CLINICAL STUDY PROTOCOL

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

(**DEVOTE: DE**nosumab biosimilar **V**ersus Prolia for post-menopausal **O**steoporosis: A randomized, double-blind, multicenter, **T**wo-arm phase 3 study comparing **E**fficacy, safety, and immunogenicity)

Title Page

B1000-PMO-03-G-02

Sponsor:	[redacted]
Sponsor Contact:	[redacted]
SAE Reporting and Data Center:	[redacted]
Version of Protocol:	Version 3.0
Date of Protocol:	31-Aug-2022
Compound Name:	Bmab 1000
Study Phase:	Phase 3

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Randomized, Double-Blind, Multicenter, Parallel-Arm Phase 3 Study to Compare the Efficacy, Pharmacodynamics, Safety, and Immunogenicity Between Bmab 1000 and Prolia in Postmenopausal Women with Osteoporosis
Protocol Number	B1000-PMO-03-G-02
Protocol Version and Date	Version 3.0, 31-Aug-2022

Protocol reviewed by:

[redacted]

Signature Date

[redacted]

Protocol Approval – Lead Statistician

Study Title	A Randomized, Double-Blind, Multicenter, Parallel-Arm Phase 3 Study to Compare the Efficacy, Pharmacodynamics, Safety and Immunogenicity Between Bmab 1000 and Prolia in Postmenopausal Women with Osteoporosis
Protocol Number	B1000-PMO-03-G-02
Protocol Date and Version	Version 3.0, 31-Aug-2022

Protocol accepted and approved by:

Lead Statistician

[redacted]

Si[redacted] Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "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".

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 31-Aug-2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Biocon Biologics UK Limited or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub investigator.

I will not supply the investigational product to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Biocon Biologics UK Limited.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

Protocol Version History	
Protocol Version	**Date**
Amendment 2	31-Aug-2022
Amendment 1	13-Apr-2022
Original Protocol	06-Jan-2022

Amendment 2 (31-Aug-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Major changes from Amendment 1 (13-Apr-2022) to Amendment 2 (31-Aug-2022) are summarized in the following table. Additional minor changes to the protocol and changes to the synopsis are not listed but were applied, as applicable. Minor editorial or formatting changes are not included in this summary table.

Section # and Name	**Description of Change**	**Brief Rationale**
Title page, Signature page, Protocol Amendment Summary of Changes, Header, and Appendix 13.3 with protocol amendment history	Updated the protocol version and date.	Reflect the new version and date.
Synopsis – Pharmacodynamic Assessments Section 13.1 Appendix: Schedule of Events	Added visit in double-blind active-controlled period (Part 1) at Week 23 (Day 162) for blood sample collection for PD testing and other relevant assessments including PK	Based on the EMA recommendation.
Section 5.8.1 Prohibited Concomitant Medications	It has been clarified that the use of COVID-19 vaccine is encouraged, although, at the discretion of PI, an interval of 7 days is advised between the COVID-19 vaccine and study drug administration due to putative adverse drug reactions.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 6.2.1.1.1 Adverse Events	Clarified that AE does not include pre-existing diseases or conditions present or detected prior to signing the ICF that does not worsen.	Clarification
Section 6.2.2 Clinical Safety Laboratory Assessments	deleted the following texts “only if urinalysis dipstick results are abnormal”.	Clarification
Section 6.2.3 Section 7.6.8.4 Physical Examinations	Clarified that significant findings and illnesses to be reported after signing the ICF.	Clarification
Section 7.6.2 (Table 7-3) Summary of Statistical Methods, Including Sensitivity Analyses Section 7.6.3.4 Sensitivity Analysis for Estimand 1a EMA (Co-Primary Efficacy)	Updated text for sensitivity analysis of estimand 1a EMA (co-primary efficacy) to reflect missing data imputed under MI MAR approach, penalties and Rubin’s method used for results. Removed sensitivity analysis for Estimand 1a (US FDA) as it is not required since sensitivity included in other estimands that are explored.	Based on the US FDA recommendation.
Section 7.6.2 (Table 7-3) Summary of Statistical Methods, Including Sensitivity Analyses Section 7.6.3.1 Main Estimation of Estimand 1a US FDA (Efficacy) Section 7.6.3.5 Multiple Imputation Model Under Missing at Random Section 7.6.3.5.1 Penalties for Non-Inferiority and Non-Superiority Section 7.7 Handling of Missing Data	Added missing data imputed under MI MAR approach, penalties to reflect non-inferiority and non-superiority nulls, and results pooled using Rubin’s method and two one-sided tests. Clarified that sensitivity analysis is not required as explored in other estimands.	Based on the US FDA recommendation.
Section 7.6.4.1 Secondary BMD Endpoints	Clarified that Estimand 1a-US FDA (Efficacy) will be performed but without the penalty being applied.	Based on the US FDA recommendation.

Section # and Name	Description of Change	Brief Rationale
Section 7.6.9 Other Analyses	The occurrence and time to intercurrent events will be considered and compared for the treatment groups.	Based on the US FDA recommendation.
Table 13-1 (Schedule of Events)	Added a footnote to clarify that FSH is not required for women with surgical menopause as their postmenopausal status will be confirmed via their medical history.	Clarification

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Protocol Synopsis

Protocol Number: B1000-PMO-03-G-02

Title: A Randomized, Double-Blind, Multicenter, Parallel-Arm Phase 3 Study to Compare the Efficacy, Pharmacodynamics, Safety, and Immunogenicity Between Bmab 1000 and Prolia in Postmenopausal Women with Osteoporosis

Sponsor: Biocon Biologics UK Limited
16, Great Queen Street
Covent Garden
London, WC2B 5AH
United Kingdom

Study Phase: Phase 3

Study Sites: Approximately 480 patients will be enrolled at approximately 47 sites in Europe and the United States.

Indication: Postmenopausal women with osteoporosis

Rationale:

Bmab 1000 is currently being developed as a proposed biosimilar to Prolia. This is a randomized, double-blind, multicenter, parallel-arm, Phase 3 study that will be conducted as a part of the clinical development program of Bmab 1000 and will assess the therapeutic equivalence in efficacy, safety, and PD of Bmab 1000 compared with US-licensed Prolia.

The design of this study considers the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues, the US FDA Guidance on Scientific Considerations in Demonstrating Biosimilarity to a reference product, and PMDA Guideline on the Quality, Safety and Efficacy Assurance of Follow-on Biologics.

This study protocol is designed to allow a global study that would address the needs of various regulatory bodies. For EMA, the PD endpoint AUEC of sCTX from baseline to 26 weeks is considered as Co-primary endpoint, while, for US FDA, this endpoint is considered as a key secondary endpoint. For US FDA, after completion of double-blind active-controlled period (Day 1 to Week 52 [pre-dose]), the study is designed to include the

transition period (Week 52 to Week 78), where patients who have received Prolia will be re-randomized to receive either Bmab 1000 or Prolia.

The study population in this study was selected to be representative of the clinical studies supporting the development and marketing of the reference product (Prolia), and to align with the indications approved for the reference product.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of Bmab 1000 is provided in the IB. Bmab 1000 will have the same pharmaceutical formulation and strength as Prolia (60 mg). The proposed dosing regimen is in line with the approved labeling for Prolia. The proposed safety monitoring is deemed to be sufficient to monitor potential risks of Bmab 1000 administration. In view of the structural and biological similarity, Bmab 1000 is expected to display a safety profile similar to Prolia. Based upon the proven safety profile of Prolia, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

Objectives and Estimands:

The primary objectives, endpoints, and estimands are presented in the table below:

Primary Objectives	Endpoints (Including Estimand Description)
To demonstrate equivalent efficacy between Bmab 1000 and Prolia based on percentage change from baseline at Week 52 in lumbar spine BMD (Co-primary for EMA and Primary for US FDA)	Endpoint: Percentage change from baseline at Week 52 in the lumbar spine BMD by DXA *(Time Frame: Baseline and Week 52)*
	Estimand 1a-EMA (Co-primary Efficacy): Difference in means (Bmab 1000 – Prolia) in % change from baseline in lumbar spine BMD by DXA after 52 weeks in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements
	Estimand 1a-US FDA (Efficacy): Difference in means (Bmab 1000 – Prolia) in composite endpoint of % change from baseline in lumbar spine BMD by DXA after 52 weeks (where % change from baseline of zero is taken for anyone who dies) in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any other osteoporosis medications are taken
To demonstrate pharmacodynamic equivalence between Bmab 1000 and Prolia based on AUEC of the bone resorption marker sCTX from baseline to week 26 (Co-primary for EMA and secondary for US FDA)	Endpoint: AUEC of sCTX from baseline to 26 weeks (*Time Frame: Baseline to Week 26)*
	Estimand 1b-EMA (Co-primary PD): Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women[a] with osteoporosis treated with a SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements

Abbreviations: AUEC, area under the effect curve; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SC, subcutaneous; sCTX, serum C-terminal telopeptide of Type 1 collagen

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

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

The secondary objectives and endpoints of double-blind active-controlled period (Part 1) are presented in the table below:

Secondary Objective(s)	Endpoints
To compare other efficacy parameters (BMD of lumbar spine, total hip and femoral neck; fracture incidence) between Bmab 1000 and Prolia	• Percentage change from baseline at Week 26 in lumbar spine BMD by DXA (*Time Frame: Baseline and Week 26)* • Percentage change from baseline at Weeks 26 and 52 in total hip BMD by DXA (*Time Frame: Baseline, Week 26, and Week 52)* • Percentage change from baseline at Weeks 26 and 52 in femoral neck BMD by DXA (*Time Frame: Baseline, Week 26, and Week 52)* • Incidence of fracture up to Week 52 (*Time Frame: Baseline up to Week 52)*
To compare bone turnover between Bmab 1000 and Prolia based on sCTX and P1NP	• C_{min} of sCTX *(Time Frame: Baseline up to Week 26)* • Serum concentrations of P1NP (*Time Frame: Baseline up to Week 52)* • PD parameters of sCTX: I_{max}, TI_{max}, AUIC *(Time Frame: Baseline up to Week 26)*
To compare safety and tolerability of 2 administrations of Bmab 1000 and Prolia 6 months apart	• Incidence of TEAEs up to 6 months after the second dose (*Time Frame: Baseline up to Week 52)* • Incidence of clinically significant changes in vital sign, physical examinations, laboratory safety tests, and ECGs up to 6 months after the second dose *(Time Frame: Baseline up to Week 52)*
To compare immunogenicity between Bmab 1000 and Prolia	• Incidence and titer of ADA, incidence of NAb up to Week 52 *(Time Frame: Baseline up to Week 52)*
To assess denosumab serum concentrations following Bmab 1000 and Prolia administration	• Denosumab concentrations at Weeks 2, 4, 12, 26, 38, and 52 (*Time Frame: Baseline up to Week 52)*

Abbreviations: ADA, anti-drug antibodies; AUEC, area under the effect curve; AUIC, the area under the % inhibition curve; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; C_{min}, minimum concentration; I_{max}, maximum % inhibition; NAb, neutralizing antibodies; P1NP, procollagen Type 1 N-terminal propeptide; sCTX, serum C-terminal telopeptide of Type 1 collagen; TEAE, treatment-emergent adverse event; TI_{max}, the time of occurrence of maximum % inhibition

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

The key secondary objectives and endpoints of transition period (Part 2, for US FDA) are presented in the table below:

Secondary Objective(s)	Endpoints
To assess the risk of hypersensitivity and adverse events up to 6 months after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia	• Incidence of TEAEs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)* • Incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)* • Incidence of deaths and SAEs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)*
To assess the risk of immunogenicity through formation of anti-drug antibodies after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia	• Incidence and titer of ADA, incidence of NAb at Week 78 split by serostatus at Week 52 *(Time Frame: from Week 52 up to Week 78)*

Abbreviations: ADA, anti-drug antibodies; ECG, electrocardiogram; Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event; TEAE, treatment-emergent adverse event

The other secondary objectives and endpoints of transition period (Part 2, for US FDA) are presented in the table below:

Other Secondary Objective(s)	Endpoints
To assess efficacy after the single transition from Prolia to Bmab 1000 compared with those to continuing on Prolia	• Percentage change from Week 52 at Week 78 in lumbar spine BMD by DXA *(Time Frame: from Week 52 up to Week 78)*
To assess efficacy of 3 doses of Bmab 1000 compared to Prolia	• Percentage change from (original) baseline at Week 78 in lumbar spine, hip and femoral neck BMD by DXA *(Time Frame: Day 1 up to Week 78)*
To assess PK and PD: i. after the single transition from Prolia to Bmab 1000 ii. on Bmab 1000 throughout each compared with those on Prolia throughout	• Serum concentrations of denosumab at Week 56, 64, and 78 (PK) *(Time Frame: from Week 56 up to Week 78)* • Serum concentrations of CTX at Week 78 (PD) (*Time Frame: Week 78)*
To assess the adverse events on Bmab 1000 throughout compared to Prolia throughout	• Incidence of TEAEs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)* • Incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)* • Incidence of deaths and SAEs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)*
To assess the risk of immunogenicity through formation of anti-drug antibodies on Bmab 1000 throughout compared to Prolia throughout	• Incidence and titer of ADA, incidence of NAb at any point from the first dose up to Week 78 *(Time Frame: Day 1 up to Week 78)*

Abbreviations: ADA, anti-drug antibodies; ECG, electrocardiogram; Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; CTX, carboxy-terminal cross-linking telopeptide of Type 1 collagen; serious adverse event; TEAE, treatment-emergent adverse event

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Each patient must meet all of the following criteria to be enrolled in this study:

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: Patients meeting any of the following criteria will be excluded from the study:

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), drugs being investigated 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 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 acetylsalicylic acid), anticonvulsants (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, and anabolic steroids within the last 3 months before screening. Direct oral anticoagulants will be allowed. Receipt of PPI for >1 year 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), eg, 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 the 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 s (as determined by central reading of lateral spine X-ray during the screening period). Severe vertebral 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 (eg, 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 results 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 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%. The investigator is recommended to contact medical monitor and/or sponsor.)

    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.

Study Design:

This is a randomized, double-blind, multicenter, parallel-arm, Phase 3 study to compare the efficacy, PK, PD, safety, and immunogenicity of Bmab 1000 and Prolia in postmenopausal women with osteoporosis.

The study will consist of 3 study periods: Screening period; Part 1, double-blind active-controlled period; and Part 2, transition period.

Screening Period (from Day –28 to Day –1)

Screening evaluations will be completed within 28 days prior to the randomization.

Part 1, Double-Blind Active-Controlled Period (from Week 0 [Day 1] to Week 52 Pre-dose)

In the double-blind active-controlled period, eligible patients will be 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 will be followed-up for 26 weeks after the second dose. The randomization will be stratified by [redacted]

Part 2, Transition Period (from Week 52 to Week 78 [EoS Visit]):

All patients who complete Part 1 will undergo the re-randomization process prior to the study treatment administration at Week 52. Prior to dosing at Week 52, patients in the Prolia arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia at Week 52. This is done to obtain data after single switch in patients who have been treated with Prolia. To maintain the study blinding, the patients in the original Bmab 1000 arm will also go through the re-randomization procedure; however, they will continue to receive Bmab 1000.

The re-randomization will take place within the original strata used for the randomization at baseline. All applicable assessments including efficacy, PK, PD, safety including immunogenicity will be performed as per Schedule of Events.

End-of-study visit will be at Week 78 post randomization (Month 18).

An Independent Safety Review Committee (ISRC) will periodically review the safety data to ensure safety of patients is protected. The ISRC will consist of therapeutic area experts (at least 3 members) who are independent of this study conduct. The initial meeting of the ISRC will be conducted after the first 10% of patients have completed Day 15 visit. The ISRC will continue to review the emerging safety data.

The ISRC will review the unblinded safety data to determine if the incidence of a serious adverse drug reaction was unacceptably high in the Bmab 1000 arm (or notably higher than

the Prolia arm) such that continued administration of the product would present an unacceptable risk to patients.

The roles, responsibilities, and review process will be defined in the ISRC Charter.

Duration of Treatment:

The patients will receive the study treatment on Day 1 and at Week 26 and Week 52. The maximum study duration for a patient will be approximately 18 months (excluding screening).

Efficacy Assessments:

Bone Mineral Density: Bone mineral density will be assessed by DXA scan at screening, Week 26, Week 52, and Week 78. All DXA scans will be analyzed by the central imaging vendor.

Fracture: Lateral spine X-ray will be assessed at a central imaging center at screening, Week 26, and Week 52. Additional radiographs will be performed as required during the study for confirmation of suspected new clinical fractures. Any new fractures confirmed by the central imaging vendor will be recorded as an adverse event.

Pharmacokinetic Assessments:

Blood samples for measuring serum concentrations of denosumab will be collected at Day 1 (pre-dose), Day 15, Day 29, Day 85, Day 162, Day 183 (pre-dose), Day 267, Day 365 (pre-dose), Day 393, Day 449, and Day 547.

Pharmacodynamic Assessments

Blood samples for PD parameters (sCTX, P1NP) will be collected at Day 1 (pre-dose), Day 3, Day 15, Day 29, Day 85, Day 141, Day 162, Day 183 (pre-dose), Day 267, Day 365 (pre-dose), and Day 547.

