BIOSIMILAR MULTI-DISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA 351(k)
Application Number	BLA 761436
Submit Date	September 14, 2024
Received Date	September 16, 2024
BsUFA Goal Date	September 16, 2025
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology Division of Oncology 1/ Office of Oncologic Diseases
Review Completion Date	See DARRTS stamped date
Product Code Name	Bmab 1000
Proposed Non-Proprietary Name[1]	Denosumab-kyqq
Proposed Proprietary Name[1]	Bosaya (proposed interchangeable biosimilar to US-Prolia); Aukelso (proposed interchangeable biosimilar to US-Xgeva)
Pharmacologic Class	Receptor Activator Of Nuclear Factor Kappa B (RANK) Ligand (RANKL) Inhibitor
Applicant	BioconBiologics UK Limited
Applicant Proposed Indication(s)	Bosaya (proposed interchangeable biosimilar to US-Prolia): • Treatment of postmenopausal women with osteoporosis at high risk for fracture. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

[1] Section 8 of the Biosimilar Mutli-Disciplinary Evaluation and Review discusses the acceptability of the proposed proper and proprietary names, which are conditionally accepted until such time that the application is approved.

	Aukelso (proposed interchangeable biosimilar to US-Xgeva): • Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Recommendation on Regulatory Action	Approval of Bmab 1000 as a biosimilar to US-Prolia and US-Xgeva. Provisional determination that Bmab 1000 meets the applicable standards of interchangeability with US-Prolia and US-Xgeva. Approval as interchangeable is precluded due to unexpired first interchangeable exclusivity for Jubbonti and Wyost.

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CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error and Prevention Analysis
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health
OTBB = Office of Therapeutic Biologics and Biosimilars

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multi-Disciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products

OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation

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1 Executive Summary

1.1 Product Introduction

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (i.e., RANKL). It is marketed in the United States under the trade names Prolia (60 mg/1 mL in a pre-filled syringe [PFS]) and Xgeva (120 mg/1.7 mL or 70 mg/mL in a single-dose vial). The indications and strength of US-Prolia are different from the indications and strength of US-Xgeva.

The Applicant proposes Bmab 1000 as an interchangeable biosimilar product to US-Prolia and US-Xgeva, and the proposed proprietary names are Bosaya and Aukelso, respectively.

The Applicant seeks the same indications for Bmab 1000 as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for Bmab 1000 will be the same as those of US-Prolia and US-Xgeva, which are listed below:

Bosaya:

- Strength: 60 mg/1 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Dosing regimen: 60 mg administered subcutaneously once every 6 months
- Indications:
    - Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
    - Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
    - Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
    - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
    - Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

Aukelso:

- Strength: 120 mg/1.7 mL
- Dosage form: injection
- Route of administration: subcutaneous
- Indications and associated dosing regimen:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected subcutaneously [SC] every 4 weeks)
  - Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy)
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (120 mg injected SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy).

1.2 Determination under section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable

1.3 Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL (receptor activator of the nuclear factor kappa-B ligand), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone.

This BLA contains sufficient data and information to demonstrate that Bmab 1000 has the same mechanism(s) of action as those of US-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment of Bmab 1000 and US-Prolia and US-Xgeva. The data provided support the conclusion that Bmab 1000 is highly similar to US-Prolia and US-Xgeva.

US-Prolia is licensed in 60 mg/1 mL in a pre-filled syringe (PFS) and US-Xgeva is licensed in 120 mg/1.7 mL or 70 mg/mL in a single-dose vial.

Bmab 1000 is proposed as below:

For subcutaneous injection:

- Single-dose prefilled syringe containing 60 mg denosumab-kyqq in 1mL solution
- Single-dose vial containing 120 mg denosumab-kyqq in 1.7 mL (70 mg/mL) solution

Bmab 1000 has the same route of administration, strengths, and dosage form as US-Prolia and US-Xgeva.

Additionally, the conditions for use for which the Applicant is seeking licensure have been previously approved for US-Prolia and US-Xgeva.

1.4 Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Biocon Biologics Limited (FEI: 3003981475) proposed for Bmab 1000 (denosumab-kyqq) drug substance and drug products manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage by Remote Regulatory Assessment (RRA).

1.5 Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

1.6 Biosimilarity and Interchangeability Assessment

Table 1. Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[2]	
Summary of Evidence	• The comparative analytical assessment included comparisons between Bmab 1000 and US-Prolia and between Bmab 1000 and US-Xgeva. • Bmab 1000 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components. • Bmab 1000 has the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	
Summary of Evidence	• The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity
Assessment of Residual Uncertainties	• There are no residual uncertainties from the pharmacology/toxicology assessment

[2] Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	• Pharmacokinetic (PK) similarity between Bmab 1000 and US-Prolia was demonstrated in healthy subjects in Study B1000-NHV-01-G-01 and supports demonstration of no clinically meaningful differences between Bmab 1000 and US-Prolia. • Because of demonstrated analytical similarity between B1000 and US-Xgeva and US-Prolia, PK data from Study B1000-NHV-01-G-01 also support the conclusion that Bmab 1000 would be expected to have similar PK as US-Xgeva. Comparative PK data generated with the 60 mg/1 mL (US-Prolia) strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL (US-Xgeva) strength. • The presence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were compared between Bmab 1000 and US-Prolia in healthy subjects (Study B1000-NHV-01-G-01) and female subjects with postmenopausal osteoporosis (Study B1000-PMO-03-G-02). The incidence of immunogenicity was comparable across treatment groups in both studies. Therefore, the data support that Bmab 1000 has no clinically meaningful differences from US-Prolia and US-Xgeva.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	• The Applicant conducted a randomized, double-blind comparative clinical study (Study B1000-PMO-03-G-02) in 478 post-menopausal women with osteoporosis to compare the PK, pharmacodynamics (PD), efficacy, safety, and immunogenicity of Bmab 1000 and US-Prolia. Patients were randomized to receive Bmab 1000 or US-Prolia 60 mg injected SC every six months for one year (Part 1). After one year, patients initially assigned to US-Prolia during Part 1 of the study were re-randomized to either continue US-Prolia or transition to Bmab 1000. Patients who received Bmab 1000 during Part 1 continued their treatment with Bmab 1000. Patients were followed for six months after the third dose of study drug.

	• This study demonstrated that Bmab 1000 and U.S.-Prolia have similar efficacy with respect to the percent change from baseline in bone mineral density (BMD) for lumbar spine at Week 52. The 90% confidence interval (CI) for the difference in mean change were within the pre-specified equivalence margin of ±1.45%. • The safety profiles of Bmab 1000 and U.S.-Prolia were comparable. The adverse events observed were consistent with the known safety profile of denosumab (as labeled in the U.S.-Prolia USPI). There were no meaningful differences in the incidence of specific adverse events between Bmab 1000 and U.S.-Prolia, and the small differences in incidences of some of the treatment emergent adverse events (TEAE) that were observed in the Bmab 1000 and U.S.-Prolia arms was likely due to chance. • The study also demonstrated similarity of Bmab 1000 and US-Prolia with respect to the pharmacokinetics of denosumab, pharmacodynamic effect on biomarkers of bone turnover, and immunogenicity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Switching Study	
Summary of Evidence	• FDA determined that a switching study is unnecessary to support a demonstration of interchangeability for Bmab 1000. • The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1000 and US-Prolia, or Bmab 1000 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.

Any Given Patient Evaluation	
Summary of Evidence	• The Applicant has provided adequate data and information, including the analytical and clinical data, to support a demonstration that Bmab 1000 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• Division of General Endocrinology (DGE) and the Division of Oncology 1 (DO1) have determined that the Applicant has provided adequate scientific justification and agrees with the Applicant's justification for extrapolation to the other indications listed in the US-Prolia and US-Xgeva USPIs being sought for licensure based on: 1) the mechanism of action of denosumab, 2) the analysis of the known safety and immunogenicity profiles of denosumab across each of the indications being sought, and 3) the assessment of any differences in expected toxicities for each indication. • The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of Bmab 1000 as interchangeable biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: ○ Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. ○ Treatment to increase bone mass in men with osteoporosis, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

	○ Treatment of glucocorticoid-induced osteoporosis who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. ○ Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer. ○ Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer ○ Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors ○ Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity ○ Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.
Assessment of Residual Uncertainties	• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of Bmab 1000 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the above indications.

1.7 Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that Bmab 1000 is highly similar to U.S.-Prolia and U.S.-Xgeva, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Bmab 1000 and U.S.-Prolia, or between Bmab 1000 and U.S.-Xgeva, in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that Bmab 1000 can be expected to produce the same clinical result as U.S.-licensed Prolia and U.S.-licensed Xgeva in any given patient. The risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1000 and U.S.-Prolia or between Bmab 1000 and U.S.-Xgeva is not greater than the risk of using U.S.-Prolia or U.S.-Xgeva without alternation or switch. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information,

demonstrates that Bmab 1000 is biosimilar to U.S.-Prolia and U.S.-Xgeva and meets the statutory criteria to be an interchangeable with U.S.-Prolia and U.S.-Xgeva as follows:

- Bmab 1000, 60 mg/mL injection for SC use in a single-dose PFS as an interchangeable biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- Bmab 1000, 120 mg/1.7 mL injection for SC use in a single-dose vial as an interchangeable biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

for each of the following indications for which US-Prolia and US-Xgeva have been previously approved and for which the Applicant is seeking licensure of Bmab 1000:

US-Prolia:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

US-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that Bmab 1000 meets the statutory interchangeability criteria for any condition of use as described above. However, pursuant to section 351(k)(6) of the PHS Act, FDA is unable to approve Bmab 1000 as interchangeable

because of unexpired first interchangeable exclusivity (FIE) for US-licensed Jubbonti and Wyost. FDA has previously determined that FIE for Jubbonti and Wyost will expire on October 29, 2025. Refer to the Purple Book at https://purplebooksearch.fda.gov/.

Therefore, BLA 761436 will be administratively split to facilitate an approval action for Bmab 1000 as biosimilar to US-Prolia and US-Xgeva ("Original 1") and a provisional determination that Bmab 1000 would be interchangeable with US-Prolia and US-Xgeva ("Original 2"), but for unexpired exclusivity.

The review team recommends approval of Bmab 1000 as a biosimilar product as follows:

- Bmab 1000, 60 mg/mL injection for SC use in a single-dose PFS is biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- Bmab 1000, 120 mg/1.7 mL injection for SC use in a single-dose vial is biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

The review team also recommends a Provisional Determination that:

- Bmab 1000, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- Bmab 1000, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

BLA 761436/Original 2 will receive a Provisional Determination letter. The Applicant is expected to submit an amendment seeking approval no more than six months prior to the expiration of such exclusivity or when the Applicant believes that BLA 761436 Original 2 will become eligible for approval.

The CDTL and Division Signatory agree with the above assessment and recommendation.

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Cross Disciplinary Team Leader, DGE

2 Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory History Related to Submission

Pre-IND 153805 for this product was opened in February 2021 with the submission of a Biosimilar Biological Product Development (BPD) Type 2 meeting request. The initial pre-IND meeting occurred on May 21, 2021, during which the development of Bmab 1000 as a biosimilar product to US-licensed Prolia and US-licensed Xgeva was discussed.

Key interactions between FDA and the Applicant are summarized in Table 2.

Table 2. Regulatory Milestones

Date	Event	Comments
5/21/2021	BPD Type 2 Meeting	Discussed development program, including the comparative analytical assessment plan, the nonclinical development plan, and the clinical development plan. FDA provided recommendations for the study design of the PK and comparative clinical studies.
2/11/2022	Study may proceed letter from FDA	FDA communicated that the PK study may proceed and recommended that the protocol exclude patients with serum 25-OH vitamin D level <20 ng/dL and include procedures for managing hypocalcemia. FDA also provided guidance for the comparative analytical assessment between Bmab 1000 and US-licensed Prolia and Xgeva.
3/10/2022	Advice letter from FDA	FDA provided feedback for the comparative clinical study, which included clinical and statistical recommendations.
11/9/2022	Advice letter from FDA	FDA communicated that a switching study would not be necessary to support interchangeability.
2/17/2023	BPD Type 2a Meeting	FDA clarified that the advice letter dated November 9, 2022, specifically pertains to conducting a switching study. The Applicant should include a single transition assessment in the comparative clinical study to support demonstration of biosimilarity.
6/1/2023	Advice letter from FDA	FDA communicated the necessity of addressing statutory requirements in the application to support a demonstration of interchangeability for Bmab 1000.
4/26/2024	BPD type 4 meeting (preliminary comments; video conference was cancelled)	Discussed planned 351(k) BLA submission. FDA provided feedback regarding the Applicant's proposed approach to submission of stability data and shipping validation study protocol. FDA recommended that the completed 78-week comparative clinical study report should be included with the initial BLA submission, rather than only including transition data in a subset of the population (as proposed by the Applicant).
8/2/2024	Advice letter from FDA	FDA communicated that two months of post-transition safety data for the entire study population of the comparative clinical study should be submitted at the time of BLA submission, with the remaining follow up data to be submitted at the 120-day safety update.

2.2 Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

No in vivo nonclinical studies were submitted for Bmab 1000.

Table 3. Relevant Clinical Studies

Study Identity	EudraCT number	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
B1000-NHV-01-G-01	2021-006461-38	Compare the pharmacokinetics, pharmaco-dynamics, safety, and immunogenicity between Bmab 1000 and US-Prolia	Double-blind, randomized, 2-arm, single-dose, parallel-group, active-controlled study	Healthy adult patients	Bmab 1000 60 mg SC once (n = 94) US-Prolia 60 mg SC once (n = 95)
Comparative Clinical Study					
B1000-PMO-03-G-02	2021-006545-36	Compare the efficacy, safety, pharmacokinetics and pharmaco-dynamics of Bmab 1000 and US-Prolia	Randomized, multi-center (EU and US), double-blind study involving two treatment periods.	Women with post-menopausal osteoporosis	**Part 1** (52 weeks): • US-Prolia 60 mg SC q6 mo (241 patients randomized, 240 received study drug) • Bmab 1000 60 mg SC q6 mo (N=238) **Part 2** (26 weeks): • US-Prolia 60 mg SC q6 mo (N=104) • Bmab 1000 60 mg SC q6 mo (N=322)

Authors:

Carly Gordon, MD
Clinical Reviewer, DGE

Shivangi Vachhani, MD
Clinical Team Leader

3 Summary of Conclusions of Other Review Disciplines

3.1 Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761436 for Bosaya and Aukelso manufactured by BioconBiologics UK Limited. The data submitted in this application are adequate to support the conclusion that the manufacture of Bosaya and Aukelso are well-controlled and lead to products that are safe, pure, and potent. The comparative analytical data support a demonstration that Bosaya and Aukelso are highly similar to US-licensed Prolia and US-licensed Xgeva, respectively, notwithstanding minor differences in clinically inactive components. It is recommended that these products be approved for human use under conditions specified in the package inserts with the post market commitment to improve the container closure integrity test (CCIT) method for Bmab 1000 pre-filled syringe (PFS) (see section 11.2). Refer to OPQ memo in DARRTS dated September 05, 2025.

3.2 Devices

Bosaya is supplied as a drug-device combination product, and each prefilled syringe contains 60 mg of Bmab 1000. Aukelso is supplied as a single-dose vial, and hence, is not considered a drug-device combination product.

3.2.1 Center for Devices and Radiological Health (CDRH)

Based on the assessment of the needle safety feature of the proposed combination product, Bosaya, CDRH recommends approval.

3.2.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis (DMEPA 1) evaluated the Use-Related Risk Analysis (URRA) and comparative analyses (CA) to determine if human factors (HF) validation study results and comparative use human factors (CUHF) results are needed to support the marketing application for Bmab 1000 (Bosaya) 60 mg/mL PFS as an interchangeable biosimilar to U.S.-licensed Prolia. The DMEPA 1 team concluded that Biocon does not need to submit HF validation study and CUHF study results. Refer to the DMEPA 1 review dated March 26, 2025, in DARRTS.

3.3 Office of Study Integrity and Surveillance (OSIS)

OSIS audits were requested for two clinical sites (Biotrial Rennes in Brittany, France, and Biotrial Inc in Newark, New Jersey) and one analytical site (b) (4) OSIS determined that inspections are not needed for the all requested sites, as all requested sites were recently inspected for other biologics licensing applications; Biotrial Rennes previously underwent inspection in September 2024, Biotrial Inc underwent inspection in November 2024, and (b) (4)

underwent inspection in (b) (4) OSIS concluded that data from the studies were reliable.

Refer to the Bioequivalence Establishment Inspection Report Review dated on December 4, 2024, and January 2, 2025, in DARRTS for additional details.

3.4 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of three clinical investigators (CIs) in Poland, Dr. Anna Strelecka (Site #3001), Dr. Grzegorz Kania (Site #3013), and Dr. Rafal Plebanski for the clinical comparative study B1000-PMO-03-G-02.

Based on the overall inspection results of these CIs and the regulatory assessments, OSI concluded that Study B1000-PMO-03-G-02 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication. Refer to OSI review dated July 11, 2025, in DARRTS for additional details.

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4 Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1 Nonclinical Executive Summary and Recommendation

No in vivo animal studies were conducted with Bmab 1000 (i.e., Bmab 1000-P, Bmab 1000-X).

Bmab 1000 is a recombinant human IgG2 monoclonal antibody expressed in CHO cells with high affinity and specificity for RANKL. Bmab 1000 was developed to be highly similar and interchangeable to US-Prolia (Bmab 1000-P) and US-Xgeva (Bmab 1000-X) and has the same indications, dosage form, route of administration, and dosing regimen for Prolia and Xgeva. From a nonclinical perspective, the toxicity of denosumab products is a direct function of their affinity to RANKL and related activity barring any different in clinical PK parameters. The Applicant conducted an extensive battery of comparative physicochemical and in vitro functional tests to demonstrate biosimilarity, which are considered more sensitive than animal studies in detecting differences between monoclonal antibodies. The acceptability of the analytical characterization studies to demonstrate highly similar biological activity and physicochemical properties to US-Prolia and US-Xgeva was determined by the Product Quality review.

In summary, no animal studies were needed to support a determination of biosimilarity of Bmab-1000 to Prolia and Xgeva and nonclinical data were appropriate to support

biosimilarity. Refer to the Quality section of the review for an assessment of the in vitro studies to support biosimilarity.

4.1.1 Nonclinical Residual Uncertainties Assessment

There are no nonclinical residual uncertainties.

4.2 Product Information

Product Formulation

(b) (4)

The Bmab 1000-P and Bmab 1000-X drug product formulations are qualitatively identical to the listed Prolia and Xgeva drug products as shown in Table 4.

Table 4 – Drug Product Formulation

Qualitative and quantitative composition of Bmab 1000-P, Bmab 1000-X, Prolia® and Xgeva®

Component	Function	Bmab 1000-P	Prolia®	Bmab 1000-X	Xgeva®	Reference to quality standards
		Quantity in mg or Quantity per mL	Quantity in mg or Quantity per mL	Quantity in mg or Quantity per mL	Quantity in mg or Quantity per mL	
Denosumab	Active ingredient/Drug Substance	60 mg	60 mg	70 mg	70 mg	In-house specification
(b) (4)						
Sorbitol	(b) (4)	47 mg	47 mg	47 mg	46 mg	USP-NF/Ph. Eur.
Polysorbate 20		0.1 mg	0.1 mg	0.1 mg	0.1 mg	USP-NF/Ph. Eur.
Water for Injection		Q.S. to 1 mL	Q.S. to 1 mL	Q.S. to 1 mL	Q.S. to 1 mL	USP/Ph. Eur.
Sodium hydroxide	pH adjustment	Q.S to adjust pH 5.2[3]	Q.S to adjust pH 5.2	Q.S to adjust pH 5.2[3]	Q.S to adjust pH 5.2	USP-NF/Ph. Eur.
Glacial acetic acid			-		-	USP/Ph. Eur.
(b) (4)						
USP-NF = United States Pharmacopeia-National Formulary; Ph. Eur. = European Pharmacopeia.						
(b) (4)						

Source: Applicant submission

Comments on Excipients

There are no novel excipients in the drug products. Slight quantitative differences in the drug product formulation do not present any safety concerns (Table 4).

Comments on Impurities of Concern

The Applicant provided justification and safety assessments, where appropriate, for potential drug substance impurities and extractable and/or leachable compounds identified from drug product storage in container-closure systems. Impurity specifications were considered appropriate based on 'worst case scenario' calculations that showed exposures would be below permissible daily exposures (PDEs) identified or estimated by the Applicant.

A single compound, (b) (4) was measured above the analytical evaluation threshold (AET) from a the study which was designed to determine potential leachables from the storage bag and drug product contact materials (filter, tubing, disposable bags) during the manufacturing process. The Applicant conducted a safety assessment for the 'worst case scenario' exposure of (b) (4) from drug product storage and the concentration of (b) (4) was several orders of magnitude below the estimated PDE.

There are no nonclinical safety concerns from the identified or potential impurities or extractable/leachable compounds and the proposed drug substance specifications are considered acceptable from a nonclinical safety perspective.

Authors:

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Nonclinical Reviewer

David B. Carlson, PhD
Nonclinical Supervisor

5 Clinical Pharmacology Evaluation and Recommendations

5.1 Clinical Pharmacology Executive Summary and Recommendation

Table 5: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	The Sponsor is developing the following: • Proposed interchangeable biosimilar to Prolia: BOSAYA (Bmab 1000-P), containing denosumab 60 mg in 1 mL solution (60 mg/mL) in a single-dose prefilled syringe (PFS). • Proposed interchangeable biosimilar to Xgeva: VEVZUO (Bmab 1000-X), containing denosumab

Review Issue	Recommendations and Comments
	120 mg in 1.7 mL solution (70 mg/mL) in a single-dose vial. PK similarity between Bmab 1000-P and US-Prolia was demonstrated in Study B1000-NHV-01-G-01 (healthy male and female patients). PK/PD similarity was also confirmed in the comparative clinical study B1000-PMO-03-G-0 (postmenopausal women with osteoporosis). PK data from Study B1000-NHV-01-G-01 also support the conclusion that Bmab 1000-X would be expected to have similar PK as Xgeva because comparative PK data generated with the 60 mg/1 mL strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL strength. These results support the demonstration that Bmab 1000-X and Bmab 1000-P have no clinically meaningful PK differences from their respective reference products, Xgeva and Prolia. Taken together, the results support a conclusion that Bmab 1000 has no clinically meaningful differences from Prolia and Xgeva.
Immunogenicity	Immunogenicity data from the Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02 support the conclusion that Bmab 1000 has no meaningful differences from Prolia and Xgeva. This conclusion is based on the comparable incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) across treatment groups observed in both studies. No clinically significant impact of ADAs or NAbs was observed on the PK, PD, safety, or efficacy of the study drugs. Consequently, these findings further substantiate that Bmab 1000-X and Bmab 1000-P demonstrate no clinically meaningful differences from their respective reference products, Xgeva and Prolia.

The clinical development program of Bmab 1000 included two clinical studies:

B1000-NHV-01-G-01: A Randomized, double-blind, two-arm, Single-dose, Parallel–group “Phase 1” Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and tolerability of Bmab 1000-P and Prolia in normal healthy volunteers.

B1000-PMO-03-G-02: A Randomized, Double-Blind, Multi-center, Parallel-Arm "Phase 3" Study to Compare the Efficacy, Pharmacodynamics, Safety, and Immunogenicity Between Bmab 1000-P and Prolia in postmenopausal women with osteoporosis.

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (B1000-NHV-01-G-01).

PK similarity between Bmab 1000 and US-Prolia was demonstrated given that the 90% confidence intervals (CIs) for the ratios (Bmab 1000/Prolia) of geometric means for AUC0-inf, AUC0-last and Cmax were all contained within the pre-specified equivalence limits [0.80; 1.25], as shown in Table 6.

Table 6. Summary of statistical analyses for assessment of PK similarity (B1000-NHV-01-G-01)

Parameters	Statistics	Bmab1000	Prolia	Geometric Mean Ratio* (90% CI) Bmab1000 vs. US-Prolia
AUC_{0-t}	Least Square Geometric Mean	6981469 (N=91)	6042653 (N=93)	114.85 (106.27,124.12)
AUC_{inf}	Least Square Geometric Mean	7003783 (N=90)	6059016 (N=93)	114.91 (106.38, 124.12)
C_{max}	Least Square Geometric Mean	5633.1 (N=91)	5050.9 (N=93)	111.43 (103.96,119.4)

*Presented as percent. Source: FDA analysis

In addition to study B1000-NHV-01-G-01, PK/PD similarity was confirmed in study B1000-PMO-03-G-02, which consisted of a screening period, a Double-Blind Active-Controlled Period comparing Bmab 1000 vs. Prolia (Part 1), and a transition period focusing on the safety of Bmab 1000 and Prolia after a single transition from Prolia to Bmab 1000 compared with those continuing Prolia in Part 2 (Part 2).

Study B1000-NHV-01-G-01 is the pivotal BE study for this application. This study was conducted in two clinical sites (Site #1: Biotrial Rennes located in Brittany, France; Site #2: Biotrial, Inc. located in New Jersey, United States), and clinical samples were analyzed in one analytical site (b) (4)
The FDA Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the two clincal sites and the analytical site, because these sites were inspected earlier under other BLAs, and OSIS determined that data generated from these sites were reliable.

In terms of immunogenicity assessment, the incidences of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) were comparable between Bmab 1000-P and Prolia in Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02 (refer to Section 5.4.1 for details).

In conclusion, the clinical pharmacology data submitted supports the demonstration of no clinically meaningful differences between Bmab 1000-P and Prolia, and between Bmab 1000-X and Xgeva. This evidence contributes to the overall totality of evidence supporting the biosimilarity between Bmab 1000-X and Xgeva, and between Bmab 1000-P and Prolia. The clinical pharmacology review team recommends approval of BLA 761436.

5.1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology perspective.

5.2 Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable. The Sponsor used US-Prolia in study B1000-NHV-01-G-01 and Study B1000-PMO-03-G-02.

5.3 Human Pharmacokinetic and Pharmacodynamic Studies

As summarized in Section 5.1, the Applicant submitted two clinical studies to support a demonstration that Bmab 1000 has no clinically meaningful differences from Prolia and Xgeva. The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (B1000-NHV-01-G-01) and the additional PK and immunogenicity data from the comparative clinical study (B1000-PMO-03-G-02). The Applicant collected and analyzed PD data in both clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

5.3.1 STUDY B1000-NHV-01-G-01

Clinical Pharmacology Study Design Features

The PK similarity study was a randomized, double-blind, two-arm, single-dose, parallel-group study to compare the PK, PD, safety, and tolerability of Bmab 1000-P and Prolia in healthy male and female patients. Patients were administered SC with Bmab 1000 or Prolia. This study randomized a total of 189 patients (94 patients in Bmab 1000 group and 95 patients in Prolia group). Blood samples for PK analysis were collected at 0 (pre-dose), 4, 12 hours, and 1, 2, 3, 5, 7, 9, 12, 14, 17, 28, 42, 56, 70, 84, 112, 140, 154, 168, 196, 224, 252 days post-dose. PK data were available from 184 patients (91 from Bmab group, and 93 from Prolia group) for analysis.

