Biocon Biologics UK Limited

B1000-PMO-03-G-02

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

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Statistical Analysis Plan

Final Version 1.0

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Date

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List of Abbreviations

Abbreviation	Definition
ADA	antidrug antibody
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	area under the % inhibition curve
BDRM	blind data review meeting
BLQ	below limit of quantification
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
C_{min}	minimum concentration
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trial management system
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EoS	End of Study
FAS	full analysis set
FDA	United States Food and Drug Administration
ICE	Intercurrent Events
ICF	Informed Consent Form
Imax	maximum % inhibition
IWRS	interactive web response system
LLOQ	lower limit of quantification
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MI	multiple imputation
MMRM	mixed model for repeated measures
NA	not applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency

Abbreviation	Definition
PT	Preferred term
SOC	System Organ Class
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAF	safety analysis set
SAS	statistical analysis system
SC	subcutaneous
sCTX	serum C-terminal telopeptide of Type 1 collagen
SD	standard deviation
TEAE	treatment-emergent adverse event
TI_{max}	time of occurrence of maximum % inhibition
T_{min}	time of occurrence of the minimum concentration
UK	United Kingdom
US/USA	United States/United States of America

1. Introduction

B1000-PMO-03-G-02 is a randomized, double-blind, multicenter, parallel-arm, Phase 3 study. The study will consist of 3 study periods: Screening period; Part 1, double-blind active-controlled period; and Part 2, transition period.

Bmab 1000 is a medicinal product containing denosumab as the active substance and being developed by Biocon as a biosimilar product to Prolia® (Prolia USPI 2021, Prolia SmPC 2021) which is used for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, men with osteoporosis at high risk for fracture, glucocorticoid-induced osteoporosis in men and women at high risk for fracture and for the treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures.

The purpose of B1000-PMO-03-G-02 (DEVOTE Study) is to compare the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety and immunogenicity of Bmab 1000 (proposed biosimilar to Prolia) versus Prolia® (US-sourced) in postmenopausal women with osteoporosis. After collecting the totality of evidence proving its biosimilarity to Prolia®, Bmab 1000 may provide an opportunity to improve access to treatment while delivering substantial cost savings.

Part 1(from Week 0 [Day 1] to Week 52 Predose) is to assess equivalence between Bmab 1000 and Prolia based on percentage change from baseline at Week 52 in lumbar spine bone mineral density (BMD) and pharmacodynamic equivalence between Bmab 1000 and Prolia based on area under the effect curve (AUEC) of the bone resorption marker sCTX after the first dose (0-26 weeks). Part 2 is to assess risk of hypersensitivity and adverse events (AE) 6 months after the last study treatment administration and the risk of immunogenicity through formation of antidrug antibodies after the single transition from Prolia to Bmab 1000 compared with those continuing on Prolia.

This study 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 United States Food and Drug Administration (US FDA), this endpoint is considered as a 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 subjects who have received Prolia will be re-randomized to receive either Bmab 1000 or Prolia.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives and at the same time to ensure that the data listing, summary tables, and figures which will be produced are complete and appropriate to allow valid conclusions regarding the study objectives. This document does not fully cover the details of the safety review meetings for the Independent Safety Review

Committee (ISRC). The ISRC charter and ISRC Table, Listing, and Figure Shells document will outline the sequential nature of these reviews.

This SAP is based on International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use - E3 and E9 (including E9(R1)) Guidelines

This plan should be read in conjunction with the following documents:

- Protocol Version 3.0, 31 Aug 2022
- Electronic case report form (eCRF) Version 2.0, 05 Dec 2022.

2. Objectives, Endpoints and Estimands

2.1. Primary objective, 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 subcutaneous (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:** Area under the effect curve (AUEC) of sCTX from baseline to 26 weeks [*Time Frame: Baseline to Week 26*] **Estimand 1b-EMA**(Co-primary PD): Ratio of geometric means (Bmab 1000/Prolia) in AUEC in (fasted) sCTX up to 26 weeks in postmenopausal women[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: DXA, dual-energy x-ray absorptiometry; sCTX, serum C-terminal telopeptide of Type 1 collagen.

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

a. Women may 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)

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 serum C-terminal telopeptide of Type 1 collagen (sCTX) and procollagen Type 1 N-terminal propeptide (P1NP)	• Minimum Concentration (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: maximum % inhibition (I_{max}), time of occurrence of maximum % inhibition (TI_{max}), area under the % inhibition curve (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 treatment-emergent adverse event (TEAEs) up to 6 months after the second dose [*Time Frame: Baseline up to Week 52*] • Incidence of clinically significant changes in vital sign, physical examinations, laboratory safety tests, and electrocardiogram (ECGs) up to 6 months after the second dose [*Time Frame: Baseline up to Week 52*]
To compare immunogenicity between Bmab 1000 and Prolia	• Incidence and titer of antidrug antibody (ADA), incidence of neutralizing antibodies (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: DXA, dual-energy X-ray absorptiometry.
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, for US FDA)

Secondary Objective(s)	Endpoints
To assess the risk of hypersensitivity and AE 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 serious adverse event (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: Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; sCTX, serum carboxy-terminal cross-linking telopeptide of Type 1 collagen.

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

Other Secondary Objective(s)	Endpoints
To assess efficacy after the single transition from Prolia to Bmab 1000 compared with those 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, 58, and 78 (PK) [*Time Frame: from Week 56 up to Week 78*] • Serum concentrations of sCTX at Week 78 (PD) [*Time Frame: Week 78*]
To assess the AEs 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; Nab, neutralizing antibodies; PD, pharmacodynamic; PK, pharmacokinetic; sCTX, serum carboxy-terminal cross-linking telopeptide of Type 1 collagen; serious adverse event; TEAE, treatment-emergent adverse event.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-blind, multicenter, parallel-group, 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 age ≥55 and <80 with a BMD absolute value consistent with a T-score ≤-2.5 and ≥-4.0 at the lumbar spine will be enrolled.

The study will involve a Screening Period, a Double-blind Active-controlled Period and a Transition Period/Safety Follow-Up Period.

On Day 1, 480 eligible postmenopausal women with osteoporosis will be randomly assigned (1:1) to receive either Bmab 1000 (Arm 1) or Prolia (Arm 2) via SC injection (Week 0, the same date as randomization) and at Week 26. Subjects will be followed up for 26 weeks after the second dose. The randomization will be stratified by geographical region (US,

Europe), prior use of bisphosphonate treatment (Yes, No), and age of the subject (<65, ≥65) using the IRT system.

Efficacy, PK, PD, and safety including immunogenicity data will be collected as per Schedule of Events in Appendix 17.1.

All subjects who complete the Double-blind Active-controlled will undergo the re-randomization process for the Transition Period prior to the study treatment administration at Week 52. Prior to dosing at Week 52, subjects in the Prolia arm will be randomly assigned again in a 1:1 ratio to receive either Bmab 1000 or Prolia. This is done to obtain data after single switch in subjects who have been treated with Prolia. To maintain the study blinding, the subjects 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 See Appendix 16.1.