Immunogenicity Assessments:

The immunogenicity of Bmab 1000 and Prolia will be assessed by ADA and NAb test in a validated immunoassay. Blood samples for immunogenicity assessments will be collected at

Day 1 (pre-dose), Day 15, Day 29, Day 85, Day 183 (pre-dose), Day 267, Day 365 (pre-dose), Day 393, Day 449, and Day 547.

Safety Assessments:

Safety will be assessed through the collection and evaluation of AEs, including TEAEs, SAEs, AESIs (treatment-related hypersensitivity/allergic reaction monitoring, serious infections, hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reactions), clinical laboratory assessments, physical examinations, vital sign measurements, and ECGs.

Any fracture will be recorded as an AE/SAE/AESI (as applicable).

Study Treatment, Dosage, and Route of Administration:

Bmab 1000 (60 mg) or Prolia (60 mg) will be administered subcutaneously using a PFS of 60 mg/mL solution for injection on Day 1 and at Week 26 and Week 52.

Sample Size:

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

Equivalence will be established if the 95% CI of the difference (T-R) in mean percent change in lumbar spine BMD from baseline at Week 52 is within equivalence margin of (±1.45%). Equivalence margin is derived from meta-analysis of previous similar studies, which gave the pooled denosumab treatment effect [redacted] Based on the lower bound of the 95% CI, a 1.45% margin will preserve [redacted] Assuming that the treatments are equally effective and that the common SD for percent change from baseline in lumbar spine BMD at Week 52 is [redacted] a sample size of 204 patients per treatment group (total 408 patients) ensures a power of minimum 80% with 2.5% level of significance. Considering a dropout of 15%, the total sample size required is 480 patients (240 per treatment group). Note that the US FDA require a 90% CI to establish equivalence which provides more power for this sample size (this will be reflected in the efficacy analyses).

The current sample size has high power for the (Co-primary) sCTX AUEC endpoint; 204 evaluable patients/group with a margin of 80%-125% and between-patient CV of 45% would give >95% power to demonstrate similarity.

Statistical Methods:

Analysis Sets:

The following analysis sets will be used in the statistical analyses.

Full analysis set: The FAS will consist of all randomized patients who meet the eligibility criteria and receive at least one dose of study treatment. Patients from the FAS will be analyzed under the treatment as randomized. This will be used as the analysis dataset for estimation of Estimand 1a-US FDA (Efficacy).

Modified full analysis set: The term mFAS will be used to define the analysis data set which includes a data record at each time point for all patients in the FAS but excludes data observed after the first occurrence of those intercurrent events where a hypothetical strategy is taken for (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS will be analyzed under the treatment as randomized and used as the primary analysis data set for this estimation of Estimand 1a-EMA (Co-primary Efficacy) and Estimand 1b-EMA (Co-primary PD) and other key efficacy, PD and PK analyses. For PD, data points within 8 hours of food-intake or 48-hours of intense physical activity will not be used.

Safety analysis set: The SAF will consist of all randomized patients who received at least one administration of study treatment. The SAF will be used for all safety and immunogenicity analyses. In the SAF, patients will be analyzed per the actual treatment received.

Efficacy Endpoint

Main Estimation of Estimand 1a-US FDA (Efficacy)

In order to estimate Estimand 1a-US FDA, an ANCOVA model will be fitted to the composite percent change from baseline in lumbar spine BMD (where % change from baseline of zero is taken for anyone who dies) at Week 52 on the FAS multiply imputed data

sets including terms for randomization strata, treatment, and baseline BMD included as a continuous covariate. Rubin's method will be used to pool results.

Multiple imputation will be used to produce 30 multiply imputed data sets so that any missing BMD data at Week 52 are imputed under MAR, by treatment. A penalty (delta of -1.45 and 1.45) will be applied to imputed values for the BMab 1000 group reflecting the noninferiority and non-superiority null hypotheses (H0) respectively and two separate one-sided tests at alpha=0.05 conducted (Tests 1 and 2 below, respectively):

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

H0: $\mu_{BMab\ 1000} - \mu_{Prolia} \leq -1.45\%$

H1: $-1.45\% < \mu_{BMab\ 1000} - \mu_{Prolia}$

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

H0: $\mu_{BMab\ 1000} - \mu_{Prolia} \geq +1.45\%$

H1: $\mu_{BMab\ 1000} - \mu_{Prolia} < +1.45\%$

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. The estimated mean difference in % change from baseline in lumbar spine BMD at Week 52 will be presented with 90% CI for each delta. The two one-sided tests of alpha=0.05 are equivalent to showing that each 90% CI falls within predefined equivalence margins of [–1.45%, 1.45%]. If these criteria are met, equivalence will be concluded for the US FDA submission.

Main Estimation of Estimand 1a-EMA (Co-primary Efficacy)

For the primary efficacy analysis, an MMRM will be fitted to the % change from baseline in lumbar spine BMD at Week 26 and Week 52 on the mFAS. The MMRM will include terms for randomization strata, visit by treatment, and baseline BMD included as a continuous covariate. The repeated measures on patients will be modeled with an unstructured covariance structure.

The estimated mean difference in % change from baseline in lumbar spine BMD will be presented with 95% CI at each time point.

The estimated mean difference in % change from baseline in lumbar spine BMD at Week 52 will be presented with 95% CI and equivalence concluded if this falls within predefined equivalence margins of [–1.45%, 1.45%].

Note: The main analysis method is on the mFAS and therefore does not use data after any dosing errors, treatment discontinuation or receipt of any other medications affecting bone health (except for supplements).

Main Estimation of Estimand 1b-EMA (Co-primary PD)

Comparability of sCTX levels between Bmab 1000 and Prolia will be assessed by fitting an ANCOVA to AUEC data on a log scale to give the ratio of geometric means with 95% CI. Logged pre-dose sCTX concentrations will be fitted as a covariate since baseline-adjustment is not included in the AUEC calculation, baseline eGFR will be included as a covariate since renal function is known to affect sCTX levels, and treatment group and all stratification factors will be fitted as fixed effects. Comparability between Bmab 1000 and Prolia will be concluded if the 95% CI around the geometric mean ratios for AUEC lie entirely within 80.00% - 125.00%.

Secondary Efficacy Endpoints

Secondary BMD Endpoints

An MMRM, as per the main estimation of Estimand 1a-EMA (Co-primary Efficacy), will be used to estimate the mean percent change from baseline and difference between treatments for the mFAS in lumbar spine BMD after 26 weeks, hip BMD after 26 and 52 weeks, and femoral neck BMD after 26 and 52 weeks. Similarly, ANCOVA on composite endpoint of percent change from baseline for FAS as per main estimation of Estimand 1a-US FDA (Efficacy) will be performed (see Section 7.6.3.1) but without the penalty being applied.

Analyses of BMD After Transition

BMD percentage change from baseline and percentage change at Week 78 from Week 52 will be summarized by treatment for lumbar spine, hip, and femoral neck BMD by DXA. Statistical analyses to present 95% CIs will be performed on Week 78 lumbar spine BMD in 2 separate analyses which will considering either original baseline or Week 52 baseline as a covariate.

Summary of Fractures

Any incidence of fractures up to and including Week 52 and from Week 52 to Week 78 will be summarized with descriptive statistics.

Secondary Pharmacodynamic Endpoints

Serum C-terminal telopeptide of Type 1 collagen and P1NP concentrations will be listed, summarized with descriptive statistics by treatment and visit, and presented graphically, as appropriate.

C_{min} for sCTX will be analyzed in a similar manner to sCTX AUEC as a secondary PD endpoint on mFAS. In addition, PD parameters estimated for sCTX using change from baseline observations (ie, Imax and AUIC) will be analyzed in a similar manner to sCTX AUEC as additional secondary PD endpoints on mFAS.

Following the transition period, serum concentrations of CTX and P1NP at Week 78 will be summarized for those transitioning to Bmab 1000 and those continuing on Bmab 1000, compared to those continuing on Prolia.

Secondary Pharmacokinetic Endpoints

Serum denosumab concentrations will be listed and summarized with descriptive statistics at each visit. Pharmacokinetic parameter estimation and formal statistical analyses of PK data are not planned in this study; however, population PK and/or PK/PD modeling may be performed and reported separately from the main clinical study report, if deemed necessary.

Following the transition period, serum concentrations at Week 78 will be summarized.

Secondary Immunogenicity Endpoints

Incidence and titer of anti-drug antibody, incidence of neutralizing antibody up to Week 52 will be summarized by treatment and timepoints per the Schedule of Events. Similar summaries will be presented for the transition period, split by Week 52 serostatus, to compare the transition to Bmab 1000 against continuing on Prolia.

Safety Analysis

Treatment-emergent adverse events and serious adverse events recorded during the study will be summarized by system organ class, preferred term, and treatment, and will include the total number of events with number and percentage of patients with adverse events. Adverse events and medical history will be coded using the most current version of MedDRA.

Summaries of the number and percentage of patients (and number and percentage of events) for study treatment-related adverse events, severe adverse events, serious adverse events, adverse events with an outcome of death, and adverse events leading to discontinuation of the study treatment will be provided by treatment.

Incidence and grade of AESI including treatment-related hypersensitivity/allergic reaction, serious infections, hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reactions from baseline (Day 1) through the EoS will be summarized by treatment group.

Descriptive statistics and listings will be presented for other safety assessments, ie, vital signs, clinical laboratory assessments, abnormal physical examination findings, ECGs, and concomitant medications.

Following completion of the Transition Period, summaries will be produced for incidence of TEAEs, deaths, and SAEs from the third dose to Week 78, and incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG, and vital signs will also be summarized for the same period.

Version and Date of Protocol: Version 3.0, 31-Aug-2022

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
AUEC	area under the effect curve
AUIC	the area under the % inhibition curve
BMD	bone mineral density
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
C_{min}	minimum concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal telopeptide of Type 1 collagen
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoS	end-of-study
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT3	free tri-iodothyroinine
FT4	free throxine

Abbreviation	Definition
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG2	immunoglobulin G2
I_{max}	maximum % inhibition
IRB	institutional review board
ISRC	independent safety review committee
IWRS	interactive web response system
LOCF	last observation carried forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MI	multiple imputation
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
NYHA	New York Heart Association
OTC	over-the-counter
P1NP	procollagen Type 1 N-terminal propeptide
PD	pharmacodynamic
PFS	prefilled syringe
PK	pharmacokinetic

Abbreviation	Definition
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	proton-pump inhibitor
PVG	pharmacovigilance
RANKL	receptor activator of nuclear factor kappa-B ligand
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAF	safety analysis set
SAS	statistical analysis system
SC	subcutaneous
sCTX	serum C-terminal telopeptide of Type 1 collagen
SD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TI_{max}	the time of occurrence of maximum % inhibition
T_{min}	time of occurrence of the minimum concentration
UK	United Kingdom
ULN	upper limit of normal
UN	United Nations
US	United States
WHO	World Health Organization

1 Introduction

1.1 Background

Osteoporosis, a systemic skeletal disease characterized by low BMD and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures, is a global public health concern (Klibanski *et al.*, 2001). With 200 million individuals estimated to have osteoporosis worldwide, around 9 million fragility fractures each year are noted, with a fracture occurring every 3 seconds causing pain, disability, loss of independence and death (IOF 2019). This includes 1.6 million hip fractures, which result in the most morbidity, mortality, and healthcare costs. The 1.4 million individuals who sustain compression fractures of the vertebrae endure back pain, loss of height and adversely affect the quality of life. Traumatic fractures of the wrist and femoral neck are also common osteoporotic fractures, which cause a substantial clinical and economic burden for society. As the world population is ageing fast, UN projects that by 2050, 2.1 billion people will be over 60 years of age and at risk of osteoporosis. In case of the hip fracture alone, it is expected that the cases will range from 7 million to 21 million by 2050 (IOF 2019).

Many pharmacological agents for treating osteoporosis have been evaluated in large clinical trials and proven to reduce fracture risk. The aim of the pharmacological intervention is to decrease the incidence of fractures. Earlier approved classes of drugs for this indication are antiresorptive agents (bisphosphonates, HRT, and selective estrogen receptor modulators); the parathyroid hormone analog teriparatide that has an anabolic effect on bone tissue, and strontium ranelate that increases bone formation and decreases bone resorption (Tella and Gallagher 2014; Chang *et al.*, 2018).

1.2 Denosumab

Denosumab is marketed in the US and Europe by Amgen under the brand name Prolia as a single-use prefilled syringe (PFS) containing 60 mg of denosumab in 1 mL of solution (60 mg/mL) and will be used as a reference treatment in this study.

Denosumab is a fully human IgG2 monoclonal antibody to RANKL, a cytokine expressed by cells of the osteoblast lineage that is a key regulator of osteoclastic bone resorption. By binding and neutralizing RANKL, denosumab inhibits osteoclast differentiation, activity, and survival, thereby decreasing bone resorption in cortical and trabecular bone. Prolia® is indicated for the treatment of following conditions in patients with high risk of fracture:

postmenopausal women with osteoporosis at high risk for fracture, men with osteoporosis at high risk for fracture, glucocorticoid-induced osteoporosis in men and women at high risk for fracture, men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (Prolia USPI 2021; Prolia SmPC 2021).

1.3 Bmab 1000

Bmab 1000 is a proposed biosimilar to Prolia and is a monoclonal antibody of IgG_2 consisting of 2 identical heavy chains, each comprising of 448 amino acids (including C-terminal lysine) and 2 identical light chains, each comprising of 215 amino acids. The average mass of intact Bmab 1000 is 147.4 kDa, which is similar to denosumab in Prolia. Bmab 1000 is produced in suspension culture in the CHO cell line. Qualitatively and quantitatively, the formulation composition for Bmab 1000 is identical to the reference product Prolia. The final formulation is filled into a PFS containing 60 mg of Bmab 1000 in 1 mL of solution (60 mg/mL).

1.4 Clinical Studies

1.4.1 Bmab 1000

Physicochemical, analytical, and preclinical (functional assays) characterizations and comparability evaluations have shown Bmab 1000 to be of similar structure, biological activity and quality profile as that of Prolia.

To date, no clinical studies have been initiated with Bmab 1000. As part of the biosimilar development program and in accordance with the applicable biosimilar guidelines, the following clinical studies are planned to be conducted with Bmab 1000:

- Study B1000-NHV-01-G-01: A Randomized, Double-blind, Two-arm, Single-dose, Parallel-Group Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Bmab 1000 and Prolia® in Normal Healthy Male Volunteers.
- Study B1000-PMO-03-G-02 (present study): 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.

In the absence of any clinical data pertaining to Bmab 1000 and considering the biosimilar development pathway, relevant efficacy and safety data from clinical studies conducted with Prolia (denosumab) are summarized in the section below.

Further detailed information can be found in the Investigator's Brochure (IB).

1.4.2 Prolia

The efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. Women with a baseline BMD T-score between –2.5 and –4.0 at either the lumbar spine or total hip were enrolled. A total of 3902 women were enrolled in placebo group and 3886 women were enrolled in Prolia (60 mg) group (Prolia USPI 2021).

Prolia significantly reduced the incidence of new morphometric vertebral fractures at 3 years (primary efficacy variable) compared with the placebo (2.3% versus 7.2%, respectively; $P<0.0001$). The absolute risk reduction was 4.8%, and relative risk reduction was 68%. Prolia significantly reduced the incidence of hip fracture at 3 years compared with the placebo (0.7% versus 1.4%, respectively; $P = 0.04$). The age-adjusted absolute risk reduction was 0.3% and a relative risk reduction was 40%. Prolia significantly reduced the incidence of nonvertebral fracture at 3 years compared with the placebo (6.5% versus 8.0%, respectively; $P = 0.01$). The absolute risk reduction was 1.5%, and relative risk reduction was 20%. Treatment with Prolia significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck (Prolia USPI 2021).

In clinical trials, treatment with Prolia reduced the level of sCTX by approximately 85% by 3 days, with maximal reductions occurring by 1 month. Within 1 to 3 months after dosing, the sCTX levels were below the limit of quantitation in 39% to 68% of patients. At the end of dosing interval, the suppression of sCTX partially reduced from a maximal reduction of ≥87% to ≥ 45%. This indicated reversibility of the effects of Prolia on bone remodeling. After further dosing, these effects were sustained. Similar effect was also observed for the level of P1NP (Prolia USPI 2021).

The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis (Prolia USPI 2021).

1.5 Study Rationale

Bmab 1000 is currently being developed as a proposed biosimilar to Prolia. For a proposed biosimilar to be approved, it must be proven that there are no clinically meaningful differences between the biosimilar and the reference innovator product. The PK, PD, and safety profile of Bmab 1000 and the US-licensed Prolia will be compared to demonstrate PK equivalence in a Phase 1 study in healthy volunteers (Study B1000-NHV-01-G-01).

The current randomized, double-blind, multicenter, parallel-arm study will be conducted as a part of the clinical development program of Bmab 1000 and will assess the therapeutic equivalence in efficacy, safety, and PD of Bmab 1000 compared with US-licensed Prolia.