Clinical Pharmacology Study Endpoints

- **Primary PK endpoints**: area under the concentration curve from 0 to last observation/infinity (AUC0-last/AUC0-inf) and maximum observed study drug

concentration (Cmax). To demonstrate PK similarity, the 90% CI of the geometric LS mean ratios needs to fall within 80-125%.

- **PD endpoints:** area under the effect-time curve (AUEC) of percent change from baseline (%CfB) in serum type 1 collagen carboxy terminal telopeptide (CTX). The 90% CI of the geometric LS mean ratios needs to fall within 80-125% to demonstrate PD similarity.
- **PK Datasets Analyzed:** A total of 184 patients (91 from Bmab group, and 93 from Prolia group) for PK analysis.

Bioanalytical PK Method and Performance

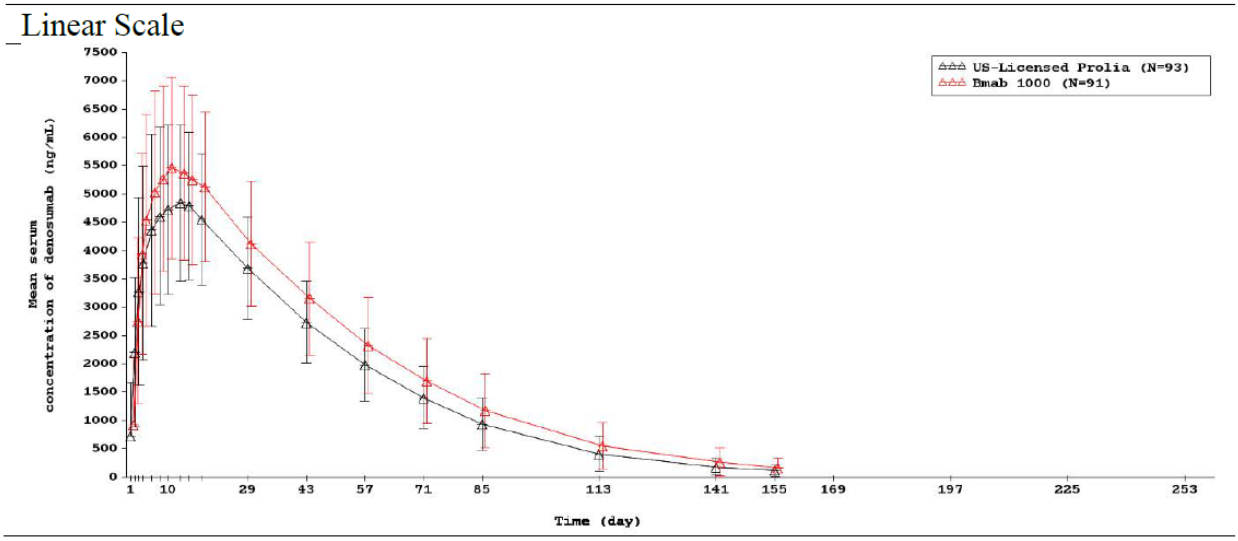
An electrochemiluminescence immunoassay (ECLIA) was used to determine the free or partially bound denosumab concentration in human serum. An MSD Multi-array 96 well Plate was first coated with an anti-denosumab antibody and incubated for 14-72 hours. Following a blocking step to minimize non-specific binding, serum samples, standards, and quality controls were added to the wells. After incubation, a sulfo-tag-labeled anti-idiotype detection antibody was applied, enabling electrochemiluminescent signal generation. The plate was subsequently washed and treated with glutaraldehyde, then read buffer was added. Signal detection was carried out using the MESO QuickPlex SQ 120 reader, producing relative light units proportional to analyte concentration.

This method was fully validated over a range of 3 to 75 ng/mL for denosumab in accordance with the Bioanalytical Method Validation Guidance from the Agency, and is considered suitable for the assessment of serum concentrations of denosumab. Refer to the Appendix 13.4.1 for more detailed information on method validation.

PK Similarity Assessment

The mean study drug serum concentration-time profiles are similar for all treatment groups (Figure 1). For the primary PK parameters (AUC0-last, AUC0-inf, and Cmax), the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (Table 7). Reviewer's analysis confirmed that the primary PK parameters met the pre-specified criteria for PK similarity (see Table 6 above).

Figure 1. Denosumab serum concentrations vs. time profile in Study B1000-NHV-01-G-01



Source: CSR of Study B1000-NHV-01-G-01, Figure 2

Table 7. Geometric mean ratio and 90% CI for primary PK parameters between the two treatment groups

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

*: Geometric lsmean.

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

Source: CSR of Study B1000-NHV-01-G-01, Table 9

Five patients (Patients [redacted](b) (6)) were withdrawn from the study due to early termination (see Table 8 below). The Applicant excluded these patients with early termination to avoid bias in the PK similarity assessment for AUC_{0-inf} and AUC_{0-t}.

Reviewer's comments: The Applicant's subject exclusion on the analysis of AUC_{0-inf} and AUC_{0-t} is adequate. Therefore, the reviewer did not conduct the sensitivity analysis on AUC_{0-inf} and AUC_{0-t} by including patients with early termination. For Cmax analysis, the reviewer noted that the PK profiles of three patients (Patients [redacted](b) (6)) among these five may allow reliable estimation of C_{max}. Therefore, the reviewer conducted sensitivity analysis for Cmax by including the aforementioned three patients, and found the Cmax also met the similarity criteria. Overall, the reviewer agreed with the Applicant's conclusion on PK similarity analysis for AUC and Cmax.

Table 8. Patients Excluded from Similarity Assessment

PK endpoints	Subject ID	Treatment	Reasons for exclusion
C_{max}, AUC_{0-inf}, AUC_{0-t}	(b) (6)	US-Prolia	Early Termination after Day 29.
C_{max}, AUC_{0-inf}, AUC_{0-t}		US-Prolia	Early Termination after Day 13.
C_{max}, AUC_{0-inf}, AUC_{0-t}		Bmab1000	Early Termination after Day 85.
C_{max}, AUC_{0-inf}, AUC_{0-t}		Bmab1000	Early Termination after Day 13.
C_{max}, AUC_{0-inf}, AUC_{0-t}		Bmab1000	Early Termination after Day 29.

Bioanalytical PD Method and Performance

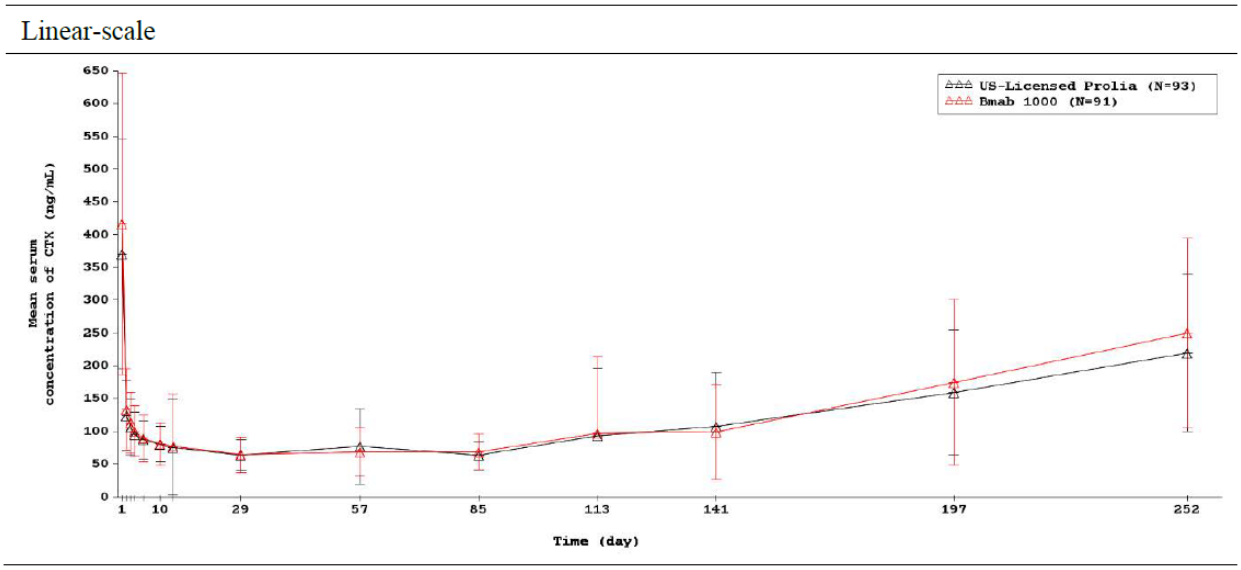
CTX in human serum (s-CTX) was quantified using a validated immunoassay. In this assay, samples were incubated with biotinylated monoclonal anti-β-CrossLaps antibody. β-CrossLaps present in the samples was captured by biotinylated monoclonal anti-β-CrossLaps antibody. Ruthenium complex-labeled monoclonal anti-β-CrossLaps antibody was then used to detect β-CrossLaps. When voltage was applied, the ruthenium complex produced an ECL signal. The resulting ECL was measured by a photomultiplier and the results were determined via master curve generated by the instrument.

All validation parameters passed the acceptance criteria, and the assays are considered appropriate for the quantification of CTX in human serum. The validated range of CTX measurement is 10-5000 pg/mL. A summary of the bioanalytical validation report to assess the PD marker can be found in the Clinical Pharmacology Appendices (Section 14).

PD Similarity Assessment

For the PD parameter in Study B1000-NHV-01-G-01, the arithmetic median percent change from baseline in s-CTX concentrations versus nominal time curves on linear scale is presented for treatment groups in Figure 2. The PD profiles for s-CTX were similar between Bmab 1000-P and Prolia.

Figure 2. Median Percent Change from Baseline for Serum Concentration of s-CTX versus Time



Source: CSR of Study B1000-NHV-01-G-01, Figure 3

In conclusion, the Applicant provided adequate clinical pharmacology data to establish PK similarity.

5.3.2 STUDY B1000-PMO-03-G-02

Clinical Pharmacology Study Design Features

This is a randomized, double-blind, multicenter, parallel-arm "Phase 3" study to compare the efficacy, pharmacodynamics, safety, and immunogenicity between Bmab 1000-P and Prolia in women with postmenopausal osteoporosis. It comprised 3 periods: Screening Period (from Day -28 to Day -1), Double-Blind Active-Controlled Period (Part 1, from Week 0 [Day 1] to Week 52 Predose, including two doses of the study drug on Day 1 and at Week 26) and a Transition Period (Part 2, from Week 52 to Week 78 [end-of-study {EoS} Visit]).

In Part 1, eligible patients were randomly assigned (1:1) to receive either Bmab 1000 (60 mg) or Prolia (60 mg) via SC injection on Day 1 (Week 0, the same date as randomization) and at Week 26. Patients were followed-up for 26 weeks after the second dose. All patients who completed Part 1 underwent the re-randomization process prior to the study drug administration at Week 52. Prior to dosing at Week 52, patients in the Prolia arm were randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia at Week 52. This was done to obtain data after a single switch in patients who had been treated with Prolia. To maintain the study blinding, the patients in the original Bmab 1000 arm also underwent the re-randomization procedure; however, they continued to receive Bmab 1000 treatment in Part 2.

During Part 1, comparative efficacy between Bmab 1000 and Prolia was evaluated based on the lumbar spine bone mineral density (BMD) measured at Week 52, after

administration of 2 doses (primary objective). Part 2 focused on the safety of Bmab 1000 and Prolia after the single transition from Prolia to Bmab 1000 compared with those continuing Prolia in Part 2.

BMD assessments were done at screening, Week 26, Week 52 and Week 78 (EOS). The PK samples were collected on Weeks 0 (baseline), 2, 4, 12, 23, 26 (predose), 38, 52 (predose), 56, 64, and 78. The PD samples were collected on Week 0 (Day 1), Week 0 (Day 3), and on Weeks 2, 4, 12, 20, 23, 26, 38, 52, and 78.

PK Assessment

The serum concentrations of study drug were similar between Bmab 1000-P and Prolia-treated patients, at all tested time points during Part 1 and Part 2 of the study (Table 9, Table 10, Figure 3).

Table 9. Summary of Serum Concentrations of Study Drug for Part 1 of Study B1000-PMO-03-G-02 (ng/mL)

Study Week (Day)	Summary Statistic	Treatment Bmab 1000-P (N=237)	Prolia (N=235)
Week 0 (D1)	n	237	234
	Mean	0.0230	1.71
	SD	0.354	17.8
	CV%	1539.5	1040.3
	Median	0	0
	Minimum	0	0
	Maximum	5.45	248
Week 2 (15)	n	199	194
	Mean	4970	4755
	SD	1581	1617
	CV%	31.8	34.0
	Median	4910	4690
	Minimum	453	1110
	Maximum	10500	11900
Week 4 (D29)	n	217	209
	Mean	4209	3972
	SD	1275	1287
	CV%	30.3	32.4
	Median	4210	3840
	Minimum	613	1020
	Maximum	7940	8600
Week 12 (D85)	n	210	195
	Mean	1373	1260
	SD	731	600
	CV%	53.3	47.6
	Median	1290	1250
	Minimum	84.6	4.75
	Maximum	3790	2870
Week 23 (D162)	n	197	193
	Mean	133	120
	SD	203	204
	CV%	152.4	169.5
	Median	38.2	36.2
	Minimum	0	0
	Maximum	907	1760
Week 26 (D183)	n	186	174
	Mean	54.4	40.3
	SD	118	88.7
	CV%	217.4	220.0
	Median	0	0
	Minimum	0	0
	Maximum	668	437
Week 38 (D267)	n	184	180
	Mean	1421	1315
	SD	758	657
	CV%	53.3	49.9
	Median	1315	1310
	Minimum	0	0
	Maximum	4300	3300
Week 52 (D365)	n	176	176
	Mean	70.2	38.6
	SD	162	81.2
	CV%	231.0	210.3
	Median	0	0
	Minimum	0	0
	Maximum	1270	434

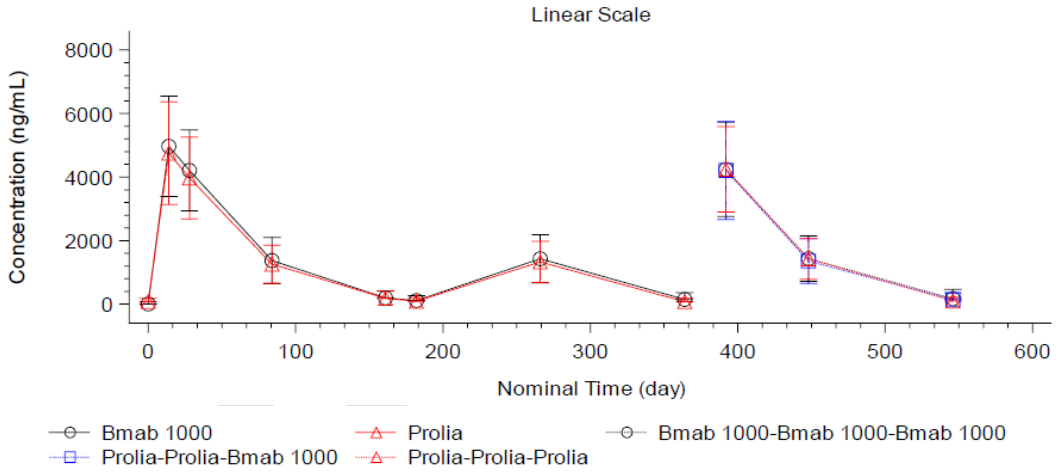
Source: CSR of B1000-PMO-03-G-02, Table 14.3.8.1.1

Table 10. Summary of Serum Concentrations of Study Drug for Part 2 of Study B1000-PMO-03-G-02 (ng/mL)

Study Week (Day)	Summary Statistic	Treatment Bmab 1000-P-Bmab 1000-P (N=218)	Prolia-Bmab 1000-P (N=104)	Prolia-Prolia (N=104)
Week 56 (D393)	n	171	80	89
	Mean	4190	4209	4242
	SD	1545	1541	1346
	CV%	36.9	36.6	31.7
	Median	4170	4165	4260
	Minimum	0	1580	1680
	Maximum	9580	8460	7930
Week 64 (D449)	n	175	83	80
	Mean	1426	1356	1426
	SD	724	706	639
	CV%	50.8	52.0	44.8
	Median	1340	1320	1375
	Minimum	0	123	135
	Maximum	4000	3700	3470
Week 78 (D547)	n	168	75	78
	Mean	89.1	69.9	61.6
	SD	226	175	107
	CV%	254.1	251.0	173.9
	Median	3.73	4.34	16.7
	Minimum	0	0	0
	Maximum	2160	1290	577

Source: CSR of B1000-PMO-03-G-02, Table 14.3.8.1.1

Figure 3. Mean (±SD) Serum Concentrations of Study Drug (Study B1000-PMO-03-G-02)



Source: CSR of Study B1000-PMO-03-G-02, Figure 14.3.8.1.1

PD Assessment

For the primary PD endpoint (AUEC of sCTX from baseline to 26 weeks), following a single administration of Bmab 1000-P to post-menopausal women with osteoporosis, sCTX AUEC up to 26 Weeks was comparable to that observed following a single administration of Prolia, with a geometric LS mean ratio (Bmab 1000-P / Prolia) of

104.12%, and the 95% CI around the GLSM ratio were contained within the acceptance limits (80.00% to 125.00%), as shown in Table 11.

Table 11. Ratio of the Geometric Means of s-CTX AUEC (Study B1000-PMO-03-G-02)

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: AUEC, area under sCTX curve; CI, confidence interval; LS, least squares. Comparability between Bmab 1000-P and Prolia was concluded if the 95% CI lie entirely within 80.00% to 125.00%.
Source: CSR of Study B1000-PMO-03-G-02, Table 14.2.3.1

In conclusion, the PK and PD data obtained in the comparative clinical study B1000-PMO-03-G-02 confirmed the PK similarity between Bmab 1000-P and Prolia observed in the comparative PK study.

5.4 Clinical Immunogenicity Studies

The clinical development program of Bmab 1000 encompassed two key studies, B1000-NHV-01-G-01 and B1000-PMO-03-G-02. Comparative immunogenicity assessments were conducted in both studies. In Study B1000-NHV-01-G-01, only ADAs were assessed. In Study B1000-PMO-03-G-02, both ADAs and NAbs were assessed.

5.4.1 Design features of the clinical immunogenicity assessment

Refer to Sections 5.3 and 6.2 for more detailed information on the design of the study.

5.4.2 Immunogenicity endpoints

Immunogenicity assessment was proposed as the secondary study endpoints in the following studies:

- Study B1000-NHV-01-G-01: Incidences of anti-drug antibodies (ADAs)
- Study B1000-PMO-03-G-02: Incidences of ADAs and neutralizing antibodies (NAbs) up to Week 78.

5.4.3 Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples

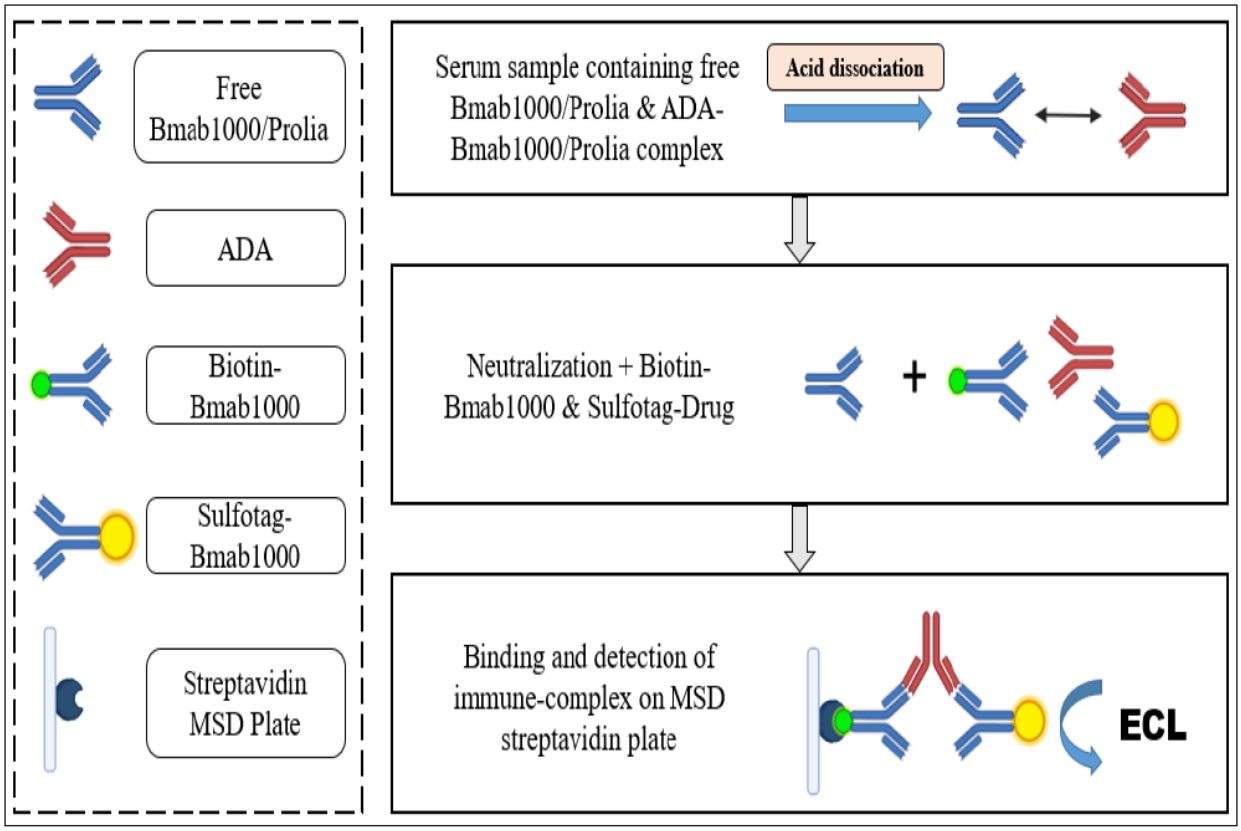
ADAs against denosumab in human serum were detected using an electrochemiluminescence (ECL) method, as shown in Figure 4 below. The test scheme for Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02 is summarized in Figure 5.

This comprised of an ADA screening test using the same bridging ECL assay in MSD format, with Bmab 1000 labeled antigen. All clinical samples were tested in an operator-blinded manner; samples which have at least one screened positive from the screening assay were then tested in a confirmatory step using the unlabeled version of the Bmab 1000 antigen.

The tolerance of the ADA assay to drug interference was evaluated using samples containing ADA against denosumab at the NC level, the LPC level (0.912 ng/mL), 100 ng/mL, and at the HPC level (400 ng/mL). These samples were pre-incubated with increasing amounts of Bmab 1000 or Prolia (i.e. 5.00, 10.0, 20.0, 50.0 µg/mL) for at least 1 hour and then analyzed in 3 duplicates per concentration in the screening format. The drug tolerance was found to be 20 µg/mL at LPC, 50 µg/mL at 100 mcg/mL and at HPC. The highest serum denosumab concentration measured in Phase 1 study B1000-NHV-01-G-01 is 11100 ng/mL and in Phase 3 study B1000-PMO-03-G-02 is 11900 ng/mL, which are much lower than the tolerance levels. This suggests that the ADA assay used in both the clinical studies is adequately tolerant to drug interference.

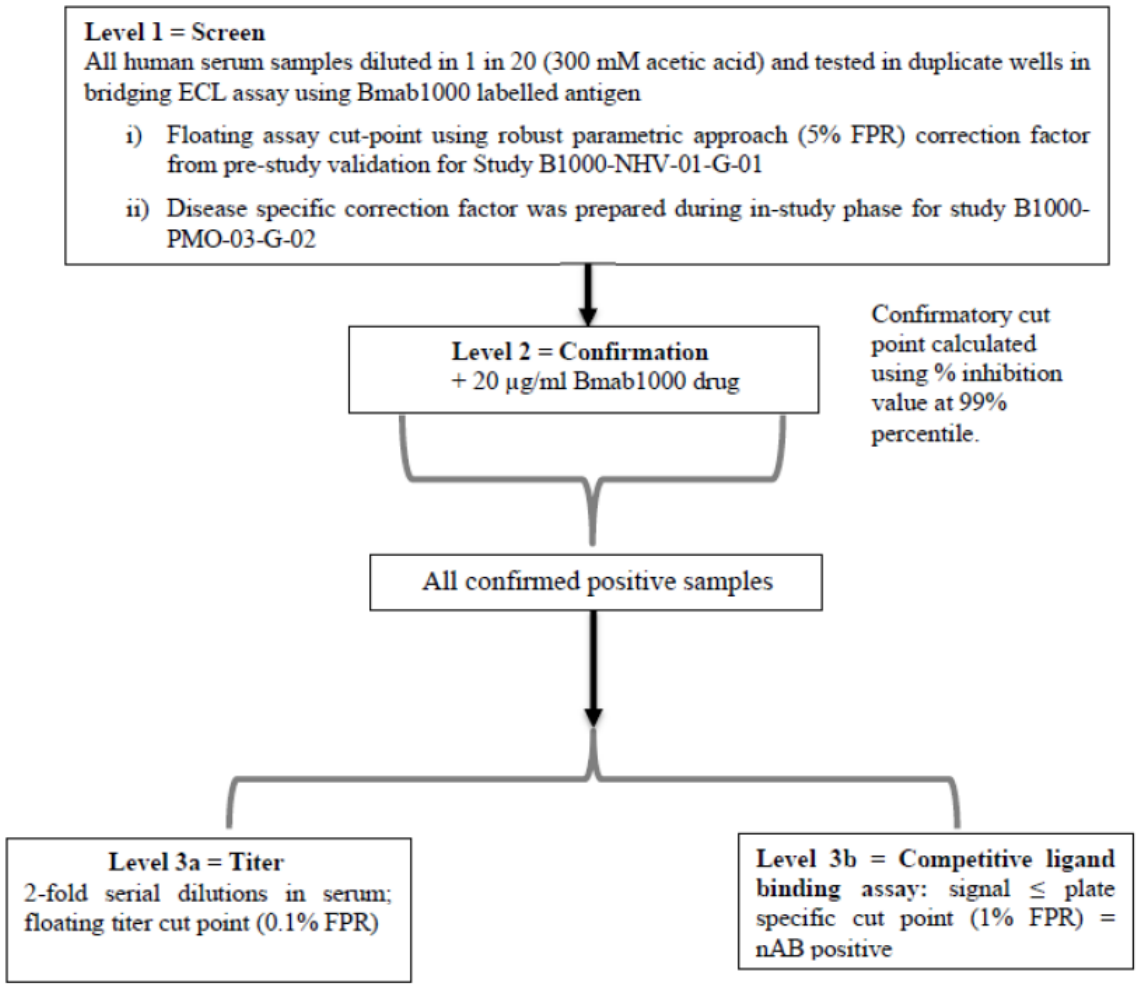
The Office of Product Quality Assessment III (OPQAIII) immunogenicity review team was consulted on the acceptability of the ADA assay. OPQAIII confirmed that the ADA assay demonstrated comparable antigenic equivalence between Prolia and Bmab1000, supporting its ability to differentiate immune responses between reference product and biosimilar treatment groups. Therefore, OPQAIII concluded that the ADA assay is suitable for its intended use.