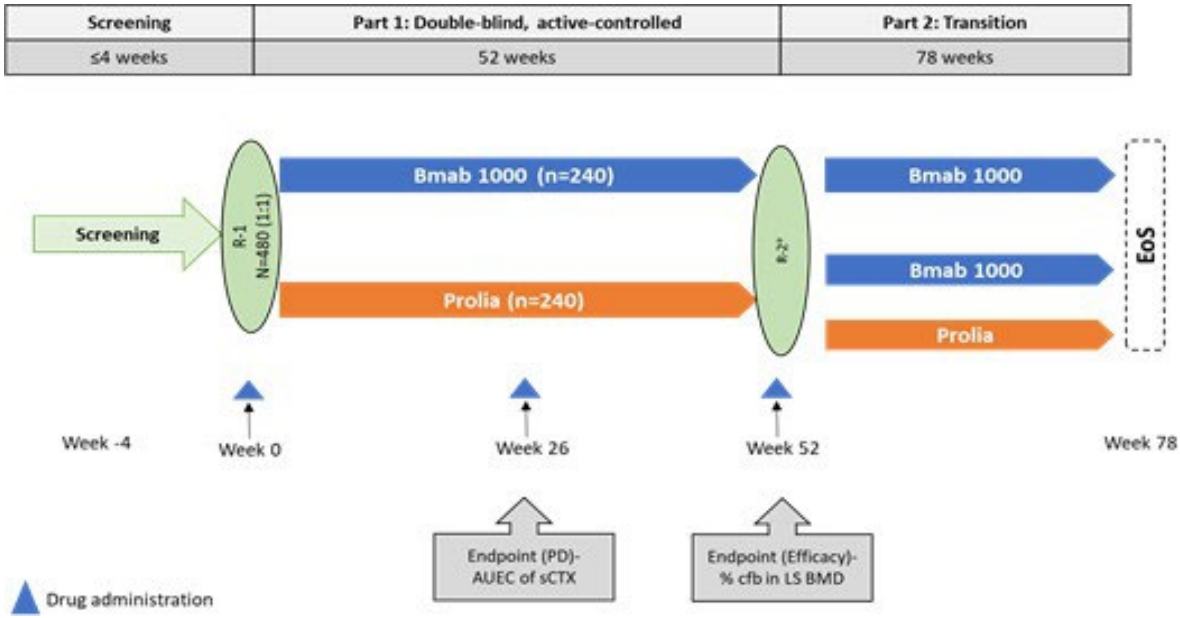
EoS visit will be at Week 78 post randomization (Month 18).
The subjects will receive the study treatment on Day 1 (Week 0), Week 26, and Week 52. The maximum study duration for a subject will be approximately 18 months (excluding screening).

An ISRC will assess the safety data periodically and will recommend to Biocon whether to continue, modify, or stop the study. This decision will be based on reviewed data (see protocol Section 7.9 for further details).

All assessments performed in the study are summarized in the schedule of events provided in the Appendix 17.1.

A schematic diagram of the overall study design is presented in Figure 1.

Figure 1 Study Design



Abbreviations: AUEC, area under the effect curve; cfb, change from baseline; 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, subjects in the Prolia arm will be re-randomized in 1:1 ratio to receive Bmab 1000 or Prolia. To maintain the blinding, subjects in Bmab 1000 arm will undergo re-randomization procedure however, they will continue to receive Bmab 1000.

4. General Statistical Considerations

Specific statistical methods will be described in the Efficacy Analysis Section 8.

Data collected in this study will be presented using summary tables, subject data listings and figures. Continuous data will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be summarized using the frequency counts and percentages in each category. Data will be listed in data listings. 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 unless otherwise specified, percentages will be calculated based on the total subjects (N) per treatment arm. For categorical variables, number of subjects with missing data will also be included.

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% Confidence Interval (CI) falls entirely within predefined margins; this approach is equivalent to two one-sided tests at the 5% significance level

The periods of the study will be summarized separately so that:

- In the Double-blind Active-controlled Period, subjects will be summarized by treatment (Bmab 1000 versus Prolia) up to week 52 (predose).

- In the Transition Period from week 52 (post dose) up to week 78/EOS, subjects will be summarized by treatment schedule (Bmab 1000-Bmab 1000 (Arm 1), Prolia-Bmab 1000 (Arm 2) and Prolia-Prolia (Arm 3)).

- Through the study including all data up to week 78/EOS, subjects will be summarized by treatment schedule (Bmab 1000-Bmab 1000 (Arm 1), and Prolia-Prolia (Arm 3)).

Non-zero percentages will be rounded to one decimal place. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of 3 decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of 3 decimal places. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected up to a maximum of 3 decimal places.

All other statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. No adjustment for Type I error will be made for multiple comparisons.

P-values will be rounded to four decimal places. If a rounded P-value is less than 0.0001 it will be reported as "<0.0001".

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the population of interest, unless otherwise specified.

All analyses (except PD analyses) will be conducted using SAS® Version 9.4 or higher.
All PD analyses will be conducted using Phoenix® WinNonlin® Version 8.3 (Certara USA, Inc., Princeton, NJ).

4.1. Sample Size

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

Equivalence will be established if the 95% CI of the difference (T-R) in mean percent change in lumbar spine BMD from baseline at Week 52 is within equivalence margin of (±1.45%). Equivalence margin is derived from meta-analysis of previous similar studies (Bone et al., 2008, Cummings et al., 2009, McClung et al., 2006) which gave the pooled denosumab treatment effect 5.35% (95% CI: 4.83% to 5.87%). Based on the lower bound of the 95% CI, a 1.45% margin will preserve 70% of the treatment effect (0.3*4.83%). Assuming that the treatments are equally effective and that the common SD for percent change from baseline in lumbar spine BMD at Week 52 is 4.5, a sample size of 204 subjects per treatment group (total 408 subjects) ensures a power of minimum 80% with two one-sided test at 2.5% level of significance. Considering a dropout of 15%, the total sample size required is 480 subjects (240 per treatment group).

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

4.2. Randomization, Stratification, and Blinding

An interactive web response system (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 participant randomization numbers to treatment codes.

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

4.2.1. Stratification

The randomization will be stratified by

- Geographical region (US, Europe)
- Prior use of bisphosphonate treatment (Yes, No)
- Age at study entry (≥55 to <65 years versus ≥ 65 to < 80 years)

4.2.2. Blinding

This study will be double-blind until the end of all follow-up procedures. The randomization codes will not be revealed to study subjects, 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 prefilled syringe (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 subject remains blinded (eg, blindfold, screen, or similar method during the dosing procedure so that the injection syringe will not be visible to the subject). Blinded staff/any other person 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 subjects have received the Week 52 assessments (prior to the third administration of study treatment) or have terminated the study before Week 52. At Week 52, the investigators, subjects and other members of staff involved with the study 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.

4.2.3. Breaking the Blind Methods for Unblinding a Subject

A subject's treatment assignment will not be unblinded until the end of all follow-up procedures (Week 78) unless medical treatment of the subject depends on knowing the study treatment the subject received. If the blind needs to be broken because of a medical emergency, the investigator may unblind an individual participant'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 subject. 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.

4.3. Intercurrent Events and Estimands

Intercurrent events (ICE) relevant in the treatment of postmenopausal women with osteoporosis by SC injection of study treatment (Bmab 1000 and Prolia) every 6 months are summarized in Table 1.

Table 1 Intercurrent Event Types (ICE))

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 of protocol for further details).
ICE2 (Discontinue - unrelated)	Treatment discontinuation for unrelated reasons (as detailed in Section 4.2.1 of protocol) 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 subcutaneous 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

*The dose must be adjusted by the Investigator

Currently, ICEs related to the COVID-19 pandemic (such as patient being unable to attend the study site because of travel restrictions and/or the site closure for study activities per regional governance, or patient is unable to attend the site because of being in isolation) are not included. These ICEs may be added as appropriate during study conduct once the extent of effect of the pandemic on the study conduct is known. Similarly, further ICEs may be added if any patients experience emergency unblinding. Relevant list of ICEs is presented in the Table 1 and will be adapted during Blind Data Review Meeting (BDRM) (if required).

As part of BDRM discussion, it was agreed that for ICE3 subjects are also included if actual dose is different from the planned dose. Subjects with a delay of receiving month 6 treatment dose of more than 30 days will be included in ICE3. Prohibited concomitant medications affecting bones were included for the definition of ICE5. Further details are specified in section 7.1.2.

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.

Estimands

Table 2 below presents the co-primary endpoints with its estimands and rationale for strategies to address ICEs.

Table 2 Estimands for the Co-Primary Endpoints with Rationale for Strategies to Address Intercurrent Events

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

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

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

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

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

4.4. Analysis Set

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

4.4.1. All Enrolled Set

The all enrolled analysis set will consist of all subjects who signed ICF.

4.4.2. All Randomized Set

The all randomized analysis set will consist of all subjects who were randomized regardless of receiving study drug.

4.4.3. Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who meet the eligibility criteria and receive at least one dose of study treatment. Any subject who did not meet eligibility criteria identified through the protocol deviation list will be also excluded from FAS. Subjects 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).

4.4.4. Re-Randomized Analysis Set

The Re-Randomized analysis set will consist of all re-randomized subjects regardless of receiving study drug at Week 52.

4.4.5. Full Analysis Set for Transition Period

The Full Analysis Set for Transition Period (FAS-TP) will consist of all re-randomized subjects who meet initial eligibility criteria and received dose at Week 52. Subjects from the FAS-TP will be analyzed under the treatment as randomized schedule of treatments.