The sponsor considers that the proposed clinical development program will be sufficient to demonstrate PK equivalence (Study B1000-NHV-01-G-01) and therapeutic equivalence and safety (Study B1000-PMO-03-G-02) of Bmab 1000 to the reference product. After collecting the totality of evidence proving its biosimilarity to Prolia, Bmab 1000 will provide an opportunity to improve access to treatment with potentially lowering health care costs.

The design of this study considers the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues (EMA 2012), the US FDA Guidance on Scientific Considerations in Demonstrating Biosimilarity to a reference product (FDA 2015), and PMDA Guideline on the Quality, Safety and Efficacy Assurance of Follow-on Biologics (PMDA 2009).

This study protocol is designed to allow a global study that would address the needs of various regulatory bodies. For EMA, the PD endpoint AUEC of sCTX from baseline to 26 weeks is considered as Co-primary endpoint, while, for US FDA, this endpoint is considered as a key secondary endpoint. For US FDA, after completion of double-blind active-controlled period (Day 1 to Week 52 [pre-dose]), the study is designed to include the transition period (Week 52 to Week 78), where patients who have received Prolia will be re-randomized to receive either Bmab 1000 or Prolia (Section 3).

1.5.1 Rationale for Study Population

International regulations (World Health Organization 2009; EMA 2012; FDA 2015; FDA 2019) suggest that proposed biosimilars shall be tested in a population representative of the approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the proposed biosimilar and the reference product.

The study population in this study was selected to be representative of the clinical studies supporting the development and marketing of the reference product (Prolia), and to align with the indications approved for the reference product.

Postmenopausal female patients aged ≥55 and <80 years with the BMD T-score at the lumbar spine (L1 to L4) ≤−2.5 and ≥−4.0 will be enrolled in this study. The age group has been selected based on the statistics that the mean age of natural menopause is 51 years in industrialized nations, compared with 48 years in poor and nonindustrialized nations. With the average life span extended to 70 years, the upper age limit is selected as 80 years (Ji and Yu 2015). The BMD T-score inclusion criteria is based on a 3-year, randomized, double-blind, placebo-controlled trial conducted in 7808 women to evaluate efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis, which had enrolled women with a baseline BMD T-score between –2.5 and –4.0 at either the lumbar spine or total hip (Prolia USPI 2021; Prolia SmPC 2021).

1.5.2 Rationale for Dose Selection

The recommended dose of Prolia is 60 mg administered as a single SC injection once every 6 months. The same dose has been selected for Bmab 1000 to allow comparisons between the reference product and the proposed biosimilar.

1.6 Benefit-Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of Bmab 1000 is provided in the IB. Bmab 1000 is being developed as a proposed biosimilar to Prolia; analytical and biological similarity has been demonstrated between Bmab 1000 and Prolia based on physicochemical and functional characterization using sensitive, orthogonal, and state of the art analytical methods and functional assays. Therefore, it is expected that efficacy, safety, and immunogenicity of Bmab 1000 will be comparable to Prolia. Bmab 1000 will have the same pharmaceutical formulation and

strength as Prolia (60 mg). The proposed dosing regimen is in line with the approved labeling for Prolia (Prolia USPI 2021). The proposed safety monitoring is deemed to be sufficient to monitor potential risks of Bmab 1000 administration. In view of the structural and biological similarity, Bmab 1000 is expected to display a safety profile similar to Prolia. Based upon the proven safety profile of Prolia, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

The benefit and risk assessments and the risk mitigation plans for COVID-19 are specified in Section 13.2.

2 Study Objectives, Endpoints, and Estimands

2.1 Primary Objectives, Endpoints, and Estimands

The primary objectives, endpoints, and estimands are presented in Table 2-1.

Table 2-1 Primary Objectives, Endpoints, and Estimands

Primary Objectives	Endpoints (Including Estimand Description)
To demonstrate equivalent efficacy between Bmab 1000 and Prolia based on percentage change from baseline at Week 52 in lumbar spine BMD (Co-primary for EMA, and Primary for US FDA)	Endpoint: Percentage change from baseline at Week 52 in the lumbar spine BMD by DXA *(Time Frame: Baseline and Week 52)*
	Estimand 1a-EMA (Co-primary Efficacy): Difference in means (Bmab 1000 – Prolia) in % change from baseline in lumbar spine BMD by DXA after 52 weeks in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements
	Estimand 1a-US FDA (Efficacy): Difference in means (Bmab 1000 – Prolia) in composite endpoint of % change from baseline in lumbar spine BMD by DXA after 52 weeks (where % change from baseline of zero is taken for anyone who dies) in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any other osteoporosis medications are taken
To demonstrate pharmacodynamic equivalence between Bmab 1000 and Prolia based on AUEC of the bone resorption marker sCTX from baseline to week 26 (Co-primary for EMA and secondary for US FDA)	Endpoint: AUEC of sCTX from baseline to 26 weeks (*Time Frame: Baseline to Week 26)*
	Estimand 1b-EMA (Co-primary PD): Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women[a] with osteoporosis treated with a SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements

Abbreviations: AUEC, area under the effect curve; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SC, subcutaneous; sCTX, serum C-terminal telopeptide of Type 1 collagen

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

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

2.2 Secondary Objectives and Endpoints of Double-Blind Active-Controlled Period (Part 1)

The secondary objectives and endpoints of double-blind active-controlled period (Part 1) are presented in Table 2-2.

Table 2-2 Secondary Objectives and Endpoints of Double-Blind Active-Controlled Period (Part 1)

Secondary Objective(s)	Endpoints
To compare other efficacy parameters (BMD of lumbar spine, total hip and femoral neck; fracture incidence) between Bmab 1000 and Prolia	• Percentage change from baseline at Week 26 in lumbar spine BMD by DXA (*Time Frame: Baseline and Week 26)* • Percentage change from baseline at Weeks 26 and 52 in total hip BMD by DXA (*Time Frame: Baseline, Week 26, and Week 52)* • Percentage change from baseline at Weeks 26 and 52 in femoral neck BMD by DXA (*Time Frame: Baseline, Week 26, and Week 52)* • Incidence of fracture up to Week 52 (*Time Frame: Baseline up to Week 52)*
To compare bone turnover between Bmab 1000 and Prolia based on sCTX and P1NP	• C_{min} of sCTX *(Time Frame: Baseline up to Week 26)* • Serum concentrations of P1NP (*Time Frame: Baseline up to Week 52)* • PD parameters of sCTX: I_{max}, TI_{max}, AUIC *(Time Frame: Baseline up to Week 26)*
To compare safety and tolerability of 2 administrations of Bmab 1000 and Prolia 6 months apart	• Incidence of TEAEs up to 6 months after the second dose (*Time Frame: Baseline up to Week 52)* • Incidence of clinically significant changes in vital sign, physical examinations, laboratory safety tests, and ECGs up to 6 months after the second dose *(Time Frame: Baseline up to Week 52)*
To compare immunogenicity between Bmab 1000 and Prolia	• Incidence and titer of ADA, incidence of NAb up to Week 52 *(Time Frame: Baseline up to Week 52)*
To assess denosumab serum concentrations following Bmab 1000 and Prolia administration	• Denosumab concentrations at Weeks 2, 4, 12, 26, 38, and 52 (*Time Frame: Baseline up to Week 52)*

Abbreviations: ADA, anti-drug antibodies; AUEC, area under the effect curve; AUIC, the area under the % inhibition curve; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; C_{min}, minimum concentration; I_{max}, maximum % inhibition; NAb, neutralizing antibodies; P1NP, procollagen Type 1 N-terminal propeptide; sCTX, serum C-terminal telopeptide of Type 1 collagen; TEAE, treatment-emergent adverse event; TI_{max}, the time of occurrence of maximum % inhibition

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

2.3 Key Secondary Objectives and Endpoints for the Transition Period (Part 2)

The key secondary objectives and endpoints of transition period (Part 2, for US FDA) are presented in Table 2-3.

Table 2-3 Key Secondary Objectives and Endpoints for the Transition Period (Part 2)

Secondary Objective(s)	Endpoints
To assess the risk of hypersensitivity and adverse events up to 6 months after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia	• Incidence of TEAEs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)* • Incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)* • Incidence of deaths and SAEs from the third dose at Week 52 and up to and including Week 78 *(Time Frame: from Week 52 up to Week 78)*
To assess the risk of immunogenicity through formation of anti-drug antibodies after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia	• Incidence and titer of ADA, incidence of NAb at Week 78 split by serostatus at Week 52 *(Time Frame: from Week 52 up to Week 78)*

Abbreviations: ADA, anti-drug antibodies; ECG, electrocardiogram; Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; SAE, serious adverse event; TEAE, treatment-emergent adverse event

2.4 Other Secondary Objectives and Endpoints of Transition Period (Part 2)

The other secondary objectives and endpoints of transition period (Part 2, for US FDA) are presented in Table 2-4.

Table 2-4 Other Secondary Objectives and Endpoints for the Transition Period (Part 2)

Other Secondary Objective(s)	Endpoints
To assess efficacy after the single transition from Prolia to Bmab 1000 compared with those to continuing on Prolia	• Percentage change from Week 52 at Week 78 in lumbar spine BMD by DXA *(Time Frame: from Week 52 up to Week 78)*
To assess efficacy of 3 doses of Bmab 1000 compared to Prolia	• Percentage change from (original) baseline at Week 78 in lumbar spine, hip and femoral neck BMD by DXA *(Time Frame: Day 1 up to Week 78)*
To assess PK and PD: i. after the single transition from Prolia to Bmab 1000 ii. on Bmab 1000 throughout each compared with those on Prolia throughout	• Serum concentrations of denosumab at Week 56, 64, and 78 (PK) *(Time Frame: from Week 56 up to Week 78)* • Serum concentrations of CTX at Week 78 (PD) (*Time Frame: Week 78)*
To assess the adverse events on Bmab 1000 throughout compared to Prolia throughout	• Incidence of TEAEs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)* • Incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)* • Incidence of deaths and SAEs from the first dose up to and including Week 78 *(Time Frame: Day 1 up to Week 78)*
To assess the risk of immunogenicity through formation of anti-drug antibodies on Bmab 1000 throughout compared to Prolia throughout	• Incidence and titer of ADA, incidence of NAb at any point from the first dose up to Week 78 *(Time Frame: Day 1 up to Week 78)*

Abbreviations: ADA, anti-drug antibodies; ECG, electrocardiogram; Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; CTX, serum carboxy-terminal cross-linking telopeptide of Type 1 collagen; serious adverse event; TEAE, treatment-emergent adverse event

3 Investigational Plan

3.1 Study Design

This is a randomized, double-blind, multicenter, parallel-arm, Phase 3 study to compare the efficacy, PK, PD, safety, and immunogenicity of Bmab 1000 and Prolia in postmenopausal women with osteoporosis.

Approximately 480 postmenopausal women aged ≥55 and <80 years with a BMD absolute value consistent with a T-score ≤−2.5 and ≥−4.0 at the lumbar spine will be enrolled.

Figure 3-1 shows the study design for the study. The study will consist of 3 study periods: Screening period; Part 1, double-blind active-controlled period; and Part 2, transition period.

Screening Period (from Day –28 to Day –1)

Screening evaluations will be completed within 28 days prior to the randomization.

Part 1, Double-Blind Active-Controlled Period (from Week 0 [Day 1] to Week 52 Pre-dose)

In the double-blind active-controlled period, eligible patients will be 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 will be followed-up for 26 weeks after the second dose. The randomization will be stratified by [redacted]

Efficacy, PK, PD, and safety including immunogenicity data will be collected as per Schedule of Events (Table 13-1).

Part 2, Transition Period (from Week 52 to Week 78 [EoS Visit])

All patients who complete Part 1 will undergo the re-randomization process prior to the study treatment administration at Week 52. Prior to dosing at Week 52, patients in the Prolia arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia at Week 52. This is done to obtain data after single switch in patients who have been treated with Prolia.

To maintain the study blinding, the patients in the original Bmab 1000 arm will also go through the re-randomization procedure; however, they will continue to receive Bmab 1000.

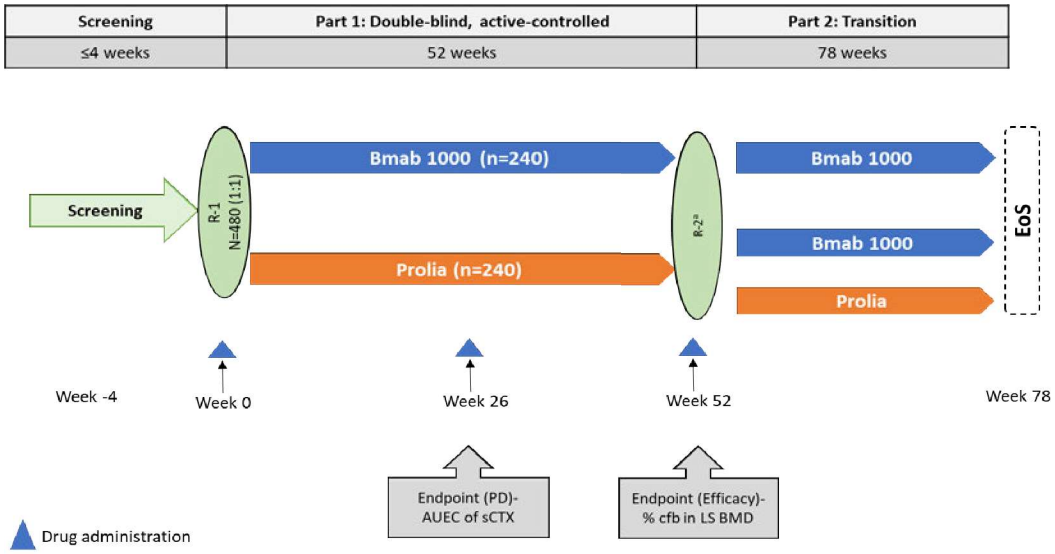
The re-randomization will take place within the original strata used for the randomization at baseline. All applicable assessments including efficacy, PK, PD, safety including immunogenicity will be performed as per Schedule of Events (Table 13-1).

End-of-study visit will be at Week 78 post randomization (Month 18).

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

The maximum study duration for a patient will be approximately 18 months (excluding screening).

Figure 3-1 Study Design



Abbreviations: AUEC, area under the effect curve; BMD, bone mineral density; cfb, change from baseline; EoS, end-of-study; LS, lumbar spine; PD, pharmacodynamic; sCTX, serum C-terminal telopeptide of Type 1 collagen; R-1, first randomization; R-2, re-randomization

a. At Week 52, patients in the Prolia arm will be re-randomized in 1:1 ratio to receive Bmab 1000 or Prolia. To maintain the blinding, patients in Bmab 1000 arm will undergo re-randomization procedure however, they will continue to receive Bmab 1000.

3.1.1 Independent Safety Review Committee

An Independent Safety Review Committee (ISRC) will periodically review the safety data to ensure safety of patients is protected (see Section 4.2.2). The ISRC will consist of therapeutic area experts (at least 3 members) who are independent of this study conduct. The initial meeting of the ISRC will be conducted after the first 10% of patients have completed Day 15 visit. The ISRC will continue to review the emerging safety data.

The ISRC will review the unblinded safety data to determine if the incidence of a serious adverse drug reaction was unacceptably high in the Bmab 1000 arm (or notably higher than the Prolia arm) such that continued administration of the product would present an unacceptable risk to patients.

The roles, responsibilities, and review process will be defined in the ISRC Charter.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Patients

Approximately 480 patients will be enrolled at approximately 47 sites in Europe and the United States. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the eligibility criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

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.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

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), drugs being investigated 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 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 acetylsalicylic acid), anticonvulsants (with the exception of benzodiazepines), systemic ketoconazole, adrenocorticotropic hormone, lithium, gonadotropin releasing hormone agonists, and anabolic steroids within the last 3 months before screening. Direct oral anticoagulants will be allowed. Receipt of PPI for >1 year 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), eg, 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 the 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 period). Severe vertebral 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 (eg, 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.

4.2 Discontinuation From Study Treatment and/or Withdrawal From the Study

4.2.1 Discontinuation From the Study Treatment

Patients may discontinue from the study treatment at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep patients in the study. If necessary, the investigator may discuss with the sponsor or its designee about any patient's reason for study treatment discontinuation. The reasons for patients discontinuing the study treatment will be recorded on the eCRF.

If the patient was dosed in error because she did not meet the eligibility criteria of the study, the patient should be discontinued from the study treatment. The patient will be followed-up for 6 months after the study treatment administration for safety.

The reason for discontinuing study treatment should be collected and categorized as related or not related as follows:

Related reasons: Related reasons for treatment discontinuation are related to intolerance to study treatment or supplements, or lack of efficacy (worsening of disease). The reasons will be categorized as below:

1. Any physical examination finding, change in vital signs, AE/SAE/AESI, or laboratory abnormality that, in the opinion of the investigator is causally related to the study treatment and can cause an excessive risk if the patient continued on treatment.
2. Use of prohibited therapy for osteoporosis.

3. Noncompliance or inability to tolerate the calcium and vitamin D supplementation that, in the opinion of the investigator, compromise possible response to therapy or risk of hypocalcemia.
4. Patient cannot tolerate study treatment (including PFS related issues with SC route of administration).
5. Lack of efficacy at investigator's discretion (BMD at the total hip or lumbar spine decreased by 7% or more).