Figure 4. Design of ADA assay format used for clinical sample analysis in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02



Source: ISI Report, Figure 2.3.2

Figure 5. Hierarchical testing scheme for ADA in Study B1000-NHV-01-G-01 and B1000-PMO-03-G-02



Source: ISI Report, Figure 2.3.1

5.4.4 Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

In Study B1000-NHV-01-G-01, blood ADA samples were collected at pre-dose, Days 10, 29, 57, 85, 169 and 253 (end of study). All the ADA samples had time-matched blood PK samples.

In Study B1000-PMO-03-G-02, blood ADA samples were collected at pre-dose, in active-controlled period (Days 1, 15, 29, 85, 183, 267, 365), in transition period (Days 393, 449) and at the end of study (Day 547). All the ADA samples had time-matched blood PK samples, and almost all time-matched blood PD samples except that PD samples were not collected on Day 393 and 449.

The immunogenicity assessment schedules in these two studies are deemed appropriate. These schedules include ADA sampling at baseline (pre-dose) and at multiple post-dose timepoints, extending beyond 5 half-lives of denosumab (according

to Prolia label, the mean half-life of denosumab is 25.4 days). This comprehensive sampling strategy allows for a thorough evaluation of the immunogenic response over time.

Furthermore, the study design incorporates concurrent measurement of drug concentrations at the same timepoints as immunogenicity sample collection. This parallel assessment of drug levels and ADA formation enhances the ability to interpret the immunogenicity data in the context of drug exposure.

The inclusion of baseline samples, multiple post-dose timepoints, and corresponding drug concentration measurements provides a robust framework for evaluating the immunogenicity profile of the study drug.

5.4.5 Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

Study B1000-NHV-01-G-01

The incidences of ADA were similar between Bmab 1000 group (100%, 94/94) and Prolia group (94%, 94/95). The number of participants with ADA+ increased until Day 57, and was stable until Day 85. All patients (100%) in both treatment groups had at least one post-baseline evaluable ADA+ assessment.

Study B1000-PMO-03-G-02

The incidences of ADAs and NAbs were similar between treatment groups.

In Part 1 (active-controlled period), the proportion of patients with ADA-positive sample at any time after initiation of treatment irrespective of the baseline result was 87.9% (420/478). The incidences were similar between both the Bmab 1000 (90.3%, 215/238) and Prolia (85.4%, 205/240) treatment groups.

In Part 2 (transition period), the 1:1 re-randomization of patients in the Prolia treatment group led to unequal (~2:1:1) number of patients in the Bmab 1000-Bmab 1000: Prolia-Bmab 1000: Prolia-Prolia treatment groups. Similar proportion of patients in all the 3 treatment groups were positive for ADA at predose Week 52 prior to dosing (32.1%, 29.8%, and 29.8% patients in the Bmab 1000-Bmab 1000, Prolia-Bmab 1000, and Prolia-Prolia treatment groups, respectively) and all patients exhibited no neutralizing capacity (NAb-negative), except for 1 patient in the Prolia-Bmab 1000 treatment group who was NAb-positive.

A total of 35 (10.9%) patients had NAb-positive results, the number of patients with NAb-positive results was higher in the Bmab 1000-Bmab 1000 (12.8% patients) treatment group compared to Prolia-Prolia (6.7% patients) treatment group. The incidence of Nab did not increase in patients who switched from Prolia to Bmab 1000, and the incidence of Nab was declining in both groups by week 78 to (almost) zero.

Reviewer's comment on observed high incidence of ADAs:

The observed ADA incidence is higher than that reported in the label of Prolia. The Prolia label states: "Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None

of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay."

It should be noted that the observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay, as emphasized in Prolia label. The Office of Product Quality Assessment III (OPQAIII) immunogenicity review team was consulted on this issue, which confirmed that the ADA assay demonstrated comparable antigenic equivalence between Prolia and Bmab1000, supporting its ability to differentiate immune responses between reference product and biosimilar treatment groups. Therefore, OPQAIII concluded that the ADA assay was suitable for its intended use, and the differences in ADA incidence between the Prolia label and the studies included in this application likely reflect differences in assay sensitivity.

5.4.6 Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product

Impact of ADA and NAb on PK/PD

B1000-NHV-01-G-01

In this study, the comparison in the primary PK parameters (AUCinf, Cmax, AUClast) was performed between the two treatment groups by post-dose ADA subgroup to evaluate the impact of immunogenicity on PK more precisely. As shown in Table 12, the denosumab serum concentrations over time were analyzed in ADA positive patients in groups of titers (quartiles) versus the ADA-negative patients. For this, the ADA titers were classified into low, moderate and high based on quartile distribution of subject titer 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 [Day 1 (predose), Day 10, Day 29, Day 57, Day 85, Day 169 and Day 253].

Table 12 Denosumab PK concentrations (ng/mL) by visit and ADA status and titer groups.

Treatment	Statistics	Denosumab concentration in ADA-Negative Subjects	Denosumab concentration in ADA-Positive Subjects	ADA-Positive (by group of titers)		
				Low	Moderate	High
Visit: D1 H00:00 (PRE-DOSE)						
US-Licensed Prolia (N=93)	n	92	1	1	0	0
	Arithmetic Mean [95% CI]	0.0 [NC]	0.0 [NC]	0.0 [NC]	NC	NC
	CV%	NC	NC	NC	NC	NC
	Median	0.0	0.0	0.0	NC	NC
	Min ; Max	0 ; 0	0 ; 0	0 ; 0	NC	NC
Bmab 1000 (N=91)	n	91	0	0	0	0
	Arithmetic Mean [95% CI]	0.0 [NC]	NC	NC	NC	NC
	CV%	NC	NC	NC	NC	NC
	Median	0.0	NC	NC	NC	NC
	Min ; Max	0 ; 0	NC	NC	NC	NC
Visit: D10 H216:00						
US-Licensed Prolia (N=93)	n	64	29	15	9	5
	Arithmetic Mean [95% CI]	4875.0 [4520.6 ; 5229.4]	4377.9 [3763.8 ; 4992.1]	4600.7 [3976.9 ; 5224.5]	3890.0 [2301.9 ; 5478.1]	4588.0 [1956.5 ; 7219.5]
	CV%	29.1	36.9	24.5	53.1	46.2
	Median	4950.0	4350.0	4720.0	3920.0	4310.0
	Min ; Max	1960 ; 7930	1220 ; 6760	2900 ; 6180	1220 ; 6650	1870 ; 6760
Bmab 1000 (N=91)	n	52	39	14	13	12
	Arithmetic Mean [95% CI]	5525.4 [5050.5 ; 6000.3]	5366.4 [4889.0 ; 5843.8]	5063.6 [4215.8 ; 5911.4]	5092.3 [4110.1 ; 6074.5]	6016.7 [5266.2 ; 6767.1]
	CV%	30.9	27.4	29.0	31.9	19.6
	Median	5535.0	5660.0	5110.0	5690.0	6430.0
	Min ; Max	2580 ; 9790	1890 ; 7440	1890 ; 7290	2140 ; 7440	4020 ; 7390
Visit: D29 H672:00						
US-Licensed Prolia (N=93)	n	15	78	23	36	19
	Arithmetic Mean [95% CI]	3492.7 [3046.7 ; 3938.6]	3726.9 [3519.7 ; 3934.2]	3498.7 [3104.1 ; 3893.3]	3768.3 [3520.6 ; 4016.1]	3924.7 [3345.8 ; 4503.6]
	CV%	23.1	24.7	26.1	19.4	30.6
	Median	3580.0	3710.0	3350.0	3730.0	3830.0
	Min ; Max	2220 ; 4640	1590 ; 6290	2190 ; 5200	1880 ; 5140	1590 ; 6290
Bmab 1000 (N=91)	n	16	75	16	40	19
	Arithmetic Mean [95% CI]	4185.6 [3499.8 ; 4871.4]	4106.5 [3858.7 ; 4354.3]	4110.6 [3541.8 ; 4679.4]	4170.8 [3822.9 ; 4518.6]	3967.9 [3434.0 ; 4501.8]
	CV%	30.7	26.2	26.0	26.1	27.9
	Median	4295.0	3970.0	3940.0	4240.0	3610.0
	Min ; Max	1990 ; 6410	1880 ; 7350	2300 ; 6100	2150 ; 7350	1880 ; 6190
Visit: D57 H1344:00						
US-Licensed	n	6	87	25	41	21
	Arithmetic	2216.7	1959.1	1769.3	2003.7	2098.0

Prolia (N=93)	Mean [95% CI]	[1568.4 ; 2864.9]	[1822.6 ; 2095.6]	[1511.6 ; 2027.0]	[1842.3 ; 2165.0]	[1715.9 ; 2480.2]
	CV%	27.9	32.7	35.3	25.5	40.0
	Median	2280.0	1970.0	1690.0	1990.0	2250.0
	Min ; Max	1320 ; 3030	539 ; 3440	601 ; 2940	1000 ; 3210	539 ; 3440
Bmab 1000 (N=91)	n	1	90	20	47	23
	Arithmetic Mean [95% CI]	3770.0 [NC]	2309.5 [2135.5 ; 2483.5]	2156.6 [1864.1 ; 2449.1]	2317.7 [2047.3 ; 2588.1]	2425.7 [2078.4 ; 2772.9]
	CV%	NC	36.0	29.0	39.7	33.1
	Median	3770.0	2215.0	2100.0	2220.0	2340.0
	Min ; Max	3770 ; 3770	610 ; 4370	782 ; 3300	610 ; 4370	1090 ; 4110
Visit: D85 H2016:00						
US-Licensed Prolia (N=93)	n	5	88	29	41	18
	Arithmetic Mean [95% CI]	836.8 [288.1 ; 1385.5]	936.1 [837.6 ; 1034.5]	867.7 [707.3 ; 1028.1]	911.8 [779.4 ; 1044.2]	1101.3 [803.0 ; 1399.7]
	CV%	52.8	49.6	48.6	46.0	54.5
	Median	1070.0	891.0	952.0	866.0	1020.0
	Min ; Max	328 ; 1220	33 ; 2160	33 ; 1520	219 ; 1740	170 ; 2160
Bmab 1000 (N=91)	n	1	90	16	48	26
	Arithmetic Mean [95% CI]	1110.0 [NC]	1173.7 [1035.6 ; 1311.7]	927.0 [686.6 ; 1167.4]	1128.1 [913.1 ; 1343.0]	1409.6 [1190.7 ; 1628.6]
	CV%	NC	56.2	48.7	65.6	38.5
	Median	1110.0	1115.0	912.0	982.5	1290.0
	Min ; Max	1110 ; 1110	83 ; 3760	91 ; 1910	83 ; 3760	328 ; 2410
Visit: D169 H4032:00						
US-Licensed Prolia (N=93)	n	2	34	5	22	7
	Arithmetic Mean [95% CI]	BLQ#	65.0 [43.1 ; 86.9]	BLQ#	55.2 [29.2 ; 81.2]	84.9 [27.8 ; 141.9]
	CV%	BLQ#	96.5	BLQ#	106.1	72.7
	Median	BLQ#	42.3	BLQ#	35.5	85.9
	Min ; Max	BLQ# ; 6	3 ; 237	BLQ# ; 217	4 ; 237	3 ; 175
Bmab 1000 (N=91)	n	1	40	3	19	18
	Arithmetic Mean [95% CI]	BLQ#	113.6 [71.5 ; 155.8]	BLQ#	114.2 [54.4 ; 173.9]	124.4 [50.2 ; 198.6]
	CV%	BLQ#	116.0	BLQ#	108.6	119.9
	Median	BLQ#	81.2	BLQ#	46.1	94.2
	Min ; Max	BLQ# ; 7	3 ; 618	BLQ# ; 108	3 ; 462	4 ; 618
Visit: D253 H6048:00						
US-Licensed Prolia (N=93)	n	0	0	0	0	0
	Arithmetic Mean [95% CI]	NC	NC	NC	NC	NC
	CV%	NC	NC	NC	NC	NC
	Median	NC	NC	NC	NC	NC
	Min ; Max	NC	NC	NC	NC	NC
Bmab 1000 (N=91)	n	0	1	0	0	1
	Arithmetic Mean [95% CI]	NC	BLQ#	NC	NC	33.2 [NC]
	CV%	NC	BLQ#	NC	NC	NC
	Median	NC	BLQ#	NC	NC	33.2
	Min ; Max	NC	BLQ# ; 33	NC	NC	33 ; 33

Note:
Low = ADA Titre <= Q1 / Moderate = Q1 < ADA Titre <= Q3 / High = ADA Titre > Q3.
#: No descriptive statistics are computed when more than half of the values are BLQ at a single time point. BLQ: below the limit of quantification (< 3 ng/mL); NC: not calculated.
Source: ISI Report, Table 3.2.5

As shown in Table 12, the distribution of denosumab concentrations as per the ADA status as well as ADA titers suggests that 95% CI of mean denosumab concentration overlapped in ADA status-positive (low/medium and high titer)/ and negative stratums. There was no trend toward decreased denosumab concentrations with increased ADA titers. In summary, the serum concentration of denosumab were not affected by the presence of ADAs.

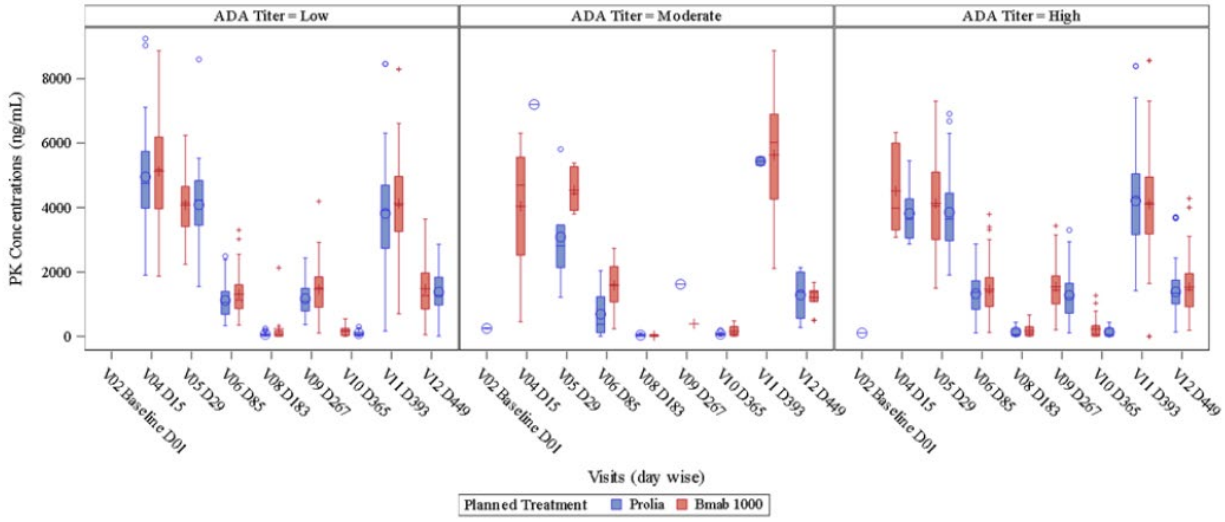
Study B1000-PMO-03-G-02

In this study, the impact of ADA status on denosumab PK and PD were evaluated.

For PK, an analysis was performed to evaluate the denosumab serum concentrations over time for ADA-positive patients in groups of titers (quartiles) and that of the ADA-negative patients for Bmab 1000 and Prolia treatment group. For this, the ADA titers were classified into low, moderate and high based on quartile distribution of subject titer values [low (<=Q1, for first 25%), medium (Q1-Q3, between 25 – 75%), high (>Q3, for last 25%) on visits where samples for immunogenicity evaluation were collected concurrently with the PK samples [Day 1 (predose), Day 15, Day 29, Day 85, Day 183 (predose), Day 267, Day 365 (predose), Day 393, Day 449, and Day 547].

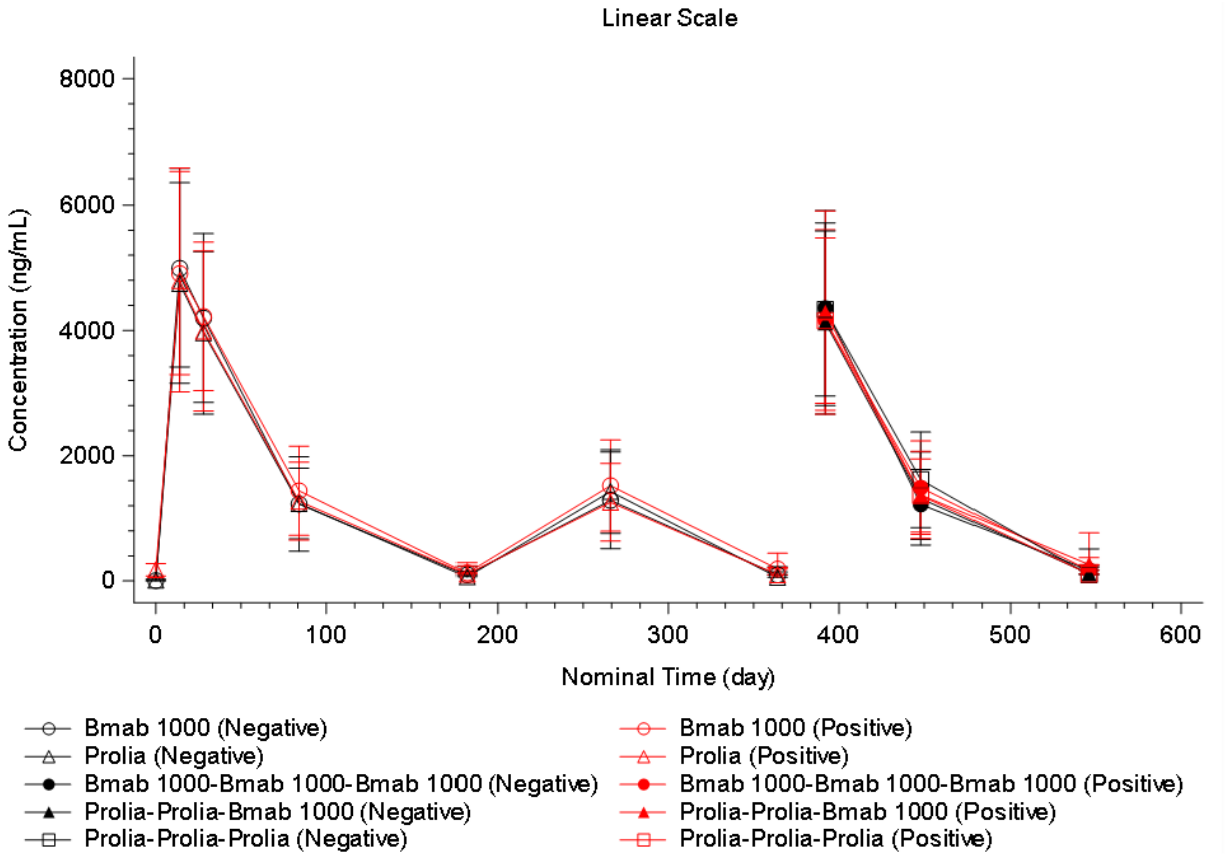
As depicted in Figure 6 and Figure 7, overtime the 95% CI of mean denosumab concentration generally overlapped in ADA status-positive (low/medium and high titre)/and negative stratums. NAb-positive incidences were low at different time points throughout the study, and therefore the denosumab concentrations in NAb-positive group were not compared to NAb-negative group. Overall, there was no trend toward decreased trough denosumab concentrations with increased ADA titers.

Figure 6: Boxplot of denosumab PK concentrations by visit and ADA titer groups (Study B1000-PMO-03-G-02)



Source: ISI Report, Figure 3.3.3

Figure 7. Posthoc mean (±SD) serum concentrations of denosumab over time by treatment and ADA status (Study B1000-PMO-03-G-02)



Source: ISI Report, Figure 3.3.4

For PD, the impact of ADA status/titer on PD marker (s-CTX concentrations) was evaluated in Study B1000-PMO-03-G-02. The s-CTX was similar irrespective of the ADA titer and are comparable between Bmab group and Prolia group (Table 13).

Table 13: Summary of s-CTX concentration (pg/mL) by ADA-status and group of titers

Treatment	Statistics	ADA-Negative	ADA-Positive	ADA-Positive (by group of titers)		
				Low	Moderate	High
Day 29						
US-Licensed Prolia (N=235)	n	137	89	49	23	17
	Mean (SD)	49.2 (22.095)	48.22 (17.542)	46.63 (14.699)	50.87 (21.768)	49.24 (19.334)
	Median	46	46	44	55	49
	Min, Max	5, 153	5, 98	21, 98	5, 81	5, 84
	Mean 95% CI	(45.46,52.93)	(44.53,51.92)	(42.41,50.85)	(41.46,60.28)	(39.29,59.18)

Treatment	Statistics	ADA-Negative	ADA-Positive	ADA-Positive (by group of titers)		
				Low	Moderate	High
Bmab 1000 (N=237)	n	122	110	49	30	31
	Mean (SD)	48.4 (19.303)	51.89 (21.44)	50.08 (21.019)	52.07 (19.442)	54.58 (24.186)
	Median	50	49	44	47	51
	Min, Max	5, 157	5, 141	5, 141	25, 115	5, 124
	Mean 95% CI	(44.94,51.86)	(47.84,55.94)	(44.04,56.12)	(44.81,59.33)	(45.71,63.45)
Day 183						
US-Licensed Prolia (N=235)	n	154	61	27	20	14
	Mean (SD)	151.69 (117.645)	87.69 (61.864)	91 (48.633)	100.45 (89.301)	63.07 (18.768)
	Median	130	75	79	75	62
	Min, Max	30, 1063	5, 372	5, 229	36, 372	27, 92
	Mean 95% CI	(132.96,170.42)	(71.84,103.53)	(71.76,110.24)	(58.66,142.24)	(52.24,73.91)
Bmab 1000 (N=237)	n	152	70	22	30	18
	Mean (SD)	147.55 (93.622)	86.6 (46.192)	99.55 (62.952)	86.73 (37.945)	70.56 (28.622)
	Median	122	71	68	75	66
	Min, Max	33, 592	27, 242	37, 242	27, 160	41, 142
	Mean 95% CI	(132.54,162.55)	(75.59,97.61)	(71.63,127.46)	(72.56,100.9)	(56.32,84.79)

Source: Table 3.3.6 of ISI Report

Impact of ADA and NAb on Safety and Efficacy

ADA Safety Analysis

The development of antidrug antibodies (ADA) primarily raises concerns about potential adverse events. Of particular concern are hypersensitivity reactions, which may occur if patients become sensitized to the drug through antibody formation. This immunological response could theoretically increase the risk of hypersensitivity-related adverse reactions upon subsequent drug exposure.

When analyzing the ADA positivity of patients treated during study B1000-PMO-03-G-02, a result of “positive” or “negative” was provided for each immunogenicity laboratory result, as well as an ADA titer level. A reference range for the titer assay was not provided, so this review evaluates immunogenicity by ADA positivity rather than titer level.

Study B1000-NHV-01-G-01

Injection sites were assessed until Day 10 i.e. on (Day 1) D1H0 (after study drug injection), 12 h, 24 h (D2), 48 h (D3), 72 h (D4), 144 h (D7) and 216 h (D10). The assessment was done for redness, bruising, swelling, itching, and pain. Two patients (1 with injection site erythema, 1 with injection site pain) in the Bmab 1000-P group and 1 subject (injection site reaction) in the Prolia group had injection site reactions. All these three patients were ADA negative at baseline and turned ADA positive after treatment. All these reactions were Grade 1 in severity and were possibly related to the study treatment. No hypersensitivity events were reported in the study. Overall, no data indicated that the ADA status had an impact on the incidence of hypersensitivity or allergic reaction.

Study B1000-PMO-03-G-02

Part 1

The incidence of treatment emergent ADA positivity at any time during Part 1 was high but similar in both the Bmab 1000 (N=213/238, 89%) and US-Prolia (N=203/240, 85%) treatment groups.

The Applicant provided an analysis of the most common safety events in newly ADA positive patients compared to patients who never developed ADA positivity during Part 1 of the study. In this analysis, the Applicant found that the incidence of TEAEs appeared to be similar in the two groups, with the most frequent system organ class (SOC) being *Infections and Infestations* for both groups. Minor differences were observed, such as *urinary tract infection* being the most frequently reported preferred term (PT) in the *Infections and Infestations* SOC among ADA-negative patients, while upper respiratory tract infection was most common in ADA-positive patients within the same SOC. These differences in individual TEAE incidence rates were minor and do not appear clinically significant.

In terms of the difference between hypersensitivity reactions in the ADA-positive and ADA-negative groups, hypersensitivity reactions were rare overall during Part 1, occurring in five patients, all in the Prolia treatment group (5/240, 2%). All five patients who experienced these reactions were ADA-positive, though notably none of the patients on Bmab 1000 who tested positive for ADAs experienced hypersensitivity reactions. Overall, due to the low incidence of hypersensitivity reactions and the high prevalence of ADA positivity, a definitive relationship between ADA status and hypersensitivity reactions cannot be established.

Part 2

The incidence of ADA positivity during Part 2 of the study in patients who were negative for ADAs at Week 52 was high but comparable for all treatment groups: 87% (N= 189/218) for the Bmab 1000/Bmab 1000 group, 84% (N= 87/104) for the US-Prolia/Bmab 1000 group, and 87% (N= 90/104) for the US-Prolia/US-Prolia treatment group.

The Applicant provided an analysis of the most common safety events in ADA-positive patients during Part 2 who were negative at week 52 compared to patients who never developed ADA positivity during Part 2 of the study. In this analysis of adverse events, the Applicant found that the incidence and pattern of preferred terms within each system organ class were similar between ADA-positive and ADA-negative groups overall during the transition period. As with Part 1, the most common events in Part 2 of the study were categorized under the *Infections and Infestations* SOC irrespective of ADA positivity status.

In addition, no hypersensitivity reactions were reported during Part 2 of the study. Therefore, the relationship between ADA positivity and hypersensitivity reactions development following transition from Prolia to Bmab 1000 could not be assessed.

Overall, it does not appear that development of anti-drug antibodies had a meaningful impact on adverse events or hypersensitivity reactions throughout Study B1000-PMO-

03-G-02, and there was no clinically meaningful difference between treatment groups in occurrence of immunogenicity.

NAb Efficacy Analysis

The primary clinical concern regarding neutralizing antidrug antibodies (NAbs) is their potential to reduce product efficacy. NAbs may bind to the drug, interfering with its ability to interact with the therapeutic target and potentially compromising its therapeutic effect.

When analyzing the NAb positivity of patients treated during study B1000-PMO-03-G-02, a result of “positive” or “negative” was provided for each immunogenicity laboratory result. A titer level was not provided.

Part 1

The incidence of treatment emergent NAb positivity at any time during Part 1 was infrequent in both the Bmab 1000 (N=7/238, 3%) and US-Prolia (N=5/240, 2%) treatment groups.

The Applicant provided an analysis of the comparative efficacy of patients who were NAb positive versus NAb negative during Part 1 of the study. Given that the number of patients who were NAb positive were so few, the population size in each subgroup (Bmab 1000 and US-Prolia treatment groups) was too small to allow for a meaningful assessment of the impact of NAb positivity on efficacy.

