f]			
Mild	24 (49.0)	28 (58.3)	52 (53.6)
Moderate	25 (51.0)	20 (41.7)	45 (46.4)

Abbreviations: BMD, bone mineral density; CTXI, type I collagen C-telopeptides; Max, maximum; Min, minimum; N, total number of patients; n, number of patients at each level of summarization; P1NP, procollagen 1 N-terminal propeptide; SD, standard deviation.

a. Corrected values were used when available.
b. Stratification factors.
c. Percentages were calculated out of those who had a lateral spine X-ray performed.
d. Percentages were calculated out of those who had a fracture detected and lateral spine X-ray performed.
e. Non-vertebrae fractures were osteoporotic fractures. All recorded fractures at screening were vertebrae.
f. Percentages were calculated out of those who have had a vertebrae fracture detected. A patient was counted once for the most severe grading if the patient had multiple fractures detected.

Source: Table 14.1.4.3

Table 23: Medical history - Safety analysis set

Table 14.1.6
Medical History
Safety Analysis Set

System Organ Class Preferred Term	Bmab 1000 (N=238) n (%)	Prolia (N=240) n (%)	Total (N=478) n (%)
Vascular disorders	108 (45.4)	108 (45.0)	216 (45.2)
Aortic arteriosclerosis	0	2 (0.8)	2 (0.4)
Arteriosclerosis	1 (0.4)	0	1 (0.2)
Deep vein thrombosis	1 (0.4)	1 (0.4)	2 (0.4)
Essential hypertension	0	1 (0.4)	1 (0.2)
Hypertension	92 (38.7)	93 (38.8)	185 (38.7)
Lymphoedema	1 (0.4)	0	1 (0.2)
Peripheral arterial occlusive disease	0	1 (0.4)	1 (0.2)
Peripheral vascular disorder	2 (0.8)	0	2 (0.4)
Peripheral venous disease	1 (0.4)	3 (1.3)	4 (0.8)
Raynaud's phenomenon	0	1 (0.4)	1 (0.2)
Subclavian artery occlusion	0	1 (0.4)	1 (0.2)
Superficial vein thrombosis	0	1 (0.4)	1 (0.2)
Varicose vein	24 (10.1)	18 (7.5)	42 (8.8)
Musculoskeletal and connective tissue disorders	106 (44.5)	109 (45.4)	215 (45.0)
Arthralgia	7 (2.9)	2 (0.8)	9 (1.9)
Arthritis	1 (0.4)	1 (0.4)	2 (0.4)
Back pain	5 (2.1)	10 (4.2)	15 (3.1)
Bone pain	1 (0.4)	0	1 (0.2)
Bursitis	0	1 (0.4)	1 (0.2)

Table 14.1.6
Medical History
Safety Analysis Set

System Organ Class Preferred Term	Bmab 1000 (N=238) n (%)	Prolia (N=240) n (%)	Total (N=478) n (%)
Musculoskeletal and connective tissue disorders (cont.)			
Exostosis	1 (0.4)	0	1 (0.2)
Extremity contracture	0	1 (0.4)	1 (0.2)
Fibromyalgia	0	1 (0.4)	1 (0.2)
Foot deformity	3 (1.3)	3 (1.3)	6 (1.3)
Intervertebral disc degeneration	1 (0.4)	1 (0.4)	2 (0.4)
Intervertebral disc disorder	15 (6.3)	15 (6.3)	30 (6.3)
Intervertebral disc protrusion	3 (1.3)	3 (1.3)	6 (1.3)
Kyphosis	2 (0.8)	1 (0.4)	3 (0.6)
Meniscal degeneration	0	1 (0.4)	1 (0.2)
Metatarsalgia	1 (0.4)	0	1 (0.2)
Nodal osteoarthritis	0	1 (0.4)	1 (0.2)
Osteoarthritis	45 (18.9)	42 (17.5)	87 (18.2)
Osteopenia	3 (1.3)	3 (1.3)	6 (1.3)
Osteoporosis	1 (0.4)	0	1 (0.2)
Pain in extremity	1 (0.4)	1 (0.4)	2 (0.4)
Polyarthritis	1 (0.4)	2 (0.8)	3 (0.6)
Rotator cuff syndrome	1 (0.4)	1 (0.4)	2 (0.4)
Scoliosis	4 (1.7)	5 (2.1)	9 (1.9)
Spinal deformity	0	1 (0.4)	1 (0.2)
Spinal osteoarthritis	48 (20.2)	56 (23.3)	104 (21.8)

Table 14.1.6
Medical History
Safety Analysis Set

System Organ Class Preferred Term	Bmab 1000 (N=238) n (%)	Prolia (N=240) n (%)	Total (N=478) n (%)
Congenital, familial and genetic disorders (cont.)			
Myocardial bridging	0	1 (0.4)	1 (0.2)
Pulmonary arteriovenous fistula	1 (0.4)	0	1 (0.2)
Type V hyperlipidaemia	1 (0.4)	2 (0.8)	3 (0.6)
Social circumstances	3 (1.3)	2 (0.8)	5 (1.0)
Menopause	1 (0.4)	0	1 (0.2)
Postmenopause	2 (0.8)	2 (0.8)	4 (0.8)

The most frequently (≥10% of total patients) reported medical history by PT were hypertension (185 [38.7%] patients); hypercholesterolaemia (114 [23.8%] patients); hypothyroidism (109 [22.8%] patients); spinal osteoarthritis (104 [21.8%] patients); osteoarthritis (87 [18.2%] patients); and hyperlipidaemia (81 [16.9%] patients). In general, the distribution of medical history by PT was balanced between both the treatment groups.

Nevertheless, it should be noted that there are low patient numbers with osteoporosis and / or postmenopause in the medical history. With submission of responses, the applicant confirmed that all studied patients were postmenopausal women according to the eligibility criteria. It was further clarified that disease characteristics as defined in the indication were not required to be captured under medical history in the eCRF. Furthermore, the definition of "postmenopausal" included patients after 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, thus explaining the lower range of years with 0.0 years.

Prior medication

A similar proportion of patients in the Bmab 1000 and Prolia groups had received at least 1 prior medication (116 [48.7%] and 117 [48.8%] patients in the Bmab 1000 and Prolia groups, respectively).

The most frequently (≥5% of total patients) reported prior medications were in the ATC level 4 of vitamin D and analogues (149 [31.2%] patients), COVID-19 vaccines (106 [22.2%] patients), and calcium (38 [7.9%] patients). Most frequently (≥2% of total patients) reported prior medications by preferred name were colecalciferol (135 [28.2%] patients), tozinameran (95 [19.9%] patients), calcium carbonate (35 [7.3%] patients), COVID-19 Vaccine Nrvv Ad (Chadox1 Ncov-19) (17 [3.6%] patients), and Vitamin D NOS (12 [2.5%] patients).

Concomitant Medication

A similar proportion of patients in the Bmab 1000 and Prolia groups received at least 1 concomitant medication (238 [100%] and 238 [99.2%] patients in the Bmab 1000 and Prolia groups, respectively).

All 478 patients (238 and 240 patients in the Bmab 1000 and Prolia groups, respectively) were given vitamin D and calcium supplementation.

Other than the vitamin D and calcium supplementation, the most frequently (≥10% of total patients) reported concomitant medications at the ATC level 4 were for HMG-CoA reductase inhibitors (165 [34.5%] patients); thyroid hormones (115 [24.1%] patients); selective beta blocking agents (104 [21.8%] patients); plain ACE inhibitors (79 [16.5] patients); anilides (65 [13.6%] patients); propionic acid derivatives (49 [10.3%] patients); and plain angiotensin II receptor blockers (48 [10.0%] patients).

Numbers analysed

Table 5-2 Number of Patients in Each Analysis Set (All Enrolled Set)

	Bmab 1000	Prolia	Total
All enrolled set[a]			1219
Randomized set[b]	238	241	479
Full analysis set[c,d]	237 (99.6)	235 (97.5)	472 (98.5)
Safety analysis set[d,e]	238 (100)	240 (99.6)	478 (99.8)

Abbreviations: ICE, intercurrent event; ICF, informed consent form.

a. All Enrolled Set consisted of all patients who signed the ICF.
b. Randomized Set consisted of all patients who were randomized regardless of receiving the study drug.
c. Full Analysis Set consisted of all randomized patients who met the eligibility criteria and received at least 1 dose of the study drug. Patients from the Full Analysis Set were analyzed under the treatment as randomized.
   Full Analysis Set=Modified Full Analysis Set, where Modified Full Analysis Set excluded data observed after the first occurrence of those ICEs with a hypothetical strategy (as specified in Section 7.1 of the study protocol [Appendix 16.1.1]).
d. Percentages were based on the number of patients randomized.
e. Safety Analysis Set consisted of all randomized patients who received at least 1 administration of study drug. Patients from the Safety Analysis Set were analyzed per actual treatment received.

Source: Table 14.1.2.1

Seven patients were removed from the Full Analysis Set (FAS): Patients with the significant protocol deviation "Selection criteria not met" were excluded from the FAS (n = 6). One patient in the Prolia group did not receive any dose (n = 1). Numbers are comprehensible.

Outcomes and estimation

Primary efficacy endpoint

Equivalence of Bmab 1000-P to Prolia at Week 52 was established as the 95% CIs of the difference in LS means %CfB in lumbar spine BMD (Bmab 1000-P - Prolia) were entirely contained within the pre-defined margins of (-1.45%, 1.45%).

Table 24: Main estimation of the primary estimand (co-primary efficacy) by MMRM: difference in means in %CfB in lumbar spine BMD at Week 52 (mFAS)

Week 52 Visit	Bmab 1000 (n=237)	Prolia (n=235)	95% CI Within Equivalence Limits[1]
n	207	206	
LS mean %CfB (SE)	5.554 (0.7546)	4.955 (0.7538)	
LS mean difference (Bmab 1000-P - Prolia)[2]	0.599		
95% CI	-0.107, 1.306		Yes

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

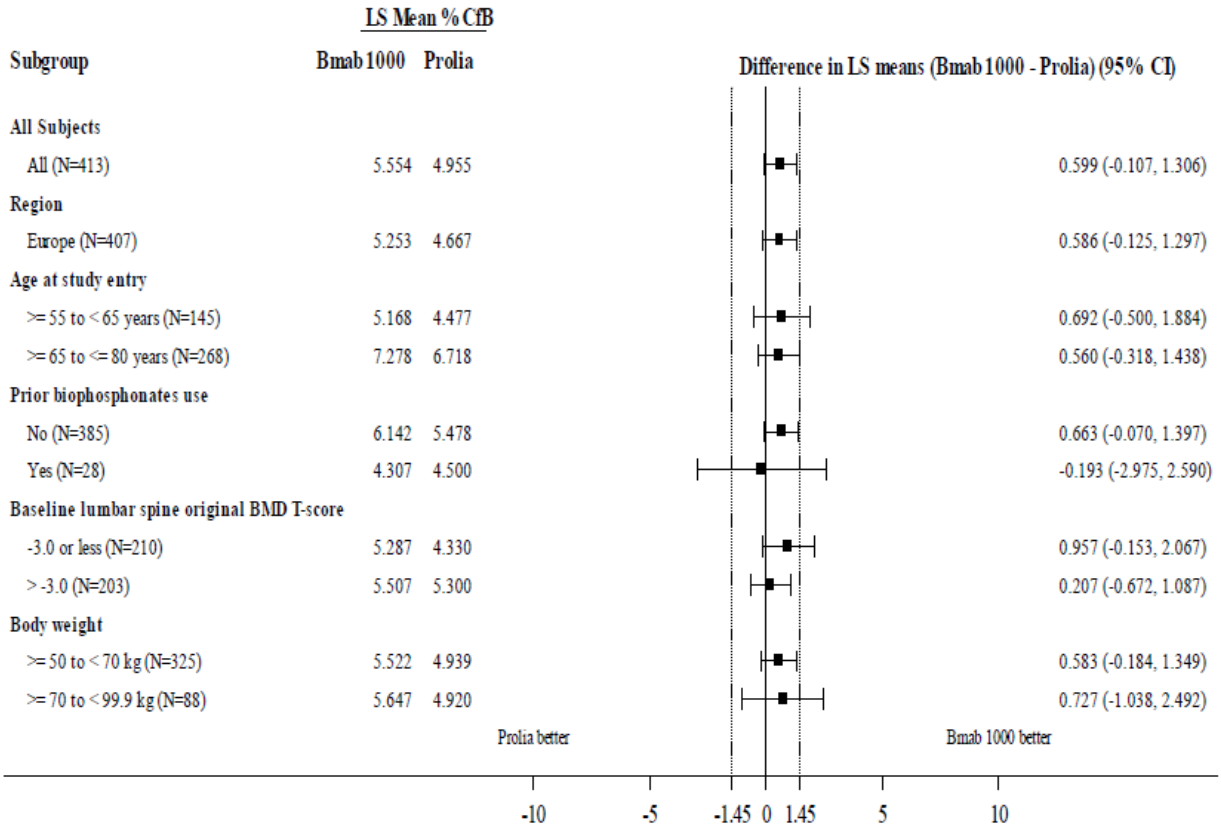
[1]Therapeutic equivalence was demonstrated if the 95% CI was entirely within the predefined margins of (-1.45%, 1.45%).

[2]Estimate of primary estimand 1a-EMA (co-primary efficacy): Difference in means (Bmab 1000-P minus Prolia) in %CfB in lumbar spine BMD by DXA after 52 weeks in post-menopausal women with osteoporosis treated with subcutaneous injections every 6 months assuming that all women received two doses without any errors or deviations in dosing and without the receipt of any other medications affecting bones, except for vitamin D and calcium supplements.

Abbreviations: BMD = bone mineral density, %CfB = percent change from baseline, CI = confidence interval, DXA = dual-energy X-ray absorptiometry, EMA = European Medicines Agency, LS = least squares, mFAS = modified full analysis set, MMRM = mixed model with repeated measures, SE= standard error.

Source: Table 6-2, CSR, B1000-PMO-03-G-02.

Figure 1: Main Estimation of Primary Estimand (Co-Primary Efficacy) by MMRM - Forest Plot, Subgroup Analysis of Difference in Means up to Week 52 (mFAS)



Sensitivity analysis for primary endpoint

MI (Multiple Imputation) under MAR (Missing At Random) approach was applied to the mFAS, and data at Week 52 were analysed using the same ANCOVA model as that for estimand 1a-FDA. The analysis by MI under MAR is well established as a flexible, general, method for the analysis of data sets with missing values and tipping point analysis (by adding penalty) assess the robustness of the assumptions used for data handling of the primary estimand by incrementally shifting the distribution of the underlying data for each treatment group separately used for imputation. In effect, it aims to explore the plausibility of missing data assumptions by finding the point at which the produced CI no longer achieves equivalence within the specified equivalence margin.

Table 25: Sensitivity analysis of primary estimand 1a-EMA (co-primary efficacy) by ANCOVA: Difference in means in %CfB in lumbar spine BMD at Weeks 26 and 52 - MI under MAR

Table 14.2.2.3
Sensitivity Analysis of Primary Estimand 1a-EMA(Co-Primary Efficacy) by ANCOVA: Difference in Means in % CfB in Lumbar Spine BMD at Weeks 26 and 52 – MI under MAR
Modified Full Analysis Set

Multiple Imputation [1] Results Using Rubin's Method [2]	Bmab 1000 (N=237)	Prolia (N=235)
Week 26		
n	237	235
LS mean % CfB (SE)	3.937 (0.7960)	3.704 (0.7946)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.234	
95% CI [2]	-0.418 ,0.886	
Week 52		
n	237	235
LS mean % CfB (SE)	5.184 (0.8504)	4.616 (0.8479)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.568	
95% CI [2]	-0.127 ,1.262	

A penalty (delta) was added to the imputed percent change in BMD values from MI assuming MAR in the Bmab 1000 group only. This approach was a sensitivity analysis for estimand 1a-EMA conducted on the mFAS and the main estimation approach for estimand 1a-FDA conducted on the FAS.

Table 26: Sensitivity analysis of primary estimand 1a-EMA (co-primary efficacy using penalty

Table 14.2.2.4
Sensitivity Analysis of Primary Estimand 1a-EMA(Co-Primary Efficacy) using Penalty: Difference in Means in % CfB in Lumbar Spine BMD by ANCOVA up to Week 52 – MI under MAR
Modified Full Analysis Set

	Multiple Imputation [2] Results Using Rubin's Method [3]		Adjusted estimate with penalty applied		
Penalties (Delta) Applied to Imputed Value in Bmab 1000 [1]	LS Mean % CfB Bmab 1000 (N=237)	LS Mean % CfB Prolia (N=235)	LS Mean Difference in % CfB Estimate [4]	95% CI	95% CI within equivalence margins? [5]
-1.45			0.385	-0.312, 1.081	Yes
0	5.184	4.616	0.568	-0.127, 1.262	Yes
1.45			0.751	0.053, 1.449	Yes

The 95% CI of the difference in LS means %CfB in the lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%) using both the sensitivity analyses suggests that the results of the co-primary estimand (estimand 1a-EMA) were robust.

Supplementary analysis for estimand 1a-EMA

To investigate assumptions of normality, the log-transformed BMD as a ratio of baseline was analysed in a similar MMRM model to the main analysis but with baseline covariate as the log BMD (using the mFAS).

Table 27: Supplementary analysis of primary estimand 1a-EMA (co-primary efficacy) MMRM on Log transformed lumbar spine BMD

Table 14.2.2.5
Supplementary Analysis of Primary Estimand 1a-EMA(Co-Primary Efficacy) MMRM on Log Transformed Lumbar Spine BMD: Geometric Mean Ratio up to Week 52
Modified Full Analysis Set

Visit	Bmab 1000 (N=237)	Prolia (N=235)
Week 26		
n	220	217
Geometric mean (SE)	1.035 (1.0072)	1.033 (1.0072)
Ratio of geometric means (Bmab 1000/Prolia) [1]	1.002	
95% CI	0.996 ,1.008	
Week 52		
n	207	206
Geometric mean (SE)	1.055 (1.0073)	1.049 (1.0073)
Ratio of geometric means (Bmab 1000/Prolia) [1]	1.006	
95% CI	0.999 ,1.013	

Supplementary analysis of the primary estimand supported the main estimation results as the 95% CI of the difference in LS means %CfB in the lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%).

Co-primary PD endpoint

The 95% CI (97.74% to 110.93%) for the geometric LS mean ratio of sCTX AUEC up to Week 26 was contained entirely within the predefined acceptance limits (80.00% to 125.00%), indicating Bmab 1000-P was equivalent to Prolia in terms of PD endpoint.

Secondary efficacy analysis (Part 1)

Lumbar Spine BMD at 26 Weeks (EMA)

Difference in means in %CfB in the lumbar spine BMD at Week 26 by MMRM for the mFAS is presented in the following table:

Table 28: Main estimation of primary estimand 1a-EMA (co-primary efficacy) by MMRM

Table 14.2.2.2
Main Estimation of Primary Estimand 1a-EMA (Co-Primary Efficacy) by MMRM: Difference in Means in % CfB in Lumbar Spine BMD up to Week 52
Modified Full Analysis Set

Visit	Bmab 1000 (N=237)	Prolia (N=235)	95% CI within equivalence margins? [2]
Week 26			
n	220	217	
LS mean % CfB (SE)	3.576 (0.7490)	3.365 (0.7478)	
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.211		
95% CI	-0.441 ,0.864		
Week 52			
n	207	206	
LS mean % CfB (SE)	5.554 (0.7546)	4.955 (0.7538)	
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.599		
95% CI	-0.107 ,1.306		Yes

Total Hip and Femoral Neck BMD at 26 and 52 Weeks (EMA)

Difference in means in %CfB in the total hip and femoral neck BMD, at Weeks 26 and 52 by MMRM, for the mFAS is presented in the following tables:

Table 29: Difference in means in % CfB up to Weeks 26 and 52 in hip BMD by MMRM

Table 14.2.4.1.2.1
Difference in Means in % CfB up to Weeks 26 and 52 in Hip BMD by MMRM
Modified Full Analysis Set

Visit	Bmab 1000 (N=237)	Prolia (N=235)
Week 26		
n	220	217
LS mean % CfB (SE)	1.546 (0.4772)	1.291 (0.4756)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.255	
95% CI	-0.162 ,0.671	
Week 52		
n	207	206
LS mean % CfB (SE)	2.385 (0.4804)	2.302 (0.4791)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.083	
95% CI	-0.364 ,0.531	

Table 30: Difference in means in % CfB up to Weeks 26 and 52 in femoral neck BMD by MMRM

Table 14.2.4.1.3.1
Difference in Means in % CfB up to Weeks 26 and 52 in Femoral Neck BMD by MMRM
Modified Full Analysis Set

Visit	Bmab 1000 (N=237)	Prolia (N=235)
Week 26		
n	220	217
LS mean % CfB (SE)	1.878 (0.6842)	1.274 (0.6815)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.604	
95% CI	0.022 ,1.186	
Week 52		
n	207	206
LS mean % CfB (SE)	2.653 (0.6939)	2.322 (0.6915)
LS Mean Difference (Bmab 1000 - Prolia) [1]	0.331	
95% CI	-0.338 ,1.000	

Incidence of Fracture up to Week 52

Summary of fracture events by timepoints for the SAF is presented in the following table:

Table 31: Summary of fractures by timepoint

Table 14.3.7.1.1
Summary of Fractures by Timepoint - Double-blind Active-controlled Period
Safety Analysis Set

	Bmab 1000 (N=238) n (%)	Prolia (N=240) n (%)	Total (N=478) n (%)
Screening			
Lateral spine X-ray performed			
Yes	238 (100)	240 (100)	478 (100)
Fracture detected [a]			
Yes	49 (20.6)	48 (20.0)	97 (20.3)
No	189 (79.4)	192 (80.0)	381 (79.7)
Type of Fracture [b]			
Vertebrae	49 (100)	48 (100)	97 (100)
Vertebrae			
Genant Grade [c]			
Mild	24 (49.0)	28 (58.3)	52 (53.6)
Moderate	25 (51.0)	20 (41.7)	45 (46.4)

<u>Secondary efficacy analysis (Part 2)</u>

Lumbar Spine BMD from Week 52 to Week 78

The Lumbar Spine BMD from Week 52 to Week 78 was assessed after re-randomisation of patients in the Prolia group to Bmab 1000 or Prolia at Week 52. Efficacy was evaluated in the following groups:

- Prolia-Prolia vs. Prolia-Bmab 1000 and
- Prolia-Prolia vs. Bmab 1000 and Bmab 1000.

Table 32: Analysis of % Cfb in lumbar spine BMD at Week 78 using ANCOVA – MI under MAR

Multiple Imputation [1] Results Using Rubin's Method [2]	Bmab 1000(Bmab 1000 in Double-blind Active-controlled Period) (N=218)	Bmab 1000(Prolia in Double-blind Active-controlled Period) (N=104)	Prolia (Prolia in Double-blind Active-controlled Period) (N=104)
%Cfb (Baseline to Week 78) [3]			
n	218	104	104
LS Mean % CfB (SE)	5.832 (0.9037)	5.431 (0.9721)	6.370 (0.9128)
LS Mean Difference (relative to Prolia arm)	-0.537	-0.939	
90% CI	-1.309 ,0.234	-1.843 ,-0.035	
%Cfb (Week 52 to Week 78) [4]			
n	218	104	104
LS Mean % CfB (SE)	0.807 (0.6606)	1.130 (0.7114)	1.328 (0.6672)
LS Mean Difference (relative to Prolia arm)	-0.520	-0.197	
90% CI	-1.085 ,0.044	-0.859 ,0.464	

BMD=Bone Mineral Density (g/cm2); % CfB=Percentage Change from Baseline; CI=Confidence Interval; LS=Least Squares; SE=Standard

Error.