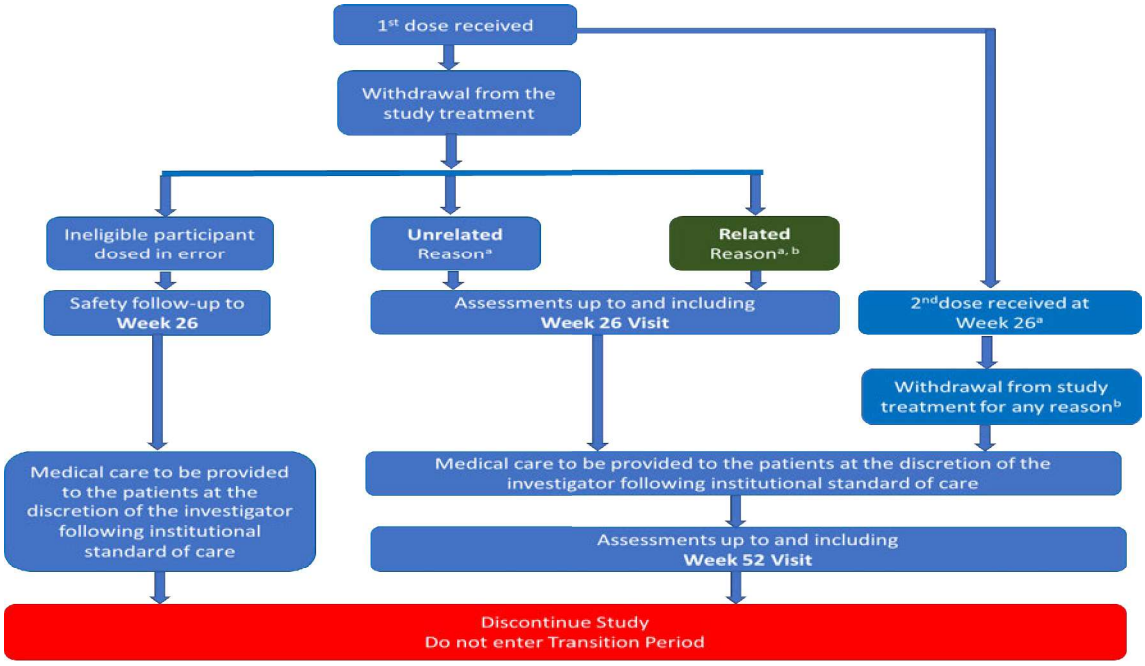
Unrelated reasons

6. AEs/SAEs not related to the study treatment and AEs not related to lack of efficacy
7. Investigator’s decision, if it is in the patient’s best interest to discontinue treatment (eg, new medical condition unrelated to osteoporosis, development of contraindication to administration of denosumab and any other reason unrelated to study treatment)
8. Administrative or logistical reasons, such as inability of the patient, the investigator, or the sponsor to continue the study

The follow-up of patients after study treatment discontinuation is described in Figure 4-1.

A good effort will be made to follow-up on patients particularly after intercurrent events.

Figure 4-1 Follow-up of Patients After Study Treatment Discontinuation



Note that Week 52 assessments are of primary importance (even if other medications administered and non-compliance with intermediate visits).

All assessments will be performed after informed consent is obtained from the patient and will only be performed in the interest of the patient.

a. Eligible patients wishing to discontinue from study treatment are encouraged to return for all assessments up to Week 52.

b. Treatment discontinued for "Related reason" = related to intolerance to study treatment or supplements, or lack of efficacy (worsening of disease).

Any ineligible patients given the initial dose in error, should be discontinued from both the study treatment and discontinued from the study after a 6-month safety follow up. Patients who discontinue the study treatment for **any other** reasons should be encouraged to return for the Week 52 visit (Table 13-1) and also intermediate visits, if feasible; they will not enter the transition period.

BMD assessment at Week 52 is important to collect even if the patient wishes to discontinue treatment after the first dose for any reason and even if they transitioned to different osteoporosis medications or have been non-compliant with intermediate visits.

Patients who discontinued the study treatment early for any reason will be followed for 6 months after the last study treatment administration for safety. If a patient cannot or is unwilling to attend any visit, a safety follow-up (eg, AEs, concomitant medication) will be conducted by telephone.

4.2.2 Pausing of Study Treatment or Enrollment or Study Termination and ISRC Review

The administration of the study treatment or further enrollment in the study may be paused/modified by Biocon based on the ISRC's recommendation. The ISRC will review the safety data and provide recommendations whether to pause/continue/modify the study (see Section 3.1.1). In case of an unforeseen situation, where the ISRC determines upon review of the emerging safety data that the continued administration of the study treatment would present an unacceptable risk to the patients, ISRC may recommend terminating the study to Biocon. Further details will be provided in ISRC Charter.

4.2.3 Withdrawal From the Study

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator also has the right to withdraw patients. The participation of patient in the study can be discontinued for the following reasons:

1. Patient withdraws consent
2. Patient's substantial noncompliance toward protocol-specified procedures/requirements (eg, unwilling to attend the critical visits – Week 26 and Week 52 visits)
3. Patient is lost to follow-up

4. Investigator's decision (serious or intolerable adverse event, new medical condition or an intercurrent illness not consistent with the protocol requirements, contraindications of use of study treatment)
5. Termination of the site or study by the sponsor or regulatory authority

For patients who discontinue the study early and do not wish to attend Week 26 and/or Week 52 visit(s) as described in Section 4.2.1, all procedures specified for EoS visit (Table 13-1) will be performed at early withdrawal visit; however, DXA scan should be performed only if the 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.

4.2.4 Lost to Follow-Up

A patient will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 2 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

If the patient continues to be unreachable, she will be considered to have withdrawn from the study. If the patient can be reached, the patient should be encouraged to return for Week 26 and/or Week 52 Visits as described in Section 4.2.1.

4.2.5 Replacements and Screen Failures

Patients who receive study treatment and discontinue before the study completion will not be replaced.

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 after minimum of 28 days from the date of COVID-19 positive test result on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study as per site and/or local regulatory guidelines. The investigator is recommended to discuss with the medical monitor and/or sponsor before rescreening the patients with positive COVID-19 test result.

For patients who meet the exclusion criteria of laboratory assessments (exclusion criterion 12), one retesting of laboratory test is allowed within the screening period; however, except for the vitamin D deficiency (exclusion criterion 12.a), the investigator is recommended to discuss with the medical monitor and/or sponsor for possibility of retesting of laboratory test.

Overall, only 1 retesting of laboratory parameter and 1 rescreening is allowed during the study. For rescreened patients, all screening procedures/tests are required to be repeated except DXA scan and lateral spine X-ray if performed within 90 days prior to rescreening. In case of history of fall or clinical signs of vertebral fracture or based on investigator's decision, DXA scan and/or lateral spine X-ray can be performed even within 90 days prior to rescreening. The rescreened patient will be assigned with a new patient identification number.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

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

First Randomization for Part 1

Patients will be randomly assigned at the baseline/randomization visit (Week 0/Day 1) to receive Bmab 1000 (test product) or Prolia (reference product) using a 1:1 allocation ratio. The first randomization to treatment assignment will be stratified by the following:

Re-Randomization for Part 2 (Transition Period)

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

The second randomization process will be conducted in all arms to maintain the study blind.

During Part 2, the randomization will be stratified by the original strata used for the randomization at baseline.

5.2 Treatments Administered

5.2.1 Bmab 1000 and Prolia

Bmab 1000 (60 mg) or Prolia (60 mg) will be administered subcutaneously using a PFS of 60 mg/mL solution for injection on Day 1, and at Week 26 and Week 52. The study treatment will be administered as an SC injection, preferably in the abdomen. Whenever possible, the same injection site should be used for all study treatment administration.

The study treatment is required to be administered by the site-qualified and trained clinical staff member(s) (eg, nurse/physician, etc.), who is designated as an unblinded study site personnel who will not be involved in any other study-related procedure(s). Patients will be blinded through the use of a blindfold, screen, or similar method during the dosing procedure so that the injection syringe will not be visible to the patient. The details regarding blinding are described in Section 5.6.

Bmab 1000 and Prolia should be visually inspected prior to its use. The study treatment solution should not be injected if it is cloudy or discolored or if it contains many particles or foreign particulate matter. To avoid discomfort at the site of injection, the PFS should be allowed to reach room temperature (up to 25ºC) before injecting and inject slowly. The entire contents of the PFS should be injected.

Further guidance and information for handling the study treatment is provided in the Pharmacy Manual.

5.2.2 Calcium and Vitamin D Supplements

During the screening period, oral vitamin D repletion is permitted at the investigator's discretion if serum 25-hydroxy vitamin D level is ≥12 and <20 ng/mL for eligibility purpose.

All patients will receive daily supplementation containing at least 1000 mg of elemental calcium and at least 400 IU vitamin D (via any route of administration) from randomization until the EoS visit (Week 78). Calcium and vitamin D are co-administered to prevent low serum calcium level while taking study treatments. The dose can be increased at investigator's discretion. Patients who are already taking calcium and vitamin D prior to the screening visit, will continue the supplements during the screening period. Information about calcium and vitamin D administration will be collected via a patient diary and will also be recorded in the source documents and eCRF.

Note: On the day of PD sample collection, patients should not take calcium supplement prior to sample collection (to be taken after sample collection).

5.2.2.1 Managing Hypercalcemia and Hypocalcemia

If a patient develops hypercalcemia during the study, the calcium and/or vitamin D supplementation may be interrupted or reduced per the investigator's discretion until the

serum calcium concentration has returned to the normal range or as per the investigator's discretion.

If a patient develops hypocalcemia, defined as albumin-adjusted total serum calcium <8.5 mg/dL (<2.125 mmol/L) during the study, appropriate additional supplementation shall be instituted as deemed acceptable by local guidelines or as per investigator's discretion to return the serum calcium concentration to within the normal range.

If a patient is intolerant of the daily calcium or vitamin D supplementation, the formulation may be changed (including taking a preferred product that the patient tolerated well earlier) or the dose can be lowered per the investigator's discretion. The intolerance as well as the resolution (eg, change in formulation or dosage) shall be recorded in both the source documents and the eCRF.

5.3 Identity of Investigational Product

Bmab 1000 is a mAb that is being developed by Biocon Biologics UK Limited as a proposed biosimilar to Prolia. Bmab 1000, is a full-length human mAb of the IgG_2 subtype produced in a mammalian cell line, CHO cells, by recombinant DNA technology. Like denosumab, Bmab 1000 consists of 2 heavy chains and 2 light chains of the kappa subclass. The average mass of intact Bmab 1000 is 147.4 kDa, which is similar to denosumab in Prolia. The International Nonproprietary Name of the commercially available reference material (Prolia) is denosumab and the ATC Classification System code is M05BX04.

The reference product, US-licensed Prolia, is supplied as sterile, preservative-free, clear, colorless to pale yellow solution for SC administration. Each 1 mL single-dose PFS of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, water for injection, and sodium hydroxide to a pH of 5.2 (Prolia USPI 2021).

Bmab 1000 is supplied as a sterile, preservative-free solution of denosumab for SC administration in a single-use PFS with a grey needle cap (1 per carton). Bmab 1000 is a colorless to pale yellow solution for injection, with a pH similar to that of Prolia and is formulated at 60 mg of denosumab in 1 mL for SC use. Each 1 mL single-dose PFS contains 60 mg denosumab (60 mg/mL solution), acetate, sorbitol and polysorbate-20. For further details, see the IB.

The following drug supplies will be used in the study:

Product	Supplied as
Bmab 1000	60 mg/mL single-dose PFS
US-licensed Prolia	60 mg/mL single-dose PFS

Abbreviation: PFS, prefilled syringe.
Note: The Bmab 1000 PFS is supplied without needle safety guard whereas Prolia PFS is supplied with needle safety guard.

5.4 Management of Clinical Supplies

5.4.1 Investigational Product Packaging and Storage

The sponsor will provide adequate supplies of Bmab 1000 and Prolia for distribution to the study sites. Bmab 1000 will be manufactured and packaged in accordance with GMP for medicinal products for use in human clinical trials and provided with a certificate of analysis. All study treatments will be labeled in accordance with GMP and local regulatory requirements.

Storage and handling requirements are identical to that for Prolia and will be followed when handling Bmab 1000. All study treatment supplies must be stored in a secured area with restricted access (eg, a locked cabinet) and in accordance with the manufacturer's instructions. They will be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and will not be frozen. The immediate containers must be kept in the outer carton until use to protect the study treatment from light and heat and avoid vigorous shaking. Once removed from the refrigerator, the product must not be exposed to temperatures above 25°C (77°F) or direct light and must be used within 14 days. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

Further guidance and information for drug product stability and storage are provided in the Pharmacy Manual.

5.4.2 Investigational Product Accountability

The investigator will maintain accurate records of receipt of all study treatments, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each patient in the study. The study treatment

accountability will be verified by the monitoring team during their monitoring visit and ensure the accountability as per the IWRS reports.

Only patients enrolled in the study may receive the study treatment and only authorized site personnel may supply or administer the investigational product. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study treatments will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused investigational products are provided in the Study Reference Manual.

The used syringes can only be destroyed if it is according to local standard operating procedures and a specific authorization is given by the sponsor. Permission will be granted by the sponsor on a study-site-by-study-site basis after reviewing the study site destruction policy. This authorization may also be granted to destroy used syringes immediately after administering the study treatment to patients in a manner that preserves the blinding. The list of destroyed syringes must be recorded.

5.4.3 Calcium and Vitamin D Supplies

Calcium and vitamin D will be supplied locally to the patient as per local regulations (see Section 5.2.2 for further information regarding doses and adjustments).

5.5 Overdose, Underdose, and Medication Errors

Since study treatments are directly administered by personnel involved in the study in controlled manner, overdose/underdose/medication error is unlikely to occur. However, in case of overdose/underdose/medication error, the management will be as per the standard of care. In case there is overdose/underdose/medication error, it must be reported to the sponsor/sponsor representative immediately (ie, within 24 hours).

In case of overdose or medication error, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5.6 Blinding

This study will be double-blind until the EoS. The randomization codes will not be revealed to study patients, investigators, and study center personnel, except for delegated unblinded staff who will handle the study treatment, and predefined unblinded sponsor and CRO personnel, until all final clinical data have been entered into the database and the database is locked and released for analysis.

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

Analyses of double-blind active-controlled period (Part 1) will include data after all patients have received the Week 52 assessments (prior to the third administration of study treatment) or have terminated the study before Week 52. At Week 52, the investigators, patients and other members of staff involved with the study will remain blinded. Randomization data, including any documentation identifying the treatment allocation, will be kept strictly confidential. An unblinding plan will give full details of who will be unblinded at Week 52 and how the flow of information is going to be handled.

5.6.1 Breaking the Blind

A patient’s treatment assignment will not be unblinded until the EoS (Week 78) unless medical treatment of the patient depends on knowing the study treatment the patient received. If the blind needs to be broken because of a medical emergency, the investigator may unblind an individual patient’s treatment allocation. The investigator should notify the sponsor or medical monitor in case of unblinding.

To the extent possible before unblinding, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through IWRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

The pharmacovigilance personnel from contract research organization's PVG will have access to the randomization code, if SUSARs, which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities. The unblinding process for SUSAR reporting will be defined in the Safety Management Plan.

5.7 Compliance With Study Treatment

Bmab 1000 and Prolia will be administered by the unblinded staff while the patient is at the study site. The date and time of each dose administered in the clinic will be recorded in the source documents and eCRF. The dose of study treatment and study patient identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study treatment. Administration of co-administered treatments (calcium and vitamin D) will be recorded daily by the patient in their diary.

Every effort will be made to encourage patients' compliance with the study visits. A dosing visit window of ± 7 days is allowed for Week 26 visit and Week 52 visit. If any study visit has to be rescheduled, subsequent visits should follow the original visit date scheduled.

5.8 Prior and Concomitant Therapies

Prior osteoporosis medications refer to medications started any time prior to screening and stopped prior to the first dose of study treatment. All other prior medications (ie, medication used for conditions other than osteoporosis) refer to medications started within 5 years prior to screening and stopped prior to the first dose of study treatment.

Concomitant medications refer to medications started prior to and continued after the first dose of study treatment or taken any time after the first dose of study treatment up to the follow-up visit.

Use of all concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Any COVID-19 vaccination must be recorded on the concomitant page of the eCRF.

5.8.1 Prohibited Concomitant Medications

Patients who have received these prohibited therapies or plan to receive these prohibited therapies will not be enrolled in the study. Patients who receive any prohibited therapy during the screening period should be considered a screen failure. Patients who are permanently discontinued from study treatment can be treated with alternative therapies at the investigator's discretion. Patients who receive any prohibited medication can be discontinued from the study treatment at the investigator's discretion. Intake of any of the following therapies by the patients while on study treatment will be considered as a protocol deviation.

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

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

Use of COVID-19 vaccine is encouraged, although, at the discretion of PI, an interval of 7 days is advised between the COVID-19 vaccine and study drug administration due to putative adverse drug reactions. Use of COVID-19 vaccines should be captured as concomitant medication.