Part 2

The incidence of NAb positivity during Part 2 of the study in patients who tested negative for NAb at Week 52 was 10% (22/218), 1% (1/103), and 5.8% (6/104) in the Bmab 1000/Bmab 1000, Prolia/Bmab 1000, and Prolia/Prolia treatment groups, respectively.

Due to the limited number of patients who developed NAbs during Part 2 of study B1000-PMO-03-G-02, especially in the group transitioning from US-Prolia to Bmab 1000, a meaningful comparison of relative bone mineral density changes from baseline between treatment groups was again not feasible for NAb-positive patients.

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6 Statistical and Clinical Evaluation and Recommendations

6.1 Statistical and Clinical Executive Summary and Recommendation

The Applicant conducted a single comparative clinical study comparing the efficacy and safety of Bmab 1000 and US-Prolia in postmenopausal women with osteoporosis (Study B1000-PMO-03-G-02). The demographic and disease characteristics of the population at baseline was similar between the two treatment groups.

The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (LS-BMD) assessed by DXA at week 52 compared to baseline. At the end of Part 1 of the study (i.e., week 52), the difference in the mean percentage change from baseline in LS-BMD between the Bmab 1000 group and the US-Prolia group was 0.39 under the non-inferiority null imputation and 0.63 under the non-superiority null imputation of missing data, with the 90% confidence interval within the pre-defined equivalence margin of +/-1.45% (see Table 19). Therefore, this study demonstrated that there is no clinically meaningful difference between the two products with respect to efficacy. There was also no meaningful difference between Bmab 1000 and US-Prolia with respect to the nature or frequency of treatment emergent adverse events.

The single transition from US-Prolia to Bmab 1000 showed maintenance of efficacy (see Table 23) and was not associated with any increase in the nature or frequency of adverse events or evidence of immunogenic response.

6.1.1 Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2 Review of Comparative Clinical Studies with Statistical Endpoints

Study B1000-PMO-03-G-02: 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.

6.2.1 Data and Analysis Quality

There are no concerns regarding data quality and integrity

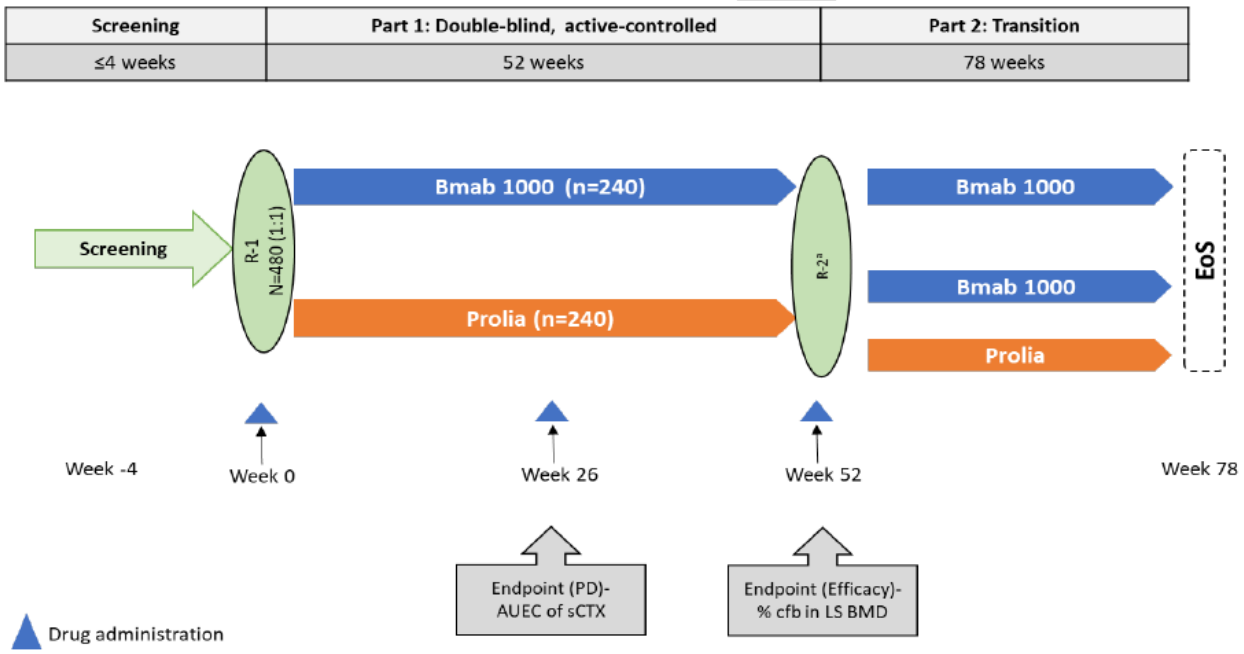
6.2.2 Study Design and Endpoints

Study B1000-PMO-03-G-02 was an international, multicenter, randomized, double-blind study consisting of two treatment periods. For the first treatment period (i.e., "Part 1"), a total of 479 female patients with post-menopausal osteoporosis (PMO) were randomized in a 1:1 ratio to receive either Bmab 1000 60 mg or US-Prolia 60 mg on Day 1 and at Week 26. Randomization on Day 1 was stratified by geographical region

(US/Europe), age group (<65 years/ ≥65 years), and prior bisphosphonates use (yes/ no).

At Week 52, patients entered Part 2 of the study. All patients in the Bmab 1000 group continued treatment with a third dose of Bmab 1000 60 mg SC. Patients who had received US-Prolia during Part 1 were re-randomized in a 1:1 ratio to either continue on US-Prolia 60 mg SC or switch to Bmab 1000 60 mg SC. Randomization at Week 52 was also stratified by the original strata used for the randomization on Day 1. Patients were followed for an additional 26 weeks. The study design is shown in Figure 8.

Figure 8. B1000-PMO-03-G-02 Study Design



Source: Figure 3-1, page 44 of B1000-PMO-03-G-02 clinical study report body

To qualify for study participation, patients had to be post-menopausal, aged 55 to 80 years, and have osteoporosis according to bone mineral density (BMD) criteria on DXA scan (absolute lumbar spine BMD T-score ≤ -2.5 and ≥ -4.0). Patients also had to be naïve to denosumab. Use of medications with bone effects, or presence of underlying conditions that could impact bone quality or density were additional exclusion criteria. Refer to Section 16.6 for complete list of entry criteria.

Bmab 1000 or US-Prolia were administered subcutaneously by blinded study staff, preferably in the abdomen. The dose used in the study is the same as the dose of US-Prolia indicated for treatment of postmenopausal osteoporosis [i.e. 60 mg injected subcutaneously (SC) every 6 months]. All patients received daily supplementation containing at least 1000 mg of calcium and at least 400 IU vitamin D from randomization until Week 78.

The study duration was 78 weeks, including 13 visits to the study clinic. Assessments included periodic testing of vital signs, ECG, and laboratory tests for safety. DXA scan was performed at screening and again at treatment weeks 26, 52, and 78. Immunogenicity assessment consisted of antidrug antibody and neutralizing antibody

testing and evaluation for injection site reactions. The complete schedule of assessments is shown in Table 50, in the Appendices.

The primary efficacy endpoint was the percentage change in lumbar spine bone mineral density (LS-BMD) assessed by DXA at Week 52 compared to baseline. The same DXA scanner was to be used for a particular patient for all study procedures, and all DXA scans were submitted to a central imaging vendor for analysis.

Key secondary endpoints include incidence of fracture up to Week 52 and the percentage change from baseline in BMD at lumbar spine assessed by DXA at Week 78.

6.2.3 Statistical Methodologies

Analysis Population

Part 1 randomized analysis set consisted of all participants who were randomized regardless of receiving the study drug. The Applicant's primary efficacy analysis was performed using the full analysis set (FAS), which was defined as all randomized participants who met the eligibility criteria and received at least 1 dose of study drug. Any participant who did not meet the eligibility criteria identified through the protocol deviation list was excluded from the FAS. The Applicant used this analysis dataset for the estimation of Estimand 1a-US FDA (Efficacy).

Primary Efficacy Analysis

The statistical hypotheses tested to assess similarity between Bmab 1000 and Prolia in terms of the percent change from baseline in LS-BMD at week 52 (Tests 1 and 2 below, respectively) is as follows:

Test 1: for non-inferiority (delta = -1.45):

H_0: $\mu_{Bmab\ 1000} - \mu_{Prolia} \leq -1.45\%$

H_1: $-1.45\% < \mu_{Bmab\ 1000} - \mu_{Prolia}$

Test 2: for non-superiority (delta = 1.45):

H_0: $\mu_{Bmab\ 1000} - \mu_{Prolia} \geq +1.45\%$

H_1: $\mu_{Bmab\ 1000} - \mu_{Prolia} < +1.45\%$

where $\mu_{Bmab\ 1000}$ and μ_{Prolia} denotes the true mean % change from baseline in lumbar spine BMD by DXA at Week 52 for Bmab 1000 and Prolia, respectively. A margin of ± 1.45% was used to determine clinical similarity.

Margin derivation for percent change from baseline in BMD for lumbar spine

The similarity margin, which was agreed upon by FDA, was based on three published clinical trials (Bone et al., 2008, Cummings et al., 2009 [pivotal FREEDOM trial], McClung et al., 2006). Based on this meta-analysis, the point estimate of the treatment

effect of the reference product was 5.35% with 95% CI (4.83%, 5.87%). The Applicant stated that the lower bound of the 95% CI is used to justify an appropriate margin:

- A margin of 1.45% retains at least 70% of the treatment effect of the reference product.

The Applicant's prespecified primary analysis of the primary endpoint, the percent change from baseline in lumbar spine BMD at week 52, was performed using an analysis of covariance (ANCOVA) model with missing data imputed using multiple imputation, assuming missing at random (MAR) by treatment. The model included treatment, stratification variables (region, age, and prior bisphosphonates use (yes/no)), visit by treatment factors and baseline lumbar spine BMD values as a continuous covariate. The Applicant stated that a percent change from baseline of zero was taken for anyone who died. One subject died in the Prolia group before Week 52.

A penalty (delta of -1.45% and 1.45%) was applied to the imputed values for the Bmab 1000 group reflecting the noninferiority and non-superiority null hypotheses (H_0), respectively, and two separate one-sided tests were performed at alpha=0.05. Comparative effectiveness between the two products is declared if both the lower and upper confidence limits for the difference in primary endpoint, based on the two one-sided tests, fall entirely within the pre-specified equivalence margins of +/-1.45%.

Reviewer's note:

The Applicant's defined the FAS set as all randomized participants who met the eligibility criteria and received at least 1 dose of study drug. Any participant who did not meet the eligibility criteria identified through the protocol deviation list was excluded from the FAS population. FDA prefers not to exclude participants who were randomized and received a study dose regardless of them not meeting the eligibility criteria. Thus, the reviewer's primary and secondary analyses used the reviewer defined modified intent-to-treat (mITT) population defined as all randomized participants who received at least one dose of study drug. Table 14 shows the reviewer defined mITT population.

Table 14. Reviewer Defined Modified Intent-to-Treat

	Bmab 1000 (1) N=238	Prolia (2) N=241	Total (N=479)
Randomized	238 (100%)	241 (100%)	479 (100%)
mITT	238 (100%)	240 (99.6%)	478 (99.8%)

Missing data

There were 12 (5%) participants with missing data in the Bmab 1000 arm and 19 (8%) in the Prolia arm at week 52. For the primary analysis using the ANCOVA model, if the week 52 BMD lumbar spine was missing, the corresponding value of the percent change from baseline was imputed assuming MAR by treatment. The imputation was run to produce 30 multiply imputed datasets.

FDA conducted an analysis on the primary endpoint using the FDA preferred analysis set with multiple imputation under the corresponding null for the two one-sided tests, testing for non-inferiority and non-superiority. To implement this imputation approach, FDA first imputed missing data of the Bmab 1000 group using all observed data from

the Prolia group and only baseline data from the Bmab 1000 group. When imputing missing values in the Prolia group, baseline data and intermediate endpoint values were included. After the multiple imputation, the imputed values of the Bmab 1000 product group were further decreased by the similarity margin 1.45% when testing non-inferiority and added by the margin when testing non-superiority.

No sensitivity analysis was conducted.

Secondary endpoints

The secondary endpoints for the mean percentage change from baseline were as follows:

- Lumbar-spine BMD by DXA after 26 weeks
- Total hip BMD (TH-BMD) after 26 and 52 weeks
- Femoral neck BMD (FN- MD) at week 26 and 52 weeks.

These continuous endpoints were analyzed using the ANCOVA model similar to the primary endpoint but without the penalty being applied. There were no multiplicity adjustments made for the secondary endpoints.

6.2.4 Subject Disposition

The majority of patients in both treatment groups completed both Part 1 and Part 2 treatment periods (see Table 15, Table 16). The primary efficacy analysis for the primary endpoint (percent change from baseline in LS-BMD at week 52) was conducted on the Full Analysis Set (FAS), which includes all randomized patients who met the eligibility criteria and received at least one dose of study treatment.

One patient assigned to the US-Prolia treatment group withdrew consent prior to dosing and was not included in the safety analysis set.

Table 15. Patient Disposition, Study B1000-PMO-03-G-02, Part 1

Disposition Status	Bmab 1000 (N=238) n (%)	US-Prolia (N=241) n (%)
Randomized	238	241
Safety Analysis Set	238 (100)	240 (99.6)
Discontinued before Week 52	20 (8.4)	32 (13.3)
Primary reason for study discontinuation		
Adverse event	4 (1.7)	3 (1.2)
Death	0	1 (0.4)
Withdrawal of consent	13 (5.5)	19 (7.9)
Lost to follow up	2 (0.8)	2 (0.8)
Significant protocol violation	0	3 (1.2)
Other	1 (0.4)	4 (1.7)
Patients Completing Part 1	218 (91.6)	208 (86.3)

Source: clinical reviewer analysis

This table differs from Table 5-1 in the B1000-PMO-03-G-02 study report (page 77) due to updates based on clinical reviewer assessment, discussed in the text below.

The most common reason for premature discontinuation in both treatment groups was patient withdrawal of consent.

Five patients discontinued the study early due to reason classified as “other”, all occurring during Part 1 of the study, one assigned to the Bmab 1000 treatment group and four assigned to US-Prolia. One of the patients assigned to Prolia discontinued the study early due to noncompliance with calcium and vitamin D supplementation. One patient assigned to Prolia discontinued the study due to fear of adverse reactions, and not due to an actual adverse event. The remaining 4 patients discontinued the study due to “Sponsor decision,” which, upon review of the patient narratives, was due to the patients being randomized despite not qualifying for study enrollment per study inclusion/exclusion criteria.

During Part 1 of the study, the Applicant indicated that four patients discontinued from the study due to significant protocol violations, one assigned to the Bmab 1000 treatment group and three assigned to US-Prolia. The three patients assigned to US-Prolia were discontinued because they were randomized despite not qualifying for study enrollment per study inclusion/exclusion criteria. The patient assigned to Bmab 1000 was discontinued due to “protocol non-compliance,” however, upon review of the narrative, appeared to be lost to follow up.

The Applicant concluded that during Part 1 of the study, two patients, both assigned to US-Prolia, discontinued from the study due to investigator decision. Upon review of the patient narratives, one patient was lost to follow up, while the other patient was removed from the study due to the adverse events of small nodular lesions in the lung and cirrhotic changes in the lungs. Thus, this patient in fact discontinued the study due to adverse events.

Table 16. Patient Disposition, Study B1000-PMO-03-G-02, Part 2

Disposition Status	**Bmab 1000/ Bmab 1000 (N=218)** n (%)	**US-Prolia/ Bmab 1000 (N=104)** n (%)	**US-Prolia/ US-Prolia (N=104)** n (%)
Re-Randomized	218	104	104
Patients treated as randomized	218 (100)	104 (100)	104 (100)
Discontinued prematurely	2 (0.9)	1 (1)	1 (1)
Primary reason for study discontinuation			
Adverse event	0	0	0
Death	0	0	0
Withdrawal of consent	2 (0.9)	1 (1)	1 (1)
Patients Completing Part 2	216 (99.1)	103 (99)	103 (99)

Source: B1000-PMO-03-G-02 study report, Table 5-2, page 78

During Part 2 of the study, the only reason for premature discontinuation was withdrawal of consent.

6.2.5 Demographics and Baseline Characteristics

Demographic characteristics were overall well-balanced between the two treatment groups (see Table 17). Baseline disease characteristics were also similar (see Table 18). In cases when there were slight differences in baseline characteristics, it is unlikely that these differences had a significant impact on the study findings.

Table 17. Demographic characteristics, Study B1000-PMO-03-G-02

Demographic variable	**Bmab 1000 (N=238)** n (%)	**US-Prolia (N=240)** n (%)
Age		
Mean (SD) years	66.7 (5.6)	66.5 (5.7)
N(%) < 65 years	84 (35.3)	88 (36.7)
N(%) ≥ 65 years	154 (64.7)	152 (63.3)
Race – N(%)		
Asian	1 (0.4)	0 (0)
White	237 (99.6)	240 (100)
Baseline weight		
Mean (SD) kg	63.4 (8.9)	63.4 (9.3)
BMI, N(%) < 25 kg/m^2	131 (55)	130 (54)
BMI, N(%) ≥ 25 kg/m^2	107 (45)	110 (46)
Geographical region – N(%)		
US	3 (1.3)	3 (1.2)
Europe	235 (98.7)	238 (98.8)
Country– N (%)		
Estonia	10 (4.2)	12 (5)
Latvia	4 (1.7)	9 (3.8)
Poland	221 (92.9)	216 (90)
United States	3 (1.3)	3 (1.2)

Source: B1000-PMO-03-G-02 study report, Table 5-7, page 83

Table 18. Baseline disease characteristics, Study B1000-PMO-03-G-02

Demographic variable	Bmab 1000 (N=238) n (%)	US-Prolia (N=241) n (%)
Prior bisphosphonate use – N (%)		
Yes	15 (6.3)	17 (7.1)
No	223 (93.7)	224 (92.9)
Baseline LS BMD (g/cm^2)		
Mean (SD)	0.77 (0.06)	0.76 (0.06)
Min, Max	0.62, 1	0.62, 1
Baseline LS T-score		
Mean (SD)	-3.06 (0.38)	-3.07 (0.38)
Min, Max	-3.92, -2.52	-3.96, -2.5

Source: B1000-PMO-03-G-02 study report, Table 5-9, page 86-87

6.2.6 Analysis of Primary Clinical Endpoint(s)

Table 19 shows the results of FDA's preferred mITT population. In this analysis, the FDA imputed missing data under the corresponding null for two one-sided tests, one test for non-inferiority and the other test for non-superiority. Results from the two tests supported the conclusion of similarity.

Table 19. Primary Analysis of Percent Change in BMD for Lumbar Spine at Week 52, mITT Population

	Bmab 1000 N=238	Prolia N=240
Baseline mean LS-BMD (SD)	0.77 (0.06)	0.76 (0.06)
Multiple imputation #1[1]		
LS Means (g/cm^2)	5.43	5.07
Treatment difference (Bmab 1000 -Prolia)	0.39	
90% CI[2]	-0.22, 0.99	
Multiple imputation #2[1]		
LS Means (g/cm^2)	5.67	5.07
Treatment difference (Bmab 1000 -Prolia)	0.63	
90% CI[2]	-0.02, 1.23	
Multiple imputation #3[1]		
LS Means (g/cm^2)	5.55	5.07
Treatment difference (Bmab 1000 -Prolia)	0.51	

90% CI[2]	-0.09, 1.11

Source: Statistical Reviewer's Analysis; adsl.xpt, miin_rand.xpt
[1]Imputation #1: Subtract the imputed values by the margin, 1.45, to test non-inferiority.
Imputation #2: Add the imputed values by the margin, 1.45, to test non-superiority.
Imputation #3: No penalty (washout imputation).
[2] Primary objective met if the 90% CI for the difference between Bmab 1000 and Prolia was contained within the pre-specified margin of (-1.45%, 1.45%) with imputation under each null.
Note: LS Means are from the analysis of covariance model with treatment (Bmab 1000, Prolia), stratification variables (region, age, and prior use bisphosphonates), baseline lumbar spine BMD as a covariate.
Note: The treatment mean difference was calculated as Bmab 1000 – Prolia.
Abbreviations: CI, confidence interval; LS, least squares; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; N, total number of participants; SD, standard deviation

6.2.7 Potential Effects of Missing Data

The FDA conducted a tipping point analysis for the primary endpoint using the FDA's preferred mITT population. The results supported the similarity conclusion. Similarity conclusion would be overturned only when the missing values assumed to be unrealistically worse in the test product group than that of the reference product group.

6.2.8 Analysis of Secondary Clinical Endpoint(s)

There were no key efficacy confirmatory secondary endpoints prespecified in this study. There were no multiplicity adjustments made for the secondary endpoints. The results for the secondary endpoints considered exploratory are shown in the appendix.

6.2.9 Other Clinical Endpoints

Additional endpoints of clinical interest included incidence of fractures at Week 52 and the percentage change from baseline in BMD at lumbar spine assessed by DXA at Week 78.

All efficacy endpoints other than the primary endpoint were summarized using descriptive statistics or frequency tables. These endpoints were intended to provide additional efficacy comparisons between Bmab 1000 and Prolia as supportive evidence relating to the primary endpoint, and no formal adjustments for multiplicity were performed.

Fractures

Lateral spine X-rays were performed at screening and at Week 26 and 52, as well as on an as-needed basis to confirm suspected fractures. All lateral spine X-rays were assessed at a central imaging center. Fractures were graded according to the semiquantitative Genant classification,[3] which is defined as below:

- Grade 0 = no fracture.
- Grade 1 = mild fracture, 20% to 25% reduction in vertebral height (anterior,

[3] Genant HK, Wu CY, van Kuijk C et al. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8(9):1137-48.

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.

Per the Applicant's analysis, two patients experienced fractures during Part 1 of the study, as detected with scheduled lateral spine X-rays (See Table 20). One 57-year-old patient in the Bmab 1000 group had a thoracic vertebrae fracture with a Genant grade of moderate detected with lateral spine X-ray at Week 26, and one 65-year-old patient had a lumbar vertebrae fracture with a Genant grade of mild detected with lateral spine X-ray at Week 52. The 57-year-old patient had no prior fracture history, and her bone mineral density (BMD) improved from her baseline 0.737 to 0.762 by week 26 when the thoracic vertebral fracture was detected. The 65-year-old patient also had no fracture history and her BMD improved from 0.841 at baseline to 0.902 at week 26 and 0.916 a week 52, when the lumbar vertebral fracture was detected.

No patient in the Prolia group had any fracture events detected with scheduled lateral spine X-rays during the study. No additional patients had any fracture events per lateral spine X-ray between Week 52 and Week 78 during Part 2 of the study.

Table 20. N (%) of patients with fractures detected with screening lateral spine X-rays, Part 1, Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	**US-Prolia (N=240)** n (%)
Patients with Fractures (%)	2 (0.8)	0
Lumbar vertebral fracture	1 (0.4)	0
Thoracic vertebral fracture	1 (0.4)	0

Source: B1000-PMO-03-G-02 study report, Table 14.3.7.1.1, page 436-438

The Applicant's analysis of the secondary efficacy endpoint (fracture incidence up to Week 52) included only fractures detected via lateral spine X-rays and did not include fracture events captured as adverse events. When evaluating fracture incidence using adverse event analysis as well as the results of lateral spine X-rays, an additional four patients with fractures were detected during Part 1 of the study (see Table 21). During Part 2 of the study, two patients had adverse events related to factures (see Table 22).

Table 21. N (%) of patients with fractures detected with screening lateral spine X-rays and treatment emergent adverse event analysis, Part 1, Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	**US-Prolia (N=240)** n (%)
Patients with Fractures (%)	4 (1.7)	2 (0.8)
Lumbar vertebral fracture	1 (0.4)	0
Thoracic vertebral fracture	1 (0.4)	0

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Hand fracture	1 (0.4)	0
Foot fracture	1 (0.4)	0
Forearm fracture	0	1 (0.4)
Patella fracture	0	1 (0.4)

Source: clinical reviewer analysis

Table 22. N (%) of patients experiencing treatment emergent adverse events of fracture, Part 2, Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000 (N=218) n (%)	US-Prolia/ Bmab 1000 (N=104) n (%)	US-Prolia/ US-Prolia (N = 104) n (%)
Patients with Fractures (%)	1 (0.5)	1 (1)	0
Spinal compression fracture	1 (0.5)	0	0
Radius fracture	0	1 (1)	0

Source: clinical reviewer analysis

Both vertebral and non-vertebral fractures were rare and occurring in very small numbers of patients throughout the trial, and similar in frequency across treatment groups. In addition, all fractures that occurred during the study were either a CTCAE Grade 1 or 2 in severity. Therefore, these data do not suggest a clinically meaningful difference in fracture incidence among the treatment groups, and any difference in incidences between the treatment groups is more likely due to chance rather than meaningful differences between the products. In addition, the fracture data from Part 2 do not suggest a clinically meaningful difference in efficacy after transitioning from US-Prolia to Bmab 1000.

LS-BMD at Week 78

The difference in means for the secondary endpoints evaluating BMD change from baseline, including the evaluation of lumbar spine BMD at week 78, were analyzed using an analysis of covariance (ANCOVA) for the FAS population, with baseline BMD as a covariate and classification variables for region, age, and prior use of bisphosphonates.

The mean percent change from baseline in lumbar spine BMD at week 78, coinciding with six months after the single transition dose, was similar among the three treatment groups (see Table 23).

Table 23. Mean % Change from Baseline to Week 78 in Lumbar Spine BMD (g/cm^2), Full Analysis Set, Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000 (N = 218)	US-Prolia/ Bmab 1000 (N = 104)	US-Prolia/ US-Prolia (N = 104)
Mean % CFB (SD)	6.6 (3.8)	6.2 (4)	7.1 (4.1)

CFB = change from baseline; SD = standard deviation
Source: B1000-PMO-03-G-02 study report, Table 14.2.4.2, page 423

Although not controlled for type I error or subject to hypothesis testing, these results suggest a maintenance of efficacy after a single transition from US-Prolia to Bmab 1000.

6.3 Review of Safety Data

6.3.1 Methods

Clinical Studies Used to Evaluate Safety

The evaluation of safety is based primarily on the comparative clinical study (study B1000-PMO-03-G-02), which evaluated safety and efficacy of Bmab 1000 and US-Prolia use in post-menopausal women with osteoporosis. However, safety data from the comparative clinical pharmacology study (study B1000-NHV-01-G-01), which enrolled healthy adults, were also examined for known risks of denosumab (e.g., hypersensitivity reactions, hypocalcemia) and to further evaluate any new safety signals that become apparent during review of the data from study B1000-PMO-03-G-02. Safety analysis was conducted using the safety analysis set (SAF), defined as all randomized patients who received at least one dose of the study drug. The size of the safety database is adequate to make a determination of clinical comparable safety between Bmab 1000 and US-Prolia.

Categorization of Adverse Events

In both study B1000-NHV-01-G-01 and B1000-PMO-03-G-02, an adverse event (AE) was defined as any untoward medical occurrence in a patient enrolled into the study regardless of a causal relationship to the study treatment. Any event absent before exposure to the study treatment or any event already present that worsens in either intensity or frequency after exposure to the study treatment was defined as a treatment emergent adverse event (TEAE). Adverse events were categorized by severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Serious adverse events (SAEs) were defined as any event that resulted in death, was immediately life-threatening, required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was

associated with a congenital anomaly or birth defect, or was otherwise considered to be medically important.