[1] Multiple Imputation model (see Section 8.4.1 in SAP) used to impute 30 values for each missing value.

[2] Rubin's method in PROC MIANALYZE used to pool estimates across the 30 multiply imputed datasets.

Note: ANCOVA model includes terms for treatment arm, 'baseline' lumbar spine BMD covariate and classification variables for: region, age and prior use of bisphosphonates.

[3] 'baseline' is defined at Day 1 in both calculation of % Cfb and baseline covariate.

[4] 'baseline' is defined at Week 52 in both calculation of % Cfb and baseline covariate.

Results from the Transition Period (Week 52 to Week 78) are in line with results up to Week 52 concluding that the transition from Prolia to Bmab 1000 did not negatively influence the %CfB in the lumbar spine BMD when analysed separate from Week 52 data.

Lumbar Spine, Hip, and Femoral Neck BMD at Week 78

To assess efficacy (from Day 1 to Week 78), the lumbar spine, hip, and femoral neck BMD were evaluated in the following groups;

- Prolia-Bmab 1000 vs. Prolia-Prolia
- Bmab 1000-Bmab 1000 vs. Prolia-Bmab 1000 and
- Bmab 1000-Bmab 1000 vs. Prolia-Prolia

Table 33: Summary of % Cfb in lumbar spine BMD, hip BMD, femoral BMD at Week 78 – Full analysis set for transition period

	Bmab 1000 (Bmab 1000 in Double-blind Active-controlled Period) (N=218)	Bmab 1000 (Prolia in Double-blind Active-controlled Period) (N=104)	Prolia (Prolia in Double-blind Active-controlled Period) (N=104)
Week 78 Lumbar Spine BMD			
n	216	103	103
Mean (SD)	6.634 (3.8204)	6.243 (3.9538)	7.151 (4.1187)
Median	6.323	6.648	7.227
Min, Max	-4.29, 19.86	-5.04, 20.95	-3.48, 16.58
Week 78 Hip BMD			
n	216	103	103
Mean (SD)	4.011 (2.7744)	4.052 (3.4300)	3.483 (2.6155)
Median	4.209	3.799	3.448
Min, Max	-6.46, 13.41	-3.19, 15.33	-3.65, 14.54
Week 78 Femoral Neck BMD			
n	216	103	103
Mean (SD)	3.666 (3.6640)	3.333 (3.5021)	2.834 (3.9551)
Median	3.323	3.580	2.508
Min, Max	-6.07, 20.00	-4.40, 14.03	-10.03, 19.61

BMD=Bone Mineral Density (g/cm2); % CfB=Percentage Change from Baseline; SD=Standard Deviation.

The LS mean %CfB (from Week 52 to Week 78) in the lumbar spine BMD was comparable for "Prolia to Prolia" and "Bmab 1000 to Bmab 1000" treatment groups (1.328 and 0.807; 90% CI: -1.085, 0.044). Results are also supportive for similar efficacy after switch from Prolia to Bmab 1000 (%CfB (from Week 52 to Week 78) in the lumbar spine BMD in "Prolia to Prolia" and "Prolia to Bmab 1000" were 1.328 and 1.130, respectively (90% CI: -0.859, 0.464).

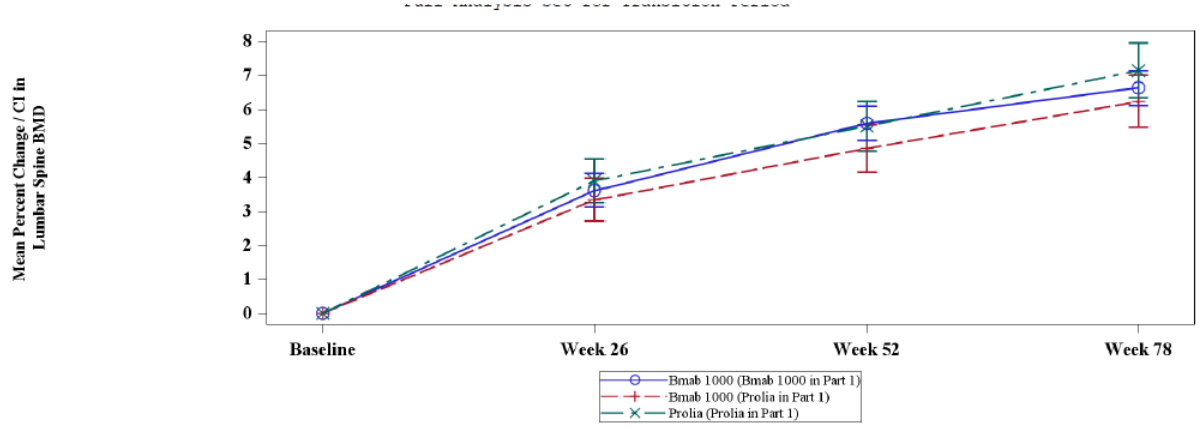
Prolia-Prolia vs. Prolia-Bmab 1000 (Baseline – Week 78)

The LS mean %CfB was 6.370 vs. 5.431 (Prolia-Prolia vs. Prolia-Bmab 1000) with a LS mean difference of -0.939 and a 90% CI: [-1.843, -0.035] not falling within the predefined limits. Nevertheless, as can be seen in Figure 8, the difference in the two groups is rather due to the period before the switch at Week 52 (green and red lines). For interpretation of the switch from Prolia to Bmab 1000 at Week 52, results of the period from Week 52 - Week78 are considered more informative, although the time period is considered very short (see above).

Prolia-Prolia vs. Bmab 1000-Bmab 1000 (Baseline – Week 78)

From Day 1 to Week 78, the LS mean %CfB in the lumbar spine BMD was 5.832 vs. 6.370 with a LS mean difference of -0.537 and a 90% CI of [-1.309, 0.234] falling within the predefined limits.

Figure 8: Percent change from baseline (Day 1) up to Week 78 in lumbar spine BMD



Bmab 1000 (Bmab 1000 in Part 1)	0 (218)	3.6 (218)	5.6 (218)	6.6 (216)
Bmab 1000 (Prolia in Part 1)	0 (104)	3.3 (104)	4.9 (104)	6.2 (103)
Prolia (Prolia in Part 1)	0 (104)	3.9 (104)	5.5 (104)	7.2 (103)

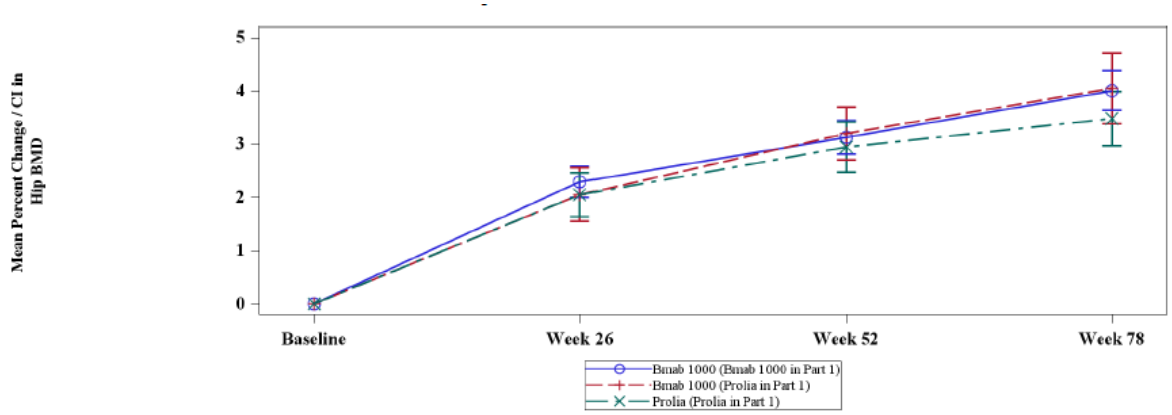
BMD=Bone Mineral Density (g/cm2).

Percent change in lumbar spine BMD(g/cm2)=100*(Post-baseline - Baseline (Day 1))/Baseline (Day 1).

Baseline is defined as last non-missing measurement prior to the first treatment injection at Day 1.

The mean percent change from baseline and number of subjects with available data at each timepoint within each treatment group are displayed below the figure. Early Termination visits for discontinued subjects and unscheduled visits collected were reallocated to the respective planned study visit as per study day (the one nearer to the planned visit day within 30 days window was allocated).

Figure 9: Percent change from baseline (Day 1) up to Week 78 in hip BMD – Full analysis set for transition period



Bmab 1000 (Bmab 1000 in Part 1)	0 (218)	2.3 (218)	3.1 (218)	4 (216)
Bmab 1000 (Prolia in Part 1)	0 (104)	2.1 (104)	3.2 (104)	4.1 (103)
Prolia (Prolia in Part 1)	0 (104)	2.1 (104)	2.9 (104)	3.5 (103)

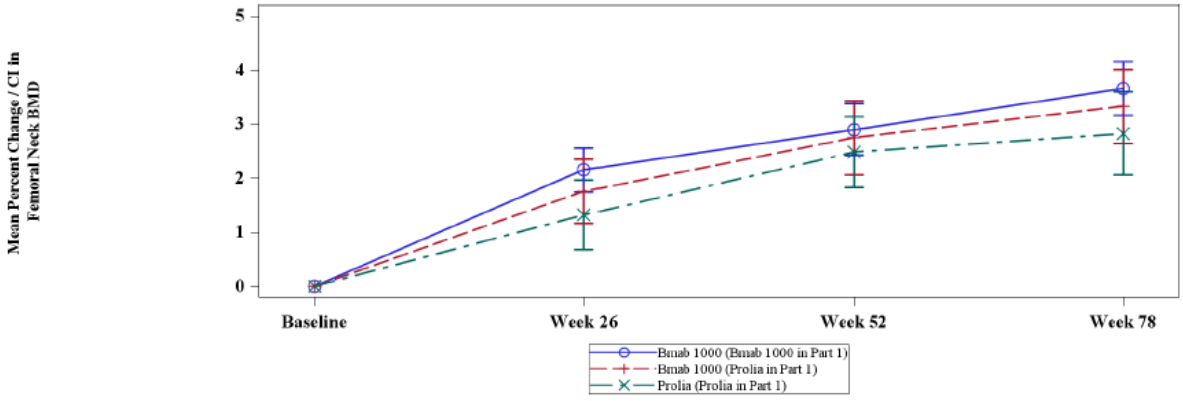
BMD=Bone Mineral Density (g/cm2).

Percent change in hip BMD (g/cm2)=100*(Post-baseline - Baseline (Day 1))/Baseline (Day 1)

Baseline is defined as last non-missing measurement prior to the first treatment injection at Day 1.

The mean percent change from baseline and number of subjects with available data at each timepoint within each treatment group are displayed below the figure. Early Termination visits for discontinued subjects and unscheduled visits collected were reallocated to the respective planned study visit as per study day (the one nearer to the planned visit day within 30 days window was allocated).

Figure 10: Percent change from baseline (Day 1) up to Week 78 in femoral neck BMD – Full analysis set for transition period



Bmab 1000 (Bmab 1000 in Part 1)	0 (218)	2.2 (218)	2.9 (218)	3.7 (216)
Bmab 1000 (Prolia in Part 1)	0 (104)	1.8 (104)	2.8 (104)	3.3 (103)
Prolia (Prolia in Part 1)	0 (104)	1.3 (104)	2.5 (104)	2.8 (103)

BMD=Bone Mineral Density (g/cm2).

Percent change in femoral neck BMD (g/cm2)=100*(Post-baseline - Baseline (Day 1))/Baseline (Day 1)

Baseline is defined as last non-missing measurement prior to the first treatment injection at Day 1.

The mean percent change from baseline and number of subjects with available data at each timepoint within each treatment group are displayed below the figure. Early Termination visits for discontinued subjects and unscheduled visits collected were reallocated to the respective planned study visit as per study day (the one nearer to the planned visit day within 30 days window was allocated).

Incidence of Fracture up to Week 78

No additional patient other than the 2 patients noted in Section 6.2.3 had any fracture event. It must be noted that no lateral spine X-ray was planned after week 52 according to the study protocol. Nevertheless, a complete clinical examination was performed at Weeks 26, 52 and also at Week 78 to

guarantee the documentation of any new fracture. Furthermore, radiographs were to be performed as required throughout the study in order to confirm suspected new fractures.

Table 34: Summary of fractures by timepoint - Transition period – Safety analysis set for transition period

Table 14.3.7.1.2
Summary of Fractures by Timepoint - Transition Period
Safety Analysis Set for Transition Period

	Bmab 1000 (Bmab 1000 in Double-blind Active-controlled Period) (N=218) n (%)	Bmab 1000 (Prolia in Double-blind Active-controlled Period) (N=104) n (%)	Prolia (Prolia in Double-blind Active-controlled Period) (N=104) n (%)	Total (N=426) n (%)
Week 52				
Lateral spine X-ray performed				
Yes	39 (17.9)	16 (15.4)	15 (14.4)	70 (16.4)
Fracture detected [a]				
Yes	0	0	0	0
No	39 (100)	16 (100)	15 (100)	70 (100)
Type of Fracture [b]				
Vertebrae	0	0	0	0
Vertebrae				
Genant Grade [c]				
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	0

[a] Percentages are calculated out of those who have had Lateral spine X-ray performed.

[b] Percentages are calculated out of those who have had a fracture detected and Lateral spine X-ray performed. All recorded fractures are vertebrae.

[c] Percentages are calculated out of those who have had a vertebrae fracture detected. A subject is counted once for the most severe grading, if the subject had multiple fractures detected.

Table 35: Summary of fractures by timepoint - Throughout the study – Safety analysis set for transition period

Table 14.3.7.1.3
Summary of Fractures by Timepoint - Throughout the Study
Safety Analysis Set for Transition Period

	Bmab 1000 (Bmab 1000 in Double-blind Active-controlled Period) (N=218) n (%)	Prolia (Prolia in Double-blind Active-controlled Period) (N=104) n (%)	Total (N=322) n (%)
Week 52			
Lateral spine X-ray performed			
Yes	211 (96.8)	103 (99.0)	314 (97.5)
Fracture detected [a]			
Yes	1 (0.5)	0	1 (0.3)
No	210 (99.5)	103 (100)	313 (99.7)
Type of Fracture [b]			
Vertebrae	1 (100)	0	1 (100)
Vertebrae			
Genant Grade [c]			
Mild	1 (100)	0	1 (100)
Moderate	0	0	0
Severe	0	0	0

[a] Percentages are calculated out of those who have had Lateral spine X-ray performed.

[b] Percentages are calculated out of those who have had a fracture detected and Lateral spine X-ray performed. All recorded fractures are vertebrae.

[c] Percentages are calculated out of those who have had a vertebrae fracture detected. A subject is counted once for the most severe grading, if the subject had multiple fractures detected.

During the procedure, the applicant confirmed that the Table 14.3.7.1.2 above includes only data from patients entering the Transition Period and X-ray assessments performed after re-randomisation and third study dose administration, whereas Table 14.3.7.1.3 includes data from patients throughout the study, thus, explaining deviating numbers of lateral spine X-ray performed at Week 52 in different tables.

Ancillary analyses

Not applicable.

2.5.5.3. Summary of main efficacy results

Table 36: Summary of efficacy for trial B1000-PMO-03-G-02

Title: A randomized, double-blind, multicenter, parallel-arm phase 3 study to compare the efficacy, pharmacodynamics, safety, and immunogenicity between Bmab 1000 and Prolia in postmenopausal women with osteoporosis		
Study identifier	Protocol Number: B1000-PMO-03-G-02 EudraCT number: 2021-006545-36 CT.gov number: NCT05345691	
Design	**Randomised, double-blind, active-controlled, parallel-arm, multicentre study**	
	Duration of main phase:	24-May-2022 (First Patient First Visit) – 19-Dec-2023 (Last Patient Last Visit for Week 52)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	15-Jun-2023 (First Patient visit at Week 52; transition Phase) – 12 June 2024 (Last Patient Last visit for Week 78)
Hypothesis	Equivalence	
Treatments groups	Bmab 1000 (Day 1 to Week 78)	**Treatment:** 60 mg/mL PFS **Double Blind Double-Blind Active-Controlled Period Duration**: From Week 0 [Day 1] to Week 52 Pre-dose): The study drug was administered on Day 1, and Week 26 **Transition Period** Duration: From Week 52 to Week 78 [EoS Visit]): The study drug was administered at Week 52 **Number of patients randomised (Day 1)**: 238
	Prolia At Week 52 (pre-dose), patients from the Prolia group were re-randomised in a 1:1	**Treatment:** 60 mg/mL PFS **Double Blind Double-Blind Active-Controlled Period Duration**: From Week 0 [Day 1] to Week 52 Pre-dose): The study drug was administered on Day 1, and Week 26

	ratio to receive either Bmab 1000 or Prolia at Week 52		**Transition Period** Duration: From Week 52 to Week 78 [EoS Visit]): The study drug was administered at Week 52. **<u>Number of patients randomised (Day 1)</u>**: 241
Endpoints and definitions	Co-Primary endpoint	The percentage change from baseline (%CfB) at Week 52 in the lumbar spine BMD by DXA Time frame: Baseline and Week 52	The %CfB in the lumbar spine BMD by DXA at Week 52. Estimand 1a-EMA (co-primary efficacy): Difference in means (Bmab 1000 – Prolia) in %CfB in the lumbar spine BMD by DXA after 52 weeks in postmenopausal women with osteoporosis treated with SC injections every 6 months assuming that all women received 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements.
	Co-Primary endpoint	Area under the effect curve (AUEC) of sCTX from baseline to 26 weeks Time frame: Baseline to Week 26	Estimand 1b-EMA (Co-primary PD): Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women with osteoporosis treated with an SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements
	Secondary endpoint	Lumbar Spine BMD	The %CfB at Week 26 in the lumbar spine BMD by DXA Time frame: Baseline and Week 26
	Secondary endpoint	Total Hip BMD	The %CfB at Weeks 26 and 52 in the total hip BMD by DXA Time frame: Baseline, Week 26, and Week 52
	Secondary endpoint	Femoral Neck BMD	The %CfB at Weeks 26 and 52 in the femoral neck BMD by DXA Time frame: Baseline, Week 26, and Week 52
	Secondary endpoint	Incidence of Fracture	Incidence of fracture up to Week 52 Time frame: Baseline up to Week 52
Database lock	30-Jan-2024 (For Week 52)		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis:** The %CfB in the lumbar spine BMD by DXA at Week 52		
Analysis population and time point description	**Modified Full Analysis Set (mFAS):** The term mFAS was used to define the analysis data set that included a data record at each time point for all patients in the Full Analysis Set but excluded data observed after the first occurrence of those intercurrent events (ICEs) where a hypothetical strategy was taken (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS were analysed under the treatment as randomised and used as the		

	primary analysis data set for estimation of estimand 1a-EMA (co-primary efficacy) Primary analysis was conducted at Week 52		
Descriptive statistics and estimate variability	**Treatment group**	**Bmab 1000**	**Prolia**
	Number of patients	**237**	**235**
	n	207	206
	LS Mean %CfB	5.554	4.955
	Standard Error (SE)	0.7546	0.7538
Effect estimate per comparison	The % CfB in the lumbar spine BMD by DXA at Week 52	**Comparison groups**	**Difference between Bmab 1000 and Prolia**
		LS mean difference (Bmab 1000 - Prolia)*	0.599
		95% CI	-0.107, 1.306
	Abbreviations: %CfB, percent change from baseline; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; LS, least squares; N, total number of patients; n, number of patients at each level of summarisation; SE, standard error. Note: The Mixed Model with Repeated Measures (MMRM) model was used, which included terms for visit by treatment, baseline BMD at the lumbar spine (as a covariate), and classification variables for: region, age, and prior use of bisphosphonates. Patient was included as a random effect. *: Estimate of primary estimand 1a-EMA (co-primary efficacy): Difference in means (Bmab 1000 minus Prolia) in %CfB in the lumbar spine BMD by DXA after 52 weeks in postmenopausal women with osteoporosis treated with subcutaneous injections every 6 months assuming that all women received 2 doses without any errors or deviations in dosing and without the receipt of any other medications affecting bones, except for vitamin D and calcium supplements		
Notes	Therapeutic equivalence would be concluded in terms of efficacy if 95% CI for the mean difference in %CfB at Week 52 in the lumbar spine BMD falls within predefined equivalence margins of (-1.45%, 1.45%).		
Analysis description	**Secondary analysis:** The %CfB in the lumbar spine BMD by DXA at Week 26		
Analysis population and time point description	**Modified Full Analysis Set (mFAS):** The term mFAS was used to define the analysis data set that included a data record at each time point for all patients in the Full Analysis Set but excluded data observed after the first occurrence of those intercurrent events (ICEs) where a hypothetical strategy was taken (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS were analysed under the treatment as randomised and used as the primary analysis data set for estimation of estimand 1a-EMA (co-primary efficacy) Analysis was conducted at Week 26 and Week 52		
Descriptive statistics and estimate variability	**Treatment group**	**Bmab 1000**	**Prolia**
	Number of patients	**237**	**235**
	n	220 (Week 26) 207 (Week 52)	217 (Week 26) 206 (Week 52)
	LS Mean %CfB	3.576 (Week 26) 5.554 (Week 52)	3.365 (Week 26) 4.955 (Week 52)

	SE	0.7490 (Week 26) 0.7546 (Week 52)	0.7478 (Week 26) 0.7538 (Week 52)
Effect estimate per comparison	The % CfB in the lumbar spine BMD by DXA	**Comparison groups**	**Difference between Bmab 1000 and Prolia**
		LS mean difference (Bmab 1000 - Prolia)*	0.211 (Week 26) 0.599 (Week 52)
		95% CI	-0.441 ,0.864 (Week 26) -0.107 ,1.306 (Week 52)
	Abbreviations: BMD=Bone Mineral Density (g/cm2); % CfB=Percentage Change from Baseline; CI=Confidence Interval; LS=Least Squares; SE=Standard Error Note: The MMRM model was used, which included terms for visit by treatment, baseline BMD at the lumbar spine (as a covariate), and classification variables for: region, age, and prior use of bisphosphonates. Patient was included as a random effect. *: Estimate of primary estimand 1a-EMA (co-primary efficacy): Difference in means (Bmab 1000 minus Prolia) in % CfB in lumbar spine BMD by DXA after 52 weeks in postmenopausal women with osteoporosis treated with subcutaneous injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements		
Notes	Therapeutic equivalence would be demonstrated if 95% CI entirely within predefined margins of [-1.45%, 1.45%]. Note: The MMRM model was used, which included terms for visit by treatment, baseline BMD at the lumbar spine (as a covariate), and classification variables for: region, age, prior use of bisphosphonates. Patient is included as a random effect		
Analysis description	**Secondary analysis:** The %CfB in total hip BMD at Weeks 26 and 52		
Analysis population and time point description	**Modified Full Analysis Set (mFAS):** The term mFAS was used to define the analysis data set that included a data record at each time point for all patients in the Full Analysis Set but excluded data observed after the first occurrence of those intercurrent events (ICEs) where a hypothetical strategy was taken (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS were analysed under the treatment as randomised and used as the primary analysis data set for estimation of estimand 1a-EMA (co-primary efficacy) Analysis was conducted at Week 26 and Week 52		
Descriptive statistics and estimate variability	**Treatment group**	**Bmab 1000**	**Prolia**
	Number of patients	**237**	**235**
	n	220 (Week 26) 207 (Week 52)	217 (Week 26) 206 (Week 52)
	LS Mean %CfB	1.546 (Week 26) 2.385 (Week 52)	1.291 (Week 26) 2.302 (Week 52)
	SE	0.4772 (Week 26) 0.4804 (Week 52)	0.4756 (Week 26) 0.4791 (Week 52)
Effect estimate per comparison	The % CfB in the total hip BMD by DXA*	**Comparison groups**	**Difference between Bmab 1000 and Prolia**
		LS mean difference (Bmab 1000 - Prolia)	0.255 (Week 26) 0.083 (Week 52)