4.4.6. Modified Full Analysis Set

The term Modified Full Analysis (mFAS) will be used to define the analysis data set which includes a data record at each time point for all subjects in the FAS but excludes data observed after the first occurrence of those ICEs 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 (for details on PD analysis, refer SAP section10.2).

4.4.7. Modified Full Analysis Set for Transition Period

The term Modified Full Analysis for Transition Period (mFAS-TP) will be used to define the analysis data set which includes a data record at each time point for all subjects in the FAS-TP but excludes data observed after the first occurrence of those ICEs 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-TP will be analyzed under the treatment as randomized schedule of treatments.

4.4.8. Safety Analysis Set

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

4.4.9. Safety Analysis Set for Transition Period

The Safety Analysis Set for Transition Period (SAF-TP) will consist of all re-randomized subjects who received at least one administration of study treatment. The SAF-TP will be used for all safety and immunogenicity analyses. In the SAF-TP, subjects will be analyzed per the actual schedule of treatments.

4.5. Other Important Considerations

4.5.1. Study Day Calculation

Study Day is defined by the number of days (positive or negative) since the first dose of study drug in the Double-blind Active-controlled Period.

The reference date for the calculation of study days will be the date of the first treatment injection on Day 1/Baseline for subjects randomized and treated or the date of randomization for subjects randomized but not treated (if any).

For events/assessments on or after the treatment start date, the study day of events/assessments from treatment start date is calculated as the date of event minus the reference date + 1. For events/assessments before treatment start date, the study day of the events/assessments is defined as the date of assessment minus the reference date.

4.5.2. Definition of Baseline

For Double-blind Active-controlled Period baseline is defined as the last non-missing measurement prior to the first treatment injection at Day 1/Baseline for subjects randomized and treated or prior to the date of randomization for subjects randomized but not treated (if any) unless stated otherwise including both scheduled and unscheduled visits and assessments.

For Transition Period analyses baseline is defined as the last non-missing assessment prior to the third study drug administration at Week 52

For throughout the study analyses, baseline will be defined as the last non-missing assessment prior to the first study drug administration. Additional analyses will be performed using transition period baseline for throughout study analyses, as specified in the applicable sections of this document.

Change from baseline and percent change from baseline are defined as follows:

$$\text{Change from Baseline} = \text{PostBaseline} - \text{Baseline}$$

$$\text{Percent Change from Baseline} = \begin{cases} \text{Baseline} \neq 0 \Rightarrow 100 \text{ x } \dfrac{\text{PostBaseline} - \text{Baseline}}{\text{Baseline}} \\ \text{Baseline} = 0 \Rightarrow \text{Missing} \end{cases}$$

4.5.3. Pre-specified Subgroups

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

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

5. Subject Disposition

5.1. Disposition

5.1.1. Screened and Screen Failure Subjects

Subject disposition for screen failures and reasons for screen failures will be presented for the Screened Set, percentages will be based on the Screened set. For screened and screen failure, only the total count will be provided. Subjects who were not randomized meeting eligibility criteria will be considered as screen failures.

Subject disposition for the Double-blind Active-controlled Period, will be presented for subjects who were randomized, not treated, treated, completed week 52, discontinued from treatment prior to week 26, discontinued from treatment prior to week 52 [with primary reasons of discontinuation], discontinued from study prior to week 52 [with primary reasons of discontinuation] or are ongoing, based on All Randomized Analysis set. Similarly, subject disposition for the Transition Period will be summarized for each treatment arm and overall for the Re-randomized analysis set. All percentages will be based on the number of subjects randomized for Double-blind Active-controlled Period and based on the number of subjects re-randomized for Transition period.

The count and percentage of subjects in each analysis set will be presented in a summary table, separately for the Double-blind Active-controlled Period and the Transition Period. Percentages will be calculated out of the number of subjects randomized and re-randomized for the Double-blind Active-controlled Period and the Transition Period, respectively.

Subject disposition data including reason for individual unblinding, analysis sets, and randomization data will be presented in data listings.

Subject disposition and discontinuation data will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be recorded within the [redacted] (CTMS) and will undergo a blinded review prior to database lock and unblinding.

The protocol deviations will be categorized as significant or non-significant in collaborative review with sponsor. 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 subject or impacts the integrity of study data.

Significant protocol deviations will be presented by planned treatment (arm) and overall in a summary table using counts and percentages by protocol deviation category and term based on All Randomized Set and Re-randomized Analysis Set for Transition Period, respectively.

All protocol deviations will be listed with date of occurrence, deviation category and deviation description. A separate listing for COVID-19 related protocol deviations will be prepared.

During blinded data review meeting, protocol deviations leading to analyses set exclusion will be evaluated and documented.

6. Demographics and Baseline Characteristics

6.1. Demographics

The demographics and baseline characteristics will be presented in tables using descriptive statistics for overall and by treatment group for each treatment period using Randomized Set and Re-Randomized Set. The demographic characteristics consist of Age (Years), Race, Ethnicity and Region. The baseline characteristics consist of height (cm), weight (kg), BMI (kg/m^2), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) collected at baseline.

Summary table (cross-tabulation) by treatment for stratification factor will be provided to show any discrepancy between what was reported through IRT vs. clinical database at baseline. This summary will be performed based on Randomized Set.

Subject demographic and baseline characteristics will be listed using the Randomized Set.

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized overall and by treatment group for each treatment period using All Randomized Set:

- Years since Menopause (years)
- Baseline Lumbar Spine BMD (g/cm^2)
- Baseline Lumbar Spine BMD T-score
- Baseline Lumbar Spine BMD T-score ($\leqslant$-3, >-3)
- Baseline Total Hip BMD (g/cm^2)
- Baseline Femoral Neck BMD (g/cm^2)
- Baseline sCTX (pg/mL)
- Baseline P1NP (µg/L)
- Vitamin D (nmol/L) [measured via laboratory test taken at baseline]
- Prior use of Bisphosphonates (Yes, No, Missing)
- Fracture History (Yes, No)
    - Type of Fracture (Vertebrae, Non-vertebrae)
        - Vertebrae - Genant grade (Normal, Mild, Moderate)

The above baseline disease characteristics will be listed by treatment using all Randomized set, in addition the following will also be listed: date of osteoporosis diagnosis, year of menopause and years since menopause. A fracture history listing will be listed by treatment

using all Randomized set, and will list the following: type of fracture, trauma severity, site of fracture, genant grade, start/end date, if it is ongoing and if the subject has had surgery on this fracture and surgical procedure/date if applicable.

6.3. Medical History

Medical history will be classified by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (Version 24.1 or higher) and summarized by SOC and PT for each treatment group and overall, for the Double-blind Active-controlled Period using the SAF analysis set. Medical history will be presented in a data listing for subjects using the SAF analysis set.

6.4. Inclusion and Exclusion Criteria

A listing, based on All Enrolled analysis set, will be included which protocol version each subject was enrolled under, and whether the met and/or did not meet the inclusion and exclusion criteria.

7. Treatments and Medications

7.1. Prior and Concomitant Medications and Therapies

7.1.1. Prior and Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using WHODRUG (dated Sep2021 or later). Summaries of all medications will be tabulated by Anatomical Therapeutic Chemical Classification System (ATC) Classification System (ATC Level 4 coding) of WHO drug and preferred term separately for prior medications and concomitant medications for each treatment group and overall.

For Double-blind Active-controlled Period, prior medications are those with the start and stop dates prior to the first dose of the Double-blind Active-controlled Period. Concomitant medications are those with start dates prior to the first dose of the Double-blind Active-controlled Period and continuing after the first dose of the Double-blind Active-controlled Period or with start dates between the first dose of the Double-blind Active-controlled Period and the first dose of the Transition Period.
For the Transition Period, concomitant medications are those with start dates prior to Day 1 of the Transition Period and continuing after Day 1 of the Transition Period or with start dates on or after Day 1 of the Transition Period.
Prior and concomitant medications will be summarized and listed for both the Double-blind Active-controlled Period and the Transition Period.

If the start date is missing, it will be assumed that the medication was used concomitantly. Details on handling partial dates (i.e. year or only year and month) are provided in Appendix 17.2.