Pre-defined adverse events of special interest (AESIs) for study B1000-PMO-03-G-02 included:

- Drug-related hypersensitivity/allergic reactions
- Serious infections
- Hypocalcemia, including but not limited to asymptomatic hypocalcemia, paresthesia or muscle stiffness, twitching, spasms and muscle cramps, QT interval prolongation, tetany, seizures and altered mental status
- Osteonecrosis of the jaw, including but not limited to jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, and gingival erosion
- Atypical femoral fracture, including but not limited to new or unusual thigh, hip, or groin pain
- Dermatologic reactions, including but not limited to dermatitis, eczema, and rash.

Safety Analyses

Safety data were not combined because the study populations and design of the two studies differed.

Study B1000-PMO-03-G-02 consisted of two treatment periods. The first period (Part 1) compared Bmab 1000 to US-Prolia, and the second period (Part 2) was designed to evaluate the safety of a transition from US-Prolia to Bmab 1000 compared to continuing US-Prolia. Safety data from the two treatment periods are presented separately.

Adverse events were coded using MedDRA version 27.0. The FDA review team identified several cases where the coding of the MedDRA preferred term from the verbatim term was inaccurate or resulted in adverse events being dropped off due to inappropriate lumping of terms. Hence, the review team modified the Applicant's translation of adverse event verbatim terms to dictionary derived terms, when needed. This led to discrepancies in the number of some adverse events compared to the data provided by the Applicant. Any occurrence when FDA modification of the Applicant's translation of event verbatim term to dictionary derived term led to a difference in adverse event rates is notated in the safety results.

6.3.2 Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Study B1000-NHV-01-G-01 enrolled healthy adult volunteers, who do not reflect the population for whom denosumab is indicated. Nonetheless, the population was considered appropriate and sensitive given the primary objectives of the study.

Study B1000-PMO-03-G-02 enrolled post-menopausal women with osteoporosis, which is one of the targeted populations for denosumab. Demographic and baseline disease characteristics of the study population are shown in Table 17 and Table 18, respectively.

Deaths

Study B1000-NHV-01-G-01

There were no deaths in this study.

Study B1000-PMO-03-G-02

There was one death in this study in a 65-year-old female randomized to the US-Prolia treatment group. This patient, who had a history of tobacco use (5 cigarettes per day from [redacted] (b) (6)) and hyperlipidemia, died of cerebrovascular accident on study day 285, 98 days after her second dose of Prolia. The death was likely related to the patient's age and social and medical history.

Serious Adverse Events

Study B1000-NHV-01-G-01

There were no serious adverse events (SAEs) reported during this study.

One adverse event of spontaneous abortion was reported in the female partner of a male participant 6 months after receiving a single dose of Bmab 1000. This event was likely not related to the Bmab 1000.

Study B1000-PMO-03-G-02

Part 1:

During Part 1 of the study, serious adverse events occurred in 14/238 (5.9%) of patients receiving Bmab 1000 and 7/240 (2.9%) of patients receiving US-Prolia (refer to Table 24).

Table 24. Serious Adverse Events, Part 1, Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Total number of patients with SAEs (%)	14 (5.9)	7 (2.9)
Malignancy OCMQ	4 (1.7)	1 (0.4)
Pancreatic carcinoma	2 (0.8)	0
Breast cancer	1 (0.4)	0
Colon cancer	1 (0.4)	0
Clear renal cell carcinoma	0	1 (0.4)
Acute coronary syndrome OCMQ*	0	2 (0.8)
Dizziness	2 (0.8)	0
Bacterial infection OCMQ	1 (0.4)	1 (0.4)
Urosepsis	1 (0.4)	0)
Staphylococcal sepsis	0	1 (0.4)
Abdominal pain	1 (0.4)	0
Allergic sinusitis	1 (0.4)	0
Barrett's esophagus	1 (0.4)	0

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Ear infection	1 (0.4)	0
Ear inflammation	1 (0.4)	0
Endometrial hyperplasia	1 (0.4)	0
Inflammatory bowel disease	1 (0.4)	0
Mastoiditis	1 (0.4)	0
Musculoskeletal disorder	1 (0.4)	0
Ovarian cyst	1 (0.4)	0
Oesophageal stenosis	1 (0.4)	0
Ureterolithiasis	1 (0.4)	0
Vestibular neuritis	1 (0.4)	0
Acute kidney injury	0	1 (0.4)
Cerebrovascular accident	0	1 (0.4)
Diverticulum intestinal	0	1 (0.4)
Schizophrenia	0	1 (0.4)
Uterine prolapse	0	1 (0.4)

Source: clinical reviewer analysis
OCMQ = OND Custom Medical Query
*Acute coronary syndrome OCMQ includes the following preferred terms: acute myocardial infarction, myocardial infarction
After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there was a small discrepancy in the incidence of some adverse events. As none of the changes resulted in a difference in adverse event incidence of more than 0.4%, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis.

Overall, there is a slight excess in SAEs in the Bmab 1000 group compared to the US-Prolia group by 7 patients, which appears to be largely related to a higher incidence of new malignancies in the Bmab 1000 group (1.7% [4/238] in the Bmab 1000 group compared to 0.4% [1/240] in the US-Prolia group). Though new malignancies are included as an adverse event in the Prolia label, the frequency of malignancy was lower in both treatment groups in study B1000-PMO-03-G-02 than the frequency of new malignancy noted in the Prolia label. Other than pancreatic carcinoma, each of the malignancies occurred in a single subject, and the events were likely due to the underlying risk factors (e.g., age) and not due to the drug. The remaining SAEs only occurred in one or two patients overall and did not occur frequently in the study overall. Therefore, the observed treatment difference in SAEs is likely due to chance, and unlikely to be clinically meaningful.

Part 2:

During Part 2 of the study, 5/218 (2.3%) patients in the Bmab 1000/Bmab 1000 group, 2/104 (1.9%) patients in the Prolia/Bmab 1000 group, and 2/104 (1.9%) patients in the Prolia/Prolia group experienced treatment-emergent serious adverse events (refer to Table 25). In general, the frequency of SAEs during Part 2 of the study were overall balanced between the treatment groups. All SAEs occurred in only one patient and did not occur frequently in the study overall.

Table 25. Serious Adverse Events, Part 2, Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000 (N=218) n (%)	US-Prolia/ Bmab 1000 (N=104) n (%)	US-Prolia/ US-Prolia (N = 104) n (%)
Total number of patients with SAEs (%)	5 (2.3)	2 (1.9)	2 (1.9)
Arterial injury	1 (0.5)	0	0
Cataract	1 (0.5)	0	0
Gastric ulcer	1 (0.5)	0	0
Non-cardiac chest pain	1 (0.5)	0	0
Osteoarthritis	1 (0.5)	0	0
Skin laceration	1 (0.5)	0	0
Abdominal pain	0	1 (1)	0
Diverticulitis	0	1 (1)	0
Atrial fibrillation	0	0	1 (1)
Invasive lobular breast carcinoma	0	0	1 (1)

Source: clinical reviewer analysis

After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there was a small discrepancy in the incidence of some adverse events. As none of the changes resulted in a difference in adverse event incidence of more than 0.5%, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis

Across the study, there were no significant patterns in the SAEs reported to indicate a potential safety signal.

Common Treatment Emergent Adverse Events

Study B1000-PMO-03-G-02

Part 1:

The most common treatment emergent adverse events (i.e., occurring in ≥3% of patients in either treatment group) were similar between treatment groups, and are largely consistent with the known safety profile of denosumab or are common in the overall population at baseline (see Table 26).

Table 26. Most common treatment emergent adverse events (incidence ≥3%), Part 1, Study B1000-PMO-03-G-02

TEAEs by OCMQs and Preferred terms	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Any TEAE, N (%)	141 (59.2)	153 (63.7)
Nasopharyngitis OCMQ	37 (15.5)	34 (14.2)
Upper respiratory tract infection	17 (7.1)	22 (9.2)

TEAEs by OCMQs and Preferred terms	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Nasopharyngitis	12 (5)	7 (2.9)
Pharyngitis	6 (2.5)	2 (0.8)
Pharyngitis streptococcal	0	2 (0.8)
Chronic sinusitis	0	1 (0.4)
Rhinitis allergic	2 (0.8)	0
Allergic sinusitis	1 (0.4)	0
Bacterial infection OCMQ	23 (9.7)	22 (9.2)
Urinary tract infection	12 (5)	10 (4.2)
Cystitis	3 (1.3)	6 (2.5)
Pharyngitis streptococcal	0	2 (0.8)
Pulpitis dental	0	2 (0.8)
Periodontitis	1 (0.4)	1 (0.4)
Mastitis	0	1 (0.4)
Rash pustular	0	1 (0.4)
Staphylococcal sepsis	0	1 (0.4)
Urinary tract infection bacterial	3 (1.3)	0
Bronchitis bacterial	1 (0.4)	0
Diverticulitis	1 (0.4)	0
Helicobacter infection	1 (0.4)	0
Upper respiratory tract infection bacterial	1 (0.4)	0
Urosepsis	1 (0.4)	0
Renal and urinary tract infection OCMQ	18 (7.6)	16 (6.7)
Urinary tract infection	12 (5)	10 (4.2)
Cystitis	3 (1.3)	6 (2.5)
Urinary tract infection bacterial	3 (1.3)	0
Urosepsis	1 (0.4)	0
Viral infection OCMQ	14 (5.9)	19 (7.9)
COVID-19	9 (3.8)	8 (3.3)
Gastrointestinal viral infection	1 (0.4)	5 (2.1)
Influenza	3 (1.3)	3 (1.3)
Viral upper respiratory tract infection	1 (0.4)	3 (1.3)
Oral herpes	1 (0.4)	2 (0.8)
Herpes zoster	1 (0.4)	1 (0.4)
Viral tracheitis	0	1 (0.4)
Herpes zoster infection neurological	1 (0.4)	0
Arthritis OCMQ	12 (5)	9 (3.8)
Spinal osteoarthritis	4 (1.7)	5 (2.1)

TEAEs by OCMQs and Preferred terms	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Osteoarthritis	9 (3.8)	4 (1.7)
Back pain OCMQ	12 (5)	9 (3.8)
Back pain	9 (3.8)	6 (2.5)
Sciatica	3 (1.3)	3 (1.3)
Lipid disorder OCMQ	9 (3.8)	18 (7.5)
Hypercholesterolaemia	6 (2.5)	12 (5)
Hyperlipidaemia	1 (0.4)	4 (1.7)
Blood cholesterol increased	1 (0.4)	1 (0.4)
Low density lipoprotein increased	0	1 (0.4)
Hypertriglyceridaemia	1 (0.4)	0
Arthralgia	9 (3.8)	13 (5.4)
Dizziness OCMQ	9 (3.8)	10 (4.2)
Dizziness	7 (2.9)	10 (4.2)
Vestibular neuronitis	2 (0.8)	0
Headache OCMQ	9 (3.8)	9 (3.8)
Headache	9 (3.8)	8 (3.3)
Migraine	0	1 (0.4)
Systemic hypertension OCMQ	6 (2.5)	9 (3.8)
Hypertension	6 (2.5)	6 (2.5)
Blood pressure increased	0	2 (0.8)
Essential hypertension	0	1 (0.4)
Hyperglycemia OCMQ	3 (1.3)	9 (3.8)
Type 2 diabetes mellitus	2 (0.8)	3 (1.3)
Glucose tolerance impaired	0	3 (1.3)
Impaired fasting glucose	1 (0.4)	2 (0.8)
Diabetes mellitus	0	1 (0.4)
Hyperglycaemia	0	1 (0.4)
Rash OCMQ	0	8 (3.3)
Rash	0	2 (0.8)
Urticaria	0	2 (0.8)
Acne	0	1 (0.4)
Dermatitis	0	1 (0.4)
Rash pustular	0	1 (0.4)
Rash vesicular	0	1 (0.4)

Source: clinical reviewer analysis
OCMQ = OND Custom Medical Query
After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there was a small discrepancy in the incidence of some adverse events. As none of the changes resulted in a difference in adverse event incidence of more than

0.5%, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis.

The most common TEAEs in Part 1 of study B1000-PMO-03-G-02 were of infectious etiology and common in the baseline population. They were also balanced across treatment groups. In cases when adverse events occurred more frequently in patients taking Bmab 1000 compared to Prolia (such as for the naspharyngitis OCMQ), the risk difference between the two treatment groups was always less than 2% and the numerical differences in actual incidence were small between the treatment groups. Therefore, the differences in incidence are more likely due to chance rather than an inherent meaningful difference in the study drugs.

Part 2:

The adverse event profile during Part 2 of study B1000-PMO-03-G-02 was also largely consistent with the known safety profile of denosumab. The most common TEAEs during Part 2 were infectious in etiology, which is a labeled adverse effect of Prolia (see Table 27).

Table 27. Most common treatment emergent adverse events (incidence ≥3%), Part 2, Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000 (N=218) n (%)	US-Prolia/ Bmab 1000 (N=104) n (%)	US-Prolia/ US-Prolia (N = 104) n (%)
Any TEAE, N (%)	55 (25.2)	29 (27.9)	27 (26.1)
Nasopharyngitis OCMQ[1]	9 (4.1)	10 (9.6)	6 (8.8)
Upper respiratory tract infection	3 (1.4)	5 (4.8)	3 (2.9)
Nasopharyngitis	3 (1.4)	4 (3.8)	3 (2.9)
Bacterial infection OCMQ[2]	7 (3.2)	3 (2.9)	1 (1)
Viral infection OCMQ[3]	4 (1.8)	4 (3.8)	6 (5.8)
Arthralgia	1 (0.5)	1 (1)	4 (3.8)

Source: clinical reviewer analysis
OCMQ = OND Custom Medical Query
[1]Nasopharyngitis OCMQ includes the following preferred terms: upper respiratory tract infection, nasopharyngitis, pharyngitis, pharyngitis streptococcal, acute sinusitis
[2]Bacterial infection OCMQ includes the following preferred terms: mastitis, diverticulitis, helicobacter gastritis, pharyngitis streptococcal, urinary tract infection, urinary tract infection bacterial, cholecystitis, cystitis
[3]Viral infection OCMQ includes the following preferred terms: COVID-19, herpes zoster, respiratory tract infection viral, oral herpes, influenza, cervicitis human papilloma virus
After the FDA review team evaluated and provided modifications to the Applicant's translation of adverse event verbatim terms to dictionary derived terms, there was a small discrepancy in the incidence of some adverse events. This resulted in an increase in incidence of arthralgia in the Prolia/Bmab 1000 group from 0% pe the Applicant's analysis to 1%, and in the Prolia/Prolia group from 1.9% per the Applicant's analysis to 3.8%. As none of the changes resulted in a difference in adverse event incidence of more than 2%, this discrepancy is unlikely to result in the FDA analysis to be significantly different from the Applicant's analysis

Incidence of total treatment emergent adverse events was balanced between the treatment groups. The only events that occurred more commonly in the group transitioning from Prolia to Bmab 1000 than in the other treatment groups were those

under the Naropharyngitis OCMQ, which were driven by a slight excess of upper respiratory tract infections and nasopharyngitis. However, the total number of patients affected are small overall and differences between the treatment groups is more likely due to chance than a meaningful difference between the products. In addition, this difference is unlikely to be clinically significant, as all cases of nasopharyngitis and upper respiratory tract infections during Part 2 of the study were either grade 1 or 2 CTCAE in severity.

Dropouts and/or Discontinuations due to Adverse Events

Study B1000-PMO-03-G-02

Part 1:

Similar proportions of patients in the two treatment groups discontinued therapy early due to treatment emergent adverse events: four patients in the Bmab 1000 group (4/238 [1.7%]) and five patients in the US-Prolia group (5/240 [2%]). All adverse events leading to treatment discontinuation occurred in less than 1% of patients (see Table 28).

Table 28. Treatment emergent adverse events leading to study drug discontinuation, Part 1, B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Total number of patients who discontinued treatment due to an adverse event	4 (1.7)	5 (2)
Pancreatic carcinoma	2 (0.8)	0
Dizziness	1 (0.4)	0
Colon cancer	1 (0.4)	0
Cerebrovascular accident	0	1 (0.4)
Schizophrenia	0	1 (0.4)
Clear cell renal cell carcinoma	0	1 (0.4)
Myalgia	0	1 (0.4)
Pain in extremity	0	1 (0.4)
Chronic obstructive pulmonary disease	0	1 (0.4)
Increased bronchial secretion	0	1 (0.4)
Pulmonary fibrosis	0	1 (0.4)
Pulmonary mass	0	1 (0.4)

Source: clinical reviewer analysis

Part 2:

No TEAEs leading to discontinuation of study drug were reported during this period of the study.

6.3.3 Additional Safety Evaluations

The Applicant included TEAEs of hypocalcemia, hypersensitivity, atypical femoral fractures, serious infections, dermatologic reactions, and osteonecrosis of the jaw as adverse events of special interest (AESI), all of which are included as labeled warnings on the US-Prolia prescribing information. Each of these AESIs will be discussed in detail below, in addition to discussion of injection site reactions, fractures (which includes the discussion of atypical femoral fractures), and laboratory findings (which includes the discussion of hypocalcemia).

Laboratory Findings

Calcium and Minerals

Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorous and magnesium). The US-Prolia prescribing information advises that calcium, phosphorous and magnesium be monitored within 14 days of injection, as the nadir for serum calcium occurs within the first two weeks following administration of denosumab.

Abnormal labs were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE toxicity grading scale for hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia is shown in Table 29. Toxicity for derangements in magnesium and calcium are based on laboratory values. For phosphorous, toxicity is graded based on clinical symptoms and requirement for intervention rather than on specific laboratory findings.

Table 29. CTCAE toxicity grading scale for hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia

	Toxicity Grade				
	1	2	3	4	5
Hypocalcemia	<LLN – 8 mg/dL	<8 – 7 mg/dL	<7 – 6 mg/dL	<6 mg/dL	Death
Hypercalcemia	>ULN – 11.5 mg/dL	>11.5 – 12.5 mg/dL	>12.5 – 13.5 mg/dL	>13.5 mg/dL	Death
Hypomagnesemia	<LLN – 1.2 mg/dL	<1.2 – 0.9 mg/dL	<0.9 – 0.7 mg/dL	<0.7 mg/dL	Death
Hypophosphatemia	No intervention indicated	Noninvasive intervention indicated	Severe/ medically significant but not immediately life-threatening; hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Source: US Department of Health and Human Services. (Nov. 27, 2017). Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

There were no meaningful differences in treatment groups in median change in chemistry parameters over time in either Study B1000-NHV-01-G-01 or Study B1000-PMO-03-G-02, and shift analysis revealed no concerns or notable differences among the treatment groups.

Hypocalcemia

Both the B1000-NHV-01-G-01 and B1000-PMO-03-G-02 clinical studies presented calcium data results for both serum calcium and albumin-corrected serum calcium. Because approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia. In those situations, a correction formula to account for the low albumin is used to estimate actual serum calcium levels. Ionized calcium is the preferred measurement but is not readily available in all laboratories.[4] However, as low albumin results were very rare and mild in severity for both study B1000-NHV-01-G-01 and study B1000-PMO-03-G-02, and there are reported inaccuracies with various correction formulas and the role for such formulas when albumin levels are normal is unclear, this review examines only serum calcium measurements, not the corrected calcium values.

Study B1000-NHV-01-G-01

Safety laboratory testing occurred at screening, post-injection day 10, 29, 85, 169, and at end of study. Safety laboratory testing consisted of biochemistry (which included albumin-adjusted serum calcium), coagulation, hematology, and urinalysis. All patients received daily supplementation containing at least 1000 mg of calcium and at least 400 IU vitamin D from screening until the end of study.

No patients developed hypoalbuminemia during study B1000-NHV-01-G-01.

During the study, hypocalcemia (i.e., serum calcium below the lower limit of normal: 8.6 mg/dL or 8.7 mg/dL, depending on the study site) occurred rarely and at similar frequency between the treatment groups during the study overall (see Table 30).

Table 30. N (%) of patients with shift in serum calcium from normal to below the lower limit of normal (<LLN) during Study B1000-NHV-01-G-01

	Bmab 1000 (N=94) n (%)	**US-Prolia (N=95)** n (%)
Serum calcium transition from normal to <LLN	4 (4.3%)	2 (2.1%)

Source: clinical reviewer analysis

Overall, hypocalcemia during study B1000-NHV-01-G-01 was mild, transitory, and asymptomatic. Other than one patient in the Bmab 1000 treatment group, who had two low calcium levels (8.2 mg/dL on day 10 and 8.5 mg/dL on day 15), all patients with hypocalcemia only had one isolated low calcium level, which immediately resolved. All

[4] Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. BMJ Open. 2018 Apr 7;8(4):e017703.

hypocalcemia events were of CTCAE Grade 1 severity, as no calcium levels were below 8 mg/dL.

TEAEs relating to hypocalcemia or its symptoms were observed in one patient. A 54 year old male patient in the Bmab 1000 treatment group experienced CTCAE Grade 1 lip paresthesia on Day 3 of the study that resolved the same day. This patient had normal calcium levels on Day -1 and Day 10 (9.4 mg/dL and 9.3 mg/dL, respectively), which were temporally the closest calcium readings to the AE of lip paresthesia, suggesting that his symptom was not due to hypocalcemia. The patient had a low calcium level on Day 29 (8.5 mg/dL), during which he was asymptomatic, and he had no further hypocalcemic events. Otherwise, no patients had any AEs that could be indicative of symptomatic hypocalcemia.

No hypocalcemia TEAEs were reported during study B1000-NHV-01-G-01.

Study B1000-PMO-03-G-02

Part 1

During the 12-month duration of Part 1 of the study, patients received study drug (i.e., either Bmab 1000 or US-Prolia) injection at study day 1 and study day 183 (week 26). Safety laboratory testing (including hematology, serum chemistry, and urinalysis) was performed at screening, at baseline, and at 12, 26, 38, and 52 weeks after treatment initiation. Albumin-adjusted total serum calcium was also checked on study Day 15 as well.

All patients received daily supplementation containing at least 1000 mg of calcium and at least 400 IU vitamin D from randomization until Week 78. The dose could have been increased at investigator's discretion, such as in the case of hypocalcemia.

As the nadir for serum calcium occurs within the first two weeks following study drug administration, serum calcium was measured at baseline and week 2. The risk of hypocalcemia is greater in patients with severe renal impairment (i.e., glomerular filtration rate <30 mL/min), and this study excluded patients with a creatinine clearance <30 mL/min at screening.

Only one patient developed hypoalbuminemia during the trial, which occurred only once during the study (a single value of 33 g/L, which was classified as CTCAE toxicity Grade 1; normal range 35 to 55 g/L).

The median change from baseline in serum calcium during Part 1 was comparable in both treatment groups at all measurements following the initial and second study drug administration (see Table 31).

Table 31. Median (min, max) change from baseline in serum calcium (mg/dL) following first and second study drug administration

	Bmab 1000	US-Prolia
Change from baseline to Week 12 Median (min, max)	-0.2 (-1.32, 1.48) N=230	-0.16 (-1.48, 0.88) N=225
Change from baseline to Week 26 Median (min, max)	-0.12 (-1, 1)	-0.2 (-0.96, 1.32)

	N=223	N=216
Change from baseline to Week 38 Median (min, max)	-0.26 (-1.6, 0.92) N=222	-0.32 (-1.2, 1.04) N=215
Change from baseline to Week 52 Median (min, max)	-0.2 (-1.2, 0.92) N=218	-0.24 (-1.12, 0.92) N=211

Source: B1000-PMO-03-G-02 Clinical study report, adapted from Table 14.3.2.3.1, pg 1266-1267

No patients had low serum calcium level at screening. Hypocalcemia (i.e., serum calcium below the lower limit of normal: 8.48 mg/dL) occurred very rarely during Part 1 of the study overall (see Table 32). All patients with hypocalcemia only had one isolated low calcium level, which immediately resolved.

Table 32. N (%) of patients with shift in serum calcium to below the lower limit of normal (<LLN) during Part 1 of Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	**US-Prolia (N=240)** n (%)
Serum calcium transition to <LLN	5 (2.1%)	1 (0.4%)

Source: clinical reviewer analysis

Among the patients with laboratory evidence of serum hypocalcemia, the degree of hypocalcemia was mild. The lowest calcium level occurring during Part 1 was 8.3 mg/dL, which occurred only in one patient in the Bmab 1000 treatment group, and all hypocalcemia cases were of CTCAE Grade 1 severity. All patients were asymptomatic on the day of their low calcium reading.

In addition, one patient assigned to Bmab 1000 and three patients assigned to Prolia had reported adverse events related to hypocalcemia during Part 1 of study B1000-PMO-03-G-02. However, calcium levels drawn on the dates hypocalcemia was reported were within the normal range and in fact these patients never had laboratory evidence of hypocalcemia. In addition, these patients did not report any possible hypocalcemia-related symptoms during the study.

Part 2

Part 2 commenced at the Week 52 study visit when patients received their third and final dose of study drug. Patients who had received US-Prolia during the Part 1 were re-randomized in a 1:1 ratio to received either US-Prolia or Bmab 1000 for their final dose. Laboratory evaluation of hematology, clinical chemistry, and urinalysis occurred prior to denosumab injection at the Week 52 visit and at the end-of-study visit (week 78, or early termination).

There were no meaningful differences between treatment groups in median change in chemistry parameters over time during Part 2. There was also no meaningful difference in median change from the Transition Period baseline (Week 52) in serum calcium to the End of Study visit (Month 78) between the three groups (see Table 33).

Table 33. Median (min, max) change in serum calcium (mg/dL) from Part 2 baseline (Week 52) to End of Study (Week 78), Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000	US-Prolia/ Bmab 1000	US-Prolia/ US-Prolia
Change from baseline to Week 78 Median (min, max)	0 (-1.36, 0.92) N=214	0 (-1, 1.2) N=102	0 (-0.8, 0.8) N=103

Source: B1000-PMO-03-G-02 Clinical study report, Table 14.3.2.3.2, pg 1325
Baseline value is defined as the last non-missing assessment taken prior to the third study drug administration at Week 52.

Hypocalcemia was again rare during Part 2 of the study. Only two patients experienced hypocalcemia during Part 2 of the study (one subject in the Bmab 1000/ Prolia group and one subject in the Bmab 1000/ Bmab 1000 group). Each subject had only one low calcium level, though one patient in the Bmab 1000/Prolia treatment group did not have a repeat calcium test after an 8.3 mg/dL calcium reading on Day 547 (early termination visit). This patient was asymptomatic on the date hypocalcemia occurred.

The lowest calcium level occurring during Part 1 was 8.3 mg/dL, as discussed above. All hypocalcemia cases were of CTCAE Grade 1 severity. All patients were asymptomatic on the day of their low calcium reading.

One patient in the Bmab 1000/ Bmab 1000 treatment group reported a TEAE of *blood calcium decreased* during Part 2. This AE occurred on Day 547, though calcium measured during the corresponding visit was 8.6 mg/dL. This subject never had a low calcium measurement during the study and never reported any symptoms that could be related to hypocalcemia.