		95% CI	-0.162 ,0.671 (Week 26) -0.364 ,0.531 (Week 52)
	Abbreviations: BMD=Bone Mineral Density (g/cm2); % CfB=Percentage Change from Baseline; CI=Confidence Interval; LS=Least Squares; SE=Standard Error Note: The MMRM model was used, which included terms for visit by treatment, baseline BMD at the Hip (as a covariate), and classification variables for: region, age, prior use of bisphosphonates. Patient is included as a random effect. *: Difference in means (Bmab 1000 minus Prolia) in CfB in Hip BMD by DXA at weeks 26 and 52 in postmenopausal women with osteoporosis treated with subcutaneous injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements		
Notes	None		
Analysis description	**Secondary analysis:** The %CfB in femoral neck BMD at Weeks 26 and 52		
Analysis population and time point description	**Modified full analysis set (mFAS):** The term mFAS was used to define the analysis data set that included a data record at each time point for all patients in the Full Analysis Set but excluded data observed after the first occurrence of those intercurrent events (ICEs) where a hypothetical strategy was taken (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS were analysed under the treatment as randomised and used as the primary analysis data set for estimation of estimand 1a-EMA (co-primary efficacy) Analysis was conducted at Week 26 and Week 52		
Descriptive statistics and estimate variability	**Treatment group**	**Bmab 1000**	**Prolia**
	Number of patients	**237**	**235**
	n	220 (Week 26) 207 (Week 52)	217 (Week 26) 206 (Week 52)
	LS Mean %CfB	1.878 (Week 26) 2.653 (Week 52)	1.274 (Week 26) 2.322 (Week 52)
	SE	0.6842 (Week 26) 0.6939 (Week 52)	0.6815 (Week 26) 0.6915 (Week 52)
Effect estimate per comparison	The % CfB in the total femoral neck BMD by DXA*	**Comparison groups**	**Difference between Bmab 1000 and Prolia**
		LS mean difference (Bmab 1000 - Prolia)	0.604 (Week 26) 0.331 (Week 52)
		95% CI	0.022 ,1.186 (Week 26) -0.338 ,1.000 (Week 52)
	Abbreviations: BMD=Bone Mineral Density (g/cm2); % CfB=Percentage Change from Baseline; CI=Confidence Interval; LS=Least Squares; SE=Standard Error Note: The MMRM model was used, which included terms for visit by treatment, baseline BMD at the femoral neck (as a covariate), and classification variables for: region, age, prior use of bisphosphonates. Patient is included as a random effect. *: Difference in means (Bmab 1000 minus Prolia) in % CfB in Femoral Neck BMD by DXA at weeks 26 and 52 in postmenopausal women with osteoporosis treated with subcutaneous injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt		

	of any other medications affecting bones except for vitamin D and calcium supplements		
Notes	None		
Analysis description	**Secondary analysis:** Incidence of fracture up to Week 52		
Analysis population and time point description	**Safety analysis set (SAF):** The SAF consisted of all randomised patients who received at least 1 administration of study drug. The SAF was used for all safety and immunogenicity analyses. In the SAF, patients were analysed per the actual treatment received. Analysis was conducted at Week 26 and Week 52.		
Descriptive statistics and estimate variability	**Treatment group**	**Bmab 1000**	**Prolia**
	Number of patients	**238**	**240**
	Lateral spine X-ray performed n (%)	222 (93.3) (Week 26) 173 (72.7) (Week 52)	213 (88.8) (Week 26) 175 (72.9) (Week 52)
	Fractures detected [a] Yes	1 (0.5) (Week 26) 1 (0.5) (Week 52)	0 (Week 26) 0 (Week 52)
	Type of Fracture [b] Vertebrae	1 (100) (Week 26) 1 (100) (Week 52)	0 (Week 26) 0 (Week 52)
	Vertebrae Genant Grade [c] Moderate Mild	1 (100) (Week 26) 1 (100) (Week 52)	0 (Week 26) 0 (Week 52)
	[a]: Percentages are calculated out of those who have had Lateral spine X-ray performed [b]: Percentages are calculated out of those who have had a fracture detected and Lateral spine X-ray performed. All recorded fractures are vertebrae [c]: Percentages are calculated out of those who have had a vertebrae fracture detected. A patient is counted once for the most severe grading, if the patient had multiple fractures detected.		
Notes	None		

2.5.5.4. Clinical studies in special populations

Not applicable.

2.5.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.5.5.7. Supportive study(ies)

Not applicable.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme of Bmab 1000 to demonstrate biosimilarity to the reference product (Xgeva/Prolia) included one phase 1 study (Study B1000-NHV-01-G-01) and one phase 3 study (Study B1000-PMO-03-G-02). The phase 1 study was a randomised, double-blind, two-arm, single-dose, parallel-group study to compare the pharmacokinetics, pharmacodynamics, safety, and tolerability of Bmab 1000 and Prolia in normal healthy volunteers (n=189). The phase 3 study was a randomised, double-blind, multicentre, parallel-arm study to compare the efficacy, pharmacodynamics, safety, and immunogenicity between Bmab 1000 and Prolia in postmenopausal women with osteoporosis (n=479).

Overall, in principle the studies outlined support approval of a biosimilar MA if comparability in physicochemical and functional parameters in quality is obtained together with clinical similarity in the given studies. In accordance with the current guidance, not all indications should be studied if comparability of the product vs the reference product can be shown for one indication. Furthermore, the outlined studies are in line with other recently approved biosimilar medicines for Prolia and Xgeva and in accordance with the advices received from EMA. The applicant has received advice from EMA (FDA and PMDA) for the clinical development programme in issues of suitable patient population, equivalence margins, endpoints, and study duration.

In both clinical studies, the applicant has used US-approved and not EU-approved Prolia as reference. As according to EMA Scientific Advice, this is endorsed provided that analytical similarity of EU and US products is also shown.

Dosing in the studies: The PK study (study B1000-NHV-01-G-01) used a single, subcutaneous therapeutic dose of 60 mg. The phase 3 clinical study (study B1000-PMO-03-G-02) included three doses of the study treatment on Day 1 and at Weeks 26 and 52 of 60 mg subcutaneous Prolia or Bmab 1000. Below is a discussion of the phase 3 study B1000-PMO-03-G-02 done to show biosimilarity between Bmab 1000 and Prolia.

Study design

Study B1000-PMO-03-G-02 was a Phase 3, randomised, double-blind, active-controlled, parallel group in post-menopausal women with osteoporosis. The study consisted of three periods: a screening period (up to 4 weeks/28 days); a double-blind, active-controlled treatment period (Week 0-52) (Part 1); and a transition period (Week 52-78) (Part 2). Patients were randomly assigned (1:1) to receive two SC injections of either Bmab 1000-P (60 mg) or Prolia (60 mg) at Week 0 and at Week 26 with a follow up of further 26 weeks after 2nd dose (Part 1 of the study; Week 0-52)). Part 1 was followed by a re-randomisation step for patients in the Prolia group at Week 52 for switching therapy between Bmab 1000-P and Prolia (Part 2). The duration of the main treatment period of 12 months (Part 1) 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 Part 2 (Transition Period; Week 52-78)) is another 6 months, and allows assessment of switching from Prolia to Bmab 1000-P, but also provides additional PK, PD, efficacy and safety data for those patients who continue on the same treatment as initially assigned. The clinical phase of Part 2 of

the study has been completed with the last patient last visit on 12 June 2024. The overall study design is deemed acceptable. The final CRS including week 78 data was submitted during the procedure.

Study population

The study enrolled postmenopausal women aged ≥55 and <80 years, with body weight ≥50 to <90 kg at screening; with evidence of osteoporosis as assessed by lumbar spine (L1-L4) absolute BMD corresponding to a T-score classification ≤−2.5 and ≥−4.0 and at least 3 vertebrae in the L1-L4 region and at least 1 hip joint is evaluable by DXA. Patients were excluded from the study if their T-score was <−4.0 at the lumbar spine, total hip, or femoral neck; had a known history of previous exposure to denosumab or known hypersensitivity to denosumab or its constituents or latex allergy or hereditary problems of fructose intolerance; used any biologic drugs within 90 days or within 5 half-lives of the drug, whichever was longer; or used systemic glucocorticosteroids or other bone active drugs within 3 months of screening. 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 choice of ambulatory postmenopausal women aged 55 and 80 years with evidence of osteoporosis (defined as a T-score classification of −2.5 to −4.0) was agreed with in a Scientific Advice procedure (EMEA/H/SA/4398/1/2020/III). The setting of lower and upper weight limits in the inclusion criteria is endorsed to enhance the homogeneity of the study population since body weight may be related to the baseline BMD, and may thus influence the treatment effect.

As 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, the age range from 55 to 80 years may introduce heterogeneity in disease severity. Thus, stratification for age was recommended in a Scientific Advice. The recommendation 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). Total exclusion of subjects with prior use of oral PBs would enhance homogeneity of the study population but would admittedly hinder recruitment. Thus, as discussed in Scientific Advice and Follow-up procedures, prior BP therapy was used as stratification factor. The exclusion criteria on other bone-modifying treatments including relevant wash-out periods were discussed during the Scientific Advice procedure and are acceptable.

Overall, postmenopausal women within the chosen age range are agreed to be a relevant homogenous and sensitive patient population to assess the biosimilarity between Bmab 1000 and the reference product in terms of efficacy. The selection criteria are relevant and acceptable and in line with those of the Prolia SmPC for the studied population and take into account contraindications and special warnings for Prolia.

Trial intervention

Bmab 1000 (60 mg) or US-Prolia (60 mg) was administered SC, preferably in the abdomen using a PFS of 60 mg/mL solution for injection on Day 1, and at Week 26. Whenever possible, the same injection site was used for the study drug administration. Prior to dosing at Week 52, patients in the Prolia arm were randomly assigned again in a ratio of 1:1 to receive either Bmab 1000 or Prolia at Week 52. All patients who were initially randomly assigned to the Bmab 1000 on Week 0 (Day 1) continued their treatment. 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 the reference product.

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

Concomitant therapies

Prohibited concomitant medications include denosumab or any other biologic treatment, treatments for osteoporosis such as bisphosphonates, other bone active drugs and long term systemic glucocorticosteroids. Prohibited concomitant medication and accepted washout periods have been described in the study protocol and were part of the exclusion criteria. Any concomitant medication deemed necessary for the welfare of the participant during the study was allowed at the discretion of the investigator. Listed prohibited concomitant medications are considered appropriate and, therefore, acceptable. Calcium and vitamin D supplements were allowed during the study. Washout period for oral bisphosphonates was 1 year and eligible patients could not have received bisphosphonates for more than 2 years. Previous intravenous bisphosphonate was not allowed. Note that randomisation was stratified for use of bisphosphonates.

Study assessment

Dual-energy X-ray absorptiometry (DXA)

BMD was assessed by DXA scan at Screening, Week 26 (Day 183 ± 7 Days) and Week 52 (Day 365 ± 7 Days) during the main treatment period as well as Week 78 (Day 547 ± 7 Days) at End of Study.

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.

According to the efficacy data, there were exclusions of individual vertebral levels in the lumbar spine assessment due to several reasons as well as corrections of the BMD values. Total spine BMD was calculated on the evaluable vertebral levels (without excluded levels) and BMD results only include corrected values. The applicant presented vertebral exclusions per visit by treatment group during the procedure. Exclusions were observed in a similar proportion in each treatment arm.

X-ray

The potential of therapeutic intervention to prevent vertebral fractures was assessed performing X-ray of the lateral spine at screening, weeks 26 and 52 and as required for confirmation of suspected fractures. All lateral spine X-rays were assessed at a central imaging centre. Any new fractures confirmed by the central imaging vendor have been recorded as an adverse event. Only fractures confirmed by the central imaging centre have been considered for the analysis.

A new vertebral fracture is defined as an increase of at least one grade in any vertebra from T4 to L4 that was normal at screening (Cummings et al., 2009). The vertebral fracture will be assessed by semi-quantitative grading at a central imaging vendor (Genant et al., 1993): Grade 0 = no fracture; Grade 1 = mild fracture, 20% to 25% reduction in vertebral height (anterior, middle, or posterior); Grade 2 = moderate fracture, greater than 25% to 40% reduction in any height; Grade 3 = severe fracture, greater than 40% reduction in any height. Information about a new nonvertebral fracture (e.g., details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture have been recorded during the study. A copy of other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the patient's individual source documents and have been submitted to the central imaging vendor for confirmation of fracture. The description of radiographic assessments is considered acceptable.

Randomisation and Blinding

An IWRS was used for the randomisation. The responsible biostatistician generated the randomisation schedule using statistical software for IWRS, which linked sequential patient randomisation numbers to treatment codes.

Randomisation for Part 1 (double-blind active-controlled period)

Patients were randomly assigned at the baseline/randomisation visit (Week 0/Day 1) to receive Bmab 1000 or Prolia using a 1:1 allocation ratio. The randomisation to treatment assignment was stratified by geographical region (US, Europe), prior use of bisphosphonate treatment (Yes, No) and age of the patient (<65, ≥65 years). The stratification factors were discussed in a Scientific Advice procedure and are deemed acceptable.

Re-Randomisation for Part 2 (transition period)

Prior to dosing at Week 52, patients in the Prolia arm were randomly assigned again in a ratio of 1:1 to receive either Bmab 1000 or Prolia at Week 52. To maintain the blinding, patients in the Bmab 1000 arm also underwent re-randomisation; however, they continued to receive Bmab 1000.

Blinding and unblinding

This study was described to be double-blind remaining blinded until the EoS (Week 78).

When all patients completed the Double-Blind Active-Controlled Period (Part 1) assessments and data were available, the study drug assignment was partly unblinded to predefined unblinded sponsor and CRO personnel. After unblinding the predefined sponsor and CRO personnel, the Week 52 CSR analysis was performed.

At Week 52, the investigators, patients, and other members of staff involved with the study remained blinded. Randomisation data, including any documentation identifying the treatment allocation, was kept strictly confidential. An unblinding plan gives the full details of who were unblinded at Week 52 and how the flow of information was being handled. Bmab 1000 was supplied as PFS without needle safety guard, whereas Prolia was supplied as PFS with needle safety guard. Thus, blinding from the primary packaging was not feasible, but the blinding was maintained at the secondary packaging level with similar packaging for both the products. Therefore, 2 different teams, i.e. blinded and unblinded teams, were assigned to maintain the blinding and handling of the study treatment administration. The predefined, unblinded site staff administered the study medication injections in such a manner that the patient remained blinded (e.g. blindfold, screen, or similar method during the dosing procedure so that the injection syringe was not visible to the patient). Blinded staff was not involved in any activities about the receipt, handling, or administration of study medication. The process of blinding is adequately described and considered acceptable. Blinding was not lifted until all final clinical data was entered and locked into a database.

Objectives, endpoints and estimands

<u>Primary objective and endpoint</u>

The applicant chose %CfB in lumbar spine BMD at week 52 and AUEC of %CfB in sCTX from baseline to week 26 as co-primary endpoint.

The estimated mean difference in %CfB in the lumbar spine BMD was presented with 95% CI at each time point. The primary efficacy analysis was based on the mFAS, and therefore, did not use data after any dosing errors, treatment discontinuation, or receipt of any other medications affecting bone health (except for supplements).

The primary estimand 1a-EMA (co-primary efficacy) is based on hypothetical strategies for the intercurrent events treatment discontinuation (related or unrelated), dosing deviation, death and medications affecting bone health (except for supplements). The same applies for estimand 1b (co-primary PD) with the exception of treatment discontinuations not being applicable as the PD endpoint is measured before the second dose. For both estimands, a treatment policy strategy applies for supplements and ADAs. For key secondary estimand (estimand 1a-US FDA) a composite strategy applies for death and a treatment policy strategy for related treatment discontinuations as well as dosing deviations, medications affecting bones, supplements and ADAs.

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 is appropriate.

The equivalence margin of (-1.45%, 1.45%) was derived from a meta-analysis of previous similar studies (Bone et al., 2008, Cummings et al., 2009 (pivotal FREEDOM trial), McClung et al., 2006), which gave the pooled denosumab treatment effect of 5.35% (95% CI: 4.83% to 5.87%). Based on the lower bound of the 95% CI, a 1.45% margin preserved 70% of the treatment effect (0.3 × 4.83%). Equivalence would be established if the 95% CI of the difference (Test-Reference) in mean percent change in the lumbar spine BMD from baseline to Week 52 was within the equivalence margin of (-1.45%, 1.45%).

sCTX was a co-primary endpoint with BMD. The 95% CI was applied for the ratio of geometric means (Bmab 1000/Prolia) in AUEC in sCTX to establish the equivalence with equivalence limits of 80.00% to 125.00% without further justification. Pharmacodynamic comparability between Bmab 1000 and Prolia were to be concluded if the 95% CI around the geometric mean ratios for AUEC lie entirely within 80.00% to 125.00%.

Overall, the endpoints of the study are endorsed, and in line with the scientific advices.

Secondary objective and endpoint

The secondary endpoints %CfB in the lumbar spine BMD at Week 26, %CfB in the total hip and femoral neck BMD at Weeks 26 and 52 and incidence of fracture up to Week 52 are considered clinically relevant and were implemented as discussed in a Scientific Advice procedure to support the primary efficacy endpoint. After the transition (Part 2) the same endpoints were assessed at week 78 (not provided). The secondary pharmacodynamic endpoints are also considered relevant and sufficient to support further the co-primary pharmacodynamic endpoint.

Efficacy data and additional analyses

Results

The original protocol version 1.0 (06 January 2022) was amended twice. Only amendment 2 was submitted after study initiation. Nevertheless, the amendments are not considered to have an impact on the study integrity.

Participant flow and numbers analysed

Numbers of patients randomised and treated were comparable between treatment groups. Slightly more patients completed Part 1 of the study in the Bmab 1000 arm (Bmab 1000 vs. Prolia: 218 (91.6%) vs. 208 patients (86.3%)). With submission of responses, the applicant provided information regarding the number of re-screened subjects (see Table 22). Re-screened and randomised patients were distributed equally between treatment groups.
Fewer patients discontinued from study prior to Week 52 in the Bmab 1000 group (Bmab 1000 vs. Prolia: 19 (8.0%) vs. 33 (13.7%)) and fewer patients discontinued from treatment in the Bmab 1000 arm (Bmab 1000 vs. Prolia: 20 (8.4%) vs. 32 (13.3%)). With submission of responses, the applicant conducted a chi-square test to compare the relative frequencies in the two treatment arms. However, the informative value of this comparison is considered to be very limited. The applicant furthermore referred to the sensitivity analyses provided in the CSR. It is acknowledged, that sensitivity analyses have been performed, in which the robustness of the results have get stressed by adding plus or minus 1.45 to the imputed values in the Bmab group. In this regard, the applicant is asked to additionally conduct a tipping point analysis for the primary estimand 1a-EMA (co-primary efficacy), in which, in one scenario, a delta is added/subtracted to the imputed values in the Bmab group (hence, for every patient who discontinued treatment prior to Week 52 in the Bmab group, irrespective of whether the value was missing or observed and then excluded due to the hypothetical intercurrent event strategy) and in another scenario, a delta is added/subtracted to the imputed values in the Prolia group. Therefore, the applicant should in each case consider increasing resp. decreasing delta from 1.45 resp. -1.45 on until the margin isn't contained in the 95% confidence interval anymore. During the procedure, the applicant provided a tipping point analysis supporting the robustness of the results of the primary analysis, especially with regard to the differences in the drop-out rates (discontinuation from study/ study treatment) in the Prolia arm compared to the Bmab1000 arm. Discrepancies in the dossier between tables were clarified concerning reasons for the discontinuation of patients from treatment prior to week 26. The applicant was further able to clarify the deviations in patient numbers and missing data. The primary reason for discontinuation from study prior to week 52 was "withdrawal of consent", which was reported more frequently in the Prolia group.

The FAS included patients who met eligibility criteria and received at least one dose of study treatment. Patients with the significant protocol deviation "Selection criteria not met" were excluded from the FAS. It consists of a total of patients (Bmab 1000:237, Prolia: 235). One patient excluded from the FAS set for having received no study intervention in the Prolia arm, whereas the remaining was due to patients not being eligible after randomisation. The patient numbers in the analysis sets are comprehensible.

The Modified Full Analysis Set (mFAS) was used for the co-primary endpoints and was defined as all patients in the FAS population but without data observed after the first occurrence of predefined intercurrent events e.g., missing dose, errors or deviations in dosing, or receipt of prohibited medication (estimand 1a for the co-primary efficacy endpoint and estimand 1b for co-primary PD endpoint, utilises a mostly hypothetical approach). The term mFAS was hence used by the applicant to denote a dataset., it includes the same patients as the FAS. Estimand 1a assumed that all patients received 2 doses without error, whereas estimand 1b needed only one dose. For the co-primary endpoint of %CfB in lumbar spine BMD 207 observations were available for the analysis in the Bmab 1000 group, and 206 in the Prolia group Numbers for the mFAS population for the co-primary endpoint of AUEC of %cfb sCTX from baseline to 26 weeks is 223 in the Bmab 1000 analyses set and 213 in the Prolia analysis set. The strategy is acceptable.

Sample size calculation

Approximately 480 women with postmenopausal osteoporosis were planned to be enrolled 1:1 (240 participants per arm, including 15% drop-out) in the study, with a power of 80% and 2 one-sided tests at 2.5% level of significance.

The sample size calculation was based on percent change from baseline (%CfB) in the lumbar spine BMD by DXA at Week 52. Assuming that the treatments are equally effective, equivalence margin was set at (-1.45%, 1.45%) with a 95% confidence interval (CI) of the difference in mean percent change in the lumbar spine BMD from baseline. Equivalence margin was derived from meta-analysis of previous similar studies, which gave a pooled denosumab treatment effect 5.35% (95% CI: 4.83% to 5.87%). The power and sample size calculations are adequate and can be followed.