Prior 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.

At each level of summarization, a subject is counted once if he/she reports one or more medications at that level. All prior and concomitant procedures will be summarized for the SAF and SAF-TP respectively.

All prior and concomitant medications will be presented in a listing.

7.1.2. Prohibited Concomitant Medications

Prohibited concomitant medications are listed in Protocol Section 5.8.

Prohibited concomitant medications will be summarized separately for the Double-blind Active-controlled Period and the Transition Period using the SAF and SAF-TP, respectively. The list of prohibited medications will be reviewed by the [redacted] and Biocon medical teams before the Week 52 DBL, who will provide the final assessment on which rules are applicable for considering a medication prohibited. The final list of ATC codes considered as prohibited is specified here:

Drug name	**ATC codes**
DENOSUMAB	M05BX Other drugs affecting bone structure and mineralization
ROMOSOZUMAB	M05BX Other drugs affecting bone structure and mineralization
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	L01FX, L01FA, L04AB, L04AA, L01FD, J06BD. L01FE, Other monoclonal antibodies and antibody drug conjugates
BISPHOSPHONATES	M05BA Bisphosphonates used after randomization
FLUORIDE [SODIUM FLUORIDE]	A12CD Alimentary Tract and Metabolism-Mineral Supplements-Other Mineral Supplements]
STRONTIUM	V03AX Other therapeutic products umc-assigned ,
TERIPARATIDE	H05AA, Parathyroid hormones and analogues official
PARATHYROID HORMONES AND ANALOGUES	H05A - Parathyroid Hormones and Analogues
TIBOLONE	G03CX - Other estrogens
ESTROGEN	G03CA - Natural and semisynthetic estrogens, plain

	official L02AA - Estrogens official
SELECTIVE ESTROGEN RECEPTOR MODULATORS	G03XC - Selective estrogen receptor modulators
CALCITONIN	H05BA, Calcitonin preparations
CALCITRIOL	A11CC04.
ANTICOAGULANTS: WARFARIN, HEPARIN,	B01AA Vitamin K Antagonists [Blood and Blood Forming Organs-Antithrombotic Agents-Antithrombotic Agents] B01AB-Heparin Group
ANTIPLATELET	B01AC - Platelet aggregation inhibitors excl. heparin (excluding Aspirin or Acetylsalicylic Acid).
ANTICONVULSANTS	N03AX, ANTIEPILEPTICS official N03AB, N03AA, N03AF, N03AD, N03AG, N02BF
SYSTEMIC KETOCONAZOLE	J02AB02 - Ketoconazole
ADRENOCORTICOTROPIC HORMONE	H01AA - ACTH
LITHIUM	N05AN, Lithium official
GONADOTROPIN RELEASING HORMONE AGONISTS	L02AE - Gonadotropin Releasing Hormone Analogues; H01CA – Gonadotropin-Releasing Hormones
ANABOLIC STEROIDS	A14AA - Androstan Derivatives [Alimentary Tract and Metabolism-Anabolic Agents For Systemic Use-Anabolic Steroids] G03XA-Antigonadotropins And Similar Agents G03BA - 3-Oxoandrosten (4) Derivatives G03BB - 5-Androstanon (3) Derivatives
SYSTEMIC GLUCOCORTICOSTEROIDS	H02AB, Glucocorticoids official (≥ 5 mg prednisone equivalent per day for ≥ 10 days).
INVESTIGATIONAL DRUGS	V98 Investigational drug
PROTON PUMP INHIBITORS	A02BC used for Longer than a Year (> 365 days)
COVID-19**	JO7BN (an interval of 7 days is advised between the COVID-19 vaccine and study drug administration)

** Excluded for ICE5 definition.

7.1.3. Vitamin D and Calcium Accountability

Compliance of Vitamin D and calcium supplements will be summarized with compliance percentages and compliance categories (⩽50, 50- ⩽60, 60- ⩽70, 70- ⩽80, 80 - ⩽100, 100 - ⩽120, >120) of subjects overall and by treatment group for each treatment period using SAF and SAF-TP, respectively.

The expected number of Vitamin D and Calcium supplementation to be taken, number of supplements taken, compliance, route, frequency and reason for discontinuation and if any adjustments made to Vitamin D or calcium were made will be presented in the listing by treatment group for each treatment period using SAF.

7.2. Study Treatments

Study treatments will be summarized separately for the Double-blind Active-controlled Period and the Transition Period using the SAF and SAF-TP, respectively. The count and percentage of subjects receiving each dose, and reason if dose is not administered, as well as a duration of follow-up for subjects receiving the second dose (for the Double-blind Active-controlled Period) or third dose (for the Transition Period) will be presented.

All study treatments administration data for the two periods (Double-b-blind Active-controlled Period and Transition Period) will be presented in a data listing, by treatment group, using SAF.

8. Efficacy Analysis

8.1. Cross-calibrated DXA Data

All statistical analysis regarding BMD will be performed based on cross-calibrated data. Non-cross-calibrated values will only be used if cross-calibrated ones are unavailable.

The only exception to this general rule is the subgroup variable specified in section 6.2 “Baseline Lumbar Spine BMD T-score (≤-3, >-3)” where the non-cross-calibrated value will be used for the analysis instead of the cross-calibrated value.

Month 12 DXA results that occurred after the administration of the third dose will not be considered for the analysis of the primary endpoint.

8.2. Description of Intercurrent Events

A swimmer’s plot will display time to each intercurrent event (ICE1-ICE5) per subject on the same plot, presented separately by treatment arm for SAF. In case there are more than 10% of subjects of who have a given intercurrent then this will not be displayed.

8.3. Summary of Statistical Methods, Including Sensitivity Analyses

Table 3 Summary of Statistical Methods, Including Sensitivity Analyses

Estimand Label	Estimand Description	Main Estimation			
		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 and penalties added to reflect non-inferiority and non-superiority nulls See Section 8.3.1 and 8.3.2. ANCOVA of % change from baseline in BMD up to Week 52 and including terms for randomization strata (i.e. actual data), treatment, baseline BMD (as a covariate). See Section 8.4.1. 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 analysis included in other estimands that are explored.
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 subjects in the FAS). For sensitivity [i], Multiple Imputation (MI) under Missing at Random (MAR) [ii] delta applied to imputation in the tipping point approach	Mixed model for repeated measures (MMRM) of % change from baseline in BMD up to Week 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]. (See Section 8.4.2.1 for further details).	[i] MI under MAR approach will be applied to the mFAS. % change from baseline BMD at timepoints up to Week 52 from each multiply imputed data set will be analyzed by Analysis of Covariance (ANCOVA) and results pooled using Rubin's method. See Section 8.4.2.2. [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 8.4.2.2. **[iii] Supplementary:** MMRM analysis of log-transformed data). See Section 8.4.2.3.

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 estimated glomerular filtration rate (eGFR) as covariates and treatment group and stratification factors as fixed effects. See Section 8.4.3.1.	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. See Section 8.4.3.2. **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. See Section 8.4.3.3.

8.4. Methodologies of Imputation

8.4.1. Multiple Imputation Model Under Missing at Random

Any post-unblinding modifications to the multiple imputation model or approaches to address missing data due to unexpected data issues after unblinding treatment will be described in the Note to File.

Data Pre-processing

Data will be transposed to give a single record per subject at each relevant scheduled timepoint (Screening, or Baseline, Month 6, and Month 12). Actual values rather than changes from baseline will be included as input into the imputation model.

Imputation Model Step 1

Multiple imputation (MI) will be used with 30 imputations so that 30 complete multiply imputed data sets are produced using SAS 9.4 (or higher) PROC MI, 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 excluding data after relevant ICEs and treating it as missing (Estimand 1a-EMA) and also to FAS (for the main estimation of Estimand 1a-US FDA).

Any intermittent missing data at Week 26 (eg, where at Screening and Week 52 data are available) will be imputed using a Markov Chain Monte Carlo approach, with single chain, non-informative prior, 200 burn-in iterations, 30 iterations between imputations in a chain and Expected-Maximization algorithm (using mcmc chain=single, the impute = monotone prior=Jeffreys options) and a non-informative prior with seed of 907876).