Hypercalcemia

Study B1000-NHV-01-G-01

No patients developed hypoalbuminemia during study B1000-NHV-01-G-01.

During the study, hypercalcemia events (i.e., serum calcium above the upper limit of normal: 10.2 mg/dL or 10.5 mg/dL, depending on the study site) in patients with normal calcium levels prior to study drug administration occurred rarely (see Table 34).

Table 34. N (%) of patients with shift in serum calcium from normal to above the upper limit of normal (>ULN) during Study B1000-NHV-01-G-01

	Bmab 1000 (N=94) n (%)	US-Prolia (N=95) n (%)
Serum calcium transition from normal to >ULN	2 (2.1%)	8 (8.5%)

Source: clinical reviewer analysis

Overall, hypercalcemia during study B1000-NHV-01-G-01 was mild, transitory, and asymptomatic. Two patients in the Bmab 1000 group experienced two hypercalcemia readings (#1S009: 10.24 mg/dL on Day 85 and 10.4 mg/dL on Day 169; #01S084: 10.24 mg/dL on Day 85 and Day 252). Otherwise, all patients with hypercalcemia only had one isolated high calcium level. All hypercalcemia events were of CTCAE Grade 1

severity, as no calcium levels were above 11.5 mg/dL. These patients also did not report adverse events, such as nausea, constipation or polyuria, that are typically attributable to hypercalcemia, suggesting that their mildly elevated calcium levels were asymptomatic.

Though numerically there were more hypercalcemia events in the Prolia group compared to the Bmab 1000 group, these events were not clinically significant and any small differences between treatment groups are likely due to chance rather than differences between the drug products.

Study B1000-PMO-03-G-02

Part 1

Events of hypercalcemia (i.e., serum calcium above the upper limit of normal: 10.5 mg/dL) in patients who did not have baseline elevated calcium levels prior to administration of study treatment occurred very rarely during Part 1 of the study overall (see Table 35).

Table 35. N (%) of patients with shift in serum calcium from normal baseline to above the upper limit of normal (>ULN) during Part 1 of Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Serum calcium transition to >ULN	6 (2.5%)	7 (2.9%)

Source: clinical reviewer analysis
The baseline calcium value was derived from either Screening or Day 1 prior to study drug initiation. Patients presenting with elevated calcium levels at the initial baseline, prior to study drug administration, who subsequently exhibit hypercalcemia during the study are unlikely to have developed this condition as a result of the study drug. Hence, these patients were excluded from this analysis. The selection of the appropriate baseline allows for a more accurate assessment of potential drug-induced hypercalcemia by distinguishing pre-existing conditions from those that may be attributable to the study drug.

Overall, hypercalcemia during Part 1 of study B1000-PMO-03-G-02 was mild, transitory, and asymptomatic.

Two patients in the Prolia group experienced two hypercalcemia readings ((b) (6): 10.6 mg/dL on Day 83 and 10.7 mg/dL on Day 549; # (b) (6): 10.9 mg/dL on Day 178 and 10.7 mg/dL on Day 302). Otherwise, all patients with hypercalcemia only had one isolated high calcium level. All hypercalcemia events were of CTCAE Grade 1 severity, as no calcium levels were above 11.5 mg/dL. These patients also did not report adverse events, such as nausea, constipation or polyuria, that are typically attributable to hypercalcemia, suggesting that their mildly elevated calcium levels were asymptomatic.

In addition, two patients (one 67 year old patient and one 69 year old patient) assigned to Bmab 1000 reported a TEAE of *blood calcium increased* during Part 1 of study B1000-PMO-03-G-02. For the 67 year old patient, the Grade 1 *blood calcium increased* event occurred on Day 1, when the calcium level was 11.1 mg/dL. This 11.1 mg/dL value was the highest calcium level during the study for this patient. This subject did not report any symptoms as adverse events during the study. Given that this elevated

calcium level occurred at baseline prior to administration of study treatment, it is clearly not related to the treatment. For the 69 year old patient, the Grade 2 *blood calcium increased* event occurred on Day 183, when the blood calcium level was 11.8 mg/dL. Notably, this patient had an elevated calcium level at baseline (11.2 mg/dL on Day 1 prior to receiving study drug), and the calcium level remained high for the entirety of the trial, with calcium values largely ranging from 11 to 11.3 mg/dL. There was no significant worsening of hypercalcemia upon initiating treatment. In addition, this patient had no reported adverse events other than the *blood calcium increased* event on Day 183.

Three additional patients, two assigned to Bmab 1000 and one assigned to Prolia, had adverse events of *hypercalcaemia*; these patients were previously identified by the laboratory evaluation for hypercalcemia and accounted for in Table 35 above.

Part 2

Few patients transitioned from normal to high calcium levels during Part 2 of study B1000-PMO-03-G-02 (see Table 36).

Table 36. N (%) of patients with shift in serum calcium from normal baseline to above the upper limit of normal (>ULN) during Part 2 of Study B1000-PMO-03-G-02

	Bmab 1000/ Bmab 1000 (N=218) n (%)	US-Prolia/ Bmab 1000 (N=104) n (%)	US-Prolia/ US-Prolia (N = 104) n (%)
Serum calcium transition to >ULN	1 (0.5%)	3 (2.9%)	0

Source: clinical reviewer analysis
The baseline calcium value was derived from either the Part 1 baseline (from Screening or Day 1 prior to study drug initiation) or Part 2 baseline (from Week 52). This approach is justified by the following rationale: patients presenting with elevated calcium levels at the initial baseline, prior to study drug administration, who subsequently exhibit hypercalcemia during the study, are unlikely to have developed this condition as a result of the study drug. This is because these patients demonstrated hypercalcemia before receiving any study intervention. The selection of the appropriate baseline allows for a more accurate assessment of potential drug-induced hypercalcemia by distinguishing pre-existing conditions from those that may be attributable to the study drug. This approach led to the exclusion of two patients (one in the Bmab 1000/Bmab 1000 group and one in the Prolia/Bmab 1000 group) from this table who had hypercalcemia on Day 1 but normal calcium level on Week 52.

Again, hypercalcemia during Part 2 of study B1000-PMO-03-G-02 was mild and asymptomatic. All elevated calcium values in patients with normal baseline calcium were Grade 1 in severity. One patient assigned to US-Prolia/Bmab 1000 treatment group previously experienced hypercalcemia during Part 1 of the study. Otherwise, all other patients with hypercalcemia during Part 2 who had normal calcium at baseline had only a single elevated calcium value. Notably, all measured hypercalcemia levels during Part 2 occurred on the final study day, so no follow up calcium levels were measured to confirm resolution of hypercalcemia.

No patients had adverse events of *hypercalcaemia* during Part 2. All patients were asymptomatic when they had elevated calcium levels.

Though the transition treatment group (US-Prolia/Bmab 1000) experienced the highest incidence of hypercalcemia during Part 2 of study B1000-PMO-03-G-02, it does not appear to be clinically significant since the severity of hypercalcemia was mild and there were no accompanying symptoms in patients who experienced hypercalcemia. Small differences between treatment groups are most likely due to chance rather than differences between the drug products.

Hypomagnesemia and hypophosphatemia

Study B1000-NHV-01-G-01

There were no meaningful differences in treatment groups in median change in any chemistry parameters over time, including phosphate, and shift analysis revealed no concerns or notable differences among the treatment groups. Study B1000-NHV-01-G-01 did not evaluate magnesium levels.

The incidence of transitions from normal at baseline to below the normal range for phosphate were similar between treatment groups (Table 37). All episodes of hypophosphatemia were Grade 1 severity per CTCAE. Given that laboratory shifts from normal to low were balanced between treatment groups and mild in severity, small differences between treatment groups are most likely due to chance rather than differences between the drug products.

Table 37. Incidence of laboratory shifts from normal to below the limit of normal in phosphate during Study B1000-NHV-01-G-01

Laboratory parameter	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Phosphate	19 (20.2%)	26 (27.4%)

Source: clinical reviewer analysis

Study B1000-PMO-03-G-02

The incidence of transitions from normal at baseline to below the normal range for phosphate were similar between treatment groups during both Part 1 (Table 38) and Part 2 (Table 39).

Shifts to below the normal range of magnesium were rare throughout the study. Only two patients experienced a low magnesium level during the study; both patients were assigned to Prolia, and the low magnesium level occurred during Part 1 of the study.

Given that laboratory shifts from normal to low were rare, in the case of magnesium, or balanced between treatment groups, in the case of phosphate, small differences between treatment groups are most likely due to chance rather than differences between the drug products.

Table 38. Incidence of laboratory shifts from normal to below the limit of normal in magnesium and phosphate, at any point during Part 1 in Study B1000-PMO-03-G-02

Laboratory parameter	Bmab 1000 (N=238)	US-Prolia (N=240)

	n (%)	n (%)
Magnesium	0	2 (0.8%)
Phosphate	17 (7.1%)	19 (7.9%)

Source: clinical reviewer analysis

Table 39. Incidence of laboratory shifts from normal at Week 52 to below the limit of normal in magnesium and phosphate, Study B1000-PMO-03-G-02, Part 2

Laboratory parameter	Bmab 1000/ Bmab 1000 (N=218) n (%)	US-Prolia/ Bmab 1000 (N=104) n (%)	US-Prolia/ US-Prolia (N = 104) n (%)
Magnesium	0	0	0
Phosphate	1 (0.5%)	2 (1.9%)	0

Source: clinical reviewer analysis

Other Laboratory Findings

Study B1000-NHV-01-G-01

One 28-year-old male patient experienced elevations in liver enzymes after administration of a single dose of Bmab 1000. On Day 10, laboratory evaluation revealed elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) to 117 U/L, 53 U/L, and 60 U/L, respectively. The ALT value was nearly 3 times the upper limit of normal (ULN 40 U/L). All abnormal values had spontaneously normalized by Day 29 of the study. Bilirubin was normal during this period. This patient had no recorded adverse events or use of concomitant medications during the trial, and no recorded past medical history.

There is no evidence that this patient's elevation in liver enzymes was drug related.

Study B1000-PMO-03-G-02

During Part 1 of the study, a 56-year-old patient who was assigned to US-Prolia during the first part of the study and Bmab 1000 during the second part of the study, experienced elevations in liver enzymes. On Day 82 of the study, approximately 12 weeks after receiving the first dose of US-Prolia, the patient had elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) over 3 times the upper limit of normal (AST of 204 U/L, ALT of 120 U/L). In addition, gamma glutamyl transferase (GGT) was also elevated to 59 U/L on Day 82, though alkaline phosphatase and bilirubin levels were normal. The Investigator recorded adverse events of ALT increased (CTCAE Grade 3) and AST increased (Grade 2) on study Day 82. These adverse events were not considered serious, and no additional actions or hospitalizations were noted. The elevated ALT, AST, and GGT values all normalized after they were rechecked on Day 92. There were no accompanying bilirubin abnormalities or jaundice, so the event does not meet Hy's Law criteria.

This patient has no medical history of liver disease. Notably, the patient has a history of acne and on Day 32 to 235 the Investigator reported an adverse event of "worsening reappearance of acne on face and scalp". The patient received treatment for the event

with itraconazole from Day 78 to Day 89, which overlaps the date of the liver enzyme elevations (Day 82).

The itraconazole US Prescribing Information includes a warning that hepatotoxicity has been associated with the use of oral itraconazole. The Prolia label does not include a similar warning. Notably, the patient's liver function test abnormalities resolved after discontinuation of itraconazole. Additionally, no similar hepatic events occurred after the administration of a second dose of Prolia on Day 187 or the first dose of Bmab1000 on Day 372. Although ALT and AST were mildly elevated on Day 547 (43 U/L and 38 U/L, respectively), these levels did not suggest a drug related liver injury. Therefore, the review team considers the use of itraconazole to be a more likely cause of this subject's liver enzyme elevation on Day 82 than the study drug.

Injection Site Reactions (ISRs)

Per protocol, in both study B1000-NHV-01-G-01 and B1000-PMO-03-G-02, study drug was injected subcutaneously preferably in the abdomen.

Study B1000-NHV-01-G-01

In study B1000-NHV-01-G-01, local tolerance at the injection site was evaluated immediately after study drug administration, and 12 hours, 24 hours, 48 hours, 72 hours, 144 hours, and 216 hours after study drug administration.

The Investigator or designee assessed for the presence of redness, bruising, swelling, itching, and pain, or other types of local reactions. Participants were asked to report sensations at the injection site to evaluate itching or pain. The severity of these parameters was evaluated using the following severity scale: None = 0; Mild =1; Moderate = 2; Severe = 3. Total scores were calculated as the sum of the severity scores of each the individual tolerability parameters (redness, bruising, swelling, itching and pain), ranging from 0 to 15, according to the Global Irritation Score (refer to Figure 10 in the Appendix). Any local injection site reaction with a score of ≥ 2 according to the rating scale was documented as an AE.

Injection site reactions were documented in 13/95 patients (13.7%) in the US-Prolia group and in 10/94 patients (10.6%) in the Bmab 1000 group. Only one patient had a moderate reaction (erythema in a 29-year-old male patient assigned to Bmab 1000 occurring immediately after administration of the study drug; symptoms resolved upon re-examination 12 hours later). One other 35-year-old female patient in the US-Prolia group had a combined score above 1 (with a reported reaction of mild redness, swelling, and pain 12 hours after study drug administration evolving to mild bruising and pain lasting until 72 hours after study drug administration), resulting in a reported adverse event of injection site reaction. All other reactions were mild.

Study B1000-PMO-03-G-02

In study B1000-PMO-03-G-02, evaluation for ISRs occurred within one hour of the end of each study treatment administration as shown in the Assessment Schedule (refer to Table 50 in the Appendix).

Injection site reactions were overall rare, mild in severity, and balanced between treatment groups throughout the study. During Part 1, 3 patients in the Bmab 1000

group had mild erythema (3/238 patients [1.3%]), and in the US-Prolia group, 2 patients had mild erythema, 2 patients had mild erythema and swelling, and 1 patient had moderate erythema (5/240 patients [2.1%]).

During Part 2, 1 patient in the Bmab 1000/Bmab 1000 group (1/218 patients [0.5%]) experienced mild erythema and 1 patient in the Prolia/Prolia group (1/104 patients [1%]) experienced mild erythema. There were no ISRs reported in the Prolia/Bmab 1000 group.

Overall, for both clinical studies, ISRs were mild in severity. Though there was greater incidence of ISRs in study B1000-NHV-01-G-01 compared to study B1000-PMO-03-G-02, incidence was equally distributed between treatment groups in each trial. Therefore, there was no clinically meaningful significant difference between the treatment groups with respect to injection site reactions.

Hypersensitivity Reactions

Hypersensitivity reaction was a protocol-specified adverse event of special interest in clinical study B1000-PMO-03-G-02. In addition, the clinical reviewer searched the safety dataset for adverse event preferred terms coding to the Anaphylaxis and Hypersensitivity narrow OND Custom Medical Queries (OCMQ) to evaluate for events of anaphylaxis and hypersensitivity in the clinical studies.

Study B1000-NHV-01-G-01

There were no events of anaphylaxis or hypersensitivity during this study, according to a search of the safety dataset for adverse event preferred terms coding to the Anaphylaxis OCMQ and Hypersensitivity OCMQ.

Study B1000-PMO-03-G-02

Part 1

There were no events of anaphylaxis in either treatment group during Part 1. Hypersensitivity reactions were rare overall. One 60-year-old patient experienced drug eruption, two patients, aged 57 and 63 years, experienced drug hypersensitivity, and two patients, aged 65 and 70 years, experienced urticaria, all in the US-Prolia group. No patients in the Bmab 1000 group experienced a hypersensitivity reaction according to the Hypersensitivity OCMQ, and no adverse events of special interest relating to hypersensitivity were reported by the Applicant.

Part 2

During Part 2, there were no events of anaphylaxis or hypersensitivity according to the Applicant's evaluation of adverse events of special interest or a search of the safety dataset for adverse event preferred terms coding to the Anaphylaxis OCMQ and Hypersensitivity OCMQ. Therefore, there was no evidence that transitioning from US-Prolia to Bmab 1000 was associated with an increase in hypersensitivity reactions.

Overall, there were no clinically significant hypersensitivity findings in either clinical study.

Fractures

Refer to Section 6.2.9 evaluating fracture incidence during study B1000-PMO-03-G-02.

The Applicant identified atypical femoral fractures as adverse events of special interest. No cases of atypical femoral fractures occurred during study B1000-PMO-03-G-02.

Serious Infections

Serious infection was a protocol-specified adverse event of special interest in clinical study B1000-PMO-03-G-02.

Study B1000-NHV-01-G-01

There were no serious adverse events reported during the study, and therefore there were no serious infections.

Study B1000-PMO-03-G-02

Part 1

Serious infections were rare overall during Part 1 of the study. Two patients in the Bmab 1000 treatment group reported a serious infection during the study: a 64-year-old patient experienced *urosepsis* and a 63-year-old patient experienced *ear infection*, *ear inflammation*, and *vestibular neuronitis*. One 75-year old patient assigned to US-Prolia reported the adverse event of *staphylococcal sepsis*.

Part 2

During Part 2, no serious adverse events were reported.

Overall, there were no clinically significant findings of serious infections in either clinical study.

Dermatologic Reactions

Dermatologic reactions were considered a protocol-specified adverse event of special interest in clinical study B1000-PMO-03-G-02.

Study B1000-NHV-01-G-01

Review of TEAEs occurring during study B1000-NHV-01-G-01 revealed that dermatologic reactions were overall rare and similarly distributed between the treatment groups (refer to Table 40).

Table 40. Dermatologic reactions, Study B1000-NHV-01-G-01

	Bmab 1000 (N=94) n (%)	**US-Prolia (N=95) n (%)**
Total number of patients with dermatologic reactions (%)	5 (5.3)	3 (3.2)
Folliculitis	1 (1.1)	0
Fungal skin infection	1 (1.1)	0

	Bmab 1000 (N=94) n (%)	US-Prolia (N=95) n (%)
Injection site erythema	1 (1.1)	0
Rash	1 (1.1)	0
Skin exfoliation	1 (1.1)	0
Alopecia	0	1 (1.1)
Injection site reaction	0	1 (1.1)
Skin infection	0	1 (1.1)

Source: clinical reviewer analysis

All dermatological reactions occurring during Study B1000-NHV-01-G-01 were either Grade 1 or Grade 2 severity and each preferred term occurred only one patient.

Study B1000-PMO-03-G-02

Part 1

Dermatologic reactions were rare overall during Part 1 of the study and similarly distributed between the treatment groups (refer to Table 41).

Table 41. Dermatologic reactions, Part 1, Study B1000-PMO-03-G-02

	Bmab 1000 (N=238) n (%)	US-Prolia (N=240) n (%)
Total number of patients with dermatologic reactions occurring during Part 1 (%)	4 (1.7)	7 (2.9)
Alopecia	2 (0.8)	0
Dermatitis atopic	1 (0.4)	0
Erythema	1 (0.4)	0
Acne	0	1 (0.4)
Dermatitis	0	1 (0.4)
Hand dermatitis	0	1 (0.4)
Rash	0	1 (0.4)
Rash pustular	0	1 (0.4)
Urticaria	0	2 (0.8)

Source: clinical reviewer analysis

All dermatological reactions occurring during Part 1 were either Grade 1 or Grade 2 severity. Except for *alopecia* and *urticaria*, which occurred in two patients each, all reported dermatologic reactions occurred only one patient.

Part 2

Two patients, both in the Bmab 1000 /Bmab 1000 treatment group, experienced dermatologic reactions according to the Applicant's AESI analysis: one patient reported the preferred term *acarodermatitis* and one patient reported the preferred term *rash pruritic*.

Overall, there were no clinically significant findings of dermatologic reactions in either clinical study.

Osteonecrosis of the jaw

Osteonecrosis of the jaw is identified as a potential adverse reaction under the Warnings and Precautions section of the USPI for Prolia. No patients in either Study B1000-NHV-01-G-01 or B1000-PMO-03-G-02 had a TEAE of osteonecrosis of the jaw.

6.4 Clinical Conclusions on Immunogenicity

The assessment of immunogenicity occurred in the comparative pharmacokinetic Study B1000-NHV-01-G-01 and the comparative clinical Study B1000-PMO-03-G-02. There was no meaningful difference between the treatment groups in either study with respect to development of anti-drug antibodies (ADAs) or neutralizing antibodies (NAbs). Furthermore, presence of ADAs or NAbs had no apparent impact on efficacy or safety outcomes. Refer to Section 5.4 for complete details of the immunogenicity assessment and conclusions from the Clinical Pharmacology review team.

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6.5 Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant's development program established that Bmab 1000, US-Prolia, and US-Xgeva share identical primary structures and comparable secondary and tertiary structures. Functional assays showed similarity between Bmab 1000, US-Prolia, and US-Xgeva with respect to pharmacologic activity. There were no meaningful differences in pharmacokinetics between Bmab 1000 and US-Prolia in the PK similarity study.

The comparative clinical study showed no meaningful difference in PK, efficacy, safety, or immunogenicity between Bmab 1000 and US-Prolia in the treatment of post-menopausal women with osteoporosis. Presence of ADAs had no impact on PK, efficacy, or safety. Although some numerical differences were observed between Bmab 1000 and US-Prolia in terms of incidences of certain adverse events, the absolute differences were not large and not considered clinically meaningful. Importantly, the adverse event profile of both products was comparable.

A transition from US-Prolia to Bmab 1000 at Week 52 was well tolerated with no meaningful impact on PK, efficacy, or safety. At six months post-transition (i.e., Week 78, the percentage change from baseline in lumbar spine BMD was comparable in the two treatment groups. There was no meaningful increase in ADA titers or incidence of NAbs after transitioning from US-Prolia to Bmab 1000.

The Applicant provided sufficient justification that Bmab 1000 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

Mechanism of Action

Across all approved indications for US-Prolia and US-Xgeva, the clinical efficacy is based on denosumab binding to RANKL and prohibiting its binding to the RANK receptor. Functional assays established that Bmab 1000 exhibits the same pharmacologic activity as US-Prolia and US-Xgeva and has identical primary structure to US-Prolia and US-Xgeva. The comparative analytixal assessment support that Bmab 1000 is highly similar to US-Prolia and US-Xgeva. Furthermore, there was no clinically meaningful difference in the effect of Bmab 1000 and US-Prolia on the serum bone turnover marker CTX and lumbar spine bone mineral density, which further supports a shared mechanism of action.

The Applicant provided adequate justification to support that Bmab has the same, known, and potential mechanisms of action, as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Pharmacokinetics

The Applicant provided adequate justification that Bmab 1000 is expected to have a similar PK profile as US-Prolia for each indication for which US-Prolia is licensed.

Immunogenicity

In the Bmab 1000 development program, immunogenicity was evaluated in populations considered sensitive for detecting clinically meaningful differences: female patients with post-menopausal osteoporosis (PMO) and healthy patients. Immunogenicity was found to be similar when comparing Bmab 1000 and US-Prolia in the PK similarity study, Study B1000-NHV-01-G-01, in healthy patients and between Bmab 1000 and US-Prolia in the comparative clinical study, Study B1000-PMO-03- G-02, in PMO women. The Applicant provided adequate justification that Bmab 1000 is expected to have a similar immunogenicity as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

Toxicity

Comparative safety was assessed in the comparative clinical study B1000-PMO-03- G-02, which was conducted in female patients with PMO. Supportive safety information was also available from the PK similarity study, Study B1000-NHV-01-G-01, in healthy patients. The Applicant provided adequate justification that Bmab 1000 is expected to have a similar safety profile as US-Prolia and US-Xgeva for each indication being sought for licensure.

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1000 and US-Prolia or US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of Bmab 1000 and US-Prolia and US-Xgeva and the results from the comparative clinical study (B1000-PMO-03- G-02) to support their justification. The Applicant also described that the results from the single transition included in Study B1000-PMO-03-G-02 provided supportive evidence that there was no meaningful difference with respect to development of ADAs or Nabs and that the presence of ADAs or NAbs had no apparent impact on efficacy or safety outcomes with switching between Bmab 1000 and US-Prolia or US-Xgeva.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between Bmab 1000 and US-Prolia or US-Xgeva to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether there could be diminished efficacy or safety issues associated with alternating or switching between use of Bmab 1000 and US-Prolia or US- Xgeva was considered unnecessary to support a demonstration of interchangeability for Bmab 1000.

Conclusion

In summary, the data and information provided by the Applicant are sufficient to demonstrate that Bmab 1000 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that the risk, in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1000 US-Prolia, or Bmab 1000 and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without alternation or switch.

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6.6 Extrapolation to Support Licensure of Non-Studied Indications

6.6.1 Division of General Endocrinology and Office of Oncology Drugs

The Applicant submitted data and information in support of a demonstration that Bmab 1000 is highly similar to US-Prolia and US-Xgeva notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between Bmab 1000 and US-Prolia, or Bmab 1000 and US-Xgeva, in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that Bmab 1000 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of Bmab 1000 and

US-Prolia or Bmab 1000 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alteration or switch.

The Applicant is seeking licensure of Bmab 1000 for the following indication(s) for which US-Prolia and US-Xgeva have been previously licensed and for which Bmab 1000 has not been directly studied:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of Bmab 1000 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved.

Therefore, the totality of the evidence provided by the Applicant supports licensure of Bmab 1000 as biosimilar to and interchangeable with US-Prolia and US-Xgeva for each of the following indication(s) for which the Applicant is seeking licensure of Bmab 1000:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to

remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Conclusions

The Division of General Endocrinology and the Office of Oncology Drugs 1 conclude that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of Bmab 1000 for all indications for which US-Prolia and US-Xgeva are licensed.

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7 Labeling Recommendations

7.1 Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-kyqq, was found to be conditionally acceptable the Agency. Referred to the Division of Medication Error Prevention and Analysis 1 (DMEPA 1) review dated June 20, 2025, in DARRTS.

7.2 Proprietary Name

The proposed proprietary names for denosumab-kyqq are conditionally approved as Bosaya (denosumab-kyqq 60 mg/mL prefilled syringe) and Aukelso (denosumab-kyqq 120 mg/1.7 mL vial). These names have been reviewed by DMEPA 1, who concluded the names are acceptable. Refer to reviews dated November 21, 2024 and March 27, 2025, in DARRTS.

7.3 Other Labeling Recommendations

This Prescribing Information (PI) review includes a summary of the rationale for major changes incorporated into the finalized PI as compared to the Applicant's draft received on September 16, 2024. The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare provider.

For Bosaya, edits were made throughout the Full Prescribing Information to align with the reference product Prolia S-219 approved May 22, 2025, and language used when referring to a biosimilar to US-Prolia. "Bosaya", "denosumab-kyqq", "denosumab", or "denosumab products" were used in place of Prolia as applicable.

For Bosaya, in addition to aligning with Prolia S-219, the following product specific edits are included in the draft Prescribing Information:

- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration: deleted language proposed by the applicant (b) (4) The language are familiar to healthcare providers or are already noted in subsection 2.3.
- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration: deleted (b) (4) The proposed instructions "(b) (4)" are not included in the Prolia labeling and are considered common knowledge to HCPs.
- 2 DOSAGE AND ADMINISTRATION/ 2.4 Preparation and Administration: deleted Applicant's proposed (b) (4) as these are familiar to HCPs.
- 3 DOSAGE FORMS AND STRENGTHS: solution characteristics described as "clear to slightly opalescent, colorless to pale yellow" as confirmed by product quality reviewer.
- 11 DESCRIPTION: updated "(b) (4)" to "glacial acetic acid" per product quality reviewer, and inactive ingredients listed by amounts (mg), not percentage (%).