5.9 Intervention After the End of the Study or Treatment Discontinuation

After the EoS or study treatment discontinuation, study treatments will not be made available to patients. Medical care, including anti-resorptive therapy, will be provided to the patients following treatment discontinuation, as per institutional standard of care if in the patient's best interest at the discretion of the investigator.

6 Study Assessments and Procedures

Before any study procedures are performed, all potential patients will sign an ICF. Additional procedural details related to the ICF are provided in Section 9.3.

Study procedures and their timing are summarized in the Schedule of Events (Table 13-1). Data handling for analysis of Schedule of Events performed outside of the allotted time window will be discussed and agreed upon on a by-patient basis in the blinded data review meeting, with the report finalized before database lock.

6.1 Efficacy Assessments

6.1.1 Bone Mineral Density

Bone mineral density will be assessed by DXA scan at the time points specified in the Schedule of Events (Table 13-1), using validated instruments. All DXA scans will be analyzed by the central imaging vendor. The same DXA instrument shall be used for all study procedures for each patient during the study. If for unforeseeable reasons the same scanner is no longer available, the study site should follow the central imaging provider's guidance on selecting an appropriate replacement scanner and follow a phantom scanning process to quantify any calibration differences. All DXA scans of lumbar spine, total hip, and femoral neck BMD will be submitted to and analyzed by the central imaging vendor.

For lumbar spine DXA scan, L1 to L4 will be measured, only excluding vertebrae that are affected by local structural change or artefact, using at least 2 vertebrae for diagnostic classification. Anatomically abnormal vertebrae may be excluded from analysis if they are clearly abnormal and nonassessable within the resolution of the system and using a 1.0 T-score difference between vertebra in question and adjacent vertebrae as a guideline in identifying vertebrae for exclusion (ISCD 2019).

For femur DXA scan, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a patient fractures the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained for the affected location.

6.1.1.1 Screening Bone Mineral Density Assessment

To determine eligibility based on BMD T-score, lumbar spine DXA scans will be analyzed.

To be eligible for the study, patients must have at least 3 evaluable vertebrae at the lumbar spine (L1 to L4) and at least 1 evaluable hip by DXA scan assessed by the central imaging vendor. Patients with unilateral metal in hip will be allowed to enroll into this study and the contralateral hip will be used for evaluation.

6.1.1.2 On-Study Bone Mineral Density Assessment

Bone mineral density changes for individual patients will be monitored during the study per the time points specified in the Schedule of Events (Table 13-1). Investigators will be alerted if a patient experiences a BMD loss from baseline of 7% or more at the lumbar spine or total hip.

6.1.2 Incidence of Fracture

To increase the potential of therapeutic intervention to prevent vertebral fractures, the lateral spine X-ray will be performed at screening, Weeks 26 and 52, and also could be performed as required for confirmation of suspected fractures. All lateral spine X-rays will be assessed at a central imaging center. Any new fractures confirmed by the central imaging vendor will be recorded as an adverse event. If necessary to support the patient's medical care, these X-rays could be read locally; however, only fractures confirmed by the central imaging center will be considered for the analysis.

A new vertebral fracture is defined as an increase of at least one grade in any vertebra from T4 to L4 that was normal at screening (Cummings *et al.*, 2009). The vertebral fracture will be assessed by semi-quantitative grading at a central imaging vendor (Genant *et al.,* 1993):

- Grade 0 = no fracture.
- Grade 1 = mild fracture, 20% to 25% reduction in vertebral height (anterior, middle, or posterior).
- Grade 2 = moderate fracture, greater than 25% to 40% reduction in any height.
- Grade 3 = severe fracture, greater than 40% reduction in any height.

Information about a new nonvertebral fracture (eg, details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture will be recorded during the study. A copy of other diagnostic image and/or radiology report, surgical report, or discharge summary will be included in the patient's individual source documents and will be submitted to the central imaging vendor for confirmation of fracture. If the radiograph or diagnostic image is not available, then, at minimum, a copy of the radiology report, surgical report, clinical notes, or discharge summary will be submitted to the central imaging vendor.

6.2 Safety Assessments

Safety will be assessed through the collection and evaluation of AEs, including TEAEs, SAEs, AESIs, clinical laboratory assessments, physical examinations, vital sign measurements, and ECGs.

6.2.1 Adverse Events

6.2.1.1 Definitions

6.2.1.1.1 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study treatment or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the study treatment.

In accordance with the above definition, AEs may include:

- Worsening (change in nature, severity, or frequency) of conditions (except for osteoporosis) present at the onset of the study
- Condition detected or diagnosed after informed consent even though it may have been present prior to the start of the study

An AE does not include:

- Laboratory results of the disease being studied, medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion) but rather the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions present or detected prior to signing the ICF that does not worsen.
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen as per investigator.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).

Patients will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as 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.

6.2.1.1.2 Adverse Drug Reaction

An ADR is defined as any noxious and unintended responses to study treatment, related to any dose administered.

6.2.1.1.3 Unexpected Adverse Drug Reaction

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product).

6.2.1.1.4 Serious Adverse Events

An SAE is defined as any event that

- results in death

- is immediately life-threatening*
- requires inpatient hospitalization or prolongation of existing hospitalization**
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

**"Inpatient hospitalization" does not imply that the patient must have had an overnight stay in the hospital. If the patient was admitted to the hospital for less than a day for the purpose of treatment or observation, the definition of "Inpatient hospitalization" is met, provided the patient is admitted solely for treatment of the event and not admitted for any other reasons including, rehabilitation, hospice care, respite care (eg, caregiver relief), skilled nursing facilities, nursing homes, social reasons, ease of compliance, day care procedures, or for medical or hospital records (insurance reimbursement) purpose. Although, brief treatment in an outpatient clinic or emergency department does not constitute "inpatient hospitalization", depending on the intervention/treatment required for the event, it may satisfy the criteria of inpatient hospitalization to be reported as an SAE.

Events NOT to be reported as SAEs are hospitalizations for the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Treatment, which was elective or preplanned, for a pre-existing condition that is unrelated to the indication under study and did not worsen
- Admission to a hospital or other institution for general care due to social or economic reasons (eg, no access to local ambulatory medical care)

6.2.1.1.5 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reactions are SAEs having a reasonable possibility of a causal relationship with the study treatment, the nature or severity of which is not consistent with the applicable product information (eg, IB or approved product labels).

6.2.1.1.6 Adverse Events of Special Interest

An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor/sponsor representative could be appropriate (ICH E2F; CIOMS VI).

The following AEs are considered as AESIs:

Treatment-related hypersensitivity/allergic reaction

All AEs related to hypersensitivity/allergic reactions including anaphylaxis after study treatment administration will be reported. Symptoms include but not limited to hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria, will be reported.

Anaphylactic Reactions

Anaphylaxis will be identified according to Sampson criteria (Sampson *et al.,* 2006). Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (eg, dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
   a. Adults: Systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Serious Infections

All AEs related to serious infections including but not limited to urinary tract infection, upper respiratory tract infections, skin infections including but not limited to erysipelas and cellulitis, abdomen infection and ear infection will be reported.

Hypocalcemia

All AEs related to hypocalcemia include but not limited to asymptomatic hypocalcemia, paresthesia or muscle stiffness, twitching, spasms and muscle cramps, QT interval prolongation, tetany, seizures and altered mental status will be reported.

Osteonecrosis of the jaw

All AEs related to osteonecrosis of the jaw include but not limited to jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, and gingival erosion will be reported.

Atypical femoral fracture

All AEs related to atypical femoral fracture include but not limited to new or unusual thigh, hip, or groin pain will be reported.

Dermatologic reactions

All AEs related to dermatologic reactions include but not limited to dermatitis, eczema, and rashes will be reported

All AESIs must be reported to the sponsor/sponsor representative immediately (ie, within 24 hours) after site personnel first learn of the event. Further details on the reporting and management of AESIs are provided in the Safety Management Plan.

6.2.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF until the EoS.

If the investigator learns of any SAE, including a death, at any time after the EoS, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor/sponsor representative.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being.

In addition to patient observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

Adverse events will be recorded in the patient's medical records in accordance with the investigator's normal clinical practice and on the AE page of the eCRF. Serious AEs that occur during the study must be documented in the patient's medical record, on the AE/SAE page of the eCRF.

The investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms. If a clinically significant abnormal laboratory finding or other abnormal assessment meets the

definition of an AE (and SAE if serious), then the AE/SAE page of the eCRF page must be completed as appropriate. A diagnosis, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. As additional information becomes available and a diagnosis is achieved, the signs/symptoms or abnormal finding verbatim should be updated on the eCRF.

If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded on the AE/SAE page.

6.2.1.2.1 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the NCI CTCAE v5.0, based on the following general guidelines (a semicolon [;] indicates "or" within each description):

Grade 1:	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate: minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living*
Grade 3:	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**
Grade 4:	Life-threatening consequences: urgent intervention indicated
Grade 5:	Death related to AE

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care activities of daily living refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

In the course of the study, if AEs are not covered in the NCI CTCAE occur the investigator will determine the severity of these adverse events as follows:

Mild:	Awareness of symptoms but easily tolerated
Moderate:	Discomfort enough to cause interference with usual activity
Severe:	Incapacitating with inability to work or carry out usual activity
Life-threatening	Immediate risk of death at the time of event
Death:	Results in death

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

The SAE will not be closed out if it is of changing severity during the course. It will be reported with changes in the severity as it upgrades in follow-up reports such that each upgraded sequela will not be recorded as a new SAE, but continuation of same SAE and the serious and unexpected adverse reactions will be reported to the local regulatory authority/IEC within the stipulated timeline. Only the highest grade of severity will be considered for analysis purpose.

6.2.1.2.2 Assessment of Causality

The investigator's assessment of an AE's relationship to the study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The investigator's causality assessment should consider the potential etiologies for the observed AE. An AE may be related to study treatment, other concomitant medications, the underlying disease pathology, intercurrent illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the investigator should decide based on the most likely causal relationship. When a causality assessment is provided for an SAE, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available

supporting evidence, including relevant laboratory tests, histopathology evaluations, and the results of other diagnostic procedures.

The relationship or association of the study treatment in causing or contributing to the AE will be characterized using the following:

Unrelated:	There is no association between the investigational product and the reported event.
Unlikely	Time to drug intake makes a relationship improbable. Another explanation is more likely such as disease, environment, or other medication.
Possible:	Treatment with the investigational product caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the investigational product but could also have been produced by other factors.
Probable:	A reasonable temporal sequence of the event with drug administration exists and based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the investigational product seems likely. The event disappears or decreases on cessation or reduction of the dose of investigational product.
Definite:	A definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the investigational product is readministered.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Any fracture will be recorded as an AE/SAE/AESI (as applicable). All AEs will be followed to adequate resolution. The current version of MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.2.1.3.1 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.2.1.1) must be reported to [redacted] immediately (ie, within 24 hours) after site personnel first learn of the event. Recurrent episodes, complications, or progression of the initial SAEs must be reported as follow-up to the original episode within 24 hours of the investigator knowledge. An SAE occurring at a different time interval should be reported separately as a new event. Serious AEs will be reported electronically via the eCRF. Paper SAE forms will be used as a back-up option, and the following contact information is to be used:

Name of Department: [redacted]

[redacted]

The sponsor/sponsor representative has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational product under clinical investigation. The sponsor/sponsor representative will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information from the sponsor/sponsor representative will review and then file it as appropriate and will notify the IRB/IEC, if appropriate according to local requirements.

Clarification in Reporting of Deaths

All patient deaths (regardless of relationship to study treatment) should be reported for patients on the study and recorded in the eCRF. If a patient dies after signing consent but before the first dose of the study treatment, this should also be recorded in the eCRF. Death is an outcome of an AE and not an AE in itself. All reports of patient deaths should include an AE term (other than "Death") for the cause of the death. If an AE term is not provided, the investigator will be queried to obtain the cause of death. Only in the rare occurrence that no verbatim description of an AE can be obtained from the investigative site, the "Death-Unknown cause" will be used as the event term.

6.2.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions

The sponsor/sponsor representative will promptly evaluate all SUSARs and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor/sponsor representative will assess the expectedness of these events using Bmab 1000 IB.

The sponsor/sponsor representative will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document, ie, Bmab 1000 IB, Prolia USPI/SmPC.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.2.1.4 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, the AE returns to baseline status, or the patient is lost to follow-up.

The investigator will administer appropriate treatment for the AE/SAE resolution. The investigator is responsible to ensure that follow-up includes any supplemental investigations

as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

6.2.1.5 PFS Related Issues/ Adverse Events

The PFS is used to inject Bmab 1000/Prolia. The unblinded site staff is responsible for the detection and documentation of PFS-related issues (eg, accidental needle stick injury, malfunction of injection mechanism). The PFS related AEs will be handled as mentioned in Section 6.2.1.2, 6.2.1.3, 6.2.1.4 and Table 6-1.

The unblinded site staff will promptly notify the unblinded study team as soon as possible (as per regulatory requirement) about any PFS related issues. Further details will be provided in the Pharmacy Manual.

The PFS related AEs will be assessed, from signing of ICF until the EoS, using the classification shown in below table.

Table 6-1 Classification of Assessment of PFS Related Adverse Events

Unrelated	There is no temporal association between the PFS and the reported event and event is clearly due to other causes (eg, concomitant medication, underlying disease)
Unlikely	Time to adverse event and use of PFS makes a relationship improbable. Another explanation is more likely such as disease, environment, or other medication
Possibly	The use of PFS has caused or contributed to the adverse event, ie, the event follows a reasonable temporal sequence from the time of the injection with PFS but could also have been produced by other factors
Probably	A reasonable temporal sequence of the event with the use of PFS exists and, based upon the known or previously reported complications following use of PFS, or judgment based on the investigators clinical experience, the association of the event with the PFS seems likely
Definitely	A definite causal relationship exists between the use of PFS and the adverse event, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event

6.2.2 Clinical Safety Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the Schedule of Events (Table 13-1). Blood samples do not need to be performed in a fasting state unless required in the opinion of the investigator. If PD blood samples are also being collected at the same timepoint, the safety blood samples can be collected in the fasting state along with the PD blood samples. Clinical laboratory test samples will be analyzed at the central laboratory of safety testing. For management of emergency cases (AE/SAE), assessment can be performed at local laboratory.

The following clinical laboratory analyses will be performed:

Clinical chemistry: Albumin, albumin-adjusted total serum calcium, ALP, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, FT3[a], FT4[a], low density lipoprotein cholesterol, creatine kinase–myocardial band isoenzyme, creatine phosphokinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglycerides, magnesium, phosphates, potassium, sodium, bilirubin (total, direct), total protein, uric acid, troponin I[b], serum 25-OH vitamin D, TSH[c], and intact parathyroid hormone.

a. FT3 and FT4 are required only at screening.
b. Troponin I should be tested only if clinically relevant (at investigator's discretion).
c. TSH should be tested at screening and if clinically relevant (at investigator's discretion) at any time during the study.

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelet count.

Urinalysis: Color, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D, and mineral levels (magnesium, phosphate), and any signs and symptoms of hypocalcemia will be closely sought and adequately treated at the investigator's discretion if it occurs.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline or are clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition, are **not** to be reported as AEs or SAEs.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Events (Table 13-1). If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

6.2.2.1 Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, and SARS-CoV-2

At screening, HBsAg, HBsAb, and HBcAb will be assessed in all patients as specified in Table 6-2.

Table 6-2 Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results			Eligibility
HBsAg	**HBcAb**	**HBV DNA**	
+	+/–	Not applicable	Not eligible
–	+	+	Not eligible
		–	Eligible
–	–	Not applicable	Eligible

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

If the HBsAg test result is 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; if the HBV DNA test result is negative, the patient can be included in the study. Hepatitis B analysis will be performed at the central laboratory of safety testing.

At screening, hepatitis C antibody and HIV will be assessed in all patients. If the HCV test results is positive, HCV RNA 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. Further evaluation for the patients who are enrolled based on HCV RNA test can be done depending on the investigator's discretion during the study. If the HIV test result is positive, the patient must be excluded from the study. Hepatitis C and HIV analysis will be performed at the central laboratory of safety testing.

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. If the patient has had contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.

6.2.2.2 Follicle-Stimulating Hormone

Women of childbearing potential will not be eligible for enrolment in this study. To confirm postmenopausal status, FSH levels will be measured at screening, which should be ≥40 mIU/mL with at least 12 consecutive months since spontaneous amenorrhea. Note: Women with surgical menopause will not have their postmenopausal status confirmed with FSH test but confirmation will be via their medical history.

6.2.3 Physical Examinations

Investigators should carefully evaluate patients for any indication of injection site reaction, hypersensitivity/allergic reactions, infection, hypocalcemia, osteonecrosis of jaw, atypical femoral fracture, and dermatologic reactions and treatment should be indicated in accordance with the investigator's medical judgment. Especially, a thorough oral examination (including mouth, gums, teeth, tongue) should be performed. Physical examination will be performed at the time points specified in the Schedule of Events (Table 13-1).

Information about the physical examination findings will be recorded by the investigator or designee in the eCRF and source documents. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after signing the ICF that meet the definition of an adverse event will be recorded in the eCRF and source documents.