Imputation Model Step 2

The output data set from Imputation Model Step 1 (MI1) will be the input for Step 2 using Monotone Regression. The second imputation model will generate one imputation for each of previous multiply imputed datasets of MI1 (i.e., by *_Imputation_* and analysis set) and a seed of 293654.
The MI model will include continuous terms for age, BMI, BMD at Screening, Week 26 and Week 52.

Note: Total number of doses was not included in the imputation model because of the fact that it could introduce superficial variability for subject while executing MI Model. (Please refer to BDRM minutes).

Data Post-Processing

The output dataset from the multiple imputation model requires post-processing. In particular, the composite endpoint of %CfB lumbar spine BMD will be derived.

Note that for Estimand 1a-US FDA the %CfB lumbar spine BMD is defined as zero for anyone who dies, and any imputed values will be replaced at this step.

Multiple Imputation: Analysis Phase

For Estimand 1a-US FDA and sensitivity analyses i), and ii, for Estimand 1a-EMA an ANCOVA model of %CfB lumbar spine BMD at Week 52 will be run on each of the 30 multiply imputed datasets. The ANCOVA model will comprise terms for randomization strata, treatment, baseline BMD (as a covariate).

For Estimand 1a-EMA a MMRM model of %CfB lumbar spine BMD at Week 26 and Week 52 will be run on each of the 30 multiply imputed datasets. The MMRM model will comprise terms for randomization strata, visit by treatment, baseline BMD (as a covariate).

Datasets will be produced comprising a record for each imputation of the difference in means (Bmab 1000-Prolia) with corresponding and 90/95% CI.

Multiple Imputation: Combining Phase

Difference in means with corresponding 90/95% CI from ANCOVA (for Estimand 1a-US FDA and sensitivity analyses i), and ii, for Estimand 1a-EMA) and MMRM (for Estimand 1a-EMA) of the multiply imputed datasets will be pooled using PROC MIANALYZE to produce an overall estimate (the mean of the 30 estimates) based on Rubin's formula with corresponding 90/95% CI. Subject will be included as a random effect.

8.4.2. 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 adjusted level and then the result will be pooled using Rubin's method.

Note: That both positive and negative delta shift are tested in order to stress test whether the 95% CI for the mean difference in percent change falls within equivalence margins of [-1.45, 1.45]. This approach tests the robustness of the primary analysis to missing data (including data set to missing for the hypothetical Estimand 1a).

8.5. Primary Efficacy Endpoint

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

In order to estimate the composite endpoint Estimand 1a-US FDA (where % change from baseline of zero is taken for anyone who dies), an ANCOVA model will be fitted to the composite percent change from baseline in lumbar spine BMD until Week 52 on FAS multiply imputed data sets for visit by treatment, with stratification variables (Region, age and prior use of bisphosphonates) included as classification factors, baseline BMD included as a continuous covariate and treatment. The primary efficacy analysis (Estimand 1a-US FDA) will be based on the FAS.

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 non-inferiority and non-superiority null hypotheses (H0) respectively and two separate one-sided tests at alpha=0.05 conducted (Tests 1 and 2 below, respectively) (for more details see Section 8.3.1 and 8.3.2):

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

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

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

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

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

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

where μBmab 1000 and μProlia 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.

All efficacy data will be presented in listings. BMD by DXA scan will be listed based on All Randomized Set.

The estimated mean difference in % change from baseline in BMD between treatment arms will be presented with 90% CI and equivalence will be concluded if this falls within the predefined equivalence margins of [-1.45%, 1.45%].

8.5.2. Estimand 1a-EMA (Co-primary Efficacy)

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

For the primary efficacy analysis (Estimand 1a-EMA), an MMRM will be fitted to the percent change from baseline in lumbar spine BMD until Week 52 on the mFAS. The MMRM will include stratification variables (Region, age and prior use of bisphosphonates) included as classification factors, baseline BMD included as a continuous covariate and visit by treatment. The repeated measures on subjects will be modelled with an unstructured covariance structure.

In case of non-convergence of the MMRM with UN covariance structure, the first order heterogeneous autoregressive model [ARH(1)] will be fitted instead; if this model still fails to converge then the number of covariance parameters will be reduced further and the first order autoregressive model [AR(1)] will be fitted.

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.

The primary efficacy analysis will be based 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).

The MMRM analysis will assume a missing-at-random (MAR) mechanism for missing data. The following statistical hypotheses will be tested by the primary analysis MMRM model:

H_0: $\mu_{\text{Bmab 1000}} - \mu_{\text{Prolia}} = 0$

H_1: $\mu_{\text{Bmab 1000}} - \mu_{\text{Prolia}} \neq 0$

where $\mu_{\text{Bmab 1000}}$ and μ_{Prolia} denotes the true mean percent change from baseline in BMD at Week 52 for Bmab and Prolia, respectively.

The least-squares (LS) mean percentage reduction from baseline in BMD at Week 52 will be presented for each treatment group, as well as the LS mean difference in change from baseline in BMD across treatment groups (Bmab 1000 - Prolia). The corresponding standard errors, 95% CI, and a two-sided P-value testing H_1 against H_0 will be displayed.

8.5.2.2. Sensitivity Analyses for Estimand 1a-EMA (Co-primary Efficacy)

Two sensitivity approaches will be performed:

- MI under MAR approach will be applied to the mFAS and data at Week 52 will be analyzed using same ANCOVA model as Estimand 1a-FDA (for more details see Section 8.4.1).
- A penalty will be added to the imputed % change from baseline values on mFAS and same analysis as Estimand 1a-FDA will be performed (for more details see Section 8.4.2).

8.5.2.2.1. Multiple Imputation Missing At Random ANCOVA

Multiply imputed data sets will be produced on mFAS under MAR as explained in The percent change from baseline in lumbar spine BMD by DXA will be calculated as a post processing step from BMD values and analyzed by ANCOVA. Results will be pooled using Rubin's method.

8.5.2.2.2. Penalty Under Multiple Imputation Missing At Random (ANCOVA)

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.

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

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.

8.5.3. Estimand 1b-EMA (Co-primary PD)

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

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

8.5.3.2. Sensitivity of Estimand 1b-EMA (Co-primary PD)

Standardized AUEC (sAUEC) are standardized by time and divided by baseline sCTX (see Section 10.2 for details). Thus, a sAUEC value of 0.15 is interpreted as the overall sCTX level as a ratio of its baseline and would indicate an overall 85% reduction from baseline (ie, 85% inhibition). An ANCOVA analysis (with same fixed effect terms as Section 8.5.3.1 above) of log-transformed sAUEC will be performed and geometric least squares means

(GLSM) presented with the 95% CI for GLSM (Bmab 1000/Prolia) which provided the same covariates are included should match that obtained for the primary analysis. Note that a GLSM ratio < 1 would be interpreted as lower levels of sCTX on Bmab 100 and thus higher inhibition.

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

8.5.3.3. Supplementary Analysis for Estimand 1b-EMA (Co-primary PD)

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 as fixed effects and assume an unstructured covariance over time and thus it will allow for variability across subjects 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, the area under the curve expected mean percent inhibition profile will be estimated as a weighted mean of the expected 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). Since by definition, % inhibition at Day 1 is zero for all subjects, the Day 1 data will not be included in this model (but other weights and divisor are unaffected). Subjects with partial data will be included in this model.

8.6. Secondary Efficacy Analysis

8.6.1. Secondary BMD Endpoints during Double-Blind Active-Controlled Period

A MMRM as per the main estimation of Estimand 1a-EMA (Co-primary Efficacy) (see Section 8.4.2.1) will be used to estimate the mean percentage 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 on the same endpoints (see Section 8.4.1) but without the penalty being applied.

8.6.2. BMD Endpoints After Transition period (Part 2)

BMD percentage change at Week 78 from baseline and from Week 52 will be summarized by treatment for:

- Lumbar spine BMD
- Hip BMD

- Femoral neck BMD

Statistical analyses similar to the ones presented in section 8.5.1 (ANCOVA) will be performed on Week 78 lumbar spine BMD based on FAS-TP in 2 separate analyses which will be considering either original baseline or Week 52 baseline as a covariate. Percent change from baseline up to week 78 will be presented in a graph by visit and treatment for the three BMD parameters.