For Aukelso, edits were made throughout the Full Prescribing Information to align with the reference product Xgeva S-222 approved May 30, 2025, and language used when referring to a biosimilar to US-Xgeva. "Aukelso", "denosumab-kyqq", "denosumab", or "denosumab products" were used in place of Prolia as applicable.

For Aukelso, in addition to aligning with Xgeva S-222, the following product specific edits are included in the draft Prescribing Information:

- 3 DOSAGE FORMS AND STRENGTHS: solution characteristics described as “clear to slightly opalescent, colorless to pale yellow” as confirmed by product quality reviewer.
- 11 DESCRIPTION: updated “(b) (4)” to “glacial acetic acid” per product quality reviewer, and inactive ingredients listed by amounts (mg), not percentage (%).

Authors:

LaiMing Lee, PhD
Associate Director for Labeling, DGE

Shivangi Vachhani, MD
Cross Discipline Team Leader, DGE

8 Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.1 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

Authors:

Carly Gordon, MD
Clinical Reviewer

Shivangi Vachhani, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

Author:

Carly Gordon, MD
Clinical Reviewer, DGE

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

At the time of this review, other denosumab products Jubbonti and Wyost have been approved as interchangeable biosimilars and have qualified for FIE. Bmab 1000 will be approved as a biosimilar product, as discussed in Section 1.7, and therefore is considered to have a new active ingredient for the purposes of PREA. The Applicant submitted the initial Pediatric Study Plan (iPSP) on May 30, 2023, and an agreement letter was issued on November 15, 2023.

For the following indications and populations, PREA requirements were either waived for, or inapplicable to, US-Prolia or US-Xgeva, and therefore the Applicant is not required to submit a pediatric assessment for them:

Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture,
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer,
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and
- Treatment of glucocorticoid-induced osteoporosis in pediatric patients aged 0 to <5 years of age at high risk for fracture.

Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of hypercalcemia of malignancy of refractory to bisphosphonate therapy
- Treatment of pediatric patients who are not skeletally mature with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

The applicant submitted a pediatric assessment for giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity in skeletally mature adolescents (b) (4) based on a demonstration of biosimilarity and providing adequate scientific justification to support extrapolation of

data and information to support licensure. Refer to Section 6.6 for review of the assessment.

(b) (4)

n May 22, 2025, US-Prolia (BLA 125320/S-219) updated the label (b) (4) Specifically, appropriate pediatric language has been added to Subsection 8.4 Pediatric Use of Section 8 USE IN SPECIFIC POPULATIONS of the US-Prolia label to reflect that safety and effectiveness were not established in the phase 3 clinical trial evaluating the effect of denosumab on glucocorticoid-induced osteoporosis in children aged 5 to 17 years old.

Accordingly, the Applicant fulfilled PREA requirements for this indication by including the relevant pediatric information in Bmab 100 labeling to align with changes made by US-Prolia.

PeRC discussed this application on July 22, 2025, and concurred with the Division's recommendations.

Authors:

Carly Gordon, MD
Clinical Reviewer, DGE

Shivangi Vachhani, MD
Cross Disciplinary Team Leader, DGE

11 REMS and Postmarketing Requirements and Commitments

11.1 Recommendations for Risk Evaluation and Mitigation Strategies

Prolia is currently approved with a REMS consisting of a communication plan (CP) and timetable for submission of assessments. The Prolia REMS goal is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Prolia.

On September 14, 2024, Biocon Biologics Inc. submitted a BLA with a proposed REMS for Bosaya that consisted of a CP and timetable for submission of assessments. The proposed REMS goal was to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Bosaya, similar to the US Prolia REMS at the time of the BLA submission.

The Agency sent an Information Request (IR) on February 19, 2025 and June 30, 2025 to update their REMS proposal for Bosaya to align with the Prolia REMS. Biocon Biologics Inc. submitted REMS amendments on February 27, 2025 and July 8, 2025 in response to the Agency's comments.

The Division of Risk Management (DRM) reviewed the amended REMS and found the Bosaya REMS, submitted on July 8, 2025, acceptable. The Bosaya REMS is comparable to the Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety.

The Bosaya REMS goal and objective are:

The goal of the Bosaya REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Bosaya. The following describes the objective associated with the REMS:

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Bosaya in patients with advanced chronic kidney disease

The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan elements include:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Patient Guide
- REMS website

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The Bosaya REMS assessment plan was reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

Authors:

Brian Caruth, PharmD
Risk Management Reviewer

Yasmeen Abou-Sayed, PharmD
Team Leader

11.2 Recommendations for Postmarket Requirements and Commitments

No post-marketing requirements (PMR) are anticipated for this biologics license application.

The Applicant agreed to the following PMC, developed by OPQ:

CMC PMC#1 (4889-1): To implement appropriate positive controls for the container closure integrity test (CCIT) method for Bmab 1000 pre-filled syringe (PFS) to provide the assurance that these positive controls are not subjected to potential leaks larger than the intended breach size of ≤ 20 µm diameter.

Final report submission: 12/2025

Authors:

Carly Gordon, MD
Clinical reviewer, DGE

Shivangi Vachhani, MD
Clinical Team Leader

12 Division Director Comments

12.1 Division Director (OND – Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that Bmab 1000 is biosimilar to US-Prolia and US-Xgeva. I also concur with the team's recommendation to provisionally determine that Bmab 1000 meets the standards for interchangeability under section 351(k)(4) of the PHS Act. We have not identified any deficiencies that would justify a complete response action. Although we have provisionally determined that Bmab 1000 meets the requirements for licensure as interchangeable biosimilar product, pursuant to section 351(k)(6) of the Public Health Service Act, we are unable to make such a determination because of unexpired first interchangeable exclusivity for US-licensed Jubbonti and Wyost, as discussed in Section 1.7 above. Accordingly, I also concur with the review team's recommendation to provisionally determine that:

- Bmab 1000, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- Bmab 1000, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

These Bmab 1000 products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have previously been approved and for which the applicant is seeking licensure:

U.S.-Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures

- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

U.S.-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

When action is taken for this BLA, it will be administratively split to facilitate an approval action for Bmab 1000 as a biosimilar product ("Original 1") and a provisional determination that Bmab 1000 is an interchangeable biosimilar product, as described in Section 1.7 above ("Original 2"). The Applicant is expected to submit an amendment seeking approval of BLA 761436/Original 2 no more than six months prior to the expiration of exclusivity, or when the Applicant believes that BLA 761436/Original 2 will become eligible for approval.

Author:
Theresa Kehoe, MD
Division Director, Division of General Endocrinology

13 Appendices

13.1 Financial Disclosure

Covered Clinical Study (Name and/or Number): B1000-NHV-01-G-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): B1000-PMO-03-G-02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 187		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2 Office of Clinical Pharmacology Appendices

13.2.1 Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study and the comparative clinical study, serum concentrations of study drug were measured using a validated electrochemiluminescence immunoassay (ECLIA). This method was fully validated over a range of 3 to 75 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the Agency, and is considered suitable for the assessment of serum concentrations of denosumab.

The method validation entitled “Validation of an ECLIA method for the determination of denosumab in human serum” was performed at (b) (4) . The method is described in the standard operating procedure (SOP) SM3-561 (effective date 06/05/2023). In this method, a MSD Multi-array 96 well Plate was firstly coated with an anti-denosumab antibody and incubated for 14–72 hours. Following a blocking step to minimize non-specific binding, serum samples, standards,

and quality controls were added to the wells. After incubation, a sulfo-tag-labeled anti-idiotype detection antibody was applied, enabling electrochemiluminescent signal generation. The plate was subsequently washed and treated with glutaraldehyde, then read buffer is added. Signal detection is carried out using the MESO QuickPlex SQ 120 reader, producing relative light units (RLU) proportional to analyte concentration. Table 42 shows the summary of the ECL method validation and performance in quantification of Bmab 1000 and US-Prolia.

Table 42. Summary of bioanalytical method validation and in-study performance measurement of Bmab 1000 and US-Prolia.

Materials used for calibration curve & concentration	Matrix: Human serum Tested product: Bmab 1000 Calibration concentration (in undiluted [neat] serum): 1.0 [anchor], 3.00, 6.00, 12.0, 21.0, 30.0, 45.0, 60.0, 75.0, 130 [anchor] ng/mL		
Validated assay range	3.00 to 75.0 ng/mL		
Material used for QCs & concentration	Matrix: Human serum Tested product: Bmab 1000, US Prolia QC concentrations (in undiluted [neat] serum): 3.00 (LLOQ QC), 9.00 (LQC), 15.0 (MQC), 56.0 (HQC), 75.0 (ULOQ QC), 400 (DQC 1), 4’000 (DQC 2), 9’000 (DQC 3) ng/mL		
Minimum required dilutions (MRDs)	MRD: 1:4		
Source & lot of reagents (LBA)	**Capture protein** Biotinylated anti-denosumab antibody **Detection antibody** Sulfo-tagged anti-denosumab antibody		
Regression model & weighting	5-parameter logistic (5PL) model, 1/Y² weighting		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	8	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.6 to 6.7%	Acceptable

Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at lower limit of quantitation (LLOQ)), ≤ 20%CV	Cumulative precision (%CV) from LLOQ to ULOQ	2.2 to 8.3%	Acceptable
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 5 QCs Bmab 1000 US- Prolia	 -1.9 to 2.3% 0.7 to 4.8%	Acceptable
	Inter-batch %CV Bmab 1000 US- Prolia	 ≤ 12.6% ≤ 13.6%	Acceptable
	Percent total error (TE) Bmab 1000 US- Prolia	 ≤ 14.9% ≤ 16.4%	Acceptable
Selectivity & matrix effect	The selectivity of Bmab 1000 and US- Prolia at LLOQ and HQC met target acceptance criteria recovering within ± 25% for LLOQ and ± 20% for HQC of the nominal concentration. **Selectivity** All 10 individual matrix lots for Bmab 1000 and Prolia that were investigated were within acceptance criteria. **Matrix Effect** 10 individual lots tested 10/10 passed, no quantifiable values were observed.		Acceptable
Diseased Selectivity & matrix effect	**Selectivity** All 5 individual matrix lots for Bmab 1000 and Prolia that were investigated were within acceptance criteria. **Matrix Effect** 5 individual lots tested 5/5 passed, no quantifiable values were observed.		Acceptable
Interference & specificity	Receptor activator of nuclear factor kappa-B-ligand (RANKL), anti-denosumab antibody (ADA) interference test was performed by spiking the material in pooled normal human serum matrix with or without denosumab (Bmab1000, Prolia). **[RANKL interference]**		Acceptable

	As seen from the results from Table 46 below, no RANKL interference was observed at all the three tested QC levels of both Bmab 1000 and Prolia. **[ADA interference]** No significant interference was observed with concentration of antibody up to 10.0 ng/ml at HQC level.	
Hemolysis effect	Hemolysis effect and lipemic effect were analyzed in selectivity testing. One pre-dose sample was spiked with 2% of pre-frozen whole blood, as hemolyzed sample, and one pre-dose sample was spiked with 2% of plant based oil, as lipemic sample. The assessment met the acceptance criteria.	Acceptable
Lipemic effect	See above.	Acceptable
Dilution linearity & hook effect	Dilution integrity was demonstrated for 10-, 100-, and 200-fold dilutions using the robotic liquid handling system.	Acceptable
Bench-top/process stability	Stability was demonstrated for Bmab 1000 and Prolia at MQC level after 2 h at room temperature, and at LQC level after 1 h at room temperature in whole blood.	Acceptable
Freeze-Thaw stability	Demonstrated for 6 freeze/thaw cycles at -20°C and -80°C at room temperature in polypropylene tubes with a longest single thaw period of 16 hours and a cumulative thaw period of 33 hours.	Acceptable
Long-term storage	LTS established in human serum for 608 days at –80°C, and 620 days at –20°C.	Acceptable
Parallelism	Parallelism was assessed. See results in study Performance report below.	
Method Performance in Comparative PK Study # B1000-NHV-01-G-01 (Report No. ACA36122-01)		
Assay passing rate	95.0% (227/239) Total runs: 239 (including ISR runs) Accepted runs: 227 Rejected runs: 12	Acceptable
Standard curve performance	• Cumulative accuracy (%bias) from LLOQ to ULOQ: -0.8% to 1.0% • Cumulative precision (%CV) from LLOQ to ULOQ: 1.7% to 3.2%	Acceptable
QC performance	• Cumulative accuracy (%bias): 0.0% to 3.8% • Cumulative precision (%CV): 3.1% to 5.9%	Acceptable
Method reproducibility	ISR was performed in 6.6% (297/4485) of study samples and 96.2%% (278/289) of samples met the pre-specified criteria	Acceptable

Study sample analysis/ stability	**Sample:** LTS established in human serum for 608 days at –80°C, and 620 days at –20°C All samples were analyzed within the established duration with the longest sample storage at 615 days under storage at -20°C.	Acceptable
Parallelism in Healthy Individuals	To assess parallelism, 6 individual samples with high denosumab concentration were selected and diluted to 3 concentrations (1x, 2x, 4x and 8x dilution) within the quantitation range. Five out of 6 samples met the acceptance criteria (83%). The CV was 1.0-15.3%. Therefore, the parallelism test met the acceptance criteria.	Acceptable
Method Performance in Comparative PK Study # B1000-PMO-03-G-02 (Report No. ACA36450-01)		
Assay passing rate	95.3% (221 of 232) Total runs: 232 (including ISR runs) Accepted runs: 221 Rejected runs: 11	Acceptable
Standard curve performance	• Cumulative accuracy (%bias) from LLOQ to ULOQ: -0.8% to 1.3% • Cumulative precision (%CV) from LLOQ to ULOQ: 1.0% to 3.2%	Acceptable
QC performance	• Cumulative accuracy (%bias): -3.0% to 3.4% • Cumulative precision (%CV): 4.2% to 6.2%	Acceptable
Method reproducibility	ISR was performed in 6.5% (321/4906) of study samples and % (98.8%) of samples met the pre-specified criteria	Acceptable
Study sample analysis/ stability	**Sample:** LTS established in human serum for 608 days at –80°C, and 620 days at –20°C. The first sample collection was on 15-Jun-2022 and the end of sample analysis was on 24-Jun-2024. The longest storage duration of samples was 741 days (stored under -80°C). A small portion of samples (6.7%, 718 of 10748 aliquots) were analyzed out of the established LTS window. Since the PK data in this study were analyzed for supportive purpose, the reviewer deems it acceptable that some samples were analyzed out of the established storage stability window.	Acceptable

Parallelism in Healthy Individuals	To assess parallelism, 6 individual samples with high Denosumab concentration not above ULOQ were selected and diluted to 3 concentrations (1x, 2x, 4x and 8x dilution) within the quantitation range. Five out of 6 samples met the acceptance criteria (83%). The CV was 3.6 – 9.3%. Therefore, the parallelism test met the acceptance criteria.	Acceptable

**Concentration data from impacted samples removed for PK analysis*

PK Method Comparability (biosimilar vs. reference product)

In general, the method was validated in accordance with the FDA Bioanalytical Method Validation Guidance. However, the Applicant originally only used calibration curve prepared by Bmab 1000 and US-Prolia to determine the concentration levels of QC samples prepared by the same product and reported the difference. No QC sample performance and calibration curve similarities across the two products were assessed. FDA recommended assessing the QC sample performance similarity and Calibration curve similarity based on the published white paper (Thway TM, Wang YM, Booth BP, Maxfield K, Huang SM, Zineh I. Current Perspectives on Ligand-Binding Assay Practices in the Quantification of Circulating Therapeutic Proteins for Biosimilar Biological Product Development. AAPS J. 2019 Dec 19;22(1):15). The Applicant conducted biosimilarity assessment between Bmab 1000 and US-Prolia. Bioanalytical comparability was demonstrated across all products (Table 43, Table 44, and Table 45), with absolute bias differences between quality controls prepared with Bmab 1000 and the reference product (US-Prolia) being no greater than 10%.

Table 43. Individual calibrator accuracy and precision (Standard curves prepared with Bmab 1000 were back-calculated to standard curves prepared with Prolia US).

	Bmab 1000 standard curve back-calculated to Prolia US standard curve															
	STD 9	Bias	STD 8	Bias	STD 7	Bias	STD 6	Bias	STD 5	Bias	STD 4	Bias	STD 3	Bias	STD 2	Bias
Nominal concentration (ng/mL)	3.0	%	6.0	%	12.0	%	21.0	%	30.0	%	45.0	%	60.0	%	75.0	%
RDCA36137-01_R57	2.7	-10.1	5.2	-14.2	11.0	-8.7	19.4	-7.4	27.7	-7.8	42.7	-5.0	55.6	-7.3	74.1	-1.3
28-Mar-2023	2.7	-9.5	5.4	-10.0	11.5	-4.0	20.3	-3.4	29.8	-0.7	44.4	-1.2	58.2	-2.9	74.1	-1.2
	2.7	-9.4	5.3	-12.1	10.5	-12.3	18.8	-10.3	28.0	-6.8	42.8	-5.0	58.1	-3.2	76.0	1.4
Intra-run mean conc. (ng/mL)	2.7		5.3		11.0		19.5		28.5		43.3		57.3		74.7	
Intra-run SD	0.0		0.1		0.5		0.7		1.2		1.0		1.5		1.1	
Intra-run CV [%]	0.4		2.3		4.5		3.7		4.1		2.3		2.6		1.5	
Intra-run Bias [%]	-9.7		-12.1		-8.3		-7.0		-5.1		-3.7		-4.5		-0.4	
Total Error [%]	10.1		14.4		12.9		10.8		9.2		6.0		7.1		1.9	
n	3		3		3		3		3		3		3		3	
RDCA36137-01_R58	2.8	-5.3	5.2	-13.8	11.3	-5.8	20.0	-5.0	29.2	-2.7	41.4	-8.1	57.6	-4.1	78.5	4.7
30-Mar-2023	2.7	-10.0	5.7	-5.7	12.0	0.4	21.1	0.3	30.6	1.8	43.1	-4.3	57.5	-4.1	73.8	-1.7
	2.9	-4.8	5.7	-5.3	11.9	-0.4	20.1	-4.2	29.3	-2.3	42.3	-6.0	57.5	-4.1	77.1	2.7
Intra-run mean conc. (ng/mL)	2.8		5.5		11.8		20.4		29.7		42.2		57.5		76.4	
Intra-run SD	0.1		0.3		0.4		0.6		0.8		0.9		0.0		2.4	
Intra-run CV [%]	3.1		5.2		3.4		2.9		2.5		2.0		0.0		3.2	
Intra-run Bias [%]	-6.7		-8.3		-2.0		-2.9		-1.1		-6.1		-4.1		1.9	
Total Error [%]	9.8		13.5		5.4		5.9		3.6		8.1		4.2		5.1	
n	3		3		3		3		3		3		3		3	
RDCA36137-01_R59	2.9	-4.2	5.9	-1.8	11.8	-1.6	21.3	1.5	30.4	1.2	44.1	-1.9	60.4	0.7	80.3	7.1
31-Mar-2023	2.7	-9.5	5.8	-2.7	12.1	1.1	21.5	2.3	30.3	1.1	42.6	-5.2	57.7	-3.8	78.6	4.8
	2.9	-5.0	5.6	-6.9	11.7	-2.1	20.2	-3.6	30.3	1.0	44.3	-1.7	59.9	-0.2	78.3	4.3
Intra-run mean conc. (ng/mL)	2.8		5.8		11.9		21.0		30.3		43.7		59.3		79.1	
Intra-run SD	0.1		0.2		0.2		0.7		0.0		0.9		1.4		1.1	
Intra-run CV [%]	3.0		2.8		1.8		3.2		0.1		2.1		2.4		1.4	
Intra-run Bias [%]	-6.2		-3.8		-0.9		0.0		1.1		-2.9		-1.1		5.4	
Total Error [%]	9.2		6.6		2.6		3.2		1.2		5.0		3.5		6.8	
n	3		3		3		3		3		3		3		3	
Inter-run mean conc. (ng/mL)	2.8		5.5		11.6		20.3		29.5		43.1		58.1		76.7	
Inter-run SD	0.1		0.2		0.5		0.7		0.9		0.7		1.1		2.2	
Inter-run CV [%]	2.0		4.5		4.2		3.7		3.2		1.7		1.9		2.8	
Inter-run Bias [%]	-7.5		-8.1		-3.7		-3.3		-1.7		-4.3		-3.2		2.3	
Total Error [%]	9.6		12.6		7.9		7.0		4.9		6.0		5.2		5.2	
n	9		9		9		9		9		9		9		9	

Table 44. Individual calibrator accuracy and precision (Standard curves prepared with Prolia US were back-calculated to standard curves prepared with Bmab 1000)

	Prolia US standard curve back-calculated to Bmab 1000 standard curve															
	STD 9	Bias	STD 8	Bias	STD 7	Bias	STD 6	Bias	STD 5	Bias	STD 4	Bias	STD 3	Bias	STD 2	Bias
Nominal concentration (ng/mL)	3.0	%	6.0	%	12.0	%	21.0	%	30.0	%	45.0	%	60.0	%	75.0	%
RDCA36137-01_R57	3.4	13.6	6.7	11.4	13.4	11.3	23.6	12.5	32.8	9.3	45.1	0.3	61.9	3.1	80.4	7.1
28-Mar-2023	3.4	12.8	6.3	5.2	12.9	7.2	22.4	6.5	31.4	4.6	42.6	-5.4	59.9	-0.2	80.1	6.8
	3.4	12.2	6.7	11.6	13.9	16.1	22.9	9.1	33.4	11.5	45.6	1.4	60.3	0.5	76.3	1.8
Intra-run mean conc. (ng/mL)	3.4		6.6		13.4		23.0		32.5		44.4		60.7		78.9	
Intra-run SD	0.0		0.2		0.5		0.6		1.0		1.7		1.0		2.3	
Intra-run CV [%]	0.7		3.3		4.0		2.8		3.2		3.7		1.7		2.9	
Intra-run Bias [%]	12.9		9.4		11.5		9.4		8.5		-1.2		1.1		5.3	
Total Error [%]	13.5		12.8		15.5		12.2		11.7		5.0		2.9		8.1	
n	3		3		3		3		3		3		3		3	
RDCA36137-01_R58	3.3	9.1	6.5	8.5	13.4	11.3	22.9	9.1	32.8	9.2	42.3	-6.0	61.0	1.7	78.9	5.2
30-Mar-2023	3.3	11.6	6.0	0.6	12.5	3.9	20.9	-0.3	31.2	4.1	43.1	-4.2	61.5	2.5	80.6	7.5
	3.2	5.9	6.1	2.2	12.4	2.9	22.0	4.6	32.6	8.5	43.9	-2.4	61.4	2.3	77.2	2.9
Intra-run mean conc. (ng/mL)	3.3		6.2		12.7		21.9		32.2		43.1		61.3		78.9	
Intra-run SD	0.1		0.2		0.5		1.0		0.8		0.8		0.2		1.7	
Intra-run CV [%]	2.6		4.0		4.3		4.5		2.6		1.9		0.4		2.2	
Intra-run Bias [%]	8.9		3.7		6.0		4.5		7.3		-4.2		2.1		5.2	
Total Error [%]	11.5		7.8		10.3		9.0		9.8		6.1		2.5		7.4	
n	3		3		3		3		3		3		3		3	
RDCA36137-01_R59	3.2	5.9	5.8	-2.8	12.5	3.9	21.8	3.7	30.7	2.4	41.6	-7.6	58.7	-2.2	74.3	-1.0
31-Mar-2023	3.3	10.0	5.9	-1.2	12.3	2.8	20.7	-1.3	31.3	4.4	43.4	-3.4	59.5	-0.9	77.7	3.6
	3.2	6.8	6.2	2.7	12.8	6.4	21.6	2.8	31.4	4.6	43.1	-4.3	58.5	-2.4	74.9	-0.1
Intra-run mean conc. (ng/mL)	3.2		6.0		12.5		21.4		31.1		42.7		58.9		75.6	
Intra-run SD	0.1		0.2		0.2		0.6		0.4		1.0		0.5		1.8	
Intra-run CV [%]	2.0		2.8		1.8		2.6		1.2		2.3		0.8		2.4	
Intra-run Bias [%]	7.6		-0.5		4.3		1.7		3.8		-5.1		-1.9		0.8	
Total Error [%]	9.6		3.3		6.1		4.3		5.0		7.4		2.7		3.3	
n	3		3		3		3		3		3		3		3	
Inter-run mean conc. (ng/mL)	3.3		6.3		12.9		22.1		32.0		43.4		60.3		77.8	
Inter-run SD	0.1		0.3		0.5		0.8		0.7		0.9		1.3		1.9	
Inter-run CV [%]	2.5		4.8		3.5		3.7		2.3		2.1		2.1		2.4	
Inter-run Bias [%]	9.8		4.2		7.3		5.2		6.5		-3.5		0.5		3.8	
Total Error [%]	12.3		9.0		10.8		8.9		8.8		5.6		2.6		6.2	
n	9		9		9		9		9		9		9		9	

Table 45. Biosimilarity evaluation from 3 development runs.

Summary statistics of back-calculated QCs against STDs prepared from Bmab 1000										
	QCs prepared from Bmab 1000					QCs prepared from US-Prolia				
QC level	LLOQ	LQC	MQC	HQC	ULOQ	LLOQ	LQC	MQC	HQC	ULOQ
Nominal Concentration (ng/mL)	3	6	21	60	75	3	6	21	60	75
N (total number of replicates)	6	6	6	6	6	6	6	6	6	6
Observed Mean Concentration (ng/mL)	2.9	5.8	20.3	56.3	73.4	3.2	6.2	22.0	58.8	75.2
Mean Bias or Inter-run Bias	-3.1	-3.7	-3.3	-6.1	-2.2	7.2	3.9	4.6	-2.0	0.2
Inter-run %CV	1.1	1.5	1.3	1.4	0.6	2.7	1.2	2.0	2.1	1.7
Total Error	4.2	5.1	4.6	7.5	2.7	9.8	5.1	6.6	4.0	1.9

	LLOQ	LQC	MQC	HQC	ULOQ
Bias difference, Bmab 1000 vs US-Prolia	-10.3	-7.5	-7.9	-4.2	-2.4

Summary statistics of back-calculated QCs against STDs prepared from US-Prolia										
	QCs prepared from Bmab 1000					QCs prepared from US-Prolia				
QC level	LLOQ	LQC	MQC	HQC	ULOQ	LLOQ	LQC	MQC	HQC	ULOQ
Nominal Concentration (ng/mL)	3	6	21	60	75	3	6	21	60	75
N (total number of replicates)	6	6	6	6	6	6	6	6	6	6
Observed Mean Concentration (ng/mL)	2.7	5.6	20.6	57.7	74.8	3.0	6.0	22.3	60.1	76.4
Mean Bias or Inter-run Bias	-9.3	-6.9	-2.0	-3.9	-0.3	0.7	0.6	6.3	0.2	1.9
Inter-run %CV	1.0	1.8	2.6	1.4	1.0	2.7	1.2	2.0	2.1	1.7
Total Error	10.2	8.7	4.6	5.3	1.3	3.3	1.8	8.2	2.3	3.6

	LLOQ	LQC	MQC	HQC	ULOQ
Bias difference, Bmab 1000 vs US-Prolia	-10.0	-7.5	-8.3	-4.1	-2.2

RANKL interference with Bmab1000 and Prolia drug product

Endogenous receptor activator of nuclear factor-κB ligand (RANKL) could interfere in the quantification of denosumab via competition in binding to denosumab with coated recombinant human RANKL (rhRANKL) on the plate surface. The interference can be various depending on concentrations of target (endogenous RANKL), and denosumab in samples from clinical studies. Therefore, the FDA recommended that the Applicant conduct a drug tolerance study with different levels of target (RANKL) and denosumab and provide justifications that endogenous RANKL from the study samples does not lead to significant interference in your sample analysis.