A complete physical examination will include, at a minimum, oral examination and assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. The complete physical examination will be performed at screening, baseline (Day 1), and Weeks 26, 52, and 78. Abbreviated, ie, sign/symptom-directed examination will be performed at other visits as specified in the Schedule of Events (Table 13-1). Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.2.4 Vital Signs

Vital signs will be measured at scheduled visits as indicated in the Schedule of Events (Table 13-1). Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Blood pressure and pulse measurements will be assessed after 5 minutes of rest (sitting), preferably with a completely automated device. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). On the dosing day visits, vital signs will be assessed prior to dosing. All measurements will be recorded in the eCRFs and source documents.

6.2.5 Electrocardiograms

All scheduled 12-lead ECGs will be performed at the study site after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the Schedule of Events (Table 13-1) and if the patient experienced cardiac symptoms during study treatment administration. If following the ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT/QTcF prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The investigator will then report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion.

6.2.6 Other Safety Assessments

6.2.6.1 Medical History, Disease History, and Demographic Information

The medical history (general medical history and disease medication history), disease history of postmenopausal osteoporosis, fracture history, and demographic information including gender, age, ethnicity, race, weight, and body mass index (kg/m^2) at screening (Visit 1) will be recorded in the patient's eCRF and the source documents.

6.2.6.2 Injection Site Reaction Monitoring

Injection site reactions will be assessed within 1 hour of the end of each study treatment administration, as specified in the Schedule of Events (Table 13-1). Injection site reaction will be assessed based on CTCAE v5.0.

Details will be recorded in both the source documents and the eCRF.

6.2.6.3 Hypersensitivity/Allergic Reaction Monitoring

Hypersensitivity reactions will be assessed prior to the study treatment administration (within approximately 15 minutes) and 1 hour (±10 minutes) after each study treatment administration, as specified in the Schedule of Events (Table 13-1). If patients have signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), patients or caregivers should be advised to call the study site or get immediate help.

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.

For patients who experience or develop life-threatening treatment-related anaphylactic reactions, study treatment must be stopped immediately and succeeding doses need to be discontinued.

Details will be recorded in both the source documents and the eCRF.

6.2.6.4 New York Heart Association Functional Classification

At screening, patients who have history of heart failure will be assessed for the presence of congestive heart failure according to the NYHA functional classification. Patients with congestive heart failure of class III or IV chronic heart failure will be excluded from the study. Results will be recorded in both the eCRF and source documents.

6.3 Pharmacokinetics

Pharmacokinetic blood samples for the determination of serum concentration of denosumab will be collected from patients from both study groups (Bmab 1000 and Prolia) at the time points specified in the Schedule of Events (Table 13-1). Additionally, the blood samples for method validation will also be collected on Day 1 (pre-dose).

If the blood sample is unable to be analyzed or is missing at a certain time point, some blood samples collected for PD or immunogenicity assessment at the same time point can be used for PK assessment after discussion and agreement from the sponsor.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents.

Further details about PK blood sampling collection, storage, and sample processing specification are provided in the laboratory manual.

6.4 Pharmacodynamics and Biomarkers

Concentrations of the bone turnover markers (CTX and PINP) will be measured from fasting serum samples at the time point specified in the Schedule of Events (Table 13-1). Patients will be required to refrain from intense physical activity in the 48-hour period prior to sample collection, to fast overnight for 8 hours prior to assessment, not to take calcium supplement prior to sample collection (to be taken after sample collection), and to visit the study center in the morning for PD assessment. Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents.

Further details about PD blood sampling collection, storage, and sample processing specification are provided in the laboratory manual.

6.4.1 Pharmacodynamic Endpoints

Serum concentrations of CTX and P1NP will be assessed at the time points specified in the Schedule of Events (Table 13-1).

The following PD parameters will be estimated for sCTX using noncompartmental methods, actual sampling times, and absolute (unadjusted) sCTX concentrations, as appropriate:

C_{min}	the minimum concentration (which represents the maximum PD effect)
T_{min}	the time of occurrence of the minimum concentration
AUEC	the area under the effect curve, calculated using absolute data (without baseline-adjustment) using the linear trapezoidal rule

In addition, the following PD parameters will be estimated for sCTX using noncompartmental methods, actual sampling times, and percent reduction from baseline sCTX values, as appropriate:

I_{max}	maximum % inhibition
TI_{max}	the time of occurrence of maximum % inhibition
AUIC	the area under the % inhibition curve, calculated using percent reduction from baseline data and the linear trapezoidal rule

6.5 Immunogenicity Assessments

The immunogenicity of Bmab 1000 and Prolia will be assessed by ADA and NAb test in a validated immunoassay. Blood samples for immunogenicity assessments will be collected at the time points specified in the Schedule of Events (Table 13-1). Additionally, the blood samples for method validation will also be collected on Day 1 (pre-dose).

If the blood sample is unable to be analyzed or is missing at certain time point, some blood samples collected for PK or PD assessments at the same time point can be used for immunogenicity assessment after discussion and agreement from the sponsor.

Blood samples for immunogenicity for patients with immune-related AEs will be obtained on onset date (within 24 hours after study treatment administration) of immune-related AEs (eg, rash, pruritus), if possible, or blood sample can be used if it was obtained at the same date of study treatment administration.

Analysis will be performed at the central laboratory.

Further details about immunogenicity blood sampling collection, storage, and sample processing specification are provided in the laboratory manual.

7 Statistical Considerations

The statistical analysis will be performed using SAS software Version 9.4 or later, with PD parameters estimated using Phoenix WinNonlin software Version 8.0 or later. The statistical methods for this study will be described in a detailed SAP, which will be finalized and signed off before database lock. Changes from analyses planned in the protocol will be documented in the statistical analysis plan.

7.1 Estimands and Intercurrent Events

7.1.1 Intercurrent Events

The following intercurrent events are relevant in the treatment of postmenopausal women with osteoporosis by SC injection of study treatment (Bmab 1000 and Prolia) every 6 months:

Table 7-1 Intercurrent Event Types

Label	Intercurrent Event Type
ICE1 (Discontinue - related)	Treatment discontinuation for reasons related to study treatment (tolerability) or worsening of osteoporosis (lack of efficacy) (see Section 4.2.1 for further details)
ICE2 (Discontinue - unrelated)	Treatment discontinuation for unrelated reasons (as detailed in Section 4.2.1) such as logistical issues or other emerging conditions which require treatment
ICE3 (Dosing deviation)	Missing a dose or error in delivering dose (note this treatment is administered with SC denosumab injections every 6 months)
ICE4 (Death)	Death due to any cause in this elderly population
ICE5 (Medications affecting bones)	Administration of alternative osteoporosis medications or medications affecting bone health (except vitamin D and calcium supplements considered separately in ICE6)
ICE6 (Supplements)	Adjustments to vitamin D or calcium supplements
ICE7 (ADAs)	Formation of ADAs

Abbreviations: ADA, anti-drug antibody; ICE, intercurrent event; SC, subcutaneous

In addition, food and intense physical activity can impact sCTX and the sample for this endpoint should be collected after 8 hours of fasting and no intense physical activity in the 48-hour period prior to sample collection.

7.1.2 Estimands

Table 7-2 presents the key estimands most important to regulatory decision making with rationale for strategies to address intercurrent events.

Table 7-2 Key Estimands with Rationale for Strategies to Address Intercurrent Events

	Estimand 1a-EMA (Co-primary: Efficacy)	Estimand 1a-US FDA (Efficacy)	Estimand 1b-EMA (Co-primary: PD)
Estimand Description (attributes specified in detail below)	Difference in means (Bmab 1000 – Prolia) in % change from baseline in lumbar spine BMD by DXA after 52 weeks in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements.	Difference in means (Bmab 1000 – Prolia) in composite endpoint of % change from baseline in lumbar spine BMD by DXA after 52 weeks (where % change from baseline of zero is taken for anyone who dies) in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any other osteoporosis medications are taken.	Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women[a] with osteoporosis treated with a SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements.

	Estimand 1a-EMA (Co-primary: Efficacy)	Estimand 1a-US FDA (Efficacy)	Estimand 1b-EMA (Co-primary: PD)
Treatment Conditions of Interest	Two doses of Bmab 1000 versus Prolia (without receipt of any other medications affecting bones except for vitamin D and calcium supplements)	Up to two doses of Bmab 1000 versus Prolia (irrespective of any other medications)	One dose of Bmab 1000 versus Prolia (without receipt of any other medications affecting bones except for vitamin D and calcium supplements)
Target Population	Postmenopausal women with osteoporosis		
Endpoint	Percentage change from baseline at Week 52 in lumbar spine BMD by DXA	Composite endpoint of percentage change from baseline at Week 52 in lumbar spine BMD by DXA (and taking a value of zero for someone who dies)	AUEC calculated using absolute sCTX data (without baseline-adjustment) and actual sampling times using the linear trapezoidal rule to Week 26. Samples should be collected after 8 hours of fasting and no intense physical activity in 48-hour period prior to PD sample collection.
Population Level Summary	Difference between treatments in population mean % change from baseline BMD at Week 52 (Bmab 1000 / Prolia)		Ratio of geometric means (Bmab 1000/Prolia)
ICEs and Strategies to Handle ICEs			
ICE1 (Discontinue - related)	Hypothetical	Treatment policy	Not applicable (endpoint is measured before the second dose)
ICE2 (Discontinue - unrelated)	Hypothetical	Treatment policy	Not applicable (endpoint is measured before the second dose)
ICE3 (Dosing deviation)	Hypothetical	Treatment policy	Hypothetical
ICE4 (Death)	Hypothetical	Composite	Hypothetical
ICE5 (Medications affecting bones)	Hypothetical	Treatment policy	Hypothetical
ICE6 (Supplements)	Treatment policy	Treatment policy	Treatment policy
ICE7 (ADAs)	Treatment policy	Treatment policy	Treatment policy

	Estimand 1a-EMA (Co-primary: Efficacy)	Estimand 1a-US FDA (Efficacy)	Estimand 1b-EMA (Co-primary: PD)
Rationale of Strategies to Handle ICEs	Estimand 1a-EMA (Co-primary) utilizes a mostly hypothetical approach and so is sensitive to pick up differences between treatments which will enable to demonstrate equivalence. The hypothetical strategy requires statistical modeling to estimate the difference that might exist in the scenario that those ICEs do not occur.	Estimand 1a-US FDA using a treatment policy strategy which targets the comparative effectiveness close to a real-world setting. This requires follow-up of patients to measure BMD at Week 52 irrespective of whether they have taken other osteoporosis medication or whether they discontinued treatment for any reason.	Estimand 1b-EMA (Co-primary PD) utilizes a mostly hypothetical approach and so is sensitive to pick up differences between treatments. The hypothetical strategy requires statistical modeling to estimate the difference that might exist in the scenario that those ICEs do not occur.
	It is anticipated that the occurrence of each ICE will be balanced between groups since the biosimilar treatment, Bmab 1000, should have similar properties to Prolia. It should be noted that Prolia has a good safety profile, and it is anticipated that <1% of patients will have tolerability issues or death during the year after the first dose. Note: The formation of ADAs against Prolia in the first year of treatment is not particularly common (<1%) and thus this ICE has not been specifically mentioned in the estimand description and will be ignored in estimation approaches.		

Abbreviations: ADA, anti-drug antibody; AUEC, area under the effect curve; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICE, intercurrent event; PD, pharmacodynamic; sCTX, serum C-terminal telopeptide of Type 1 collagen

Note: The screening BMD assessment will be taken as the baseline BMD assessment

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

7.1.2.1 Choice of Primary and Key Secondary Estimands

The three estimands described above (Table 7-2) are as per the recommendations from regulatory agencies.

Estimand 1a-US FDA, using a treatment policy strategy (targeting the comparative effectiveness close to a real-world setting), will be considered as primary in the submission to the US FDA but key secondary for other submissions.

In addition, EMA required addition of the Co-primary Estimand 1b-EMA (Co-primary PD). Thus, submissions will be tailored as follows with Estimand 1a-US FDA considered the primary estimand for US FDA submission and Co-primary Efficacy and PD estimands for EMA.

Estimand	US FDA	EMA
Estimand 1a-EMA (Co-primary Efficacy)	Key secondary	Co-primary
Estimand 1a-US FDA (Efficacy)	Primary	Key secondary
Estimand 1b-EMA (Co-primary PD)	Key secondary	Co-primary

7.2 Statistical Hypothesis

The statistical hypothesis associated with the difference in treatments for the primary efficacy analysis of % change from baseline in lumbar spine BMD by DXA at Week 52 is:

H_0: ($\mu_{\text{Bmab 1000}} - \mu_{\text{Prolia}} \leq -1.45\%$) or ($\mu_{\text{Bmab 1000}} - \mu_{\text{Prolia}} \geq +1.45\%$)

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

where $\mu_{\text{Bmab 1000}}$ 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.

The statistical hypothesis associated with the difference in treatments for the analysis of sCTX AUEC (from Day 1 to Day 183) is:

H_0: ($\gamma_{Bmab\ 1000}/\gamma_{Prolia} \leq 0.80$) or ($\gamma_{Bmab\ 1000}/\gamma_{Prolia} \geq 1.25$)

H_1: $0.80 < \gamma_{Bmab\ 1000}/\gamma_{Prolia} < 1.25$

where $\gamma_{Bmab\ 1000}$ and γ_{Prolia} denotes the true geometric mean sCTX AUEC for Bmab 1000 and Prolia, respectively.

7.3 Sample Size Determination

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

Equivalence will be established if the 95% CI of the difference (T-R) in mean percent change in lumbar spine BMD from baseline at Week 52 is within equivalence margin of (±1.45%). Equivalence margin is derived from meta-analysis of previous similar studies (Bone *et al.*, 2008, Cummings *et al*., 2009, McClung *et al.*, 2006) which gave the pooled denosumab treatment effect [redacted] Based on the lower bound of the 95% CI, a 1.45% margin will preserve 70% of the treatment effect [redacted] Assuming that the treatments are equally effective and that the common SD for percent change from baseline in lumbar spine BMD at Week 52 is 4.5, a sample size of 204 patients per treatment group (total 408 patients) ensures a power of minimum 80% with 2.5% level of significance. Considering a dropout of 15%, the total sample size required is 480 patients (240 per treatment group). Note that the US FDA require a 90% CI to establish equivalence which provides more power for this sample size (this will be reflected in the efficacy analyses).

Since sCTX is also a key endpoint (considered Co-primary by EMA), the power of 95% CI falling within standard equivalence limits of 80.00%-125.00% will be considered. Thus, if Bmab 1000 achieves a true inhibition level in the region of 85% (as expected), giving rise to sCTX levels around 15% of baseline, meeting these limits would equate to 80%-125% of 15% (ie, 12% to 18.75%), which would give confidence that Bmab 1000 preserves much of the Prolia inhibition rate and, on average, achieves 81.25% to 88% inhibition over a 6-month period. The current sample size has high power for the sCTX AUEC endpoint; 204 evaluable patients/group with a margin of 80%-125% and between-patient CV of 45% would give

>95% power to demonstrate similarity for the sCTX endpoint (using 95% CI equivalent to 2 one-sided tests at 2.5% level).

7.4 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Similar analysis set will be defined in the SAP for the transition phase.

7.4.1 Full Analysis Set

The FAS will consist of all randomized patients who meet the eligibility criteria and receive at least one dose of study treatment. Patients from the FAS will be analyzed under the treatment as randomized. This will be used as the analysis dataset for estimation of Estimand 1a-US FDA (Efficacy).

7.4.1.1 Modified Full Analysis Set

The term mFAS will be used to define the analysis data set which includes a data record at each time point for all patients in the FAS but excludes data observed after the first occurrence of those intercurrent events where a hypothetical strategy is taken (eg, missing a dose, errors or deviations in dosing, or receipt of any other osteoporosis medication or medication affecting bone health). Data in the mFAS will be analyzed under the treatment as randomized and used as the primary analysis data set for estimation of Estimand 1a-EMA (Co-primary Efficacy) and Estimand 1b-EMA (Co-primary PD) and other efficacy, and PK analyses. For PD, data points within 8 hours of food-intake or 48-hours of intense physical activity will not be used.

7.4.2 Safety Analysis Set

The SAF will consist of all randomized patients who received at least one administration of study treatment. The SAF will be used for all safety and immunogenicity analyses. In the SAF, patients will be analyzed per the actual treatment received.

7.5 Description of Subgroups to Be Analyzed

The following subgroups will be explored for both (co-)primary endpoints:

- Geographical region (US, Europe)

- Prior use of bisphosphonate treatment (Yes, No)
- Age (<65, ≥65 years)
- Selected baseline characteristics

Further details will be provided in the statistical analysis plan.

7.6 Statistical Analysis Methodology

Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan and will be finalized and signed off before database lock.

The majority of the CIs presented will be 95% (two-sided) CIs. For the primary efficacy and PD endpoints (for the EMA), equivalence is demonstrated if both the 95% CIs fall entirely within predefined margins; this approach is equivalent to two one-sided tests at the 2.5% significance level for each endpoint. For the primary efficacy for the US FDA, equivalence is demonstrated if the 90% CI falls entirely within predefined margins; this approach is equivalent to two one-sided tests at the 5% significance level.