Protocol deviations

Significant protocol deviations were comparable between treatment groups (Bmab 1000 vs. Prolia: 47 (19.7%) vs. 49 (20.3%). Significant protocol deviations were defined as nonadherence to the protocol or to local regulations or ICH GCP Guidelines that could or could not result in a significant, additional risk to the patient or impacts the integrity of study data. Most deviations (9,4%) were related to visit scheduling. Other deviations included concomitant or prohibited medications in 12 (5%) patients in the Bmab 1000 group and in 6 (2.5%) patients in the Prolia group. Missing endpoint assessment in 2 (0.8%) patients in the Bmab 1000 group and an 8 (3.3%) in the Prolia group. There were comparable numbers of ICH/ GCP deviations (Bmab 1000 vs. Prolia (13 (5.5%) vs. 10 (4.1%)). The protocol deviation "Selection criteria not met" led to exclusion from the FAS. The deviations related to investigators oversight included failure to report SAE or SAE follow-up information within 24 hours of awareness of the SAE to the PVG (in 2 patients) and laboratory reports not reviewed within 10 business days (in 4 patients). Deviations in "Prohibited concomitant medications" numbers between different tables were clarified with submission of responses.

In total 238 patients were randomised to Bmab and 241 to Prolia. Numbers of patients for the mFAS population for the co-primary efficacy endpoint is Bmab 1000:207, Prolia: 206. The applicant clarified that the number of patients included into the primary analysis of the primary estimand-1a EMA was 472 with n=237 in the Bmab 1000 group and n=235 in the Prolia group with 40 patients for whom BDM observation was missing at Week 52 (19 (8.0%) in Bmab 1000 resp. 21 (8.7%) in Prolia group) and additionally 19 patients (11 (4.6%) in Bmab 1000 vs. 8 (3.3%) in Prolia group) for whom the BMD values was collected but removed due to the occurrence of an ICE (for further details see below).

Intercurrent Events (ICEs)

Six different Intercurrent Events were defined with strategies to handle these ICEs. The approach is in principle acceptable and endorsed. The distribution of ICEs is balanced between treatment groups. Based on the submitted documents, it was unclear, whether and how definitions of ICEs are overlapping with or should be reflected in significant protocol deviations and if there were consequences for the reporting of significant protocol deviations for analysis sets or the analysis. With submission of responses, the applicant clarified patient numbers and differences between ICEs and protocol deviations adequately.

Patient disposition

In total 1219 was screened and hereof a total of 479 patients were included and randomised, 238 patients to Bmab 1000 and 241 patients to Prolia. Hereof all but one patient in the Prolia arm received study treatment at week 0. A rather high proportion of patients had screenings failure (n=740), the applicant should overview the reasons for screenings failure and address if it could have an impact on the validity of the results. With submission of responses, the applicant clarified the reasons for screening failures. The most frequent reason for screening failures was T-score higher or lower than requested in the eligibility criteria (n=299). Another common reason was in the category "Signed ICF, ambulatory, able to follow study instructions and comply with the protocol requirements." (n=184).

In the Bmab 1000 arm, 91.6% of the patients completed the double-blind, active-controlled period, whereas fewer 86.3% of the patients in the Prolia group completed the double-blind period. As early as

week 26, more patients discontinued from treatment in the Prolia arm (11.2%) as compared to (6.7%) in the Bmab 1000 arm. Prior to week 52, 13.3% of patients discontinued treatment in the Prolia arm compared to 8.4% of patients in the Bmab 1000 arm. The applicant should address if the difference in proportion of patients who completed treatment until week 26 and week 52, could have influenced the results of the co-primary PD endpoint and co-primary efficacy endpoint respectively. With submission of responses, the applicant conducted a chi-square test to compare the relative frequencies in the two treatment arms. However, the informative value of this comparison is considered to be very limited. The applicant furthermore referred to the sensitivity analyses provided in the CSR. It is acknowledged, that sensitivity analyses have been performed, in which the robustness of the results have get stressed by adding plus or minus 1.45 to the imputed values in the Bmab group. In this regard, the applicant was asked to additionally conduct a tipping point analysis, in which, in one scenario, a delta is added to the imputed values in the Bmab group and in another scenario, a delta is added to the imputed values in the Prolia group. An updated and corrected tipping point analysis was submitted supporting the robustness of the results of the primary analysis, especially with regard to the differences in the drop-out rates (discontinuation from study/ study treatment) in the Prolia arm compared to the Bmab1000 arm.

Demographic Data

The demographic data was well balanced between treatment groups. The mean age for Bmab 1000 vs. Prolia was 66.7 vs. 66.5 years. Numbers of patients in age subgroups (≥55 to <65 years and ≥65 to < 80 years) were comparable between treatment arms. BMD is highly related to age, why an age range from 55 to 80 years may induce some heterogeneity in the study population also due to age-related comorbidities. However, as noted in the table of baseline characteristics, the two treatment groups had comparable age (mean, median and range) and a comparable proportion were > 65 years of age, why this point will not be further pursued. Most of the patients were "White" (Bmab 1000 vs. Prolia: 237 (99.6%) vs. 241 (100%)), "Not Hispanic or Latino" (Bmab 1000 vs. Prolia: 236 (99.2%) vs. 241 (100%). Data for baseline height, weight and BMI were comparable. Height and weight were also comparable, as well as years since menopause (17.7 years in Bmab 1000 and 17.0 years in Prolia group). However, the lower range of years since menopause is 0.0 years in the Bmab 1000 arm, as also menopause in the baseline overview applies to only to 1.3% vs. 0.8% (Bmab 1000 vs. Prolia). With submission of responses, the applicant confirmed that all studied patients were postmenopausal women according to the eligibility criteria. Furthermore, the definition of "postmenopausal" included patients after 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, thus explaining the lower range of years with 0.0 years.

According to scientific literature, smoking has a significant effect on bone mineral density. Thus, the applicant was asked to provide information on the smoking status/history of patients at baseline by treatment group or justify why this factor has not been assessed. With submission of responses, the applicant clarified that information concerning baseline smoking status/history was not collected and thus, cannot be provided. As indicated by the applicant, negative effects of smoking on BMD are reported in the scientific literature. Thus, due to the missing data, a heterogeneity in the current patient population cannot be excluded and confirmation of an equal distribution would have been reassuring. But it is agreed with the applicant that the randomisation per se should account for baseline imbalance.

Baseline disease characteristics

Baseline mean (SD) lumbar spine BMD T-score was -3.056 (0.3824) in the Bmab 1000 group and -3.071 (0.3815) in the Prolia group. Around half of the patients had lumbar spine BMD T-score of ≤-3 and >-3 in both groups. Total hip and femoral neck bone mineral density was also comparable between groups. A total of 97 (20.3%) patients had fractures at baseline.

Baseline disease characteristics are considered well balanced between treatment groups.

Medical history

Medical history was provided by treatment group and was comparable between treatment groups with SOC group "Metabolism and Nutrition Disorders" being the most reported disorder. Only 44.5% vs. 45.4% of patients (Bmab 1000 vs. Prolia) showed "Musculoskeletal and connective tissue disorders" in the medical history and osteoporosis was only present in 1 subject in the Bmab 1000 group (0.4%) and not present in the Prolia group. Furthermore, menopause and postmenopause applied only to 1.3% vs. 0.8% (Bmab 1000 vs. Prolia) whereas mean years since menopause were indicated as 17.7 vs. 17.0 years (Bmab 1000 vs. Prolia). With submission of responses, the applicant confirmed that all studied patients were postmenopausal women according to the eligibility criteria. It was further clarified that disease characteristics as defined in the indication were not required to be captured under medical history in the eCRF (see above).

Prior medication

The most common prior medications were vitamin D and analogues, Covid-19 vaccines and calcium. Bisphosphonates have been used by 18 (3.8%) patients. Other listed medications were used at percentages lower than 1.3% and do most likely not have an impact on the biosimilarity assessment.

(Prohibited) Concomitant Medication in the Double-blind Active-controlled Period

Numbers of "Prohibited concomitant medications" are deviating between Table 14.1.7.3.1 "Prohibited Concomitant Medications" (number of subjects with at least one prohibited concomitant medication: 10 vs. 7 (Bmab 1000 vs. Prolia)) and Table 5-3 "Significant Protocol Deviation" (number of subjects with at least one protocol deviation – concomitant or prohibited medication: 12 vs. 6 (Bmab 1000 vs. 6)). With submission of responses, the applicant clarified deviations in patient numbers. Overall, total numbers of prohibited concomitant medications as well as numbers of subjects with at least one prohibited concomitant medication were low (Bmab 1000 vs. Prolia: 10 (4.2%) vs. 7 (2.9%)). 2.5% of patients in each treatment arm received medications from the heparin group and gabapentinoids were administered in 1.7% vs. 0.4% (Bmab 1000 vs. Prolia) of patients. Overall, numbers were low.

Co-administration of Calcium and Vitamin D

Most patients received vitamin D and calcium supplementation. Data was missing from 3 patients in the Prolia group. The majority of patients was vitamin D compliant (Bmab 1000 vs. Prolia: 92.0% vs. 86.3%) as well as calcium compliant (Bmab 1000 vs. Prolia: 91.6% vs. 86.7%). Compliance was defined compliant if overall supplement compliance taken on all scheduled visits performed within the Double-blind Active-controlled Period is greater than or equal to 80% and less than or equal to 120%. According to the protocol, patients should receive daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D (via any route of administration) from randomisation until the EoS visit (Week 78). This is in accordance with the Prolia SmPC. Number of patients being vitamin D and calcium compliant are comparable between groups and are acceptable.

Primary efficacy endpoint

The applicant assessed therapeutic equivalence in terms of efficacy and PD if 95% CI for the mean difference in %CfB at Week 52 in the lumbar spine BMD falls within predefined equivalence margins of (-1.45%, 1.45%), and the 95% CI for the geometric means ratio (Bmab 1000/Prolia) of sCTX AUEC up to 26 weeks falls completely within the range of 80.00% to 125.00%. The primary analysis was conducted on the modified analysis data set (mFAS), which included a data record at each time point for all patients in the FAS (with n=237 patients in the Bmab100 group and 235 patients in the Prolia group) but excluded data observed after the first occurrence of those ICEs where a hypothetical strategy was taken.

For the primary estimand (estimand 1a-EMA), at Week 52, the difference in LS means (95% CI) in %CfB in the lumbar spine BMD between the Bmab 1000 and Prolia groups was 0.599 (-0.107, 1.306). The 95% CI of the difference in LS means %CfB in the lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%), indicating therapeutic equivalence of Bmab 1000 to Prolia was met in terms of efficacy endpoint. The primary estimand "estimand 1a-EMA" addressed a mostly hypothetical approach. Upon request, the applicant clarified that 52 patients had at least one of the ICE's for which a hypothetical strategy was planned (ICE1-ICE5) during the double-blind treatment period considered to impact the Week 52 BMD. BMD was observed in 19 of these 52 patients and was subsequently excluded (17 patients having medications affecting bones and 5 patients receiving only one dose of study drug). The 95% CI (97.74% to 110.93%) for the geometric LS mean ratio of sCTX AUEC up to 26 weeks were contained entirely within the predefined acceptance limits (80.00% to 125.00%), indicating Bmab 1000 was pharmacodynamically equivalent to Prolia.

For the key secondary estimand, the difference in LS means (90% CI) at week 52 in %CfB in the lumbar spine BMD between the Bmab 1000 and Prolia groups was 0.593 (0.015, 1.171) (delta 0 i.e., no penalty, the primary estimate). The 90% CI of the difference in LS means %CfB in the lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%). Upon request, the applicant also provided a 95% confidence given by (-0.086, 1.289), which is as well entirely contained in the predefined margin. The results of the sensitivity analyses were similar to the results of the main analyses. Using MI under MAR approach, the LS means difference (95% CI) in %CfB at Week 52 in the lumbar spine BMD between the Bmab 1000 and Prolia groups was 0.568 (-0.127, 1.262). Using MI under MAR approach with added penalty (delta) in the Bmab 1000 group only, the LS means difference (95% CI) in %CfB in the lumbar spine BMD at Week 52 between the Bmab 1000 and Prolia groups was 0.385 (-0.312, 1.081) for delta -1.45 (non-inferiority to Prolia) and 0.751 (0.053, 1.449) for delta 1.45 (non-superiority to Prolia).

Supplementary analysis of the primary estimand investigating assumptions of normality (assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones) supported the main estimation results as the 95% CI of the difference in LS means %CfB in the lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%) (ratio of geometric means: 1.006 with 95% CI: 0.999, 1.013).

Secondary efficacy endpoints (Part 1)

The applicant assessed the difference in means in %CfB in the lumbar spine BMD at Week 26, in the total hip and femoral neck BMD at Weeks 26 and 52 and the incidence of fracture up to week 52 as secondary efficacy endpoints.

At Week 26, the mean %CfB in the lumbar spine BMD was similar for both the Bmab 1000 and Prolia groups (3.576 and 3.365, respectively). From Week 26 to Week 52, the mean %CfB in the lumbar spine BMD continued to increase and was similar for both the Bmab 1000 and Prolia groups (LS Mean Difference: 0.599 with 95% CI: -0.107, 1.306).

For both the Bmab 1000 and Prolia groups, the mean %CfB in the total hip and femoral neck BMD increased over time till Week 52. At Week 26, the mean %CfB in the femoral neck BMD was lower for the Prolia group than the Bmab 1000 group; however, at Week 52 the mean %CfB in the total hip and femoral neck BMD were similar for both Bmab 1000 and Prolia groups. The LS means difference (95% CI) in %CfB in the total hip and femoral neck BMD between Bmab 1000 and Prolia at Week 26 was 0.255 (-0.162, 0.671) and 0.604 (0.022, 1.186), respectively, and at Week 52, it was 0.083 (-0.364, 0.531) and 0.331 (-0.338, 1.000), respectively.

No patient in the Prolia group had any fracture event at Weeks 26 and 52. At Week 26, in the Bmab 1000 group, one patient had a thoracic vertebrae fracture with Genant grade of moderate. At Week 52,

in the Bmab 1000 group, one patient had a lumbar vertebrae fracture with Genant grade of mild. As numbers are low, the difference is not concerning.

A high proportion of patients had treatment emergent ADAs (87%), but incidence was comparable between both the Bmab 1000 and Prolia groups treatment groups (89.5% and 84.6% respectively). Very few patients had neutralizing antibodies n=12, (7 in the Bmab 1000 group and 5 in the Prolia group). Results on the primary efficacy endpoint by ADA status showed that the results in the ADA-positive patients remained similar to the overall main study results and vice versa.

Secondary efficacy endpoints (Part 2)

The Lumbar Spine BMD from Week 52 to Week 78 was assessed after re-randomisation of patients in the Prolia group to Bmab 1000 or Prolia at Week 52. Results from the Transition Period (Week 52 to Week 78) are in line with results up to Week 52 concluding that the transition from Prolia to Bmab 1000 did not negatively influence the %CfB in the lumbar spine BMD when analysed separate from Week 52 data.

Furthermore, the lumbar spine, hip and femoral neck BMD were evaluated from Day 1 to Week 78. The LS mean %CfB (from Week 52 to Week 78) in the lumbar spine BMD was comparable for "Prolia to Prolia" and "Bmab 1000 to Bmab 1000" treatment groups (1.328 and 0.807; 90% CI: -1.085, 0.044). Results are also supportive for similar efficacy after switch from Prolia to Bmab 1000 (%CfB (from Week 52 to Week 78) in the lumbar spine BMD in "Prolia to Prolia" and "Prolia to Bmab 1000" were 1.328 and 1.130, respectively (90% CI: -0.859, 0.464). According to the final study report, no additional fractures were reported from Week 52 to Week 78.

2.5.7. Conclusions on clinical efficacy

In study B1000-PMO-03-G-02, 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 Bmab 1000 and the US-Prolia group was 0.599 (95% CI: -0.107, 1.306). Thus, the 95% CI was contained within the predefined margin of [-1.45, 1.45], supporting the claim of biosimilarity. Furthermore, AUEC of %CfB sCTX0-m6 until Week 26 has been addressed to as co-primary endpoint. Results showed that point estimate of geometric means and corresponding 95% CI of the ratio (Bmab 1000/US-Prolia) was contained within the 80% to 125% equivalence margin, supporting the claim of biosimilarity.

All sensitivity analyses confirmed the robustness of the results of the primary endpoint analysis.

The secondary efficacy analysis of %CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures did not reveal clinically remarkable difference between Bmab 1000 and Prolia and showed similar improvement in BMD of all vertebral and non-vertebral structures over time (Week 26 to Week 52) being supportive for the primary endpoint outcome. The same applies for efficacy data provided with submission of responses covering data up to Week 78.

In summary, the provided efficacy data support the biosimilarity between Bmab 1000 and US-Prolia.

2.5.8. Clinical safety

The safety of Bmab 1000 versus Prolia has been assessed in two clinical studies: a Phase 1 study in healthy subjects (B1000-NHV-01-G-01), and a Phase 3 study in postmenopausal women with osteoporosis (PMO) (B1000-PMO-03-G-02).

The safety analysis set (SAF), defined as all randomised patients who received at least 1 administration of study drug, comprised 478 women in study B1000-PMO-03-G-02 and 189 healthy volunteers (male and female) in study B1000-NHV-01-G-01.

Safety data for Part 2 and throughout (Day 1 to week 78) the B1000-PMO-03-G-02 study were summarised based on SAF-TP.

No studies were conducted with the reference product Xgeva as comparator.

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

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

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

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

Safety data collection

All adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1.

Owing to differences between the two studies in terms of the design, patient population, treatment duration, and data collection, an integrated analysis of the safety results was not performed.

Study B1000-NHV-01-G-01

Safety and tolerability of Bmab 1000 compared to Prolia was assessed in terms of AEs, vital signs, physical examination, 12-lead electrocardiogram (ECG), safety laboratory (including biochemistry, haematology, and urinalysis) and blood samples for analysis of anti-drug antibodies (ADAs).

Participants left the study centre after completion of all required assessments on D10 and followed up on outpatient basis till the End of Study (EOS) visit at Week 36.

Study B1000-PMO-03-G-02 – Part 1 (Double-Blind Active-Controlled)

The safety and tolerability of two administrations of Bmab 1000 and Prolia were compared 6 months apart. The safety endpoints included incidence of treatment-emergent AEs (TEAEs) and incidence of clinically significant changes in vital signs, physical examinations, laboratory safety tests (haematology, clinical chemistry, and urinalysis), and ECGs up to 6 months after the second dose (0-52 weeks).

Assessments were performed at regular intervals throughout the study period according to the schedule of assessments.

Study B1000-PMO-03-G-02 – Part 2 (Transition)

Part 2 of the study assessed the risk of hypersensitivity and AEs up to 6 months after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia. The safety endpoints included incidence of treatment-emergent AEs (TEAEs) and incidence of clinically significant changes in vital signs, physical examinations, laboratory safety tests and ECGs as well as incidence of deaths and SAEs from the third dose (week 52) up to and including week 78.

2.5.8.1. Patient exposure

Study B1000-NHV-01-G-01

Bmab 1000 was administered as single 60 mg subcutaneous (SC) dose.

189 healthy subjects received the study treatment: 94 subjects received a single dose of 60 mg Bmab 1000 and 95 subjects received a single dose of 60 mg Prolia.
Study B1000-NHV-01-G-01 has been completed on 06 Oct 2023.

Study B1000-PMO-03-G-02 – Part 1 (double-blind active-controlled)

Part 1 (Double-blind, Active-controlled Period [from Week 0 (Day 1) to Week 52 pre-dose*)*: Eligible patients received study treatment (i.e. 60mg denosumab) on Day 1 (Week 0) and at Week 26 (multiple dose).

478 patients received the first dose of the randomised study drug on Day 1; a total of 43 patients discontinued from study prior to Week 26 and 435 (90.8%) patients received the second dose of the randomised study drug on Week 26.

Part 1 (up to 52 weeks) was completed on 19 Dec 2023.

Table 37: Study treatment administration - Double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

	Bmab 1000 (N=238)	Prolia (N=240)	Total (N=478)
Number of subjects receiving Dose 1, n(%)	238 (100)	240 (100)	478 (100)
Number of subjects receiving Dose 2, n(%)	222 (93.3)	213 (88.8)	435 (91.0)
Reason Dose 2 not administered, n(%)			
Adverse Event	0	0	0
Withdrawal of Consent	1 (0.4)	0	1 (0.2)
Investigator Decision	0	0	0
Protocol violation	0	0	0
Lost to Follow-up	0	0	0
Death	0	0	0
Termination of the study by sponsor	0	0	0
Other	1 (0.4)	3 (1.3)	4 (0.8)
Duration of follow-up (days) for subjects receiving Dose 2 [a]			
n	222	213	435
Mean (SD)	181.0 (12.93)	181.2 (17.62)	181.1 (15.39)
Median	183.0	183.0	183.0
Min, Max	85, 211	1, 211	1, 211

Reason Dose 2 not administered is not recorded for patients that discontinued treatment prior to Week 26.
[a] Duration of follow-up (days) is calculated as last visit date up to Week 52 - second dose date + 1.

Source Data: Listing 16.2.5.1

Study B1000-PMO-03-G-02 – Part 2 (transition)

Part 2 (Transition Period from Week 52 to Week 78): Patients who received study treatment with Prolia on Day 1 (Week 0) and at Week 26 were re-randomised before receiving a third dose at Week 52. The

patients in the Prolia group were randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia.

Part 2 (from Week 52 to Week 78) was completed on 12 Jun 2024.

All 426 patients who completed Part 1 of the study entered Part 2 of the study and received the third dose of the study drug.

Patient disposition

Study B1000-NHV-01-G-01

Table 38: Patient disposition - Study B1000-NHV-01-G-01

Status / Reason	US-Licensed Prolia	Bmab 1000	Overall
Randomized	95	94	189
Dosed	95	94	189
Fully administered	95	94	189
Partially administered	0	0	0
Completed study	93	92	185
Discontinued	2	2	4
Withdrawal by participant	1	0	1
Other**	1	2	3

Screened: having signed their informed consent.
* an alternate participant is a participant that met the eligibility criteria but was kept as potential replacement participant if needed.
** Other reasons for withdrawal were lack of compliance with the protocol, loss to follow-up, and personal relocation (leading to consent withdrawal).
Source: Table 14.1.1.1

Study B1000-PMO-03-G-02 -– Part 1 (double-blind active-controlled)

Table 39: Patient disposition - Double-blind active-controlled period (All Randomised Analysis Set) – Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	Prolia (N=241) n (%)	Total (N=479) n (%)
Randomized	238 (100)	241 (100)	479 (100)
Not treated[a]	0	1 (0.4)	1 (0.2)
Received study drug on Day 1[a]	238 (100)	240 (99.6)	478 (99.8)
Received study drug on Week 26[a]	222 (93.3)	213 (88.4)	435 (90.8)
Completed double-blind period[a]	218 (91.6)	208 (86.3)	426 (88.9)
Discontinued from treatment prior to Week 26[a]	16 (6.7)	27 (11.2)	43 (9.0)
Discontinued from treatment prior to Week 52[a]	20 (8.4)	32 (13.3)	52 (10.9)
Discontinued from study prior to Week 52[a]	19 (8.0)	33 (13.7)	52 (10.9)
Primary reasons for discontinuation from treatment prior to Week 52[a, b]			
AE	4 (1.7)	4 (1.7)	8 (1.7)
Calcium/vitamin D non-compliance or inability to tolerate	0	1 (0.4)	1 (0.2)
Investigator decision	1 (0.4)	1 (0.4)	2 (0.4)
Other[a]	15 (6.3)	26 (10.8)	41 (8.6)
Primary reasons for discontinuation from study prior to Week 52[b]			
Withdrawal of consent	13 (5.5)	19 (7.9)	32 (6.7)
Significant protocol violation (non-compliance)	1 (0.4)	3 (1.2)	4 (0.8)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Investigator decision	0	2 (0.8)	2 (0.4)
AE	3 (1.3)	4 (1.7)	7 (1.5)
Other	1 (0.4)	4 (1.7)	5 (1.0)
Doses received by patients who discontinued from study prior to Week 52[c]			
n	19	33	52
0 Dose	0	1 (3.0)	1 (1.9)
1 Dose	16 (84.2)	27 (81.8)	43 (82.7)
2 Doses	3 (15.8)	5 (15.2)	8 (15.4)

Abbreviations: AE, adverse event; EDC, electronic data capture; N, total number of patients; n, number of patients at each level of summarization; IRT, interactive response technology.