8.7. Subgroup Analyses

Subgroup analyses will be conducted for the primary estimand 1a-US FDA and 1a-EMA on FAS and mFAS respectively and the below subgroups will be examined. Other exploratory subgroups that may have implications on the treatment effect may be examined as well. Difference in means (Bmab 1000 - Prolia) will be estimated using the same analysis model as described in Section 8.2.

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

Forest plots of difference in means will be produced. The number and percentage of subjects in each subgroup level, difference in means and corresponding 95% CI will be provided. The analyses will be conducted if number of subjects in the subgroup category is more than 10% of the analysis set.
The analysis mentioned in Sections 8.5.1 and 8.5.2.1 will be repeated for the above subgroups.

9. Safety Analysis

Safety will be assessed through the collection and evaluation of AEs, including TEAEs and SAEs, Adverse Events of Special Interest (AESIs), deaths, clinical laboratory assessments, physical examinations, vital sign measurements, and ECGs. Statistical hypothesis testing will not be performed on any safety results.

Double-blind Active-controlled Period
Safety data collected up to Week 52 will be summarized by actual treatment group on SAF.

Transition Period
Analyses will be performed on SAF-TP following two different approaches:

1) Safety following the third dose at Week 52 and up to and including Week 78 will be summarized for the three treatment arms Bmab-Bmab (Arm 1), Prolia-Bmab (Arm 2), and Prolia-Prolia (Arm 3).

2) Data from first dose through to Week 78 of Bmab throughout versus Prolia throughout. i.e. Bmab-Bmab (Arm 1) vs Prolia-Prolia (Arm 3)

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to the study treatment.

Any new condition noted at or after screening up to baseline (i.e., before administration of the first dose of the study drug) will be regarded as an AE, but not a treatment emergent adverse event (TEAE), see Section 9.1.1 for further details on TEAE.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the study treatment.

Any abnormal laboratory finding, (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 judgement of the investigator will be recorded as AE or SAE if they fulfil the following:

- Results in discontinuation from the study.
- Requires treatment or any other therapeutic intervention.
- Requires further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality).
- Are clinically significant as evaluated by the investigator.

However, any laboratory results of the disease being studied, medical or surgical procedures will not be considered as an AE but rather the condition that leads to the procedure is an AE.

AEs 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.

AEs experienced by the subjects will be collected throughout the entire study and will be all listed and coded using MedDRA Version 24.1 or later.

9.1.1. Treatment Emergent Adverse Events

A TEAE is defined as any event not present before exposure to the study drug or any event already present that worsens in intensity after exposure to the study drug. This includes any occurrence that is new in onset or aggravated in severity from the baseline condition.

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

For the Transition Period, TEAE is an event observed after third dose of study drug at Week 52 until Week 78.

For the cumulative Transition safety summaries analysis for TEAE (from Day 1 through to week 78 of Bmab 1000 vs Prolia throughout), definition of TEAE will be either Double-blind Active-controlled Period or Transition Period TEAE definition (i.e. if an event observed after first dose of study drug up to Week 78 will be considered a TEAE).

Imputed AE data will be summarized, but all the original collected AE data will be presented in a listing. TEAEs will be flagged in all the AE listings and will be summarized.

In the case of missing or partially missing AE onset dates, the rules described in Section 17.2 will be applied.

9.1.2. Incidence of AEs

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment (arm).

The incidence of TEAEs and Serious TEAEs tables will include only one occurrence of a PT per subject. If a subject reports the same PT multiple times, then that PT will only be incremented by one since subject counts will be presented. As with the PT, if a subject reports multiple AEs within the same SOC, then that SOC will only be incremented by one since subject counts will be presented. Percentages will be calculated out of the number of subjects in the SAF and SAF-TP for the Double-blind Active-controlled Period and the Transition Period/cumulative safety data analysis, respectively. The number of events at each level of SOC and PT will also be summarized.

For tables showing incidence by SOC, PT and severity, SOC will be sorted in alphabetical order. Within each SOC, preferred terms will be sorted in descending order of frequency on total of all treatment groups.

The number and percentage of subjects and the number of events will also be presented by SOC and PT.

The incidence of TEAEs and Serious TEAEs will be summarized using count and percentages of subjects by treatment groups for Safety analysis sets for below time periods:

1) Baseline up to Week 52
2) Week 52 up to and including Week 78

3) Day 1 up to Week 78

All AEs, and serious AEs will be presented in a listing.

9.1.3. Relationship of AEs to Study Drug

A summary of TEAEs and Serious TEAEs related to study drug will also be presented in a table by SOC, PT and severity.

The relationships will be collected as the possibility that study drug caused the event.

The relationships are "Unrelated", "Unlikely Related", Possibly Related", "Probably Related" and "Definitely Related". TEAE that have possible, probable, or definite relationship to treatment will be considered as study drug related.

TEAEs that are missing relationship will be presented in the summary tables as "Related" to study drug but will be presented in the data listing with a missing relationship.

The TEAE data will be categorized and presented by SOC, PT, and relationship (i.e., "Related" and "Not Related") similarly to that described in Section 9.1.2.

Percentages will be calculated out of the number of subjects in the SAF and SAF-TP for the Double-blind Active-controlled Period and the Transition Period/cumulative safety data analysis, respectively.

9.1.4. Severity of AEs

The severity of the AE will be graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, based on the following general guidelines:

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; limited age-appropriate instrumental activities of daily living.
Grade 3:	Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living.
Grade 4:	Life-threatening consequences: urgent intervention indicated.
Grade 5:	Death related to AE.

If AEs are not covered in the NCI CTCAE, then severity of the AE will be graded as Mild, Moderate, Severe, Life Threatening and Death.

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. In the TEAE severity table, if a subject reported multiple occurrences of the same AE, only the most severe will be presented. AEs that are missing severity then the AE is imputed to corresponding CTCAE grade. If both severity and CTCAE grade are missing then AE is assumed to be "severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the SAF and SAF-TP for the Double-blind Active-controlled Period and the Transition Period/cumulative safety data analysis, respectively.

The TEAE data will be categorized and presented by SOC, PT and severity in a manner similar to that described in Section 9.1.2. In addition, a summary presented by SOC, PT, severity and relationship will be provided similarly to that described in Section 9.1.2.

9.1.5. Serious AEs

The seriousness of an AE should be assessed by the investigator independently from the severity of the AE. A serious AE (SAE) is any untoward medical occurrence that at any dose results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect.

AEs to be treated as SAEs by the investigator are AEs associated with inpatient hospitalization or prolongation of existing hospitalization. Hospitalization or prolongation of hospitalization (See Section 6.2.1.1.5 of Protocol) in the absence of a precipitating clinical AE is not in itself a SAE.

For missing dates, the rules stated in Section 4 will be followed.

Serious TEAEs will be categorized presented by SOC and PT in a manner similar to that described in Section 9.2.2. The number and percentage of subjects and the number of events will also be categorized by PT only and will be presented in descending order of incidence.

In addition, a summary of serious TEAEs presented by SOC, PT, and severity will be provided similarly to that described in Section 9.1.2. All SAEs will be presented in a listing.

9.1.6. Serious AEs, Related to Study Drug

The drug-related serious TEAEs data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.2.

9.1.7. AEs of Special Interest

AESIs are defined as TEAEs of special interest of scientific or medical concern.

The following AEs are considered as AESIs:

- Treatment-related hypersensitivity/allergic reaction
- Serious Infections
- Hypocalcemia
- Osteonecrosis of the jaw
- Atypical femoral fracture
- Dermatologic reactions

A summary of AESIs will be presented by SOC and PT similar to that described in Section 9.1.2.

All AESIs will be presented in a listing. The following AESI will be listed separately for SAF: Serious Infections, Dermatologic reactions and Hypocalcemia listings.

9.1.8. AEs Leading to Treatment Discontinuation and Study Discontinuation

Summary tables of TEAEs leading to study drug discontinuation and study discontinuation by primary SOC, preferred term and severity by treatment arm will be provided.

All TEAEs leading to study drug discontinuation and study discontinuation will be listed by subjects.

9.1.9. AEs Leading to Death

The summary of Grade 5 TEAEs which are leading to death will be presented. SOC will be sorted in alphabetical order. Within each SOC, total AEs of preferred terms will be sorted in descending order of frequency on total of all treatment groups.

All subjects who have an AE leading to death will be presented in a listing.