As seen from Table 46, no RANKL interference was observed at all the tested QC levels of both Bmab 1000 and Prolia (i.e. % Bias is ≤20% of nominal concentration).

Table 46 Evaluation of RANKL interference for the bioanalytical method of denosumab measurement.

Run ID	QC Level	QC concentration (ng/mL)	RANKL concentration (pg/mL)	QC level spiked with Bmab 1000 (Batch # BS21005895)			QC level spiked with Prolia US (Batch #1135692)		
				Mean RLU	Back calculated concentration (ng/mL)	% Bias	Mean RLU	Back calculated concentration (ng/mL)	% Bias
0661-0123	High QC (HQC)	56	(b) (4)	9760	(b) (4)	-7.2	10900	(b) (4)	4.7
				9864		-6.1	10879		4.4
				9729		-7.5	11221		8.1
				9563		-9.2	10504		0.5
				9436		-10.5	10552		1.0
	Low QC (LQC)	9		1567		-6.7	1750		4.0
				1578		-6.1	1599		-4.9
				1657		-1.4	1739		3.4
				1624		-3.4	1759		4.5
				1593		-5.2	1726		2.6
	Dilution QC (DQC)	9000		5763		0.6	6354		11.0
				5712		-0.3	6149		7.4
				5388		-6.0	5978		4.3
				5798		1.2	5907		3.1
				5744		0.2	6622		15.7

Note: Back calculated concentration for DQC is the final concentration after correction with dilution factor
% Bias = (Observed concentration – Nominal concentration)/Nominal concentration x 100

Pharmacodynamics

Serum CTX (s-CTX) was quantified in clinical studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02.

Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)

The PD marker, s-CTX, was measured using Elecsys kits (US Catolog#11972308160) from Roche Diagnostics on an automated Cobas 8000/6000 E system. The β-CrossLaps assay uses two monoclonal antibodies to recognize specific CTX1 degradation fragments. The assay employed a sandwich immunoassay technique where the target molecule is captured by a biotinylated monoclonal antibody and then detected by a ruthenium complex-labeled monoclonal antibody. The detection is based on electrochemiluminescence (ECL), where an applied voltage causes the ruthenium complex to emit light. This light is measured by a photomultiplier, and the concentration of the target molecule is determined using a master curve generated by the instrument. This method allows for quantitative measurement of CTX in patient samples.

The PD assay based on commercially available diagnostic kits was fully validated with respect to precision, accuracy, specificity, and tested for stability.

13.3 Statistical Appendices

Secondary Endpoints

There were no key efficacy confirmatory secondary endpoints prespecified in this study. There were no multiplicity adjustments made for the secondary endpoints. These endpoints are used as exploratory endpoints to support the primary endpoint. The results shown in Table 47, Table 48, and Table 49 are conducted on the Applicant's FAS population.

Table 47 shows the difference in means in the percent change from baseline for lumbar spine BMD at week 26. The results have a similar trend as the primary endpoint results.

Table 47. Secondary Endpoint: Percent Change in Baseline in Lumbar Spine BMD by DXA at Week 26 – Period 1 Full Analysis Set

	Bmab 1000 N=237	Prolia N=235
Baseline mean lumbar spine (SD)	0.77 (0.06)	0.76 (0.06)
LS Means (SE)	3.87 (0.79)	3.70 (0.79)
Treatment difference (Bmab 1000 -Prolia)	0.17	
90% CI[2]	-0.36 ,0.70	

Source: Final Week 78 Clinical Study Report-Protocol Number B1000-PMO-03-G-02 Table 14.2.4.1.1, page 418 Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SE, standard error

Table 48 shows the difference in means in the percent change from baseline for total hip BMD at weeks 26 and 52. The results have a similar trend as the primary endpoint results.

Table 48. Secondary Endpoint: Percent Change in Baseline in Total Hip BMD at Weeks 26 and 52 – Period 1 Full Analysis Set

	Bmab 1000 N=237	Prolia N=235
Baseline mean total hip (SD)	0.76 (0.09)	0.76 (0.10)
Week 26		
n	237	235
LS means (g/cm^2) (SE)	1.70 (0.51)	1.44 (0.51)
Treatment difference Bmab 1000-Prolia	0.26	
90% CI	-0.09, 0.60	
Week 52		
n	237	235
LS means (g/cm2) (SE)	2.22 (0.55)	2.13 (0.55)
Treatment difference Bmab 1000-Prolia	0.09	
90% CI	-0.29, 0.47	

Source: Final Week 78 Clinical Study Report-Protocol Number B1000-PMO-03-G-02 Table 14.2.4.1.2.2, page 420 Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SE, standard error

Table 49 shows the difference in means in the percent change from baseline for femoral neck BMD at weeks 26 and 52. The results have a similar trend as the primary endpoint results.

Table 49. Secondary Endpoint: Percent Change in Baseline in Femoral Neck BMD at Weeks 26 and 52 – Period 1 Full Analysis Set

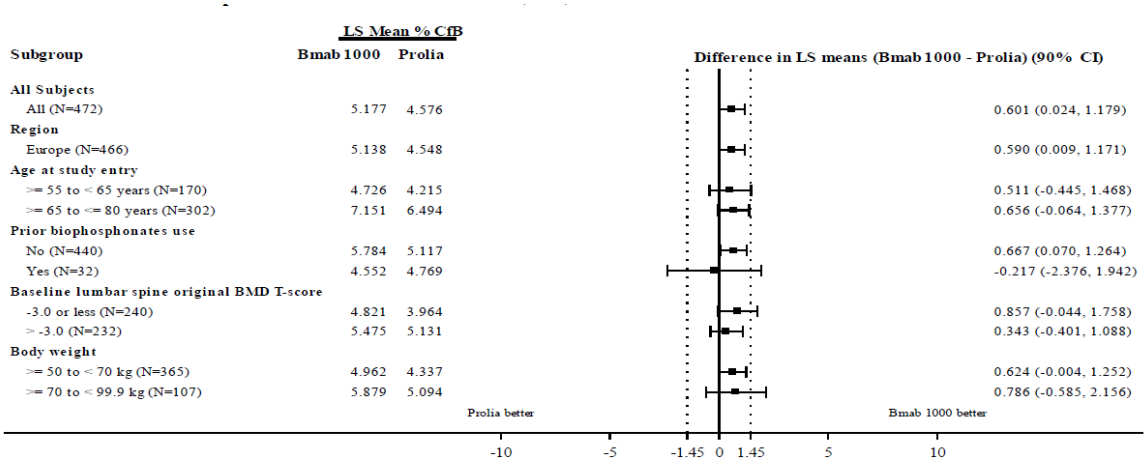
	Bmab 1000 N=237	Prolia N=235
Baseline mean total hip (SD)	0.69 (0.10)	0.69 (0.11)
Week 26		
n	237	235
LS means (g/cm^2) (SE)	2.17 (0.71)	1.48 (0.71)
Treatment difference Bmab 1000-Prolia	0.69	
90% CI	0.21, 1.17	
Week 52		
n	237	235
LS means (g/cm2) (SE)	2.14 (0.80)	1.77 (0.80)
Treatment difference Bmab 1000-Prolia	0.37	
90% CI	-0.18, 0.92	

Source: Final Week 78 Clinical Study Report-Protocol Number B1000-PMO-03-G-02 Table 14.2.4.1.3.2, page 422
Abbreviations: BMD, bone mineral density; N, total number of participants; n, total number of participants at that timepoint; SE, standard error

Subgroups

The Applicant conducted subgroup analysis for region (Europe vs. U.S.), age at study entry (≥55 to <65 and ≥65 to ≤80 years), prior bisphosphonates use (yes or no), baseline lumbar spine original BMD T-score (-3.0 or less and >-3.0), and body weight (≥50 to <70 kg and ≥70 to <99.9 kg). Due to a very small number of participants in the U.S. region subgroup, the estimates/90% CIs were not able to be calculated. Figure 9 shows the subgroup analysis of the difference in means up to Week 52. The subgroup analyses were performed using the Applicant FAS defined population.

Figure 9. Subgroup Analysis of Difference in Means up to Week 52 – MI Under MAR (FAS)



Note: ANCOVA model included terms for treatment, baseline lumbar spine BMD (as a covariate), and classification variables for: region, age, and prior use of bisphosphonates.
Estimate of Primary Estimand 1a-US FDA: Difference in means (Bmab 1000 minus Prolia) in the composite endpoint of %CfB in the lumbar spine BMD by DXA after 52 weeks (for patients who died the %CfB was taken as 0) in postmenopausal women with osteoporosis treated with subcutaneous injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing, and whether any other osteoporosis medications were taken.
Therapeutic equivalence was demonstrated if 90% CI fell entirely within the predefined margins of (-1.45%, 1.45%).
The number of patients in the region subgroup for US was very low, and the respective model was producing error; therefore, this subgroup was not included in the output.

Source: Final Week 78 Clinical Study Report-Protocol Number B1000-PMO-03-G-02 Figure 6-1, page 97

13.4 Clinical Appendices

Table 50. Schedule of Assessments, Study B1000-PMO-03-G-02

	Screening	Double-Blind Active-Controlled Period (Part 1)									Transition Period (Part 2)			Early Study Withdrawal[a]/ EoS
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**7a**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week	**-28 to -1**	**Wk0/ D1**	**Wk0/ D3**	**Wk2/ D15**	**Wk4/ D29**	**Wk12/ D85**	**Wk20/ D141**	**Wk23/ D162**	**Wk26/ D183**	**Wk38/ D267**	**Wk52/ D365**	**Wk56/ D393**	**Wk64/ D449**	**Wk78/ D547**
Allowed Window			**±1D**	**±2D**	**±5D**	**±5D**	**±5D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
Study Month	**-1**				**1**	**3**	**5**	**5**	**6**	**9**	**12**	**13**	**15**	**18**
Informed consent[b]	X													
Eligibility check	X	X[c]												
Randomization[d]		X									X			
Demographics, medical history, previous medication	X													
NYHA functional classification (in patients with heart failure)	X													
Follicle-stimulating hormone[e]	X													
Height	X								X		X			
Body weight	X	X			X	X			X		X			X
Physical examination[f]	X	X	X		X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X		X	X	X	X	X	X	X			X
12-lead ECG[h]	X	X							X	X	X			X

	Screening	Double-Blind Active-Controlled Period (Part 1)									Transition Period (Part 2)			Early Study Withdrawal[a]/ EoS
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**7a**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week	**-28 to -1**	**Wk0/ D1**	**Wk0/ D3**	**Wk2/ D15**	**Wk4/ D29**	**Wk12/ D85**	**Wk20/ D141**	**Wk23/ D162**	**Wk26/ D183**	**Wk38/ D267**	**Wk52/ D365**	**Wk56/ D393**	**Wk64/ D449**	**Wk78/ D547**
Allowed Window			**±1D**	**±2D**	**±5D**	**±5D**	**±5D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
Study Month	**-1**				**1**	**3**	**5**	**5**	**6**	**9**	**12**	**13**	**15**	**18**
Safety/laboratory test[i]	X	X				X			X	X	X			X
Albumin-adjusted total serum calcium[j]	X	X		X		X			X	X	X			X
Hepatitis B, C and HIV test[k]	X													
SARS-CoV-2[l]	X	As required												
Serum FT3/FT4/TSH	X													
Lateral spine X-ray[m]	X								X		X			
Radiography[n]		As required												
DXA scan[o]	X								X		X			X
Study treatment (Bmab 1000 or Prolia) administration		X							X		X			
Dispense patient diary		X												
Patient diary review of vitamin D and calcium intake			X	X	X	X	X	X	X	X	X	X	X	X
Hypersensitivity/allergic reaction[p], injection site reaction monitoring[q]		X							X		X			
Calcium and vitamin D supplement[r]		Daily												

	Screening	Double-Blind Active-Controlled Period (Part 1)										Transition Period (Part 2)		Early Study Withdrawal[a]/ EoS
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**7a**	**8**	**9**	**10**	**11**	**12**	**13**
Study Week	**-28 to -1**	**Wk0/ D1**	**Wk0/ D3**	**Wk2/ D15**	**Wk4/ D29**	**Wk12/ D85**	**Wk20/ D141**	**Wk23/ D162**	**Wk26/ D183**	**Wk38/ D267**	**Wk52/ D365**	**Wk56/ D393**	**Wk64/ D449**	**Wk78/ D547**
Allowed Window			**±1D**	**±2D**	**±5D**	**±5D**	**±5D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**	**±7D**
Study Month	**-1**				**1**	**3**	**5**	**5**	**6**	**9**	**12**	**13**	**15**	**18**
Blood sampling for denosumab PK		X[s,t]		X	X	X		X	X[s]	X	X[s]	X	X	X
Blood sampling for immunogenicity (ADA and NAb)		X[s,t]		X	X	X			X[s]	X	X[s]	X	X	X
Blood sampling for PD testing[u]		X[s]	X	X	X	X	X	X	X[s]	X	X[s]			X
Adverse events[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA, anti-drug antibody; BMD, bone mineral density; COVID-19, Corona virus disease 2019; D, day; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; EoS, end-of-study; FT3, free tri-iodothyroinine; FT4, free throxine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Nab, neutralizing antibody; NYHA, New York Heart Association; P1NP, procollagen Type 1 N-terminal propeptide; PK, pharmacokinetic; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2; sCTX, serum C-telopeptide of Type 1 collagen; TSH, thyroid stimulating hormone; Wk, Week

Note: Patients who early discontinue study treatment will be followed as described in Section 4.2.1.

a. For patients who discontinue the study early and do not wish to attend Week 26 and/or Week 52 as described in Section 4.2.1, all procedures specified for EoS visit Table 13-1will be performed at early withdrawal visit; however, DXA scan should be performed only if last DXA scan was not performed within 90 days prior to the early withdrawal visit. Lateral spine X-ray can be performed if clinically indicated.

b. Informed consent must be obtained before any study-related procedures are performed.

c. Eligibility confirmation by investigator before randomization will be based on assessment of inclusion/exclusion criteria.

d. Patients will be randomly assigned to 1 of 2 treatment groups (either Bmab 1000 or Prolia) on Day 1 prior to the study treatment administration. Second randomization will be performed prior to the study treatment administration on Week 52. Patients who are initially randomized to Bmab 1000 on Day 1 will continue to receive Bmab 1000. Patients who are initially randomized to Prolia on Day 1, will be re-randomized in a ratio of 1:1 to Bmab 1000 or Prolia.

e. Not required for women with surgical menopause as their postmenopausal status will be confirmed via their medical history.

f. A complete physical examination will include, at a minimum, oral examination and assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems and will be performed at screening, baseline (Day 1) and at Weeks 26, 52 and 78. Abbreviated, ie, sign/symptom-directed physical examinations will be performed at other visits.

g. Vital signs (blood pressure and pulse rate in a semi-supine position, body temperature, and respiratory rate) will be measured after 5 minutes of rest (sitting). On the dosing day visits, vital signs will be assessed prior to dosing.

h. All scheduled 12-lead ECGs must be performed at the study site after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be conducted at the investigator's discretion.

i. Safety laboratory tests include hematology, serum chemistry, and urinalysis. See Section 6.2.2 for the list of clinical laboratory tests.

j. Blood samples for albumin-adjusted total serum calcium will be collected as a part of safety/laboratory tests when the sampling visits of serum calcium coincide with safety/laboratory tests.

k. At screening, hepatitis B will be assessed in all patients. If a patient has HBsAg positive, the patient will be excluded from the study. If a patient has HBsAg negative and HBcAb positive, an HBV DNA test will be performed at screening. If the HBV DNA test result is positive, the patient will be excluded from the study. At screening, hepatitis C antibody will be assessed in all patients. If hepatitis C antibody test result is positive, an HCV RNA test will be performed at screening. If the HCV RNA test result is positive, the patient will be excluded from the study; If the HCV RNA test result is negative, the patient can be included in the study at the investigator's discretion. HIV test will be assessed in all patients at screening. If the HIV test result is positive, the patient will be excluded from the study.

l. At the screening visit, a COVID-19 test will be performed as per site and/or local regulatory guidelines. Patients who have a COVID-19 positive test result and were asymptomatic or mildly symptomatic will be allowed to be rescreened as described in Section 4.2.5. Systematic COVID-19 screening tests will be performed locally based on the site guidelines and on the investigator's discretion throughout the study period. If COVID-19 is confirmed after randomization, the investigator will discuss case-by-case with the sponsor and/or medical monitor.

m. Lateral spine X-rays will be assessed by central imaging center. Lateral spine X-rays could be performed as required for confirmation of suspected fractures.

n. Radiography will be performed as required for confirmation of suspected fractures. Radiography will be analyzed at a central imaging vendor.

o. BMD will be assessed by DXA using validated instruments. Assessment of lumbar spine, total hip, and femoral neck BMD assessments will be performed using the same DXA instrument for each patient throughout the study period. Assessments will be performed at a central imaging vendor. Note: The screening BMD assessment will be taken as the baseline BMD assessment.

p. Hypersensitivity reactions will be assessed before the start of the study treatment administration (within approximately 15 minutes) and at 1 hour (± 10 minutes) after each study treatment administration. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids and respiratory support including inhalational therapy, oxygen and artificial ventilation must be available and any types of ECG can be performed. If the patient experiences any hypersensitivity signs and symptoms outside the study site, the patient can visit the study site for further assessment.

q. Injection site reactions will be assessed within 1 hour of the end of each study treatment administration.

r. All patients will be instructed to take daily supplementation containing calcium and vitamin D as described in Section 5.2.2.

s. Blood sample for PK, PD, and immunogenicity should be collected up to 30 minutes prior to study treatment administration.

t. Blood samples for PK and immunogenicity method validation will be collected up to 30 minutes prior to study treatment administration on Day 1.

u. Blood sample for PD markers: this includes bone turnover markers, sCTX and P1NP. Samples will be collected in the morning with fasting of at least 8 hours and patients will be required to refrain from intense physical activity in the 48-hour period prior to sample collection.

v. Includes PFS related issues.

Source: Module 5.3.5.1, B1000-PMO-03-G-02 study synopsis, Table 13-1, page 393-397

Entry Criteria, Study B1000-PMO-03-G-02

Inclusion Criteria

1. Willingness to sign the written ICF, ambulatory, able to follow study instructions and comply with the protocol requirements, and not visually impaired as per the investigator's opinion to participate in the trial.
2. 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.
3. 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 center for this purpose.
4. At least 3 vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA at screening.
5. Patients with body weight ≥50 to <90 kg at screening.

Exclusion Criteria

1. Patients with T-score of <-4.0 at the lumbar spine, total hip, or femoral neck.
2. Known history of previous exposure to denosumab (Prolia, Xgeva, or any biosimilar denosumab).
3. Use of any biologic drugs (with the exception of insulin and insulin analogue and GLP-1 receptor agonists) within 90 days or within five half-lives of the drug, whichever is longer prior to the screening.
4. Known hypersensitivity to denosumab or its constituents or latex allergy or hereditary problems of fructose intolerance.
5. 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), teriparatide or any parathyroid hormone analogs, tibolone, oral or transdermal estrogen, selective estrogen receptor modulators, calcitonin, and cinacalcet.
6. Systemic glucocorticosteroids (≥5 mg prednisone equivalent per day for ≥10 days) within the past 3 months before screening. Topical and nasal corticosteroids are allowed.
7. Other bone active drugs including but not limited to anticoagulants, antiplatelet (with the exception of acetlysalicylic 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 continuously will be allowed only after 3 months of washout prior to the screening. Patients receiving PPI for ≤1 year continuously are not allowed if they plan to continue the use of PPI during the study such that the continuous use of PPI will be >1 year.
8. Patients with ongoing serious infections including cellulitis, or infection requiring parenteral antibiotics within 4 weeks prior to the first administration of the study treatment, or oral antibiotics within 2 weeks prior to the first administration of the study treatment.
9. Evidence of any of the following per the patient's history, DXA, or X-ray review and/or current disease:
   a. Patient in bed rest for 2 or more weeks during the last 3 months prior to screening
   b. Current hyperthyroidism or hypothyroidism (patients on stable thyroid treatment will be allowed). Patients with subclinical hyperthyroidism (TSH <0.1 mIU/L) or subclinical hypothyroidism (≥10 mIU/L) will be excluded
   c. History and/or current hyperparathyroidism or hypoparathyroidism
   d. Patients who have had recurrent episode of hypocalcemia in the past which, as per the investigator, is a risk to her participation in the trial
   e. Current hypocalcemia or hypercalcemia based on albumin-adjusted serum calcium
   f. Any bone disease including bone metastasis or metabolic disease (except for osteoporosis) e.g., osteomalacia or osteogenesis imperfecta, rheumatoid arthritis, Paget's disease, ALP elevation (at investigator's discretion), Cushing's disease, clinically significant hyperprolactinemia (at investigator's discretion), fibrous dysplasia, malabsorption syndrome which may interfere with interpretation of the results
   g. Malignancy (except squamous cell carcinoma, basal cell carcinoma, cervical or breast ductal carcinoma in situ) within the last 5 years from screening visit
   h. Height, weight, and girth which may preclude accurate DXA measurements
   i. Advanced scoliosis or extensive lumbar fusion which would preclude vertebral fracture assessment
   j. History and/or presence of one severe or 3 or more moderate vertebral fractures (as determined by central reading of lateral spine X-ray during

the screening periods). Severe vertabral fracture (Grade 3) is defined as >40% vertebral height loss, and moderate vertebral fracture (Grade 2) is defined as 25% to 40% vertebral height loss

k. History and/or presence of hip fracture or bilateral hip replacement or history of atypical femoral fracture
l. Presence of an active healing fracture according to assessment of investigator
m. History of severe skeletal pain with bisphosphonates which, as per the investigator, is a risk to her participation in the trial
n. Oral/dental or periodontal conditions: Prior history or current evidence of osteomyelitis, osteonecrosis of the jaw (or risk of developing osteonecrosis of the jaw as per the investigator's opinion), osteonecrosis of the external auditory canal; active dental or jaw condition which requires oral surgery; planned invasive dental procedure (dental implants); or non-healed dental or oral surgery
o. Any organic or psychiatric disorder or laboratory abnormality or underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal, which, in the opinion of the investigator, will prevent the patient from completing the study or interfere with the interpretation of the study results, or will put the patient into unacceptable risk for participating in the trial
p. History of presence of a severe allergic reaction (e.g., anaphylaxis)
q. Personal/family history of prolonged QT interval syndrome or family history of sudden death.

10. New York Heart Association Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease or ECG abnormalities, which can be judged as clinically significant at the investigator's discretion.
11. Patient has a planned surgical intervention during the study period except those related to the underlying disease and which, in the opinion of the investigator, will put the patient at further risk or hinder the patient's ability to maintain compliance with study treatment and the visit schedule.
12. One of the following laboratory test result at screening:
    a. Vitamin D deficiency (serum 25-hydroxy vitamin D level <20 ng/mL). For eligibility purpose, oral vitamin D repletion is permitted at the investigator's discretion if serum 25-hydroxy vitamin D level is ≥12 and <20 ng/mL and vitamin D level is allowed to be retested once post repletion within the screening period
    b. Creatinine clearance <30 mL/minute (as estimated by the Cockcroft-Gault equation); severe renal impairment of eGFR <30 mL/min
    c. Liver transaminases: Serum AST ≥3.0 × ULN. Serum ALT ≥3.0 × ULN. Bilirubin ≥1.5 × ULN (isolated bilirubin ≥1.5 × ULN is acceptable if bilirubin is fractionated, and direct bilirubin is <35%)
    d. Hemoglobin <10 g/dL

13. Allergy to vitamin D or calcium supplements, or intolerant to long-term calcium or vitamin D supplementation, or history malabsorption of calcium or vitamin D supplements.
14. Participation in a drug study within 90 days or 5 half-lives of the previous drug (if known), whichever is longer, prior to drug administration.
15. Known case of active hepatitis B, hepatitis C or HIV infection. Has a hepatitis B, hepatitis C or HIV positive test result at screening. A patient with past hepatitis B or C virus infection is allowed if recovered by the time of the screening visit. At screening, hepatitis B will be assessed in all patients. If a patient has HBsAg positive, the patient will be excluded from the study. If a patient has HBsAg negative and HBcAb positive, an HBV DNA test will be performed at screening. If the HBV DNA test result is positive, the patient will be excluded from the study. At screening, hepatitis C antibody will be assessed in all patients. If hepatitis C antibody test result is positive, an HCV RNA test will be performed at screening. If the HCV RNA test result is positive, the patient will be excluded from the study; If the HCV RNA test result is negative, the patient can be included at the investigator's discretion.
16. Evidence of alcohol or substance-abuse within the last 12 months prior to screening that the investigator believes would interfere with understanding or completing the study.
17. Confirmed or suspected with infection with SARS-CoV-2 from screening to randomization, or who has been diagnosed with COVID-19 (as per site and/or local regulatory guidelines) or history of COVID-19 infection requiring oxygen supplementation in the last 8 weeks prior to screening or had contact with a COVID-19 patient 14 days prior to screening and within the screening period up to randomization.
18. Patient has received live virus vaccine within 4 weeks prior to screening or within the screening period up to randomization.

Figure 10. Global Irritation Score

Each injection site will be assessed by the Investigator or their designee for any local reaction according to the following scales.

Redness

Grade Description

0 = NONE: no visible redness

1 = MILD: ≤ 2 cm redness

2 = MODERATE: > 2 to ≤ 5 cm redness

3 = SEVERE: greater than 5 cm redness

Bruising

Grade Description

0 = NONE: no visible bruising

1 = MILD: ≤ 2 cm bruising

2 = MODERATE: > 2 to ≤ 5 cm bruising

3 = SEVERE: greater than 5 cm bruising

Swelling

Grade Description

0 = NONE: no swelling detected

1 = MILD: palpable 'firmness' only

2 = MODERATE: ≤ 4 cm swelling

3 = SEVERE: > 4 cm swelling

Itching

Grade Description

0 = NONE

1 = MILD

2 = MODERATE

3 = SEVERE

Pain

Grade Description

0 = NONE

1 = MILD

2 = MODERATE

3 = SEVERE

The subjects will be asked about the degree of itching or pain that they are experiencing. The score is the sum of these points, ranging from 0 to 15. A local injection site reaction with a score of ≥ 2 according to the rating scale will be documented as an AE.

Source: Study B1000-NHV-01-G-01 protocol, page 154

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/s/

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