7.6.1 General Considerations

Data collected in this study will be presented using summary tables, patient data listings and figures. For ordinal-scaled variables, a combination of presentations may be employed as appropriate: frequency and percentage of observations within a category and means and SDs of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on the N of the patient level analysis set (FAS or SAF) and number of patients with missing data will also be included.

After the transition is complete, 2 sets of descriptive statistics will be presented to explore:

1) The single transition from Prolia to Bmab 1000 compared to continuing on Prolia focusing on the transition period from Week 52 to Week 78

2) Data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout.

7.6.2 Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

Table 7-3 presents a summary of statistical methods including sensitivity analyses.

Table 7-3 Summary of Statistical Methods, Including Sensitivity Analyses

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1a-EMA (Co-primary Efficacy)	Difference in means (Bmab 1000 – Prolia) in % change from baseline in lumbar spine BMD by DXA after 52 weeks in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months assuming that all women receive 2 doses without any errors or deviations in dosing and without receipt of any other medications affecting bones except for vitamin D and calcium supplements.	mFAS	mFAS removes data occurring after ICEs for which the hypothetical strategy is used (keeping all patients in the FAS). For sensitivity [i], MI under MAR [ii] delta applied to imputation in the tipping point approach	MMRM of % change from baseline in BMD at Weeks 26 and 52 including terms for randomization strata, visit by treatment, baseline BMD (as a covariate). The estimated mean difference in % change from baseline in BMD will be presented with 95% CI at each time point, and the result at Week 52 compared to margins of [–1.45, 1.45].	[i] MI under MAR approach will be applied to the mFAS (see Section 7.6.3.5 for details). % change from baseline BMD at timepoints up to Week 52 from each multiply imputed data set will be analyzed by ANCOVA and results pooled using Rubin's method. [ii] MI under MAR will be used to impute missing data where a penalty will be added to the imputed % change from baseline values. This will be a delta for Bmab 1000, of –1.45 and 1.45 (see Section 7.6.3.5.1 for further details). **[iii] Supplementary:** MMRM analysis of log-transformed data (see Section 7.6.3.7).

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1a-US FDA (Efficacy)	Difference in means (Bmab 1000 - Prolia) in composite endpoint of % change from baseline in lumbar spine BMD by DXA after 52 weeks (where % change from baseline of zero is taken for anyone who dies) in postmenopausal women[a] with osteoporosis treated with SC injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any other osteoporosis medications are taken.	FAS	The composite endpoint defines % change from baseline of zero for anyone who dies. Observed data analyzed without any imputation or removal of data points	Missing data imputed under MI MAR approach (Section 7.6.3.5) and penalties added to reflect non-inferiority and non-superiority nulls (Section 7.6.3.1). ANCOVA of % change from baseline in BMD at Weeks 26 and 52 and including terms for randomization strata, treatment, baseline BMD (as a covariate). Results pooled using Rubin's method and two one-sided tests. The estimated mean difference in % change from baseline in BMD will be presented with 90% CI for each delta.	Not required since sensitivity included in other estimands that are explored.

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1b-EMA (Co-primary: PD)	Ratio of geometric means (Bmab 1000/Prolia) in AUEC in sCTX up to 26 weeks in postmenopausal women[a] with osteoporosis treated with a SC injection without any dosing error and no receipt of any other medications affecting bones except for vitamin D and calcium supplements.	mFAS	No imputation will be performed	Log-transformed AUEC will be analyzed using an ANCOVA model with baseline log sCTX and baseline eGFR as covariates and treatment group and stratification factors as fixed effects	sCTX AUEC will be transformed to standardize the AUEC by the number of days (ie, divided by 183-1=182), then divided by baseline sCTX prior to log transformation. ANCOVA analysis will give the same 95% CI for geometric mean ratio as the primary analysis, but the geometric means can be transformed to represent a % inhibition scale. **Supplementary**: A MMRM analysis will be performed to estimate the mean % reduction (interpreted as % inhibition) of each treatment and mean difference at each time point with 95% CI. In addition, this same model will be used to estimate the overall % inhibition to 6 months for each treatment group and the mean difference with 95% CI.

Abbreviations: ANCOVA, analysis of covariance; AUEC, area under the effect curve; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; FAS, full analysis set; ICE, intercurrent event; mFAS, modified full analysis set; MAR, missing at random; MI, multiple imputation; MMRM, mixed model for repeated measures; PD, pharmacodynamic; sCTX, serum carboxy-terminal cross-linking telopeptide of Type 1 collagen; SC, subcutaneous

Note: The screening BMD assessment will be taken as the baseline BMD assessment.

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

7.6.3 Analysis of Primary Efficacy Endpoints

7.6.3.1 Main Estimation of Estimand 1a-US FDA (Efficacy)

In order to estimate Estimand 1a-US FDA, an ANCOVA model will be fitted to the composite percent change from baseline in lumbar spine BMD at Week 52 on FAS multiply imputed data sets including terms for randomization strata, treatment, and baseline BMD included as a continuous covariate. Rubin's method will be used to pool results.

Multiple imputation will be used to produce 30 multiply imputed data sets so that any missing BMD data at Week 52 are imputed under MAR, by treatment (see Section 7.6.3.5). A penalty (delta of –1.45 and 1.45) will be applied to imputed values for the BMab 1000 group reflecting the noninferiority and non-superiority null hypotheses (H0) respectively and two separate one-sided tests at alpha=0.05 conducted (Tests 1 and 2 below, respectively):

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

$H0: \mu_{BMab\ 1000} - \mu_{Prolia} \leq -1.45\%$

$H1: -1.45\% < \mu_{BMab\ 1000} - \mu_{Prolia}$

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

$H0: \mu_{BMab\ 1000} - \mu_{Prolia} \geq +1.45\%$

$H1: \mu_{BMab\ 1000} - \mu_{Prolia} < +1.45\%$

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. The estimated mean difference in percent change from baseline in lumbar spine BMD will be presented with 90% CI for each delta. The two one-sided tests of alpha=0.05 are equivalent to showing that each 90% CI falls within predefined equivalence margins of [–1.45%, 1.45%]. If these criteria are met, equivalence will be concluded for the US FDA submission.

7.6.3.2 Main Estimation of Estimand 1a-EMA (Co-primary Efficacy)

For the primary efficacy analysis, an MMRM will be fitted to the % change from baseline in lumbar spine BMD at Week 26 and Week 52 on the mFAS. The MMRM will include terms for randomization strata, visit by treatment, and baseline BMD included as a continuous covariate. The repeated measures on patients will be modeled with an unstructured covariance structure.

The estimated mean difference in % change from baseline in lumbar spine BMD will be presented with 95% CI at each time point.

If at Week 52, the 95% CI falls within predefined equivalence margins of [–1.45%, 1.45%], equivalence will be concluded for the EMA submission.

Note: The main analysis method is on the mFAS and therefore does not use data after any dosing errors, treatment discontinuation or receipt of any other medications affecting bone health (except for supplements).

7.6.3.3 Main Estimation of Estimand 1b-EMA (Co-primary PD)

Comparability of sCTX levels between Bmab 1000 and Prolia will be assessed by fitting an ANCOVA to AUEC data on a log scale (mFAS) to give the ratio of geometric means with 95% CI. Logged pre-dose sCTX concentrations will be fitted as a covariate since baseline-adjustment is not included in the AUEC calculation, baseline eGFR will be included as a covariate since renal function is known to affect sCTX levels, and treatment group and all stratification factors will be fitted as fixed effects. Comparability between Bmab 1000 and Prolia will be concluded if the 95% CI around the geometric mean ratios for AUEC lie entirely within 80.00% - 125.00%.

7.6.3.4 Sensitivity Analysis for Estimand 1a-EMA (Co-primary Efficacy)

A sensitivity approach will be performed the mFAS (targeting Estimand 1a-EMA) in a similar approach using penalties to the main analysis on FAS (targeting Estimand 1a-US FDA):

Multiply imputed data sets will be produced on mFAS under MAR as explained in Section 7.6.3.5. The percent change from baseline in lumbar spine BMD will be calculated

as a post processing step from BMD values and analyzed by ANCOVA. Results will be pooled using Rubin's method.

In addition, the robustness of the results in both of the one-sided hypotheses will be assessed by adding penalties (delta of –1.45 and 1.45) to all imputed values in the BMab 1000 group (Section 7.6.3.5.1).

7.6.3.5 Multiple Imputation Model Under Missing at Random

Multiple imputation will be used to produce 30 multiply imputed data sets so that any missing BMD data at Week 26 or Week 52 are imputed under MAR, by treatment. This approach will be applied to mFAS (for sensitivity aligned to Estimand 1a-EMA, excluding data after relevant intercurrent events and treating it as missing) and also to FAS (for the main estimation of Estimand 1a-US FDA).

The MI approach will comprise of 2 steps by analysis set and treatment group:

1. Any intermittent missing data at Week 26 (eg, where Week 0 and Week 52 data are available) will be imputed using a Markov Chain Monte Carlo approach, using the impute = monotone option in SAS Version 9.4 (or higher) PROC MI.

2. A single imputation will be performed on each of the 30 multiply imputed data sets from Step 1. This step will use a monotone regression approach.

The MI model will include continuous terms for age, body mass index, BMD at Week 0, Week 26 and Week 52, total number of doses received.

Full details of the MI models will be provided in the statistical analysis plan.

7.6.3.5.1 Penalties for Non-Inferiority and Non-Superiority

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

A penalty will be added to the Week 52 imputed percent change from baseline in lumbar spine BMD values (but not to data observed) for the Bmab 1000 group only. Note this

applies to missing data and to data removed as irrelevant for the hypothetical Estimand 1a-EMA. It will consider delta of –1.45 and 1.45 representing values under the non-superiority null and non-inferiority null, respectively. ANCOVA is performed for each multiply imputed dataset at each delta level and then the result will be pooled using Rubin's method.

Note: That both positive and negative values of delta are tested in order to stress test whether the 90% CI and 95% CI for the mean difference in percent change meets each of the lower and upper bounds of the equivalence margins of [–1.45, 1.45].

Further exploratory analysis may be described in the SAP to investigate a penalty applied only where treatment (ie, 2nd dose) was discontinued for related reasons or other alternative medications received.

7.6.3.6 Sensitivity and Supplementary Analyses of Estimand 1b-EMA (Co-primary PD)

Sensitivity: sCTX AUEC will be transformed to standardize the AUEC by the number of days (ie, divided by 183-1=182), then divided by baseline sCTX. In doing so, a resulting value of 0.15 would indicate an overall 85% reduction from baseline (ie, 85% inhibition), hence an ANCOVA analysis of log-transformed value (adjusted for time and baseline) will give the same 95% CI for geometric mean ratio as the primary analysis, but the geometric means can be transformed [100 × (1-ratio)] to represent a percent inhibition scale.

Supplementary: An MMRM analysis using all relevant unlogged percent reduction sCTX data will be performed to estimate the mean percent reduction (interpreted as percent inhibition) of each treatment and mean difference at each time point with 95% CI. The model will include baseline sCTX and treatment by time point interaction and allow for variability to be different at each time point. In addition, this same model will be used to estimate the overall % inhibition to 6 months for each treatment group and the mean difference with 95% CI. Specifically, AUEC is a weighted mean percent inhibition; if we assume nominal sampling days of 1, 3, 15, 29, 85, 141, 162 and 183 then the weights (based on linear trapezoidal rule) would be 1, 7, 13, 35, 56, 38.5, 21 and 10.5, respectively, with divisor of 182 to standardize by overall time (calculated using ESTIMATE statement in PROC MIXED in SAS).

A sensitivity analysis using LOCF will be performed as requested by PMDA.

7.6.3.7 Supplementary Analysis for Estimand 1a-EMA (Co-primary Efficacy)

In order to investigate assumptions of normality, the log-transformed BMD as a ratio of baseline will be analyzed in a similar MMRM model to the main analysis but with baseline covariate as the log BMD (using the mFAS). The least squares mean and difference will be back-transformed to present geometric mean ratios of baseline, and 95% CI for the ratio of geometric means (Bmab 1000/Prolia). Residual plots will be produced and compared to the main analysis.

7.6.4 Analysis of Secondary Efficacy Endpoints

7.6.4.1 Secondary BMD Endpoints

An MMRM as per the main estimation of Estimand 1a-EMA (Co-primary Efficacy) (see Section 7.6.3.2) will be used to estimate the mean percent change from baseline and difference between treatments for the mFAS in:

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

Similarly, ANCOVA on composite endpoint of percent change from baseline for FAS as per main estimation of Estimand 1a-US FDA (Efficacy) will be performed (see Section 7.6.3.1) but without the penalty being applied.

7.6.4.2 Analyses of BMD After Transition

BMD percentage change from baseline and percentage change at Week 78 from Week 52 will be summarized by treatment for lumbar spine, hip, and femoral neck BMD by DXA.

Statistical analyses to present 95% CIs will be performed on Week 78 lumbar spine BMD in 2 separate analyses which will be considering either original baseline or Week 52 baseline as a covariate. Further details will be given in SAP.

7.6.4.3 Summary of Fractures

Any incidence of fractures up to and including Week 52 and from Week 52 to Week 78 will be summarized with descriptive statistics.

7.6.5 Analyses of Secondary Pharmacodynamic Endpoints

Serum C-terminal telopeptide of Type 1 collagen and P1NP concentrations will be listed, summarized with descriptive statistics by treatment and visit, and presented graphically, as appropriate.

C_{min} for sCTX will be analyzed in a similar manner to sCTX AUEC (see Section 7.6.3.3) as a secondary PD endpoint on mFAS. In addition, PD parameters estimated for sCTX using change from baseline observations (ie, I_{max} and AUIC) will be analyzed in a similar manner to sCTX AUEC (see Section 7.6.3.3) as additional secondary PD endpoints on mFAS.

Following the transition period, serum concentrations of CTX and P1NP at Week 78 will be summarized for those transitioning to Bmab 1000 and those continuing on Bmab 1000, compared to those continuing on Prolia.

7.6.6 Analyses of Secondary Pharmacokinetic Endpoints

Serum denosumab concentrations will be listed and summarized with descriptive statistics at each visit. Pharmacokinetic parameter estimation and formal statistical analyses of PK data are not planned in this study; however, population PK and/or PK/PD modeling may be performed and reported separately from the main clinical study report, if deemed necessary.

Following the transition period, serum concentrations up to Week 78 will be summarized.

7.6.7 Analyses of Secondary Immunogenicity Endpoints

Incidence and titer of anti-drug antibody, incidence of neutralizing antibody up to Week 52 will be summarized by treatment and timepoints as shown in the Schedule of Events (Table 13-1).

Similar summaries will be presented for the transition period, split by Week 52 serostatus, to compare the transition to Bmab 1000 against continuing on Prolia.

7.6.8 Safety Analyses

7.6.8.1 Adverse Events

Treatment-emergent adverse events and serious adverse events recorded during the study will be summarized by system organ class, preferred term, and treatment, and will include the total number of events with number and percentage of patients with AEs. Adverse events and medical history will be coded using the most current version of MedDRA.

Summaries of the number and percentage of patients (and number and percentage of events) for study treatment-related AEs, SAEs, AEs with an outcome of death, and AEs leading to discontinuation of the study treatment will be provided by treatment.

Incidence and grade of AESI including treatment-related hypersensitivity/allergic reaction, serious infections, hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, and dermatologic reactions from baseline (Day 1) through the EoS will be summarized by treatment group.

7.6.8.2 Clinical Laboratory Assessments

Clinical safety laboratory data will be summarized descriptively by treatment and scheduled visits. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by treatment. Summaries of safety laboratory parameters will include the first meaningful measurement of each scheduled assessment, but repeat assessments done at the same study time point will not be included in summary calculations (unless performed to provide missing data). Laboratory data will also be listed by treatment, patient, and visit. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values will be generated. Shift tables by treatment will be provided when appropriate.

7.6.8.3 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and body temperature will be summarized by treatment at baseline and at each scheduled visit. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of change from baseline for each parameter by treatment.

7.6.8.4 Physical Examination

Abnormal physical examination findings that suggest a clinically significant worsening will be reported as adverse events and the number and percentage of patients with normal or abnormal results will be presented at scheduled visits by treatment. Clinically significant findings noted prior to signing of ICF will be recorded as medical history and the number and percentage of patients with clinically significant findings will be presented by treatment.

7.6.8.5 Electrocardiograms

The number and percentage of patients with normal or abnormal or abnormal and clinically significant results will be presented at scheduled visits by treatment. Descriptive statistics for continuous variables will be provided at scheduled visits together with a summary of changes from baseline for each parameter by treatment.

The ECG data will also be presented in listings by patient and summarized by collection date and time.

7.6.8.6 Transition Safety

Safety following the third dose at Week 52 and up to and including Week 78 will be summarized in order to assess any risk of transition to Bmab 1000 versus continuing on Prolia. Additional safety data captured in the transition period for the group that receives Bmab 1000 throughout will also be summarized.

Therefore, following completion of the transition period, summaries will be produced for incidence of TEAEs, deaths, and SAEs from the third dose to Week 78, and incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG, and vital signs will also be summarized for the same period.

7.6.9 Other Analyses

The occurrence and time to intercurrent events will be considered and compared for the treatment groups.