9.1.10. Death

Deaths and reason for death will be presented in the AE overview summary table and will be presented in a listing.

9.1.11. Overview summary

An overview summary of the number and percentage of subjects with any TEAE, study drug-related TEAE, serious TEAE, study drug-related serious TEAE, AESI, serious AESI, TEAE leading to treatment discontinuation, TEAE leading to study discontinuation, AE leading to death, and all deaths will be provided by treatment (arm) for Double-blind Active-controlled Period and Transition Period for SAF and SAF-TP respectively.

9.2. Clinical Laboratory Evaluations

All summaries will be based on SI units. Blood and urine samples collected for clinical laboratory values (hematology, clinical chemistry, coagulation and urinalysis) will be analysed by the central laboratory. However, in listings results with both conventional and standard units will be populated.

Central laboratory safety parameters will be carried out in accordance with the schedule of procedures in Section 17.1, will be used for analysis in the study.

In the Double-blind Active-controlled Period, a summary table presenting observed values and changes from baseline will be presented for clinical laboratory tests with numeric values. Change from baseline to each scheduled post-baseline visit will be presented by treatment arm.

Shift tables summarising the baseline and post-baseline timepoints results for clinical laboratory tests with categorical values will be displayed in cross-tabulations.

Shift tables summarising the baseline and post-baseline timepoints for analysis ranges of clinical laboratory tests will be displayed in cross-tabulations. Additionally, the worst post-baseline result categorized based on analysis range will be presented.

For the cumulative Transition safety data analysis, Laboratory (as described in Section 9.1) change from baseline summaries, will be presented for the three treatment arms, and data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout (i.e. Bmab 1000-Bmab 1000 (Arm 1) vs Prolia-Prolia (Arm 3))

Listings of clinical laboratory data will be provided for two periods (Double-blind Active-controlled Period and Transition Period) using the SAF analysis set. Laboratory data collected at unscheduled visits will be included in listings.

9.2.1. Hematology

The laboratory tests like Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelet count will be included in hematology summary tables.

All hematology data by subject will be presented in a listing.

9.2.2. Clinical Chemistry

The laboratory tests like albumin, albumin-adjusted total serum calcium, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, FT3, FT4, 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, serum 25-OH vitamin D, TSH, and intact parathyroid hormone will be included in clinical chemistry summary tables.

All chemistry data by subject will be presented in a listing.

9.2.3. Urinalysis

The laboratory tests: color, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination will be included in clinical urinalysis summary tables.

All urinalysis data by subject will be presented in a listing.

9.3. Vital Signs Measurements

Summary tables presenting observed values and changes from baseline will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), pulse rate (Beats/Min), and respiratory rate (Breaths/Min), by treatment group at each visit for the SAF analysis set. Change from baseline to each scheduled post-baseline visit will be presented. Change from baseline will only be calculated for subjects having non-missing baseline and post-baseline measurements.

For the cumulative Transition Vital Signs (as described in Section 9.1) change from baseline summaries, will be presented for the three treatment arms, and data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout (i.e. Bmab 1000-Bmab 1000 (Arm 1) vs Prolia-Prolia (Arm 3)).

The incidence of clinically significant changes in vital sign will be summarized using count and percentages of subjects by treatment groups for SAF analysis set for below time periods:

- Baseline up to Week 52
- Week 52 up to and including Week 78
- Day 1 up to Week 78

The following are typical ranges used:

- Systolic blood pressure (mmHg): ⩾140 mmHg/⩽90 mmHg with increase/decrease from baseline of ⩾20 mmHg
- Diastolic blood pressure (mmHg): ⩾100 mmHg/⩽50 mmHg with increase/decrease from baseline of ⩾15 mmHg
- Heart rate (beats/min): ⩾100 bpm/⩽50 bpm with increase/decrease from baseline of ⩾15 bpm
- Respiratory rate (breaths/min): ⩾25 breaths pm/⩽12 breaths pm
- Temperature (° C): ⩾37.5 ° C /⩽36 ° C

All vital signs measurements for two periods (Double-blind Active-controlled Period and Transition Period) will be presented in a data listing using the SAF analysis set.

9.4. Physical Examination

Physical examination will be collected on the CRF: a complete physical examination will be collected at the screening, baseline (Day 1), and at Weeks 26, 52 and 78. A symptom-specific physical examination will be collected for other visits.

A table will summarize complete physical examination results. Each visit captures the status of a body system and any finding associated with the body system as Normal, Abnormal not clinically significant (NCS), Abnormal clinically significant (CS), and Not Assessed. The summary will include the number and percentage of subjects with Abnormal NCS or Abnormal CS findings for the following body systems and overall: head and neck, oral cavity exam, cardiovascular, respiratory, abdomen, brief neurological, general appearance, skin exam, other (only added in listing), by scheduled visit and treatment arm.

Change from baseline to each scheduled post-baseline visit will be presented. Change from baseline will only be calculated for subjects having non-missing baseline and post-baseline measurements.

In the Double-blind Active-controlled Period, changes from baseline (Day 1) in interpretation results will be presented in a shift table by visit for the following categories: Normal, Abnormal NCS, Abnormal CS. Similarly, in the Transition Period, changes from Week 52 will be presented by visit.

Both complete and symptom-specific physical examination results will be presented in a listing together with abnormality specification when provided for two periods (Double-blind Active-controlled Period and Transition Period) using the SAF analysis set.

9.5. Electrocardiogram

A 12-lead ECG will be performed after the subject has rested in a supine position for at least 5 minutes at the timepoints specified in Schedule of Events (Appendix 16.1). Each scheduled visit captures ECG interpretation results as Normal, Abnormal NCS, and Abnormal CS.

In the Double-blind Active-controlled Period, changes from baseline (Day 1) in ECG interpretation results will be presented in a shift table by visit for the following categories: Normal, Abnormal NCS, Abnormal CS. Similarly, in the Transition Period, changes from Week 52 will be presented by visit.

For the cumulative Transition ECG (as described in Section 9.1) change from baseline summaries, will be presented for the three treatment arms, and data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout (i.e. Bmab 1000-Bmab 1000 (Arm 1) vs Prolia-Prolia (Arm 3)).

All ECG interpretation results will be presented in a listing together with abnormality specification when provided for two periods (Double-blind Active-controlled Period and Transition Period) using the SAF analysis set.

9.6. Other Safety Data

9.6.1. Injection Site Reactions

Hypersensitivity/allergic reactions monitoring will be assessed before the start of the study drug administration (within 15 minutes) and at 1 hour (± 10 minutes) after the end of the study drug administration at baseline (Day 1), Week 26 and Week 52.

In the Double-blind Active-controlled Period, all hypersensitivity/allergic reactions data will be summarized in a table. Similarly, hypersensitivity/allergic reaction summaries will be produced in the Transition Period and will be presented by visit. Summaries will display anatomical location, laterality, symptom/reaction by severity.

For the cumulative Transition Hypersensitivity/allergic reactions (as described in Section 9.1) summaries, will be presented for the three treatment arms, and data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout (i.e. Bmab 1000-Bmab 1000 (Arm 1) vs Prolia-Prolia (Arm 3)).

Hypersensitivity will also be presented in a data listing for two periods (Double- blind Active-controlled Period and Transition Period) using the SAF analysis set.

9.6.2. Summary of fractures

In the Double-blind Active-controlled Period, all incidence of fractures will be summarized with descriptive statistics by treatment group. Similarly, in the Transition Period, incidence of fractures from Week 52 will be presented by visit and treatment group.

For the cumulative Transition incidence of fractures (as described in Section 9.1) summaries, will be presented for the three treatment arms, and data from first dose through to Week 78 of Bmab 1000 throughout versus Prolia throughout (i.e. Bmab 1000-Bmab 1000(Arm 1) vs Prolia-Prolia (Arm 3)).

10. Pharmacokinetics and Pharmacodynamics

10.1. Pharmacokinetics

Data listings will be presented using the FAS; all summaries will be presented using the mFAS.

Serum denosumab concentrations below the limit of quantification (BLQ) and missing values will be handled as below:

- Concentration values that are BLQ will be reported as provided by the bioanalytical data in the PK data listings.
- Serum concentration values that are BLQ will be treated as zero at individual time points for the calculation of summary statistics (e.g. mean, SD, etc.).
- Mean concentrations will be reported as BLQ if all concentration values are BLQ, and SD and CV% will be reported as not applicable (NA).
- Missing concentration values will be excluded from the calculation of concentration summary statistics.
- For graphical presentations, all BLQs will be set to missing.