Note: For patients who were successfully re-screened, data collected during previous screening was not included in this summary.

There is a discrepancy in the number of randomized patients among IRT (480 patients) and EDC (479 patients), because 1 patient was a screen failure randomized in error. For statistical analyses, this patient was counted as a screen failure, and the patient was not included in the All Randomized Analysis Set.

a. Numbers were displayed according to the planned treatment arm for patients who received at least 1 dose of the study drug, and percentages were based on the number of patients randomized. Only treated patients were included in the counts related to drug discontinuations.

b. The most common "other" reasons for study drug discontinuation prior to Week 52 was "withdrawal of consent".

c. Percentages were based on the number of patients discontinued from study prior to Week 52.

Source: Table 14.1.1.2

Study B1000-PMO-03-G-02 – Part 2 (Transition)

Table 40: Patient disposition - Part 2 (Re-randomised analysis set for transition period)

	Bmab 1000-Bmab 1000 (N=218) n (%)	Prolia-Bmab 1000 (N=104) n (%)	Prolia-Prolia (N=104) n (%)	Total (N=426) n (%)
Total number of patients				
Not treated[a]	0	0	0	0
Treated[b]	218 (100)	104 (100)	104 (100)	426 (100)
Completed Week 78	216 (99.1)	103 (99.0)	103 (99.0)	422 (99.1)
Discontinued from study prior to Week 78[c]	2 (0.9)	1 (1.0)	1 (1.0)	4 (0.9)
Primary reasons for discontinuation from study prior to Week 78[d]				
Withdrawal of consent	2 (0.9)	1 (1.0)	1 (1.0)	4 (0.9)

a. All re-randomized patients who did not received the dose of study drug at Week 52.
b. All re-randomized patients who received a dose of study drug at Week 52.
c. All re-randomized patients who discontinued during Part 2 and prior to Week 78.
d. Percentages were based on the number of patients entering Part 2.
Source: Table 14.1.1.3

2.5.8.2. Adverse events

Study B1000-NHV-01-G-01

Overall, 99 (52.4%) participants experienced at least one TEAE and a total of 221 TEAEs were reported: 110 TEAEs in 47 (50.0%) participants in the Bmab 1000 group and 111 TEAEs in 52 (54.7%) participants in the Prolia group.

Table 41: Summary of adverse events (safety set) - Study B1000-NHV-01-G-01

	US-Licensed Prolia®		Bmab 1000		Overall	
	(N=95)		(N=94)		(N=189)	
	n (%)	nae	n (%)	nae	n (%)	nae
At least one AE	52 (54.7)	113	48 (51.1)	112	100 (52.9)	225
At least one TEAE	52 (54.7)	111	47 (50.0)	110	99 (52.4)	221
At least one TEAE with severity*:						
Grade 1	32 (33.7)	54	38 (40.4)	63	70 (37.0)	117
Grade 2	33 (34.7)	57	23 (24.5)	47	56 (29.6)	104
At least one TEAE with relationship to study treatment:						
Not related	50 (52.6)	98	41 (43.6)	85	91 (48.1)	183
Not related	41 (43.2)	66	31 (33.0)	63	72 (38.1)	129
Unlikely	20 (21.1)	32	14 (14.9)	22	34 (18.0)	54
Related	9 (9.5)	13	16 (17.0)	25	25 (13.2)	38
Possible	7 (7.4)	11	15 (16.0)	22	22 (11.6)	33
Probable	2 (2.1)	2	3 (3.2)	3	5 (2.6)	5
At least one serious related TEAE	0	0	0	0	0	0
At least one related TEAE leading to drug withdrawal	0	0	0	0	0	0
At least one related TEAE leading to study discontinuation	0	0	0	0	0	0
At least one related TEAE leading to death	0	0	0	0	0	0
At least one related TEAE with severity*:						
Grade 1	6 (6.3)	10	13 (13.8)	18	19 (10.1)	28
Grade 2	3 (3.2)	3	5 (5.3)	7	8 (4.2)	10
At least one TEAE with outcome:						
Recovered/resolved	52 (54.7)	110	47 (50.0)	109	99 (52.4)	219
Recovering/resolving	1 (1.1)	1	1 (1.1)	1	2 (1.1)	2
At least one serious TEAE	0	0	0	0	0	0
At least one TEAE leading to drug withdrawal	0	0	0	0	0	0
At least one TEAE leading to study discontinuation	0	0	0	0	0	0
At least one TEAE leading to death	0	0	0	0	0	0
Any death	0	0	0	0	0	0

*: NCI-CTCAE grade version 5.0. For any term that is not specifically listed in the CTCAE scale, severity is assigned a grade of 1 through 5 using the CTCAE guidelines defined in the protocol.
n: number of participants with at least one Adverse Event (AE); For a given preferred term, n also corresponds to the number of AEs whatever the number of occurrences during the studied period.
(%): (n/N)*100.
nae: number of occurrences of an AE.

TEAE: A treatment-emergent adverse event is an adverse event not present prior to administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.
Source: Table 14.3.1.1

Common TEAEs by SOC and PT

Table 42: Display of participants presenting TEAE, for SOCs and PTs in at least 5% of the overall safety population (Safety Set) – Study B1000-NHV-01-G-01

		US-Licensed Prolia®		Bmab 1000		Overall	
		(N=95)		(N=94)		(N=189)	
System Organ Class*	Preferred Term*	n (%)	nae	n (%)	nae	n (%)	nae
ALL	**ALL**	**52 (54.7)**	**111**	**47 (50.0)**	**110**	**99 (52.4)**	**221**
Gastrointestinal disorders	ALL	15 (15.8)	20	20 (21.3)	26	35 (18.5)	46
	Constipation	4 (4.2)	4	8 (8.5)	8	12 (6.3)	12
Infections and infestations	ALL	23 (24.2)	32	18 (19.1)	26	41 (21.7)	58
	Nasopharyngitis	10 (10.5)	12	9 (9.6)	9	19 (10.1)	21
Musculoskeletal and connective tissue disorders	ALL	14 (14.7)	17	15 (16.0)	19	29 (15.3)	36
	Back pain	5 (5.3)	5	7 (7.4)	7	12 (6.3)	12
Nervous system disorders	ALL	13 (13.7)	16	11 (11.7)	13	24 (12.7)	29
	Headache	12 (12.6)	14	9 (9.6)	10	21 (11.1)	24
General disorders and administration site conditions**	All	7 (7.4)	7	6 (6.4)	7	13 (6.9)	14
Respiratory, thoracic and mediastinal disorders**	All	4 (4.2)	4	5 (5.3)	5	9 (4.8)	9

*: MedDRA Dictionary version 26.1.
**: No PT reached a 5% occurrence threshold in this SOC.
n: number of participants with at least one Treatment-Emergent Adverse Event (TEAE); For a given preferred term, n also corresponds to the number of TEAEs whatever the number of occurrences during the studied period.
(%): (n/N)*100.
nae: number of occurrences of a TEAE.
Source: Table 14.3.1.3.1

TEAEs by severity

Table 43: TEAE severity in SOCs present for at least 5% of the overall population (Safety Set) – Study B1000-NHV-01-G-01

	US-Licensed Prolia (N=95)				Bmab 1000 (N=94)			
	Grade 1**		Grade 2**		Grade 1**		Grade 2**	
System Organ Class*	n (%)	nae	n (%)	nae	n (%)	nae	n (%)	nae
ALL	32 (33.7)	54	33 (34.7)	57	38 (40.4)	63	23 (24.5)	47
Gastrointestinal disorders	10 (10.5)	13	7 (7.4)	7	15 (16.0)	19	7 (7.4)	7
Infections and infestations	9 (9.5)	9	15 (15.8)	23	10 (10.6)	11	12 (12.8)	15
Musculoskeletal and connective tissue disorders	10 (10.5)	12	4 (4.2)	5	12 (12.8)	14	4 (4.3)	5
Nervous system disorders	3 (3.2)	3	11 (11.6)	13	5 (5.3)	6	6 (6.4)	7
General disorders and administration site conditions	4 (4.2)	4	3 (3.2)	3	5 (5.3)	6	1 (1.1)	1
Respiratory, thoracic and mediastinal disorders	3 (3.2)	3	1 (1.1)	1	4 (4.3)	4	1 (1.1)	1

*: MedDRA Dictionary version 26.1.

**: NCI-CTCAE version 5.0. For any term that is not specifically listed in the CTCAE scale, severity is assigned a grade of 1 through 5 using the CTCAE guidelines defined in the protocol.

n: number of subjects with at least one Treatment-Emergent Adverse Event (TEAE); For a given preferred term, n also corresponds to the number of TEAEs whatever the number of occurrences during the studied period.

(%): (n/N)*100.

nae: number of occurrences of a TEAE.

A treatment-emergent adverse event is an adverse event not present prior to administration of the study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

Source: Table 14.3.1.3.2

Treatment related TEAEs (Adverse drug reactions)

Table 44: IMP-related TEAEs (Safety Set) – Study B1000-NHV-01-G-01

	Prolia (N=95)		Bmab 1000-P (N=94)	
Preferred Term	**n (%)**	**nAE**	**n (%)**	**nAE**
Back pain	1 (1.1)	1	3 (3.2)	3
Myalgia	1 (1.1)	1	3 (3.2)	3
Pain in extremity	0	0	3 (3.2)	3
Headache	2 (2.1)	2	2 (2.1)	2
Constipation	1 (1.1)	1	2 (2.1)	2
Abdominal pain	1 (1.1)	1	2 (2.1)	2
Haemorrhoids	0	0	2 (2.1)	2
Arthralgia	1 (1.1)	2	1 (1.1)	1
Abdominal distension	0	0	1 (1.1)	1
Injection site erythema	0	0	1 (1.1)	1
Injection site pain	0	0	1 (1.1)	1
Musculoskeletal chest pain	0	0	1 (1.1)	1
Paraesthesia	0	0	1 (1.1)	1
Restless legs syndrome	0	0	1 (1.1)	1
Skin exfoliation	0	0	1 (1.1)	1
Injection site reaction	1 (1.1)	1	0	0
Joint stiffness	1 (1.1)	1	0	0
Skin infection	1 (1.1)	1	0	0
Dry mouth	1 (1.1)	1	0	0
Hyperhidrosis	1 (1.1)	1	0	0

n: number of subjects with at least one Treatment-Emergent Adverse Event (TEAE); For a given preferred term, n also corresponds to the number of TEAEs whatever the number of occurrences during the studied period.

(%): (n/N)*100.

nAE: number of occurrences of a TEAE.

Source: Table 14.3.1.3.4, CSR, B1000-NHV-01-G-01.

Table 45: Treatment-related TEAEs by severity - Study B1000-NHV-01-G-01

	US-Licensed Prolia® (N=95)		Bmab 1000 (N=94)		Overall (N=189)	
	n (%)	**nae**	**n (%)**	**nae**	**n (%)**	**nae**
At least one related TEAE with severity*:						
Grade 1	6 (6.3)	10	13 (13.8)	18	19 (10.1)	28
Grade 2	3 (3.2)	3	5 (5.3)	7	8 (4.2)	10

Injection site reactions

No severe injection site reaction was observed during the study.

Two assessments led to TEAE (a grade 1 injection site erythema in the Bmab 1000 group, and a grade 1 injection site reaction in the Prolia group).

A grade 1 injection site pain in the Bmab 1000 group was reported on D21, i.e., after the last injection site scheduled assessment.

Study B1000-PMO-03-G-02 – Part 1 (double-blind active-controlled)

A total of 660 TEAEs were reported in 293 (61.3%) patients (304 TEAEs in 59.2% patients and 356 TEAEs in 63.3% patients in the Bmab 1000 and Prolia groups, respectively).

Table 46: Overall summary of TEAEs – Double-blind active-controlled period (SAF) – Study B1000-PMO-03-G-02

Number of Patients With	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Any TEAEs	141 (59.2) [304]	152 (63.3) [356]	293 (61.3) [660]
Any study drug-related TEAEs	19 (8.0) [23]	27 (11.3) [35]	46 (9.6) [58]
Any serious TEAEs	14 (5.9) [18]	7 (2.9) [9]	21 (4.4) [27]
Any study drug-related serious TEAEs	0	0	0
Any AESIs	8 (3.4) [9]	13 (5.4) [14]	21 (4.4) [23]
Any serious AESIs	2 (0.8) [3]	1 (0.4) [1]	3 (0.6) [4]
Any related AESIs	5 (2.1) [5]	6 (2.5) [6]	11 (2.3) [11]
Any TEAEs leading to treatment discontinuation	4 (1.7) [4]	5 (2.1) [7]	9 (1.9) [11]
Any TEAEs leading to study discontinuation	3 (1.3) [3]	2 (0.8) [2]	5 (1.0) [5]
Any TEAEs leading to death	0	1 (0.4) [1]	1 (0.2) [1]
Any deaths	0	1 (0.4) [3]	1 (0.2) [3]

Abbreviations: AE, adverse event; AESI, adverse events of special interest; E, event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients at each level of summarization; SAF, safety analysis set; TEAE, Treatment-Emergent Adverse Event.

Notes: Percentages were based on the number of patients in the SAF within each treatment.
[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
For Double-Blind Active-Controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.
TEAEs that had possible, probable, or definite relationship to treatment were considered as drug-related.
If the relationship of an AE was missing, the AE was summarized as drug-related.
The following AEs were considered as AESI: drug-related hypersensitivity/allergic reaction, serious infections, hypocalcaemia, osteonecrosis of the jaw, atypical femoral fracture, dermatologic reaction.
Adverse events were coded using MedDRA, Version 26.1.
Source: Table 14.3.1.1.1

Common TEAEs by SOC and PT

Table 47: TEAEs reported for ≥2% of patients in either group using PT presented by SOC and PT – Double-blind active-controlled period (safety analysis set) - Study B1000-PMO-03-G-02

System Organ Class Preferred Term	Bmab 1000-P (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Total number of TEAEs	**304**	**356**	**660**
Number of patients with at least 1 TEAE	**141 (59.2)**	**152 (63.3)**	**293 (61.3)**
Infections and infestations	**76 (31.9) [109]**	**72 (30.0) [102]**	**148 (31.0) [211]**
Upper respiratory tract infection	17 (7.1) [20]	22 (9.2) [24]	39 (8.2) [44]
Urinary tract infection	12 (5.0) [12]	10 (4.2) [10]	22 (4.6) [22]
Nasopharyngitis	12 (5.0) [14]	7 (2.9) [7]	19 (4.0) [21]
COVID-19	9 (3.8) [9]	8 (3.3) [8]	17 (3.6) [17]
Bronchitis	6 (2.5) [7]	5 (2.1) [5]	11 (2.3) [12]
Cystitis	3 (1.3) [3]	6 (2.5) [7]	9 (1.9) [10]
Pharyngitis	6 (2.5) [8]	2 (0.8) [2]	8 (1.7) [10]
Laryngitis	5 (2.1) [5]	1 (0.4) [1]	6 (1.3) [6]
Sinusitis	0	5 (2.1) [5]	5 (1.0) [5]
Musculoskeletal and connective tissue disorders	**40 (16.8) [55]**	**33 (13.8) [43]**	**73 (15.3) [98]**
Arthralgia	9 (3.8) [11]	13 (5.4) [15]	22 (4.6) [26]
Back pain	9 (3.8) [9]	6 (2.5) [6]	15 (3.1) [15]
Osteoarthritis	9 (3.8) [10]	4 (1.7) [4]	13 (2.7) [14]
Spinal osteoarthritis	4 (1.7) [4]	5 (2.1) [5]	9 (1.9) [9]
Pain in extremity	5 (2.1) [6]	3 (1.3) [3]	8 (1.7) [9]
Nervous system disorders	**18 (7.6) [22]**	**31 (12.9) [35]**	**49 (10.3) [57]**
Dizziness	7 (2.9) [7]	10 (4.2) [11]	17 (3.6) [18]
Headache	9 (3.8) [10]	8 (3.3) [9]	17 (3.6) [19]
Metabolism and nutrition disorders	**13 (5.5) [14]**	**27 (11.3) [31]**	**40 (8.4) [45]**
Hypercholesterolaemia	6 (2.5) [6]	12 (5.0) [12]	18 (3.8) [18]
Investigations	**12 (5.0) [15]**	**15 (6.3) [18]**	**27 (5.6) [33]**
Blood parathyroid hormone increased	2 (0.8) [2]	6 (2.5) [6]	8 (1.7) [8]
Vascular disorders	**7 (2.9) [7]**	**9 (3.8) [9]**	**16 (3.3) [16]**
Hypertension	6 (2.5) [6]	5 (2.1) [5]	11 (2.3) [11]

Notes: In SOC and PT summarization, a patient was counted once if the patient reported 1 or more events.
[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
Percentages were based on the number of patients in the SAF within each treatment.
For Double-blind Active-controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.
Adverse events were coded using MedDRA, Version 26.1.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.
Source: Table 14.3.1.2.1, CSR, B1000-PMO-03-G-02.

TEAEs by severity

Most of the TEAEs were Grade 1 or Grade 2 in severity. Treatment-emergent AEs of Grade 1 severity were reported in 292 (44.2%) patients [124 (40.8%) and 168 (47.2%) patients in the Bmab 1000 and Prolia groups, respectively) and TEAEs of Grade 2 severity were reported in 339 (51.4%) patients [164 (53.9%) and 175 (49.2%) patients in the Bmab 1000 and Prolia groups, respectively].

Table 48: Grade 3 or higher TEAEs by PT - Double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

Preferred Term	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Total number of TEAEs n (%)	**304**	**356**	**660**
Grade 3[a]	15 (4.9)	11 (3.1)	26 (3.9)
Grade 4[a]	1 (0.3)	1 (0.3)	2 (0.3)
Grade 5[a]	0	1 (0.3)	1 (0.2)
Number of patients with at least 1 TEAE n (%)	**141 (59.2)**	**152 (63.3)**	**293 (61.3)**
Grade 3	11 (4.6)	8 (3.3)	19 (4.0)
Grade 4	1 (0.4)	1 (0.4)	2 (0.4)
Grade 5	0	1 (0.4)	1 (0.2)
Grade 3 TEAEs			
Acute kidney injury	0	1 (0.4) [1]	1 (0.2) [1]
Acute myocardial infarction	0	1 (0.4) [1]	1 (0.2) [1]
Alanine aminotransferase increased	0	1 (0.4) [1]	1 (0.2) [1]
Barrett's oesophagus	1 (0.4) [2]	0	1 (0.2) [2]
Blood creatine phosphokinase increased	1 (0.4) [1]	0	1 (0.2) [1]
Breast cancer	1 (0.4) [1]	0	1 (0.2) [1]
Clear cell renal cell carcinoma	0	1 (0.4) [1]	1 (0.2) [1]
Colon cancer	1 (0.4) [1]	0	1 (0.2) [1]
Coronary artery disease	0	1 (0.4) [1]	1 (0.2) [1]
Diverticulum intestinal	0	1 (0.4) [1]	1 (0.2) [1]
Hypertension	0	1 (0.4) [1]	1 (0.2) [1]
Inflammatory bowel disease	1 (0.4) [1]	0	1 (0.2) [1]
Musculoskeletal disorder	1 (0.4) [1]	0	1 (0.2) [1]
Myalgia	0	1 (0.4) [1]	1 (0.2) [1]
Myocardial infarction	0	1 (0.4) [1]	1 (0.2) [1]
Noninfective mastoiditis	1 (0.4) [1]	0	1 (0.2) [1]
Oesophageal perforation	1 (0.4) [1]	0	1 (0.2) [1]
Ovarian cyst	1 (0.4) [1]	0	1 (0.2) [1]
Pancreatic carcinoma	1 (0.4) [1]	0	1 (0.2) [1]
Pharyngitis	1 (0.4) [1]	0	1 (0.2) [1]
Schizophrenia	0	1 (0.4) [1]	1 (0.2) [1]
Ureterolithiasis	1 (0.4) [1]	0	1 (0.2) [1]
Urosepsis	1 (0.4) [1]	0	1 (0.2) [1]
Uterine prolapse	0	1 (0.4) [1]	1 (0.2) [1]
Vestibular neuronitis	1 (0.4) [1]	0	1 (0.2) [1]
Grade 4 TEAEs			
Pancreatic carcinoma	1 (0.4) [1]	0	1 (0.2) [1]
Staphylococcal sepsis	0	1 (0.4) [1]	1 (0.2) [1]
Grade 5 TEAE			
Cerebrovascular accident	0	1 (0.4) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients at each level of summarization; PT, preferred term; SAF, Safety Analysis Set; TEAEs=Treatment-emergent adverse events.

Notes: At each level of summarization, a patient was counted once for the worst CTCAE grade if the patient reported 1 or more events, and all events were counted independently of the worst CTCAE. If the severity of an AE was missing, the AE was summarized as Grade 3.

CTCAE: Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.

[E] represents the number of AEs at each level of summarization.

n represents the number of patients at each level of summarization.

Percentages were based on the number of patients in the SAF within each treatment.

For Double-Blind Active-Controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the study drug by investigator.

The severity of AEs was rated using CTCAE, Version 5.0.

Adverse events were coded using MedDRA, Version 26.1.

a. The percentages were calculated based on the number of events.

Source: Table 14.3.1.4.1

Treatment related TEAEs (Adverse drug reactions)

Table 49: Treatment-related TEAEs by PT reported for >1 patient in total population – Double-blind Active-Controlled Period (SAF) - Study B1000-PMO-03-G-02

Preferred Term	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Total number of TEAEs	304	356	660
Related[a]	**23 (7.6)**	**35 (9.8)**	**58 (8.8)**
Number of patients with at least 1 TEAE n (%)	141 (59.2)	152 (63.3)	293 (61.3)
Related	**19 (8.0)**	**27 (11.3)**	**46 (9.6)**
Injection site erythema	3 (1.3) [3]	4 (1.7) [4]	7 (1.5) [7]
Blood parathyroid hormone increased	1 (0.4) [1]	3 (1.3) [3]	4 (0.8) [4]
Adjusted calcium decreased	1 (0.4) [1]	2 (0.8) [2]	3 (0.6) [3]
Alopecia	3 (1.3) [3]	0	3 (0.6) [3]
Arthralgia	1 (0.4) [1]	2 (0.8) [2]	3 (0.6) [3]
Back pain	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Myalgia	0	2 (0.8) [2]	2 (0.4) [2]
Hypocalcaemia	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Injection site swelling	0	2 (0.8) [2]	2 (0.4) [2]
Upper respiratory tract infection	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Urinary tract infection	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Spinal pain	2 (0.8) [2]	0	2 (0.4) [2]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients at each level of summarization; PT, preferred term; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

Notes: In PT summarization, a patient was counted once if the patient reported 1 or more events.
[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
Percentages were based on the number of patients in the SAF within each treatment.
For Double-Blind Active-Controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.