7.6.9.1 Demographic and Baseline Disease Characteristics

If permitted by local regulation, the following demographic data will be summarized: age (in years, at the time of signing the ICF), race, ethnicity, height, weight, and body mass index.

Demographics and baseline disease characteristics will be summarized descriptively by treatment.

Patient disposition will be summarized by treatment, including the reasons for discontinuation. The number of patients in each analysis set will be displayed by treatment.

7.6.9.2 Medical History

Medical history will be coded according to the latest version of MedDRA and will be summarized by system organ class and preferred term.

7.6.9.3 Study Treatment Exposure

Study treatment administrations will be summarized and listed by treatment in the main period and transition.

7.6.9.4 Prior and Concomitant Medications

The number and percentage of patients with prior and concomitant medications will be tabulated by ATC Classification System of WHO drug, preferred term, and treatment. A medication’s usage will be considered concomitant if it was started or continued after administration of the study medication. If the start date is missing, it will be assumed that the medication was used concomitantly. Details on handling partial dates (ie, year or only year and month) will be described in the statistical analysis plan.

7.6.9.5 Vitamin D and Calcium Accountability

Vitamin D and calcium use will be summarized and listed by treatment.

7.6.10 Protocol Deviations

Protocol deviations will be summarized and listed. A separate listing for COVID-19 related protocol deviations will be prepared.

7.7 Handling of Missing Data

The extent of missing data and study withdrawal will be assessed via risk-based monitoring. Study procedures will be in place to minimize missing data for the primary endpoints; for example, patients who wish to withdraw from study treatment or take another osteoporosis medication will still be encouraged to attend Week 52 visit (Section 4.2.1).

The MMRM for Estimand 1a-EMA (Section 7.6.3.2) assume any missing data are MAR and the robustness of this assumption explored in sensitivity analyses (Section 7.6.3.4). Reasons for discontinuation of treatment will be collected as far as possible so that sensitivity analysis can take account of reasons related to treatment or osteoporosis differently to those unrelated.

In addition, ANCOVA analyses will be applied to multiply imputed data sets where imputed values for the Bmab 1000 group, will be penalized by -1.45 (representing the non-inferiority null) for testing whether it is non-inferior to Prolia and penalized by 1.45 (representing the non-superiority null) for testing whether it is non-superior to Prolia (see Sections 7.6.3.1 and 7.6.3.5.1).

Where a hypothetical strategy is taken in the estimand, data will be excluded after the first occurrence of intercurrent event (eg, dosing error, or receipt of any other osteoporosis medication for Estimand 1a-EMA and Estimand 1b-EMA) and treated as missing.

If a different approach is required for handling missing data due to COVID-19 or other issues, it will be documented in the statistical analysis plan prior to unblinding.

7.8 Interim Analyses

No formal interim analyses of efficacy data are planned for this study.

There will be 2 main analysis points after each study period is complete:

- Double-blind active-controlled period: Analyses include data after all patients have received the Week 52 assessments (prior to the third administration of study treatment) or have terminated the study before Week 52. Analyses in the clinical study report will include all data up to and including the Week 52 visit.

- Transition period: Analyses up to transition period Week 78 will be reported in a Clinical Study Addendum after all patients have completed all final assessments and the complete database is locked.

An unblinding plan will give full details of who will be unblinded at Week 52 and how the flow of information is going to be handled.

7.9 Independent Safety Review Committee

An ISRC (see Section 3.1.1) will be appointed for this study. Further details will be provided in the ISRC Charter.

8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (eg, CRO).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diary cards, laboratory reports, ECG strips, etc.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter patient data into eCRF. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable sponsor’s standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using WHO Drug.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before patients participate in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Patient Information and Consent

A written informed consent in compliance with all applicable regulatory requirements, ICH GCP, and ethical principles that have their origin in Declaration of Helsinki shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. If applicable, an informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for

review and approval before the start of the study. If the ICF is revised during the course of the study, all active patients must be reconsented by signing the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF. The authorized person obtaining the informed consent also signs the ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Patient medical records need to state that written informed consent was obtained.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the IRB/IEC, or other applicable regulatory agencies.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Data Protection

All personal data collected related to patients, investigators, or any person involved in the study, which may be included in the sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

10.3 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to

promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

10.4 Investigator Documentation

Prior to the beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR by providing all essential documents.

10.5 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins, as per local requirements.

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment (Bmab 1000). These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.9 Publications and Results Disclosures

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The study administrative structure will include sponsor representatives, CRO, third-party vendors, laboratories, and other personnel as per the requirements of the study.

11.1 Monitoring

11.1.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit. Site monitoring is conducted to ensure that the rights of patients are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on the sponsor or designee standards, ICH E6, and all applicable, regulatory guidelines.

11.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by

the sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC and to the regulatory authorities where required, along with any applicable changes to the ICF, for approval before patients can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the patient or impacts the integrity of study data.

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of study conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training may also be performed throughout the study during routine site monitoring activities.

11.3 Study or Study Site Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The sponsor may suspend or stop the study at specific study sites due to (but not limited to) failure of the investigator to enroll patients into the study at an acceptable rate, failure of the investigator to comply with regulatory authority or ICH guidelines, or submission of knowingly false information.

The study can be paused/ continued/modified by the ISRC, based on the review of safety data (Refer Section 3.1.1 for details).

The EoS is defined as the date on which the last patient completes the last visit (includes follow-up visit).

If the study is prematurely terminated or suspended, the sponsor or investigator shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

11.4 Clinical Study Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the final data are summarized and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports. The primary CSR will be based on data up to Week 52 (with option of including transition period data if needed), this will be followed by the transition period CSR with applicable data (up to Week 78).

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results without giving individual patient level data.

Upon completion of the final report, the sponsor will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers, as per local requirements.

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13Appendices

13.1 Appendix: Schedule of Events

Table 13-1 Schedule of Events

	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.

13.2 Risk Assessment and Mitigation Plan due to COVID-19

The novel SARS-CoV-2 was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as COVID-19. On 11 March 2020, the WHO declared the SARS-CoV-2 infection outbreak a global pandemic and to date more than 5 million deaths have been reported globally (World Health Organization COVID-19 Dashboard 2021).

Due to the global impact of the COVID-19 pandemic, the sponsor is taking proactive measures to guarantee that all site staff and patients involved in the trial are secure and the patients remain in the study until their last visit, with continuation of treatment during the study period.

During COVID-19 pandemic, any potential measures or changes will be handled according to the local regulations. If the COVID-19 pandemic wanes off, there is no need to amend the protocol in terms of any specific information relating to COVID-19, including if some tests/procedures are not required anymore.

Benefit and Risk Assessment on Study Population

Considering the most common symptoms of COVID-19 are fever, dry cough, and tiredness (World Health Organization Q&A on COVID-19) and the irrelevance between cause of COVID-19 and osteoporosis disease itself, osteoporosis symptoms and disease itself have a low chance to deteriorate directly due to COVID-19. Furthermore, no high risk was seen for COVID-19 complications in women older than 50 years for postmenopausal or aromatase inhibitor-induced osteoporosis, and the patients are recommended to maintain the denosumab treatment for the management of osteoporosis during the COVID-19 outbreak (Gittoes *et al.*, 2020). However, the irrelevance cannot be concluded since no studies have been conducted and there were a few research studies reporting the increased risk for respiratory infections following denosumab treatment (Formenti *et al.*, 2020).

Moreover, it has yet to be concluded that calcium and vitamin D, which is a protocol defined co-administration, may have beneficial effects to treat COVID-19. To date, it has been shown that the patients with osteoporosis may be protected from SARS-CoV-2 by vitamin D independently of the pharmacologic antiosteoporotic treatments (Bilezikian *et al.*, 2020).

Basically, the quarantine of COVID-19 should be carried out based on the SOP of each site and local regulatory guidelines. Taking all these facts into consideration, the risks of COVID-19 infection for each patient are not expected to increase by participating in this study. Yet due to the possibility of increasing the safety risk by being involved in the study, a systematic risk assessment will be conducted during the study by the sponsor through a sufficient discussion with the investigators.

Mitigation Plans

Study Treatment Management

To cope better with the sudden imposition of movement restriction and/or increased shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient study treatment will be supplied to cover patient visits for longer periods. Inter-country study treatment transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, the sponsor will prepare site-to-site transfer of study treatment from nearby clinical sites in case an agile resupply is required (eg, more patients are enrolled at a site than anticipated but additional supplied study treatment is not sufficient to meet demand). Vitamin D and calcium supplements will also be supplied to patient's home.

Rescheduling of Visit and Study Treatment Administration Schedule of Patients

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. If the patient has had contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines. In the case of a patient who has contact with COVID-19 patient 14 days prior to screening and within the screening period up to randomization, the patient should not be enrolled in the study. If the patient has contact with COVID-19 patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.

Investigators will promptly notify the sponsor if any unfavorable situation has occurred in relation to local COVID-19 status (eg, site shut down, lock down of city, cohort isolation, etc.). For sites where the patients are unable to travel or use public transportation, the sponsor will support the patients with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can be proceeded at the earliest possible opportunity. Pre-approval is required for reimbursement.

The patients require face-to-face interactions for study treatment administration. Therefore, in the event patients cannot visit the study center on the scheduled day for injection, the treatment schedule will be adjusted following Section 5.7. However, if study treatment administration cannot be carried out within an allowed visit window or a missed dose is expected, whether to continue with the subsequent study treatment will be discussed with the sponsor, ensuring the compliance with the trial protocol to such an extent that an ongoing benefit-risk assessment for the clinical trial and patients is still possible.

Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The investigator will keep following up with patients regarding any safety issues (AEs, concomitant medication) by telephone call before the patients visit the site.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than under normal circumstances, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed.

COVID-19 Vaccine

The study indication, study treatment, and assessments are not expected to be impacted by vaccination. However, COVID-19 vaccine is prohibited within 14 days prior to and 14 days after study treatment administration on Day 1, Week 26, and Week 52.

DXA Scan and X-ray Assessments

For BMD assessment, only validated bone densitometers will be allowed during the study, and the same DXA instrument shall be used for all study procedures for each patient during the study. However, in COVID-19 pandemic situation, if the patients are restricted in their

ability to travel to the sites and/or the sites are locked down, the alternative imaging centers can be considered to acquire the DXA scans. The alternative center should follow the central imaging provider's guidance on selecting an appropriate replacement scanner and a phantom scanning process to quantify any calibration differences. All DXA scans will be submitted to and analyzed by the central imaging vendor.

For vertebral fractures, the lateral spine X-ray will be performed at time points specified in Schedule of Events (Table 13-1) and may be performed in the alternative imaging centers in COVID-19 pandemic situation (site shut down, lock down of city etc.). The lateral spine X-ray for vertebral fracture as well as copies of other diagnostic image and related source documents should be submitted to the central imaging vendor for confirmation of fracture. And, if X-ray is necessary to support the patient's medical care, the X-rays also could be read locally.

The nonvertebral fractures may be assessed by alternative imaging centers in COVID-19 pandemic situation. The information about new nonvertebral fractures (eg, details regarding the type of fracture and other pertinent data) and level of trauma causing the fracture will be recorded from the alternative centers. A copy of other diagnostic image and/or radiology report, surgical report, or discharge summary will also be included in the patient's individual source documents and should be submitted to the central imaging vendor for confirmation of fracture. For further details on the source documents for nonvertebral fractures, see Section 6.1.2.

Site Monitoring and Audit

In cases where a monitoring visit cannot be performed because of the prevailing COVID-19 situation, centralized monitoring will be performed by the sponsor and/or CRO as alternatives particularly if this acceptable by local regulations, for the sites where the first patient is randomized but the first monitoring visit is not performed. Manual data review on the eCRF will be performed and if any mistakes or deviations are observed, proper guidance will be provided to prevent them happening in the future. Sponsor and/or CRO will review the data entered in the eCRF continuously and ensure queries are raised and support the sites as necessary. If necessary, sponsor/CRO will create and review reports based on CRF data to check study progress for each patient as per protocol and perform management of sites in case of any noted deficiency.

Other potential measures will be taken to assure the safety and welfare of trial patients , maintaining compliance with GCP, and minimizing risks to trial integrity during the COVID-19 pandemic, such as implementation of decentralized clinical trial methodologies. Any potential measures or changes will be handled according to the regulations.

Audits are required to ensure quality assurance throughout the study period in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. In cases where an audit cannot be performed due to the COVID-19 pandemic situation, the sponsor will postpone audits or consider performing remote audits after careful consideration of the COVID-19 pandemic situation according to guidance on the management of clinical trials during the COVID-19 (coronavirus) Pandemic (European Medicines Agency 2021). Audits will be conducted only when permitted under national, local and/or organizational social distancing restrictions.

Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to centralized monitoring plan and risk based monitoring plan. After data collection, missing data on the primary efficacy analysis due to COVID-19 will be analyzed as specified in Section 7.7 with other missing cases.

13.3 Appendix: Protocol Amendment History

Amendment 1 (13-Apr-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Major changes from Original Protocol (06-Jan-2022) to Amendment 1 (13-Apr-2022) are summarized in the following table. Additional minor changes to the protocol and changes to the synopsis are not listed but were applied, as applicable. Minor editorial or formatting changes are not included in this summary table.

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, Protocol Amendment Summary of Changes, and Header	Updated the protocol version and date.	Reflect the new version and date.
Synopsis – Rationale Section 1.5 Study Rationale	Clarified that: For EMA, the PD endpoint AUEC of sCTX from baseline to 26 weeks is considered as Co-primary endpoint, while, for US FDA, this endpoint is considered as a key secondary endpoint.	To provide further clarity.
Throughout Section 2 and 7	Changes to estimand labels with EMA and US FDA descriptors to add clarity on the purpose of each: Estimands 1a, 2, and 1b changed to 1a-EMA (Co-primary Efficacy), 1a-US FDA (Efficacy), and 1b-EMA (Co-primary PD), respectively.	Regulatory feedback suggests that EMA and US FDA regulators are looking for different estimands as primary (or Co-primary).
Synopsis - Objectives and Estimands Section 2.1 Primary Objectives, Endpoints, and Estimands	Efficacy objective stated as primary for US FDA submission whilst efficacy and PD objectives are Co-primary for EMA. Furthermore, Estimand 1a-US FDA now uses the treatment policy strategy for discontinuation from treatment for **any reason.**	To address the US FDA recommendations to modify the primary estimand and clarify that only EMA require the Co-primary objectives.

Section # and Name	Description of Change	Brief Rationale
Synopsis - Study Design Section 3.1.1 Independent Safety Review Committee, and Section 7.9 - Independent Safety Review Committee	An Independent Safety Review Committee will be used for review of safety data to decide whether to pause/continue/modify the study.	To address the US FDA recommendation to specify safety findings that would require study termination.
Section 5.9 Intervention After the End of the Study or Treatment Discontinuation	Clarified that anti-resorptive therapy will be provided to patients after the end of study or treatment discontinuation.	To address the US FDA recommendation to provide anti-resorptive therapy upon end of study.
Synopsis - Safety Assessments Section 6.2.1.3 Reporting Adverse Events	Clarified that any fracture will be recorded as an AE/SAE/AESI (as applicable).	To address the US FDA recommendation to record any fracture that occurs during the study as an AE.
Section 6.2.1.5 PFS related Issues /Adverse Events	Added the details about the assessment and reporting of PFS related issues/AEs	To address the US FDA recommendation to include an assessment of PFS related AEs.
Synopsis - (Co-)primary Efficacy Endpoint, Secondary BMD Endpoints. Section 7.1.2 Estimands, Table 7-2 Key Estimands with Rationale for Strategies to Address Intercurrent Events, Section 7.1.2.1 Choice of Primary and Key Secondary Estimands, Synopsis Sample Size, Section 7.3 Sample Size Determination	Clarified what would be considered as primary, Co-primary or secondary estimands for US FDA and EMA submissions. Furthermore, Estimand 1a-US FDA now uses the treatment policy strategy for discontinuation from treatment for any reason.	To address the US FDA recommendations to modify the primary estimands such that the data collected should be close to a real-world setting.
Synopsis - Statistical Methods-Analysis Sets, Main Estimation of Estimand 1a-EMA (Co-primary Efficacy), Main Estimation of Estimand 1a-US FDA (Efficacy) Section 7 Statistical Analysis Methodology Section 7.6.4.1 Secondary BMD Endpoints	Clarified which analysis sets will be used for Estimand 1a-EMA, Estimand 1a-US FDA, and Estimand 1b-EMA (Co-primary PD) analyses. Removed mFAS2 so that FAS is used instead for estimation of Estimand 1a-US FDA. Renamed mFAS1 as mFAS. Both 90% and 95% CIs will be presented for primary efficacy.	To address the US FDA recommendations to modify the primary estimands such that the data collected should be close to a real-world setting.
Synopsis - Analyses of BMD After Transition and Section 7.6.4.2 Analyses of BMD After Transition	Added that 95% CIs will be presented for the analyses of BMD after transition.	To provide clarity that 95% CIs will be presented for this endpoint.

Section # and Name	Description of Change	Brief Rationale
Section 13.1 Appendix: Schedule of Events, Table 13-1 Schedule of Events	Added a footnote to clarify about collection of PFS related issues	To address the US FDA recommendation to include an assessment of PFS related AEs.