Adverse events were coded using MedDRA, Version 26.1

a. The percentages were calculated based on the number of events.

Source: Table 14.3.1.3.1

Table 50: Treatment-emergent adverse events by severity and relationship - Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%) [E]		Prolia (N=240) n (%) [E]		Total (N=478) n (%) [E]	
System Organ Class Preferred Term Severity	Related	Unrelated	Related	Unrelated	Related	Unrelated
Total number of TEAEs [a]	23	281	35	321	58	602
Grade 1	16(69.6)	108(38.4)	24(68.6)	144(44.9)	40(69.0)	252(41.9)
Grade 2	7(30.4)	157(55.9)	10(28.6)	165(51.4)	17(29.3)	322(53.5)
Grade 3	0	15 (5.3)	1 (2.9)	10 (3.1)	1 (1.7)	25 (4.2)
Grade 4	0	1 (0.4)	0	1 (0.3)	0	2 (0.3)
Grade 5	0	0	0	1 (0.3)	0	1 (0.2)
Number of subjects with at least one TEAE	19 (8.0)	139(58.4)	27(11.3)	147(61.3)	46 (9.6)	286(59.8)
Grade 1	12 (5.0)	32(13.4)	17 (7.1)	52(21.7)	29 (6.1)	84(17.6)
Grade 2	7 (2.9)	95(39.9)	9 (3.8)	86(35.8)	16 (3.3)	181(37.9)
Grade 3	0	11 (4.6)	1 (0.4)	7 (2.9)	1 (0.2)	18 (3.8)
Grade 4	0	1 (0.4)	0	1 (0.4)	0	2 (0.4)
Grade 5	0	0	0	1 (0.4)	0	1 (0.2)

Injection site reactions

Injection site reactions (symptom/reaction as erythema/redness and/or swelling/hardness) were reported in 6 patients after the first dose on Day 1 (3 patients each in the Bmab 1000 and Prolia treatment group) and in 3 patients after the second dose at Week 26 (1 patient in the Bmab 1000

treatment group and 2 patients in the Prolia treatment group). Except for 1 moderate injection site reaction in 1 patient from the Prolia group, all other injection site reactions were mild. All injection site reactions resolved within 2-3 days of onset.

Study B1000-PMO-03-G-02 – Part 2 (transition)

Summary of AEs

Table 51: Overall summary of TEAEs – Part 2 (SAF-TP)

Number of Patients With	Bmab 1000-Bmab 1000 (N=218) n (%) [E]	Prolia-Bmab 1000 (N=104) n (%) [E]	Prolia-Prolia (N=104) n (%) [E]	Total (N=426) n (%) [E]
Any TEAEs	55 (25.2) [79]	29 (27.9) [40]	27 (26.0) [37]	111 (26.1) [156]
Any study drug-related TEAEs	6 (2.8) [7]	2 (1.9) [2]	4 (3.8) [5]	12 (2.8) [14]
Any serious TEAEs	5 (2.3) [5]	2 (1.9) [2]	2 (1.9) [2]	9 (2.1) [9]
Any study drug-related serious TEAEs	0	0	0	0
Any AESIs	3 (1.4) [3]	0	0	3 (0.7) [3]
Any serious AESIs	0	0	0	0
Any related AESIs	2 (0.9) [2]	0	0	2 (0.5) [2]
Any TEAEs leading to treatment discontinuation	0	0	0	0
Any TEAEs leading to study discontinuation	0	0	0	0
Any TEAEs leading to death	0	0	0	0
Any deaths	0	0	0	0

[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
Percentages were based on the number of patients in the SAF-TP within each treatment.

For Part 2, TEAE was an event observed after third dose of study drug at Week 52 until Week 78 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.
TEAEs that have possible, probable, or definite relationship to treatment were considered as drug-related.
If the relationship of an AE was missing, the AE was summarized as drug-related.
The following AE were considered as AESI: treatment-related hypersensitivity/allergic reaction, serious infections, hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reaction.
AEs were coded using MedDRA, Version 27.0.
Source: Table 14.3.1.1.2

Common TEAEs by SOC and PT

Table 52: TEAEs reported for ≥2% of patients in any group using PT presented by SOC and PT – Part 2 (SAF-TP)

System Organ Class Preferred Term	Bmab 1000-Bmab 1000 (N=218) n (%) [E]	Prolia-Bmab 1000 (N=104) n (%) [E]	Prolia-Prolia (N=104) n (%) [E]	Total (N=426) n (%) [E]
Total number of TEAEs[a]	79	40	37	156
Number of patients with at least 1 TEAE[a]	55 (25.2)	29 (27.9)	27 (26.0)	111 (26.1)
Infections and infestations	24 (11.0) [24]	18 (17.3) [23]	16 (15.4) [18]	58 (13.6) [65]
COVID-19	2 (0.9) [2]	2 (1.9) [2]	3 (2.9) [3]	7 (1.6) [7]
Nasopharyngitis	3 (1.4) [3]	4 (3.8) [5]	3 (2.9) [3]	10 (2.3) [11]
Sinusitis	0	1 (1.0) [1]	3 (2.9) [3]	4 (0.9) [4]
Upper respiratory tract infection	3 (1.4) [3]	5 (4.8) [5]	3 (2.9) [3]	11 (2.6) [11]

Notes: In SOC and PT summarization, a patient was counted once if the patient reported 1 or more events.
[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
Percentages were based on the number of patients in the SAF-TP within each treatment.
For Part 2, TEAE was an event observed after third dose of study drug at Week 52 until Week 78 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE is considered as related to the drug by investigator.
Adverse events were coded using MedDRA, Version 27.0.
a. Total number of TEAEs and number of patients with at least 1 TEAE are based on the overall SAF-TP.
Source: Table 14.3.1.2.2

TEAEs by severity

Table 53: Grade 3 or higher TEAEs by PT – Part 2 (SAF-TP)

Preferred Terms	Bmab 1000-Bmab 1000 (N=218) n (%) [E]	Prolia-Bmab 1000 (N=104) n (%) [E]	Prolia-Prolia (N=104) n (%) [E]	Total (N=426) n (%) [E]
Total number of TEAEs n (%)[a]	**79**	**40**	**37**	**156**
Grade 3[b]	3 (3.8)	1 (2.5)	1 (2.7)	5 (3.2)
Grade 4[b]	0	0	0	0
Grade 5[b]	0	0	0	0
Number of patients with at least 1 TEAE n (%)[a]	**55 (25.2)**	**29 (27.9)**	**27 (26.0)**	**111 (26.1)**
Grade 3	2 (0.9)	1 (1.0)	1 (1.0)	4 (0.9)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Grade 3 TEAEs				
Abdominal pain	0	1 (1.0) [1]	0	1 (0.2) [1]
Gastric ulcer	1 (0.5) [1]	0	0	1 (0.2) [1]
Arterial injury	1 (0.5) [1]	0	0	1 (0.2) [1]
Skin laceration	1 (0.5) [1]	0	0	1 (0.2) [1]
Invasive lobular breast carcinoma	0	0	1 (1.0) [1]	1 (0.2) [1]

Notes: At each level of summarization, a patient was counted once for the worst CTCAE grade if the patient reported 1 or more events, and all events were counted independently of the worst CTCAE. If the severity of an AE was missing, the AE was summarized as Grade 3.

CTCAE: Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.

[E] represented the number of AEs at each level of summarization.

n represented the number of patients at each level of summarization.

Percentages were based on the number of subjects in the SAF-TP within each treatment.

For Part 2, TEAE was an event observed after third administration of study drug at Week 52 until Week 78 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.

The severity of AEs was rated using CTCAE, Version 5.0.

AEs were coded using MedDRA, Version 27.0.

a. Total number of TEAEs and number of patients with at least 1 TEAE are based on the overall SAF-TP.

b. The percentages were calculated based on the number of events.

Source: Table 14.3.1.4.2

Treatment related TEAEs (Adverse drug reactions)

Table 54: Treatment-related TEAEs by PT – Transition Period (SAF-TP)

Preferred Term	Bmab 1000-Bmab 1000 (N=218) n (%) [E]	Prolia-Bmab 1000 (N=104) n (%) [E]	Prolia-Prolia (N=104) n (%) [E]	Total (N=426) n (%) [E]
Total number of TEAEs	79	40	37	156
Related[a]	**7 (8.9)**	**2 (5.0)**	**5 (13.5)**	**14 (9.0)**
Number of patients with at least 1 TEAE n (%)	55 (25.2)	29 (27.9)	27 (26.0)	111 (26.1)
Related	**6 (2.8)**	**2 (1.9)**	**4 (3.8)**	**12 (2.8)**
Cystitis	1 (0.5) [1]	0	0	1 (0.2) [1]
Mastitis	0	0	1 (1.0) [1]	1 (0.2) [1]
Upper respiratory tract infection	1 (0.5) [1]	0	0	1 (0.2) [1]
Arthralgia	0	0	1 (1.0) [1]	1 (0.2) [1]
Groin pain	0	0	1 (1.0) [1]	1 (0.2) [1]
Myalgia	1 (0.5) [1]	0	0	1 (0.2) [1]
Myofascial pain syndrome	0	0	1 (1.0) [1]	1 (0.2) [1]
Pain in extremity	0	1 (1.0) [1]	0	1 (0.2) [1]
Blood calcium decreased	1 (0.5) [1]	0	0	1 (0.2) [1]
Blood creatine phosphokinase increased	1 (0.5) [1]	0	0	1 (0.2) [1]
Blood parathyroid hormone decreased	1 (0.5) [1]	0	0	1 (0.2) [1]
Dizziness	0	1 (1.0) [1]	0	1 (0.2) [1]
Injection site erythema	0	0	1 (1.0) [1]	1 (0.2) [1]
Rash pruritic	1 (0.5) [1]	0	0	1 (0.2) [1]

Notes: In PT summarization, a patient was counted once if the patient reported 1 or more events.
[E] represented the number of adverse events at each level of summarization.
Percentages were based on the number of patients in the SAF-TP within each treatment.
[a] The percentages were calculated based on the number of events.
For Transition Period, TEAE was an event observed after third administration of study drug on Week 52 until Week 78 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the drug by investigator.
Adverse Events were coded using MedDRA, Version 27.0.
a. The percentages were calculated based on the number of events.
Source: Table 14.3.1.3.2

Treatment related TEAEs by severity

All study-drug related TEAEs were of Grade 1 or Grade 2 severity.

Injection site reactions

Injection site reactions (symptom/reaction as erythema/redness) were reported in 2 patients (1 patient each in Bmab 1000-Bmab 1000 and Prolia-Prolia treatment group) after the third dose at Week 52; both injection site reactions were mild and resolved within 1 day of onset.

2.5.8.3. Serious adverse events, deaths, and other significant events

Serious adverse events (SAE)

Study B1000-NHV-01-G-01

None of the subjects experienced SAEs in this study.

Study B1000-PMO-03-G-02 02 – Part 1 (double-blind active-controlled)

The incidence of serious TEAEs was low (4.4% of total patients) and a total of 27 serious TEAEs were reported in 21 patients (14 patients in the Bmab 1000 group and 7 patients in the Prolia group). None

of the serious TEAEs in either treatment group was considered as related to the study drug by the investigator.

Although the number of serious events appears nominally higher in Bmab 1000 group, upon further evaluation it can be concluded that the majority of the events could be attributed to pre-existing dispositions such as age-related factors and underlying medical conditions.

The majority of the serious TEAEs were of Grade 3 severity (18 serious TEAEs in 14 patients). Two serious TEAEs in 2 patients and 1 serious TEAE in 1 patient, respectively, were of Grade 4 and Grade 5 severity. The investigator considered none of the serious TEAEs in either treatment group related to the study drug. In addition, none of the events were of a nature that could be attributed to the mechanism of action of denosumab.

Except for the serious TEAEs of pancreatic carcinoma and dizziness (in 2 patients, each), no other serious TEAE was reported in >1 patient.

Table 55: Serious TEAEs by SOC and PT - Double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

System Organ Class Preferred Term	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Number of serious TEAEs	**18**	**9**	**27**
Number of patients with at least 1 serious TEAE	**14 (5.9)**	**7 (2.9)**	**21 (4.4)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.7) [4]**	**1 (0.4) [1]**	**5 (1.0) [5]**
Breast cancer	1 (0.4) [1]	0	1 (0.2) [1]
Clear cell renal cell carcinoma	0	1 (0.4) [1]	1 (0.2) [1]
Colon cancer	1 (0.4) [1]	0	1 (0.2) [1]
Pancreatic carcinoma	2 (0.8) [2]	0	2 (0.4) [2]
Gastrointestinal disorders	**3 (1.3) [3]**	**1 (0.4) [1]**	**4 (0.8) [4]**
Abdominal pain	1 (0.4) [1]	0	1 (0.2) [1]
Barrett's oesophagus	1 (0.4) [1]	0	1 (0.2) [1]
Diverticulum intestinal	0	1 (0.4) [1]	1 (0.2) [1]
Inflammatory bowel disease	1 (0.4) [1]	0	1 (0.2) [1]
Infections and infestations	**2 (0.8) [2]**	**1 (0.4) [1]**	**3 (0.6) [3]**
Staphylococcal sepsis	0	1 (0.4) [1]	1 (0.2) [1]
Urosepsis	1 (0.4) [1]	0	1 (0.2) [1]
Vestibular neuronitis	1 (0.4) [1]	0	1 (0.2) [1]
Nervous system disorders	**2 (0.8) [2]**	**1 (0.4) [1]**	**3 (0.6) [3]**
Cerebrovascular accident	0	1 (0.4) [1]	1 (0.2) [1]
Dizziness	2 (0.8) [2]	0	2 (0.4) [2]
Reproductive system and breast disorders	**2 (0.8) [2]**	**1 (0.4) [1]**	**3 (0.6) [3]**
Endometrial hyperplasia	1 (0.4) [1]	0	1 (0.2) [1]
Ovarian cyst	1 (0.4) [1]	0	1 (0.2) [1]
Uterine prolapse	0	1 (0.4) [1]	1 (0.2) [1]
Cardiac disorders	**0**	**2 (0.8) [2]**	**2 (0.4) [2]**
Acute myocardial infarction	0	1 (0.4) [1]	1 (0.2) [1]
Myocardial infarction	0	1 (0.4) [1]	1 (0.2) [1]
Renal and urinary disorders	**1 (0.4) [1]**	**1 (0.4) [1]**	**2 (0.4) [2]**
Acute kidney injury	0	1 (0.4) [1]	1 (0.2) [1]
Ureterolithiasis	1 (0.4) [1]	0	1 (0.2) [1]
Ear and labyrinth disorders	**1 (0.4) [2]**	**0**	**1 (0.2) [2]**
Ear inflammation	1 (0.4) [1]	0	1 (0.2) [1]
Noninfective mastoiditis	1 (0.4) [1]	0	1 (0.2) [1]
Musculoskeletal and connective tissue disorders	**1 (0.4) [1]**	**0**	**1 (0.2) [1]**
Musculoskeletal disorder	1 (0.4) [1]	0	1 (0.2) [1]
Psychiatric disorders	**0**	**1 (0.4) [1]**	**1 (0.2) [1]**
Schizophrenia	0	1 (0.4) [1]	1 (0.2) [1]
Respiratory, thoracic and mediastinal disorders	**1 (0.4) [1]**	**0**	**1 (0.2) [1]**
Allergic sinusitis	1 (0.4) [1]	0	1 (0.2) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients at each level of summarization; PT, preferred term; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: Percentages were based on the number of patients in the SAF within each treatment.

[E] represents the number of AEs at each level of summarization.

n represents the number of patients at each level of summarization.

In SOC and PT summarization, a patient was counted once if the patient reported 1 or more events.

For Double-Blind Active-Controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the study drug by investigator.

Adverse events were coded using MedDRA, Version 26.1.

Source: Table 14.3.1.6.1

Table 56: Serious treatment-emergent adverse events by severity double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

System Organ Class Preferred Term Severity	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Number of Serious TEAEs [a]	18	9	27
Grade 1	1 (5.6)	0	1 (3.7)
Grade 2	5 (27.8)	0	5 (18.5)
Grade 3	11 (61.1)	7 (77.8)	18 (66.7)
Grade 4	1 (5.6)	1 (11.1)	2 (7.4)
Grade 5	0	1 (11.1)	1 (3.7)
Number of subjects with at least one Serious TEAE	14 (5.9)	7 (2.9)	21 (4.4)
Grade 1	0	0	0
Grade 2	4 (1.7)	0	4 (0.8)
Grade 3	9 (3.8)	5 (2.1)	14 (2.9)
Grade 4	1 (0.4)	1 (0.4)	2 (0.4)
Grade 5	0	1 (0.4)	1 (0.2)

Study B1000-PMO-03-G-02 – Part 2 (transition)

A total of 9 patients (Bmab 1000-Bmab 1000: 5; Prolia-Bmab 1000: 2; and Prolia-Prolia: 2) reported 9 serious TEAEs (Bmab 1000-Bmab 1000: 5; Prolia-Bmab 1000: 2; and Prolia-Prolia: 2). None of the TEAEs were considered as study drug-related.

Table 57: Serious TEAEs by SOC and PT – Part 2 (SAF-TP)

System Organ Class Preferred Term	Bmab 1000-Bmab 1000 (N=218) n (%) [E]	Prolia-Bmab 1000 (N=104) n (%) [E]	Prolia-Prolia (N=104) n (%) [E]	Total (N=426) n (%) [E]
Number of serious TEAEs	**5**	**2**	**2**	**9**
Number of patients with at least 1 serious TEAE	**5 (2.3)**	**2 (1.9)**	**2 (1.9)**	**9 (2.1)**
Gastrointestinal disorders	**1 (0.5) [1]**	**1 (1.0) [1]**	**0**	**2 (0.5) [2]**
Abdominal pain	0	1 (1.0) [1]	0	1 (0.2) [1]
Gastric ulcer	1 (0.5) [1]	0	0	1 (0.2) [1]
Cardiac disorders	**0**	**0**	**1 (1.0) [1]**	**1 (0.2) [1]**
Atrial fibrillation	0	0	1 (1.0) [1]	1 (0.2) [1]
Eye disorders	1 (0.5) [1]	0	0	1 (0.2) [1]
Cataract	1 (0.5) [1]	0	0	1 (0.2) [1]
General disorders and administration site conditions	**1 (0.5) [1]**	**0**	**0**	**1 (0.2) [1]**
Non-cardiac chest pain	1 (0.5) [1]	0	0	1 (0.2) [1]
Infections and infestations	**0**	**1 (1.0) [1]**	**0**	**1 (0.2) [1]**
Diverticulitis	0	1 (1.0) [1]	0	1 (0.2) [1]
Injury, poisoning and procedural complications	**1 (0.5) [1]**	**0**	**0**	**1 (0.2) [1]**
Arterial injury	1 (0.5) [1]	0	0	1 (0.2) [1]
Musculoskeletal and connective tissue disorders	**1 (0.5) [1]**	**0**	**0**	**1 (0.2) [1]**
Osteoarthritis	1 (0.5) [1]	0	0	1 (0.2) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**1 (1.0) [1]**	**1 (0.2) [1]**
Invasive lobular breast carcinoma	0	0	1 (1.0) [1]	1 (0.2) [1]

Notes: Percentages were based on the number of patients in the SAF-TP within each treatment.
[E] represents the number of AEs at each level of summarization.
n represents the number of patients at each level of summarization.
In SOC and PT summarization, a patient was counted once if the patient reported 1 or more events.

Deaths

Study B1000-NHV-01-G-01

No death was reported in the Phase 1 study.

Study B1000-PMO-03-G-02 (part 1 and 2)

In the Phase 3 study (B1000-PMO-03-G-02), one death was reported due to a TEAE of cerebrovascular accident in the Prolia group by Week 52. Given the patient's medical background (previous smoker, recent history of non-serious AE of hyperlipidaemia) and lack of temporal association the event of cerebrovascular accident is assessed as not related.

Adverse events of special interest (AESI)

AESI were only defined for the Phase 3 trial and included treatment-related hypersensitivity/allergic reaction, serious infections, hypocalcaemia, osteonecrosis of the jaw, atypical femoral fracture and dermatologic reactions.

Study B1000-NHV-01-G-01

Even though no AESIs were prespecified for the Phase 1 study, the same AEs which were prespecified as AESIs in the Phase 3 study and reported in the Phase 1 study are briefly described below.

In general, the AESI rate was low. No AESI related to hypocalcaemia, treatment-related hypersensitivity, serious infections, osteonecrosis of the jaw, and atypical femoral fracture was reported in the study.

One dermatological allergic skin reaction (qualifies for both AESI terms "dermatological reaction" as well as "allergic reaction") was reported. The other AESIs in the SOC of skin and subcutaneous disorders included one event of "skin exfoliation" and one event of "rash," both reported for Bmab 1000. All the reported AESIs were Grade 1 or 2 in severity, and all these events were resolved by the end of the study. No safety concerns regarding AESI were noted in the study.

Study B1000-PMO-03-G-02 02 – Part 1 (double-blind active-controlled)

A total of 23 treatment-emergent- AESIs were reported in 21 (4.4%) patients (9 AESIs in 3.4% patients in the Bmab 1000 group and 14 AESIs in 5.4% patients in the Prolia group). Except for adjusted calcium decreased (in 4 patients), alopecia, hypocalcaemia, and urticaria (in 2 patients, each), no other treatment-emergent- AESI was reported in >1 patient.

Of the 23 treatment-emergent AESIs in 21 patients, 4 treatment-emergent AESIs in 3 patients were serious (2 patients in the Bmab 1000 group and 1 patient in the Prolia group). The serious AESIs were vestibular neuronitis, ear inflammation, and urosepsis in the Bmab 1000 group and staphylococcal sepsis in the Prolia group.

The majority of AESIs were Grade 1 [12 (2.5%) patients] or Grade 2 [6 (1.3%) patients] in severity. Number of AESIs with severity ≥Grade 3 was low. Grade 3 AESIs of urosepsis and vestibular neuronitis were reported in 1 patient each in the Bmab 1000 group. One Grade 4 treatment-emergent AESI of staphylococcal sepsis was reported in 1 patient in the Prolia group.

Drug-related hypersensitivity/allergic reaction of Grade 1 injection site erythema was reported in 1 patient in the Prolia treatment group. The injection site erythema resolved within 1 day of onset.

Table 58: TEAEs of special interest by severity, SOC, and PT - Double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

System Organ Class Preferred Term Severity	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Number of AESI TEAEs	**9**	**15**	**24**
Grade 1[a]	2 (22.2)	11 (73.3)	13 (54.2)
Grade 2[a]	5 (55.6)	3 (20.0)	8 (33.3)
Grade 3[a]	2 (22.2)	0	2 (8.3)
Grade 4[a]	0	1 (6.7)	1 (4.2)
Number of patients with at least 1 AESI TEAE	**8 (3.4)**	**14 (5.8)**	**22 (4.6)**
Grade 1	2 (0.8)	10 (4.2)	12 (2.5)
Grade 2	4 (1.7)	3 (1.3)	7 (1.5)
Grade 3	2 (0.8)	0	2 (0.4)
Grade 4	0	1 (0.4)	1 (0.2)
Grade 1 AESI TEAE			
Adjusted calcium decreased	0	3 (1.3) [3]	3 (0.6) [3]
Hypocalcaemia	1 (0.4) [1]	1 (0.4) [1]	2 (0.4) [2]
Urticaria	0	2 (0.8) [3]	2 (0.4) [3]
Alopecia	1 (0.4) [1]	0	1 (0.2) [1]
Blood calcium decreased	0	1 (0.4) [1]	1 (0.2) [1]
Drug hypersensitivity	0	1 (0.4) [1]	1 (0.2) [1]
Hand dermatitis	0	1 (0.4) [1]	1 (0.2) [1]
Rash	0	1 (0.4) [1]	1 (0.2) [1]
Grade 2 AESI TEAE			
Acne	0	1 (0.4) [1]	1 (0.2) [1]
Adjusted calcium decreased	1 (0.4) [1]	0	1 (0.2) [1]
Alopecia	1 (0.4) [1]	0	1 (0.2) [1]
Dermatitis	0	1 (0.4) [1]	1 (0.2) [1]
Dermatitis atopic	1 (0.4) [1]	0	1 (0.2) [1]
Ear inflammation	1 (0.4) [1]	0	1 (0.2) [1]
Erythema	1 (0.4) [1]	0	1 (0.2) [1]
Rash pustular	0	1 (0.4) [1]	1 (0.2) [1]
Grade 3 AESI TEAE			
Urosepsis	1 (0.4) [1]	0	1 (0.2) [1]
Vestibular neuronitis	1 (0.4) [1]	0	1 (0.2) [1]
Grade 4 AESI TEAE			
Staphylococcal sepsis	0	1 (0.4) [1]	1 (0.2) [1]

Notes: The following adverse events are considered as AESI: drug-related hypersensitivity/allergic reaction, serious infections, hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reaction.

CTCAE: Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.

[E] represents the number of AEs at each level of summarization.

n represents the number of patients at each level of summarization.

Percentages were based on the number of patients in the SAF within each treatment.

For Part 1, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the study drug by investigator.

At each level of patient summarization, a patient was counted once for the worst CTCAE grade if the patient reported 1 or more events, and all events were counted independently of the worse CTCAE grade.

If the severity of an AE was missing, the AE was summarized as Grade 3.

The severity of AEs was rated using CTCAE, Version 5.0.

Adverse Events were coded using MedDRA, Version 27.0.

a. The percentages were calculated based on the number of events.

Source: Table 14.3.1.9.1

Table 59: Posthoc treatment-emergent AESI by relationship to study drug (excerpt)

System Organ Class Preferred Term Relationship	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Total number of TEAEs of Special Interest[a]	9	15	24
Not Related	4 (44.4)	9 (60.0)	13 (54.2)
Related	5 (55.6)	6 (40.0)	11 (45.8)
Number of subjects with at least one TEAE of Special Interest	8 (3.4)	14 (5.8)	22 (4.6)
Not Related	3 (1.3)	8 (3.3)	11 (2.3)
Related	5 (2.1)	6 (2.5)	11 (2.3)

Study B1000-PMO-03-G-02 – Part 2 (transition)

Three patients reported 3 AESIs (acarodermatitis, blood calcium decreased, and rash pruritic, in 1 patient, each; all non-serious); all in Bmab 1000-Bmab 1000 treatment group. The AESIs of blood calcium decreased and rash pruritic (1 patient each) were considered as study drug-related. None of the treatment-emergent AESIs were serious. All 3 AESIs resolved.

2.5.8.4. Laboratory findings

Study B1000-NHV-01-G-01

No relevant trends were noted for mean change from baseline for any haematology, coagulation parameters, blood chemistry, and urinalysis parameters. There was no clinically relevant change in calcium corrected for albumin.

Study B1000-PMO-03-G-02 – Part 1 *(double-blind active-controlled)*

Haematology

Treatment-emergent AEs in the SOC blood and lymphatic system disorders were reported in 6 (1.3%) patients [3 (1.3%) patients each in the Bmab 1000 and Prolia groups].

Treatment-emergent AEs of iron deficiency anaemia, macrocytosis, and thrombocytopenia were reported in 1 patient each in the Bmab 1000 group. Anaemia, leukopenia, lymphadenitis, and neutropenia were reported in 1 patient each in Prolia group. All the TEAEs were considered not related to the study drug.

Clinical Chemistry

Treatment-emergent AEs related to changes in clinical chemistry parameters were reported under the SOC of metabolism and nutrition disorders [40 (8.4%) patients] and investigations [27 (5.6%) patients]. Of these, the TEAEs of blood parathyroid hormone increased [Bmab 1000 1 patient (0.4%); Prolia 3 patients (1.3%)], adjusted calcium decreased [Bmab 1000 1 patient (0.4%); Prolia 2 patients (0.8%)], hypocalcaemia [1 patient each (0.4%)], and blood calcium decreased [Prolia 1 patient (0.2%)] were considered related to the study drug.

Urinalysis

Treatment-emergent AE of haematuria in 1 patient in Bmab 1000 group and leukocyturia in 1 patient in the Prolia group were reported during the double-blind, active-controlled period, and both TEAEs were considered not related to the study drug.

Study B1000-PMO-03-G-02 – Part 2 (transition)

Haematology

Treatment-emergent AEs in the SOC of blood and lymphatic system disorders were reported in 2 patients and included leukopenia and neutropenia (1 patient in the Prolia-Bmab 1000 treatment group) and anaemia (1 patient in the Prolia-Prolia treatment group); none were considered as study drug-related.

Clinical Chemistry

Treatment-emergent AEs related to changes in clinical chemistry parameters were reported under the SOCs of metabolism and nutrition disorders (6 patients) and investigations (9 patients). Of these, the TEAEs of blood parathyroid hormone increased, blood calcium decreased, and blood creatine phosphokinase increased in 1 patient each were considered related to the study drug.

Urinalysis

No urinalysis related TEAEs were reported.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Not applicable

2.5.8.7. Immunological events

For more detailed information please refer to section 3.3.1.2 Immunogenicity of this AR.

Study B1000-NHV-01-G-01

Immunogenicity between Bmab 1000-P and Prolia was assessed in terms of the incidence and titre of ADAs. Serum samples for immunogenicity assessment were collected at Day 0, Day 10, Day 29, Day 57, Day 85, Day 169, and Day 253.

The incidence of final ADA in the Prolia group and in the Bmab 1000 group closely matched throughout the study: the number of participants with ADA+ increased until D57 (91 [98.9%] participants in the Bmab 1000 group and 87 [93.5%] participants in the Prolia group), and was stable until D85 (91 [98.9%] participants in the Bmab 1000 group and 88 [94.6%] participants in the Prolia group). The number of participants with ADA+ were decreased until the EOS visit, when 5 (5.4%) participants in the Bmab 1000 group, and 2 (2.2%) participants in the Prolia group, were positive. All subjects (100%) in both treatment arm have at least one post-baseline evaluable ADA+ assessment.

The evolution of ADA titres over time in both treatment groups were similar. The ADA titres increased until D57, with a mean ± SD value of 530.42 ± 270.59 versus 498.38 ± 273.14 and sustained higher until D85 with a mean ± SD value of 532.58 ± 272.79 versus 444.72 ± 273.72, in the Bmab 1000 group and in the Prolia group, respectively.

Similar to ADA incidence rate, ADA titres decreased by the EOS visit in both treatment groups with mean ± SD value of 161.20 ± 125.23 in the Bmab 1000 group, and 81.30 ± 7.78 in the Prolia group.

Study B1000-PMO-03-G-02 – Part 1 *(double-blind active-controlled)*

Immunogenicity between Bmab 1000-P and Prolia was assessed in terms of the incidence and titre of ADA and the incidence of NAb. Serum samples for immunogenicity assessment were collected at Day 1 (pre-dose), Day 15, Day 29, Day 85, Day 183 (pre-dose), Day 267, and Day 365 (pre-dose).

Five patients (2 and 3 patients in the Bmab 1000 and Prolia groups, respectively) were positive for ADA at baseline (pre-dose) and all 5 patients exhibited no neutralizing capacity (Nab negative).

During the Double-Blind Active-Controlled Period, the proportion of patients with ADA-positive (420 [87.9%] patients) and treatment-emergent ADA-positive (416 [87.0%] patients) was high and similar between both the Bmab 1000 and Prolia groups treatment groups. The number of patients with nAb was very low (12 [2.5%] patients) and were similar between both groups.

Treatment-emergent ADA were reported in 416 (87.0%) patients (213 [89.5%] and 203 [84.6%] patients in the Bmab 1000 and Prolia groups, respectively). Of the 420 patients with ADA-positive, for 12 patients (7 and 5 patients in the Bmab 1000 and Prolia groups, respectively), the detected ADAs exhibited the neutralizing capacity (Nab positive).

Of all patients who experienced injection site reactions (N=6), none had reported positive ADA status on the day of reaction except for 1 patient from the Bmab 1000 treatment group. This patient reported injection site reaction post second dose administration on Week 26. The event was Grade 1 in severity and recovered in a day. The patient was positive ADA post dosing on Day 1 (week 1) and at week 52, however, the patient did not have hypersensitivity reaction during this time. The patient was transiently positive for ADA and remained Nab non-reactive throughout the study.

None of the patients who reported injection site reactions on Day 1 were ADA positive at baseline; they were ADA negative on Day 14 postdose and continued to be ADA negative till Day 85 (12 weeks).

Study B1000-PMO-03-G-02 – Part 2 (transition)

Serum samples for immunogenicity assessment were collected on Day365 (predose), Day 393, Day 449, and Day 547.

Similar proportion of patients in all the 3 treatment groups were positive for ADA at predose Week 52 (32.1%, 29.8%, and 29.8% patients in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively).

Of the 426 patients in Part 2, 366 (85.9%) patients were ADA-positive; and the proportion was similar for all the 3 treatment groups (86.7%, 83.7%, and 86.5% patients in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively).

At Week 52, 1% patients in the Prolia-Bmab 1000 treatment group and no patients in the Bmab 1000-Bmab 1000 or Prolia-Prolia treatment group had NAb-positive results. Similar to Part 1, the proportion of patients with NAb-positive results was low for all patients in Part 2 (29 [6.8%] patients) with Bmab 1000-Bmab 1000 (10.1% patients) and Prolia-Prolia (5.8% patients) treatment groups. Importantly, the number of patients with NAb-positive result did not increase in patients transitioned from Prolia to Bmab 1000 (1.0% patients).

Two patients who reported injection site reactions (one in each group) had positive ADA on the day of reaction (Day 365 [Week 52]). The ADA status returned to negative within 28 days; and continued to be negative till Day 547 (Week 78).

None of the patients who transitioned from Prolia to Bmab 1000 reported any injection site reaction.

None of the patients in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000 or Prolia-Prolia treatment groups reported any drug-related hypersensitivity/allergic reactions.

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

Not applicable

2.5.8.9. Discontinuation due to adverse events

Study B1000-NHV-01-G-01

No subject was discontinued from the study due to a TEAE.

Study B1000-PMO-03-G-02 – Part 1 (double-blind active-controlled)

Discontinuation from study treatment

The study treatment was discontinued in 9 (1.9%) patients due to TEAEs (4 and 5 patients in the Bmab 1000 and Prolia groups, respectively).

Five of the 9 patients discontinued the study treatment due to serious TEAEs [3 patients in the Bmab 1000 group (pancreatic carcinoma in 2 patients and colon cancer in 1 patient) and 2 patients in the Prolia group (clear cell renal cell carcinoma and cerebrovascular accident in 1 patient each)]. These 5 patients were discontinued from the study (3 and 2 patients in the Bmab 1000 and Prolia groups, respectively.

Table 60: TEAEs leading to treatment discontinuation by SOC and PT – double-blind active-controlled period (SAF) - Study B1000-PMO-03-G-02

System Organ Class Preferred Term	Bmab 1000 (N=238) n (%) [E]	Prolia (N=240) n (%) [E]	Total (N=478) n (%) [E]
Number of TEAEs leading to treatment discontinuation	**4**	**7**	**11**
Number of patients with at least 1 TEAE leading to treatment discontinuation	**4 (1.7)**	**5 (2.1)**	**9 (1.9)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (1.3) [3]**	**1 (0.4) [1]**	**4 (0.8) [4]**
Clear cell renal cell carcinoma	0	1 (0.4) [1]	1 (0.2) [1]
Colon cancer	1 (0.4) [1]	0	1 (0.2) [1]
Pancreatic carcinoma	2 (0.8) [2]	0	2 (0.4) [2]
Nervous system disorders	**1 (0.4) [1]**	**1 (0.4) [1]**	**2 (0.4) [2]**
Cerebrovascular accident	0	1 (0.4) [1]	1 (0.2) [1]
Dizziness	1 (0.4) [1]	0	1 (0.2) [1]
Musculoskeletal and connective tissue disorders	**0**	**1 (0.4) [1]**	**1 (0.2) [1]**
Myalgia	0	1 (0.4) [1]	1 (0.2) [1]
Psychiatric disorders	**0**	**1 (0.4) [1]**	**1 (0.2) [1]**
Schizophrenia	0	1 (0.4) [1]	1 (0.2) [1]
Respiratory, thoracic and mediastinal disorders	**0**	**1 (0.4) [3]**	**1 (0.2) [3]**
Chronic obstructive pulmonary disease	0	1 (0.4) [1]	1 (0.2) [1]
Pulmonary fibrosis	0	1 (0.4) [1]	1 (0.2) [1]
Pulmonary mass	0	1 (0.4) [1]	1 (0.2) [1]

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients at each level of summarization; PT, preferred term; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Notes: In SOC and PT summarization, a patient was counted once if the patient reported 1 or more events.

Percentages were based on the number of patients in the SAF within each treatment.

[E] represents the number of AEs at each level of summarization.

n represents the number of patients at each level of summarization.

For Double-Blind Active-Controlled Period, TEAE was an event observed after first administration of study drug on Day 1 until Week 52 and no more than 6 months after last administration of study drug in case of early treatment discontinuation unless the TEAE was considered as related to the study drug by investigator.

Adverse Events were coded using MedDRA, Version 26.1.

Source: Table 14.3.1.10.1

Study B1000-PMO-03-G-02 – Part 2 (transition)

None of the patients in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000 and Prolia-Prolia treatment groups reported a TEAE leading to treatment discontinuation.

Discontinuation from study

Study B1000-PMO-03-G-02 02 – Part 1 (double-blind active-controlled)

7 patients (4 [1.7%] and 3 [1.2%]patients in the Bmab 1000 and Prolia groups, respectively) discontinued the study due to adverse events.

None of the patients discontinued the study due to TEAE.

2.5.8.10. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

Safety data collection

The clinical safety of Bmab 1000 versus Prolia has been assessed in two clinical studies: a Phase 1 study in healthy subjects (B1000-NHV-01-G-01), and a Phase 3 study in postmenopausal women with osteoporosis (PMO) (B1000-PMO-03-G-02) which consisted of 2 Parts

- Part 1: double-blind active controlled, administrations of 2 doses at baseline and at week 26
- Part 2: transition period, re-randomisation of Prolia group patients and 3rd dose at week 52.

In both studies the therapeutic dose of 60 mg was investigated. No studies were conducted with the reference product Xgeva as comparator.

Safety data collection occurred at reasonable and regular timepoints during both studies. Coding of AEs by MedDRA version 26.1. is adequate.

Owing to differences between the two studies in terms of the design, patient population, treatment duration, and data collection, an integrated analysis of the safety results was not performed. This is acceptable.

The safety analysis set (SAF), defined as all randomised patients who received at least 1 administration of study drug, comprised 478 women in study B1000-PMO-03-G-02 and 189 healthy volunteers (male and female) in study B1000-NHV-01-G-01. In addition, 426 patients who completed Part 1 of the study and entered Part 2 of the study received a third dose of the study drug (SAF-TP). The safety database is considered sufficiently large for the purpose of a similarity exercise.

Exposure

In the Phase 1 study B1000-NHV-01-G-01 all randomised patients were exposed to the study drug and received a single dose of 60mg denosumab, which were N=94 in the Bmab 1000 group and N=95 in the Prolia group. The total duration of study, excluding screening, was approximately 36 weeks.

Study B1000-NHV-01-G-01 has been completed on 06 Oct 2023.

In the Phase 3 study B1000-PMO-03-G-02 one patient of the randomised set did not receive study treatment, thus the safety set comprised N=238 patients in the Bmab 1000 arm and N=240 patients in

the Prolia arm. A total of 43 patients discontinued from study prior to Week 26 with more patients in the Bmab 1000 arm receiving a second dose of study drug at week 26 compared to the Prolia arm (93.3% vs 88.8%). It is stated in the CSR that reasons for not administering Dose 2 were not recorded for patients that discontinued treatment prior to week 26. Although this is unfortunate, it is not considered of concern as the overall number of patients receiving the second dose is sufficient in both treatment arms (and even higher in the Bmab 1000 arm).

The double-blind active controlled Part 1 of the study (up to 52 weeks) was completed on 19 Dec 2023 and Part 2 (transition period from Week 52 to Week 78) was completed on 12 Jun 2024.

Results

Treatment-emergent adverse events (TEAE)

In study B1000-NHV-01-G-01 approximately half of the patients experienced at least one TEAE.

In the Bmab 1000 group slightly fewer events were observed compared to Prolia (50.0% vs 54.7%). The severity of these events was evenly distributed between Grade 1 and 2 in the Prolia arm, while in the Bmab 1000 arm the majority of events was Grade 1. Except for one event in each treatment group (depression due to death of a family member (Prolia group; unrelated) and Grade 2 hypothyroidism (Bmab 1000 group; unlikely related to IMP)), all events had the outcome recovered/resolved.

There were no events of higher severity, serious TEAE, TEAEs leading to discontinuation or deaths.

The most common SOCs were "gastrointestinal (GI) disorders", "infections and infestations" and "musculoskeletal and connective tissue disorders" with the most commonly reported PTs 1) constipation, abdominal pain and diarrhoea, 2) nasopharyngitis, COVID-19 and pharyngitis, 3) back pain, myalgia and arthralgia.

There were some minor numerical imbalances between the treatment arms for "GI disorders" (Bmab 1000 21.3%; Prolia 15.8%) and "infections and infestations" (Bmab 1000 19.1%; Prolia 24.2%). The former are mainly driven by Grade 1 events in the Bmab 1000 group with an identical rate of Grade 2 events compared to Prolia while for the latter the driver were Grade 2 events in the Prolia arm. Besides that, the rate of Grade 1 and 2 events was overall balanced between the treatment arms.

Overall, the observed TEAEs were in alignment with the known safety profile of denosumab.

As opposed to the phase 1 study, in study B1000-PMO-03-G-02 the number of overall and related TEAEs was slightly lower in the Bmab1000 group compared to Prolia (59.2% vs 63.3% and 8.0% vs 11.3%, respectively).

The most common TEAE by SOC overall were "infections and infestations", "musculoskeletal and connective tissue disorders" and "nervous system disorders". The most commonly reported PTs were 1) upper respiratory tract infection, urinary tract infection and nasopharyngitis, 2) arthralgia, back pain, osteoarthritis and 3) dizziness and headache.

While the number of TEAEs by SOC and PT was largely comparable between the treatment arms, there were minor imbalances for the SOCs "nervous system disorders" and metabolism and nutrition disorders" with higher occurrence in the Prolia arm, while the SOC "musculoskeletal and connective tissue disorders" was more commonly reported in the Bmab1000 arm with back pain, osteoarthritis and pain in extremity reported slightly more often. However, these adverse events are common and known and the difference in numbers between the treatment arms is not considered of concern. Moreover, in the Bmab 1000 group nasopharyngitis, pharyngitis and laryngitis were reported more

commonly all of which are common cold symptoms and hence unlikely to be related to the study treatment.

The majority of these TEAEs was Grade 1 (Prolia: 47.2% vs Bmab 1000: 40.8%) and 2 (Prolia: 49.2% vs Bmab 1000: 53.9%). A marginally higher number of Grade 3 TEAEs was reported for the Bmab 1000 group (4.9%) compared to Prolia (3.1%) but there was no indication of any pattern as all TEAEs occurred only once. One Grade 4 TEAEs was reported in each group (Bmab 1000: pancreatic carcinoma, Prolia: Staphylococcus sepsis), and one Grade 5 event occurred in the Prolia group none of which was related to study treatment.

Overall, no major differences have been observed that would raise concern regarding similarity of Bmab 1000 to Prolia.

Treatment related TEAE

It is noted, that in the healthy volunteer study B1000-NHV-01-G-01 the number of patients with treatment-related TEAEs was almost twice as high in the Bmab 1000 group (9 out of 95 patients (9.5%)) compared to the Prolia group (16 out of 94 patients (17.0%)).

The difference was mainly driven by musculoskeletal disorders (back pain, myalgia, pain in extremity), abdominal disorders (constipation, abdominal pain, haemorrhoids) and nervous disorders (headache), the majority of which are known (common and very common) adverse drug reactions associated with denosumab. Most of these events was Grade 1 in severity and expectable in the population. Other PTs occurred only once in both treatment groups without a clear pattern observed.

Interestingly, the findings of the Phase 1 study are not observed in the Phase 3 study B1000-PMO-03-G-02 where the respective PTs occurred less frequently and with similar percentages in both treatment arms. Thus, the imbalance of treatment-related TEAEs in the Phase 1 trial is not considered to be attributed to relevant differences between Bmab1000 and Prolia.

In study B1000-PMO-03-G-02 fewer patients in the Bmab 1000 arm experienced TEAEs that were considered related to study treatment compared to the Prolia group (7.6% vs 9.8%).

These differences were mainly attributed to laboratory parameters and injection site reactions which occurred more frequently in the Prolia group. Apart from that the number of related TEAEs was overall comparable between the treatment groups. Except for one Grade 3 event of myalgia in the Prolia group, all other events were Grade 1 and 2 in severity.

In both studies the number of patients experiencing injection site reactions was low and comparable between the treatment arms.

Overall, the observed treatment-related TEAEs were in accordance with the known safety profile of denosumab. No new or unexpected AE were seen and none of the severe AE could be attributed to the MoA of denosumab. No differences in AEs were seen between treatment groups questioning biosimilarity.

Serious adverse events and deaths

In study B1000-NHV-01-G-01 no serious adverse events or deaths were reported.

In study B1000-PMO-03-G-02 the number of patients experiencing a serious TEAEs was twice as high in the Bmab1000 group compared to Prolia. However, none of them was considered related to the treatment. The largest imbalances were noted for the SOCs "neoplasms benign, malignant and unspecified" and "gastrointestinal disorders". Besides pancreatic carcinoma all events only occurred once. Hence, no clear pattern can be identified that would lead to the assumption of a different safety profile of Bmab 1000 compared to Prolia regarding the occurrence of serious TEAE. Of the 18 events in

the Bmab arm 1 events was Grade 1, 5 events were Grade 2, 11 events were Grade 3 and 1 event was Grade 4 in severity.

Narratives for all SAE have been provided. For the majority of PTs a relationship to the study treatment can be clearly excluded given the mode of action of denosumab and the timely occurrence of these events. This applies especially to neoplasms and cardiac disorders. There are some PTs that are known side effects of denosumab treatment, e.g. ear inflammation, abdominal pain, musculoskeletal disorder, urosepsis. However, after review of the respective narratives a relationship to the study treatment could be reasonably excluded as these events were mainly attributable to pre-existing medical conditions. In cases without prior medical history as reason, the narratives provided sufficient information to rule out a relationship.

One death occurred in the Prolia group: a Grade 5 cerebrovascular event in a 65-year old female with a medical history of smoking and a recent diagnosis of Grade 2 hyperlipidaemia. The event was not considered related to the study treatment.

Adverse events of special interest

AESI were only defined for the Phase 3 trial and included treatment-related hypersensitivity/allergic reaction, serious infections, hypocalcaemia, osteonecrosis of the jaw, atypical femoral fracture and dermatologic reactions. The chosen terms are deemed appropriate taking into account the safety profile of denosumab.

In study B1000-NHV-01-G-01 no AESI were predefined. However, using the definition of the Phase 3 trial, three events of dermatological reaction occurred in the Bmab 1000 group that qualified as AESI. One event each was considered related (skin exfoliation), possibly related (rash on torso and arms) and not related (allergic rash during screening) to study treatment.

In study B1000-PMO-03-G-02 fewer patients experienced AESI in the Bmab 1000 group compared to Prolia (N=8 (3.4%) vs. N=13 (5,4%)). The majority of these events were Grade 1 and 2 in severity and occurred only once with the exception of the following PTs: adjusted calcium decreased (N=3) and urticaria (N=2). Two Grade 3 events were reported in the Bmab 1000 group (urosepsis and vestibular neuronitis) and one Grade 4 event was reported in the Prolia group (staphylococcus sepsis). Of the events observed three were possibly related (Grade 2 alopecia, Grade 2 erythema, Grade 2 adjusted calcium decreased) and one event was considered definitely related (Grade 1 hypocalcaemia). All events were reported as recovered at the time of data cut-off.

Discontinuation due to adverse events

In study B1000-NHV-01-G-01 there were no discontinuations from treatment or study due to AEs.

In study B1000-PMO-03-G-02 the number of patients discontinuing treatment due to an AE was overall low and comparable between the treatment arms (Bmab 1000 N=4 (1.7%) and Prolia N=5 (2.1%). The same applies for the number of patients who discontinued from the study (Bmab 1000 N=3 (1.3%) and Prolia N=4 (1.7%).

In the Bmab group none of the AEs was considered related to treatment while 2 events in the Prolia group were considered probably and possibly related to the study drug (myalgia and COPD, respectively).

Immunogenicity

Immunogenicity results showed that almost all patients in the Phase 1 and Phase 3 trials were ADA-positive at one time during the study: Phase 1: Prolia 93.5% and Bmab 1000 98.9%; Phase 3: Prolia 85.4% and Bmab 1000 90.3%. As assays have evolved since the initial MA of the originator, this could be attributed to the use of a highly sensitive assay. It is reassuring that the incidence of ADA-positive

patients is largely comparable between the treatment arms and only a minor part were neutralizing Abs. The observed high rate of ADA positive patients does not seem to have an impact on patient safety.

Study B1000-PMO-03-G-02 – Part 2 (transition)

A transition as conducted in Part 2 of the pivotal Phase 3 study is not a prerequisite in the context of a comparability exercise for approval of a biosimilar in the EU. Nevertheless, the collected data are considered supportive in this regard.

Data for Part 2 were presented for the three treatment groups separately from week 52 to week 78 as well as throughout the study, i.e. from Day 1 to week 78. Results were overall comparable between the three treatment groups with similar incidences of overall TEAEs, related TEAEs and serious TEAEs. AESIs only occurred in the Bmab 1000-Bmab 1000 group but with a very low incidence (1.4%). No new safety signals were detected.

2.5.10. Conclusions on clinical safety

Based on the provided data of the two clinical studies, one in healthy volunteers (study B1000-NHV-01-G-01) and one in female PMO patients (B1000-PMO-03-G-02), no unexpected safety concerns were detected for Bmab 1000. The observed safety findings correspond to the known safety profile of the reference product Prolia and were overall balanced between treatment arms.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 61: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 62: Summary table of risk minimisation activities and pharmacovigilance activities by safety concern

Safety concern	Routine risk minimisation measures	Pharmacovigilance Activities
Hypocalcaemia	**Routine risk minimisation measures:** • SmPC sections 4.4 where recommendation regarding correction and monitoring of calcium levels is provided. • SmPC section 4.2, 4.3 and 4.8 • PL Section 2 and 4 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for hypocalcaemia. **Additional pharmacovigilance activities:** • None
Skin infection leading to hospitalisation	**Routine risk minimisation measures:** • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for infections. **Additional pharmacovigilance activities:** • None
Osteonecrosis of jaw	**Routine risk minimisation measures:** • SmPC Section 4.4 where oral hygiene and dental management guidance is provided. • SmPC Section 4.8 • PL Section 2 and 4 **Additional risk minimisation measures:** • Patient reminder card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for ONJ. **Additional pharmacovigilance activities:** • None
Hypersensitivity Reactions	**Routine risk minimisation measures:** • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for hypersensitivity. **Additional pharmacovigilance activities:**

		• None
Atypical Femoral Fracture	**Routine risk minimisation measures:** • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided. • SmPC Section 4.8 • PL Section 2 and 4 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for Atypical Femoral fracture. **Additional pharmacovigilance activities:** • None
Hypercalcemia in Paediatric patients receiving denosumab and after treatment discontinuation	**Routine risk minimisation measures:** • SmPC Section 4.2. • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None
Important potential risk		
Fracture healing complications	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for fracture healing complications **Additional pharmacovigilance activities:** • None
Infection	**Routine risk minimisation measures:** • SmPC Section 4.8 • PL Section 4 **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for infections. **Additional pharmacovigilance activities:** • None

Cardiovascular events	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None
Malignancy	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for malignancy. **Additional pharmacovigilance activities:** • None
Missing information		
None		

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

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

2.8.2. Additional monitoring

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

Bmab-1000-P and Bmab-1000-X are investigational medicinal products developed as biosimilar products to the reference products Prolia and Xgeva (INN: denosumab), respectively. The active pharmaceutical ingredient in Bmab-1000-P and Bmab-1000-X is denosumab. The project code for the proposed biosimilar denosumab drug substance (DS) is Bmab-1000, while the project codes for the proposed biosimilar drug products (DP) of Prolia and Xgeva are Bmab-1000-P and Bmab-1000-X, respectively.

This MAA is an application for the proposed biosimilar Evfraxy to Prolia 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 was originally approved in the European Union on 26/05/2010 (marketing authorisation holder: Amgen Europe B.V.).

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. The prevention of this RANKL/RANK interaction is the main mechanism of action of denosumab across all its approved indications.

The reference product Prolia received approval for one presentation (Prolia 60 mg/1.0 mL solution (60 mg/mL) for injection in pre-filled syringe for s.c. use).

The applicant proposes one presentation of the biosimilar Bmab-1000-P under the name Evfraxy: 60 mg/1.0 mL solution (60 mg/mL) for injection in pre-filled syringe.

Evfraxy (also referred to as Bmab 1000) contains the active substance denosumab and is being developed as a proposed biosimilar product to Prolia.

The proposed indications for Bmab 1000 are the same as those approved for Prolia:

- Treatment of osteoporosis in post-menopausal 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.

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

Quality aspects

A comprehensive similarity exercise following the general principles outlined in "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/247713/2012) was performed. EMA/CHMP scientific advice has been followed in the presented similarity exercise.

Bmab 1000 (Bmab 1000-P and Bmab 1000-X), US-licensed and EU-approved Prolia and Xgeva (EU/US) have been compared. Bmab 1000-P has the same amino acid sequence, formulation, dosage form, and product strengths as reference product Prolia. Bmab 1000-X has the same amino acid sequence, formulation, dosage form, and product strengths as reference product Xgeva.

The comparative testing included analysis of biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, general properties and thermal stability studies. Appropriate analytical methods have been utilised to ensure an understanding of Prolia and Xgeva(EU/US) product profile and Bmab 1000 (Bmab 1000-P and Bmab 1000-X).

Non-clinical aspects

The non-clinical programme supporting the similarity of Bmab1000 (Bmab 1000-P and Bmab 1000-X) with reference products Prolia and Xgeva (EU/US) includes a comprehensive battery of *in vitro* pharmacodynamic characterisation studies comparing key biological activities.

In general, a step-wise approach following the general principles outlined in "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/ 2010) was performed.

Clinical aspects

Clinical Phase 1 Study B1000-NHV-01-G-01: A randomised, double-blind, 2-arm, single-dose, parallel-group study in healthy volunteers to evaluate the PK, PD, safety, tolerability, and immunogenicity of Bmab 1000 after a single 60 mg SC injection (prefilled syringe) in comparison with US-licenced Prolia. This was the pivotal PK similarity study designed in accordance with the EMA guideline [EMA/CHMP/BMWP/403543/2010].

A total of 189 healthy male and female subjects (Bmab 1000 n=94, US-Prolia n=95) were enrolled and randomised in a 1:1 ratio to receive either 60 mg SC Bmab 1000 or Prolia on Day 1. Post dosing, all participants were followed up for 36 weeks where blood samples were collected at scheduled timepoints for PK, PD, immunogenicity, and safety laboratory assessments. The participants were observed for a 36-week period for safety monitoring.

The primary objective was to demonstrate pharmacokinetic (PK) bioequivalence of Bmab 1000 versus US-Licensed Prolia. The 90% CI for the Bmab 1000 and to reference ratio of Prolia was tested against bioequivalence criteria and if it fell within the range of 80.00% to 125.00% for log-transformed Cmax, AUC0-t and AUC0-inf then PK bioequivalence would be concluded. Secondary objectives included additional PK parameters, PD assessments, safety and immunogenicity.

Clinical Phase 3 Study B1000-PMO-03-G-02: A randomised, double-blind, multicentre, parallel-arm, Phase 3 study to compare the efficacy, PD, safety, and immunogenicity between bmab 1000 and US-licenced Prolia in post-menopausal women with osteoporosis. A total of 479 postmenopausal women with osteoporosis were randomised in a 1:1 ratio for the main treatment period (52 weeks). The randomisation to treatment assignment was stratified by geographical region (US, Europe), prior use of bisphosphonate treatment (Yes, No) and age of the patient (<65, ≥65 years). In the transition period (week 52-78) subjects receiving US-licenced Prolia were re-randomised to receive either bmab 1000 or US-licenced Prolia. The subjects received in total three SC doses of 60 mg bmab 1000 or US-licenced Prolia. Overall, the design of the study is acceptable and has been discussed in CHMP

Scientific Advice. Generally, the design is in agreement with the advice received and supports the biosimilarity development. Updated data from Part 2 were submitted during the procedure.

For the demonstration of efficacy, %CfB at Week 52 in the lumbar spine BMD by DXA from baseline to Week 52 was assessed. Equivalence would be established if the 95% CI of the difference (Test-Reference) in mean percent change in the lumbar spine BMD from baseline to Week 52 was within the equivalence margin of (-1.45%, 1.45%). The co-primary endpoint included furthermore the AUEC of sCTX from baseline to 26 weeks. Bioequivalence was established if the ratio of GLSM and corresponding 95% CI are contained within the predefined bioequivalence range of 0.80 to 1.25. Secondary endpoints included additional efficacy, PD, safety and immunogenicity parameters.

The safety profiles of Bmab-1000-P, Bmab-1000-X and the respective reference products were assessed in the Phase I study as well as in the Phase III study.

3.2. Results supporting biosimilarity

Quality

A 3-way, side-by side comparability study was conducted to compare the biosimilar with the EU reference product, the biosimilar with the US reference product, and the EU reference product with the US reference products. The presented data of US reference products is considered supportive information and it serves to bridge the data for the comparative clinical studies that have been conducted with the US product. Acceptable number of reference product batches for setting acceptance criteria for similarity evaluation has been used.

A broad panel of orthogonal standard and sophisticated state-of-the-art methods has been applied for biosimilarity evaluation to address primary structure, product-related substances and impurities, higher order structure, general properties, biological activity (see also non-clinical section below), degradation studies and the targeted similarity assessment with the necessary level of depth. Methods were fully qualified/validated.

The presented analytical data demonstrate analytical similarity of the proposed biosimilar and the EU reference products Prolia and Xgeva. Minor differences have been observed and appropriately assessed by the applicant regarding their potential impact on clinical performance of the product. The observed differences are not expected to adversely impact clinical performance of the product.

Non-clinical

General similarity between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva (EU/US) has been demonstrated.

Clinical

PK

In the pivotal PK study (B1000-NHV-01-G-01), the point estimates [90% CIs] for test to reference ratios of Cmax, AUC0-t and AUC0-inf were as follows: Cmax: 111.43 [103.96; 119.43]; AUC0-t: 115.07 [106.45; 124.39]; AUC0-inf: 115.08 [106.53; 124.33] and thus, contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among bmab 1000 and US-licenced Prolia.

PD

The geometric LS means for the Phase 3 co-primary PD endpoint, s-CTX AUEC over the initial 26 weeks in mFAS population, were 11954.89 and 11481.40 for bmab 1000 and US-licenced Prolia group,

respectively. The geometric LS mean ratio was 104.12% with the 95% CI [97.74, 110.93] being entirely contained within the pre-defined equivalence limits of 80.00% to 125.00%. Results indicate PD similarity of bmab 1000 and US-licenced Prolia in the patient population.

Secondary PD endpoints Cmin, Tmin, sAUEC, Imax, TImax, and AUIC of sCTX as well as sCTX and P1NP mean serum concentration vs time curves in study B1000-PMO-03-G-02 were highly comparable for both products.

In the pivotal PK study the point estimates (95% CIs) of Test/Reference GLSMs ratio derived for Emax and AUEC0-253days were 103.43 [91.56; 116.84] and 104.59 [94.38; 115.91], respectively. Although no acceptance limits were predefined, the 95% CIs of GLSMs ratio for PD parameters (AUEC0-253 days and Emax), were entirely contained within the standard bioequivalence range of 80.00-125.00%. Overall, PD results from the phase 1 study in healthy volunteers support the claim on biosimilarity between bmab 1000 and US-licenced Prolia.

Efficacy

At Week 52, the difference in LS means (95% CI) in %CfB in lumbar spine BMD between the Bmab 1000-P and Prolia groups was 0.599 (-0.107, 1.306). The 95% CI of the difference in LS means %CfB in lumbar spine BMD was entirely contained within the predefined margin of (-1.45%, 1.45%), indicating therapeutic equivalence of Bmab 1000-P to Prolia was met in terms of the efficacy endpoint.

The secondary efficacy analysis of %CfB BMD of vertebral (Lumbar spine) and non-vertebral (Total Hip and Femoral Neck) structures did not reveal clinically remarkable difference between Bmab 1000 and Prolia and showed similar improvement in BMD of all vertebral and non-vertebral structures over time (Week 26 to Week 52) being supportive for the primary endpoint outcome.

Results at Week 78 support previous efficacy analyses.

Safety

In the Phase 1 study B1000-NHV-01-G-01 the safety profile in healthy volunteers was comparable between Bmab 1000 and Prolia. Frequencies and pattern of TEAE gave no cause for concern.

The observed higher frequency of treatment-related TEAEs in the Bmab 1000 was not observed in the Phase 3 trial. Hence, this finding is not considered to be attributed to relevant differences between Bmab1000 and Prolia.

There were no Grade 3 TEAE, serious TEAE, TEAEs leading to discontinuation or deaths.

In the Phase 3 study B1000-PMO-03-G-02 the number of overall and related TEAEs was slightly lower in the Bmab1000 group compared to Prolia. Despite minor imbalances between the treatment arms, the most commonly observed TEAEs by SOC and PT were in alignment of the known safety profile of denosumab. The majority of events was Grade 1 and 2 in severity.

A marginally higher number of Grade 3 TEAEs was reported for the Bmab 1000 group (4.9%) compared to Prolia (3.1%) but there was no indication of any pattern as all TEAEs occurred only once.

The number of patients experiencing a serious TEAE was twice as high in the Bmab1000 group compared to Prolia. However, none of them was considered related to study treatment which was supported by the provided narratives, that could reasonably exclude any relationship as these events were mainly attributable to pre-existing medical conditions.

Fewer patients in the Bmab 1000 arm reported AESI compared to Prolia. The number of patients discontinuing treatment due to an AE was overall low and comparable between the treatment arms

Based on the provided safety data of two clinical studies, no unexpected safety concerns were detected. The observed safety findings correspond to the known safety profile of the reference products Prolia and Xgeva. No major differences have been observed that would raise concern regarding similarity of Bmab 1000 to Prolia.

Immunogenicity

ADA incidence rates were comparable between bmab 1000 and Prolia at each time point investigated in both, healthy subjects and post-menopausal women with osteoporosis.

3.3. Uncertainties and limitations about biosimilarity

Quality

None

Non-clinical

None

Clinical

PK

None

PD

None

Efficacy

None

Safety

None

Immunogenicity

None

3.4. Discussion on biosimilarity

Quality

Prolia (Bmab 1000-P) (60 mg PFS) is developed as a proposed biosimilar product to EU-approved Prolia. In parallel, Vevzuo (Bmab 1000-X) (120 mg Vial) is developed as a proposed biosimilar product to EU-approved Xgeva. The analytical similarity exercise was designed to integrate the characterisation of both formulations of Bmab 1000 to demonstrate overall biosimilarity of Bmab 1000 to the RMPs.

In general, a sound and well-established biosimilarity evaluation was performed. The recommendations from the scientific advice addressing the design and conduct of the biosimilarity evaluation have been considered. A 3-way, side-by side comparability study was conducted to compare the biosimilar with the EU reference product, the biosimilar with the US reference product, and the EU reference product with the US reference products. The presented data of US reference products is considered supportive information and it serves to bridge the data for the comparative clinical studies that have been

conducted with the US product. Acceptable number of reference product batches for setting acceptance criteria for similarity evaluation has been used.

A broad panel of orthogonal standard and sophisticated state-of-the-art methods has been applied for biosimilarity evaluation to address primary structure, product-related substances and impurities, higher order structure, general properties, biological activity, degradation studies and the targeted similarity assessment with the necessary level of depth. Methods were fully qualified/validated.

The presented biological and physiochemical comparability data support the claim of biosimilarity for Bmab 1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva (EU/US). All biological activities relevant to the primary mechanism of action, including RANKL binding, inhibition of NF-κB activation, and inhibition of RANKL-induced osteoclast differentiation, are similar.

Overall, all observed differences in Bmab1000 (Bmab 1000-P and Bmab 1000-X) compared to reference products Prolia and Xgeva (EU/US) were adequately discussed and shown not to affect the biological function related to the mechanism of action. Therefore, the presented quality data supports the biosimilarity between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva (EU/US).

Non-clinical

A comprehensive battery of *in vitro* pharmacodynamical characterisation studies was performed to compare the key biological activities of Bmab 1000 DP (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva (EU/US).

The assays assessed the primary pharmacodynamics of Bmab 1000 (denosumab) that directly impact clinical effects, including RANKL binding, inhibition of NF-κB activation, and inhibition of RANKL-induced osteoclast differentiation. In addition, binding to various Fc receptors (including FcRn) and complement factor C1q. All methods used in the functional similarity exercise were qualified or validated and suitable for the intended purpose.

Results obtained across the various comparative assays demonstrate that Bmab1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva are highly similar in terms of primary pharmacodynamics. Consequently, the applicant has sufficiently demonstrated biological/functional similarity between Bmab1000 (Bmab 1000-P and Bmab 1000-X) and reference products Prolia and Xgeva (EU/US).

Clinical

PK

In healthy subjects receiving a single 60 mg denosumab dose, the 90% CIs for test to reference ratios of Cmax, AUC0-t and AUC0-inf were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for the pair-wise comparison among bmab 1000 and US-licenced Prolia. Thus, PK biosimilarity has been demonstrated.

It is noted that the upper bound of the 90% CI for AUC0-t and AUC0-inf was very close to the upper limit of the acceptance range and for all 3 parameters the lower limit of 90%CI was above 100% (Cmax: 111.43 [103.96; 119.43]; AUC0-t: 115.07 [106.45; 124.39]; AUC0-inf: 115.08 [106.53; 124.33]). Furthermore, somewhat higher denosumab concentrations have been observed for bmab 1000 vs US-licenced Prolia at each time point investigated in healthy subjects and osteoporosis patients. Notably, dissimilarity of partial AUC113-253 was observed in the pivotal PK study, with bmab 1000 values being approximately 40% higher compared to Prolia. As AUC113-253 constitutes less than 3% of the AUC0-t, the impact on exposure is considered negligible. Overall, the slightly higher mean denosumab concentration obtained with the biosimilar in both, healthy subjects and patients, is not

expected to have a negative impact on efficacy. Furthermore, the safety margin of denosumab is broad: denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1,080 mg over 6 months), and no additional adverse reactions were observed.

PD

In the osteoporosis population, AUEC over the initial 26 weeks of the bone resorption marker s-CTX were highly comparable for bmab 1000 and US-licenced Prolia group. The geometric LS mean ratio was 104.12% with the 95% CI [97.74, 110.93] being entirely contained within the pre-defined equivalence limits of 80.00% to 125.00%. Furthermore, all secondary PD endpoints and concentration time profiles for s-CTX and P1NP were comparable between both treatment groups in both, healthy subjects and osteoporosis patients. CTX is not validated to correlate with a clinically important outcome, however, both co-primary endpoints complement each other and provide evidence for similarity in terms of efficacy. Thus, PD results support the claim on similarity in terms efficacy.

Efficacy

In summary, the provided clinical data support the biosimilarity between Bmab 1000 and US-Prolia.

Safety

A sufficiently large number of patients was treated with Bmab 1000 and the reference medicinal product Prolia in the two clinical studies. The overall study duration of 52 weeks in the Main Period of the Phase 3 study is considered adequate for the purpose of similarity assessment.

Overall, the submitted safety data are considered supportive for demonstration of biosimilarity.

Immunogenicity

High ADA incidence rates were determined in both, patient and healthy population, by the use of a highly sensitive assay. As ADA incidence was comparable in both products, the high rates are not of concern per se. No apparent correlation of antibody development with pharmacokinetics, clinical response or adverse event has been observed.

3.5. Extrapolation of safety and efficacy

Evfraxy (Bmab-1000-P) and Vevzuo (Bmab-1000-X) were developed as biosimilar products to the reference products Prolia and Xgeva. The active substance of Bmab-1000-P, Bmab-1000-X 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 of denosumab 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 may be allowed.

The extrapolation is further supported by the fact that the known PK, PD, 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 Evfraxy (Bmab 1000) and the reference product.

Based on the above, the safety and efficacy profile of Evfraxy (Bmab 1000) as assessed in the PMO indication can, in principle, be extrapolated to all indications applied for.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Evfraxy is considered biosimilar to Prolia. 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 Evfraxy is favourable in the following indication(s):

> Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Evfraxy significantly reduces the risk of vertebral, non-vertebral and hip fractures.
>
> Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Evfraxy significantly reduces the risk of vertebral fractures.
>
> Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

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 medical prescription.

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 card regarding osteonecrosis of the jaw is implemented.