PK samples are scheduled for collection on Week 0 (Day 1); Week 2 (Day 15 ± 2 days), Week 4 (Day 29 ± 5 days), Week 12 (Day 85 ± 5 days), Week 23 (Day 162 ± 7 days), Week 26 (Day 183 ± 7 days), Week 38 (Day 267 ± 7 days), Week 52 (Day 365 ± 7 days), Week 56 (Day 393 ± 7 days), Week 64 (Day 449 ± 7 days), and Week 78 (Day 547 ± 7 days).

PK collections that have an actual sampling time that deviates from the predefined collection windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

The concentration data will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, and maximum) by treatment and visit (Weeks 2, 4, 12, 23, 26, 38, 52, 56, 64, and 78) for each study part, where applicable. Mean serum concentration versus scheduled time profiles by treatment will be presented in figures on both linear and semi-logarithmic scales.

If deemed appropriate, the effects of ADA incidence on the PK concentration data up to Week 52 will be assessed. Denosumab concentration summaries by treatment and visit will be presented for each of the subject ADA statuses defined in Section 11.

Mean denosumab serum concentration versus scheduled time profiles by treatment may also be presented graphically for each of the subject defined ADA statuses.

The serum denosumab concentration data will be displayed to the same precision as received from the bioanalytical laboratory in all data listings. Summary statistics will be displayed to 3 significant figures (<1000) or to the nearest whole number (>1000), with the exception of n, which will be shown as an integer.

10.2. Pharmacodynamics

Data listings will be presented using the FAS; all summaries will be presented using the mFAS. All statistical analysis will be based on the mFAS.

Serum sCTX and P1NP concentrations below the limit of quantification (BLQ) and missing values will be handled as below:

- Concentration values will be reported as provided in the PD data listings using scheduled collection times; data imputations used for the generation of PD parameters will not be reported.
- Concentration values that are BLQ will be reported as provided in the bioanalytical data in the PD data listings.
- Serum concentration values that are BLQ will be treated as ½ lower limit of quantification (LLOQ) at individual time points for the calculation of summary statistics (e.g. mean, SD, etc.).
- Mean concentrations will be reported as BLQ if all concentration values are BLQ, and SD and CV% will be reported as not applicable (NA).
- Missing concentration values will be excluded from the calculation of concentration summary statistics and will be presented as '-' in the data listings. Missing concentrations will include unavailable visit/concentration/UTP (unable to perform bioanalysis) or not reported.
- For calculation of PD parameters, BLQ values will be set to ½ LLOQ.
- Missing concentration values will be treated as missing in the derivation of PD parameters. Missing concentrations will include unavailable visit/concentration/UTP (unable to perform bioanalysis) or not reported.
- For graphical presentations, all BLQs will be set to ½ LLOQ.

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

PD collections that have an actual sampling time that deviates from the predefined collection windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Serum sCTX and P1NP concentrations will be listed and summarized using descriptive statistics (n, mean, SD, CV%, median, minimum, and maximum) by treatment and visit for each study part, where applicable. 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. Individual sCTX concentration versus actual time and mean sCTX and P1NP concentration versus scheduled time profiles by treatment will be presented in figures on both linear and semi-logarithmic scales.

Serum PD data for sCTX and P1NP will also be presented as %inhibition in data listings, summaries, and plots. %inhibition will be derived as below, where "predose" is the baseline concentration measurement assumed to occur at time zero and "postdose" is the concentration at each timepoint:

- %inhibition = maximum of zero and [predose – postdose / predose]*100

Note that this ensures %inhibition is not negative and is set to zero in the case of rebound effect.

The serum sCTX and P1NP concentration data will be displayed to the same precision as received from the bioanalytical laboratory in all data listings. Summary statistics will be displayed to 3 significant figures (<1000) or to the nearest whole number (>1000), with the exception of n, which will be shown as an integer.

PD parameters will be analyzed using noncompartmental methods and actual sampling times. In cases where an actual sampling time is not recorded, the nominal time will be used. All PD parameters will be calculated using Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS® (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher.

To support the derivation of the AUEC and AUIC, the following terminology is defined but will not be reported.

C_{last}	Last observed concentration of the first dosing interval
T_{last}	Last time point of the first dosing interval with observation C_{last}
$C_{(last-1)}$	Penultimate observed concentration of the first dosing interval
$T_{(last-1)}$	Penultimate time point with observation $C_{(last-1)}$
CSlope	Slope calculated from the last 2 observations as: $[C_{last}-C_{(last-1)}]/[T_{last}-T_{(last-1)}]$
C_{182imp}	Imputed concentration at exactly 182 days post-dose, calculated by interpolation or extrapolation from the last 2 observations of the first dosing interval in mFAS (provided $T_{(last-1)}$ and T_{last} are both >130 days) using the below formula: $C_{last}+CSlope*(182-T_{last})$
C_0	Baseline (predose) concentration measurement assumed to occur at time zero
I_{last}	Last observed inhibition of the first dosing interval %inhibition = maximum of zero and $[(C_0 – C_{last})/ C_0] * 100$
$I_{(last-1)}$	Penultimate observed inhibition of the first dosing interval %inhibition = maximum of zero and $[(C_0 – C_{(last-1)})/ C_0] * 100$
ISlope	Slope calculated from $[I_{last}-I_{(last-1)}]/[T_{last}-T_{(last-1)}]$
I_{182imp}	Imputed inhibition at exactly 182 days post-dose, calculated by interpolation or extrapolation from the last 2 observations of the first dosing interval in mFAS (provided $T_{(last-1)}$ and T_{last} >130 days) using the below formula: $I_{last}+ISlope*(182-T_{last})$

The following PD parameters will be estimated for sCTX in the first dosing interval using absolute (without baseline-adjustment) sCTX concentrations in the mFAS:

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

The following PD parameters will be estimated for sCTX using %inhibition sCTX values:

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

Note that for the derivation of AUIC, negative %inhibition sCTX values (i.e., where post-baseline > baseline) will be set to 0. This will remove the contribution of the rebound area from the estimation of the AUIC. Additional PD parameters, such as truncated AUECs or AUICs over a common time period across all subjects, may be calculated as required.

Where the predose sample is missing within a profile, no imputation of predose (C_0) will be performed and estimation of AUEC and %inhibition parameters will not be performed or reported. For PD parameter estimation, data points within 8 hours of food-intake or 48 hours of intense physical activity will not be used.

The PD parameters will be individually listed and summarized using descriptive statistics (n, geometric mean, geometric CV%, mean, SD, CV%, median, minimum, and maximum). For T_{min} and TI_{max}, n, median, minimum, and maximum will be reported.

PD parameters and summary statistics will be displayed to 3 significant figures (<1000) or to the nearest whole number (>1000), with the exception of n, which will be shown as an integer, and T_{max} and TI_{max}, which will be displayed to 2 decimal places.

11. Immunogenicity Assessments

The immunogenicity of Bmab 1000 and Prolia will be analysed in the Double-blind Active-controlled Period by treatment and combined treatment group in the Transition Period by treatment arms. Additionally, immunogenicity data throughout the study (Baseline to the end of Transition Period (Week 78)) will be analysed.

Analysis of immunogenicity data will be based on ADA evaluable subjects defined as all SAF or SAF-TP subjects with baseline and at least one post-baseline immunogenicity assessment within the Double-blind Active-controlled Period, the Transition Period and Throughout study period, respectively.

The formation of ADAs against Bmab 1000 or Prolia will be assessed in blood samples (Day 1, Week 26 and Week 52) up to 30 minutes before the study drug administration. All other samples at week 2, 4, 12, 38, 56, 64 and week 78 will be collected as close as possible to the scheduled time point within windows as specified in the schedule of events (Appendix 17.1). The ADA and Nab levels will be measured using validated methods. In case of positive results in the ADA evaluation, the ADA titer will be evaluated, also the Nab will be tested.

Validated ADA test methods enable characterization of samples into ADA positive vs. ADA negative.

Subject ADA status during double-blind period is defined based on the sample ADA status as follows:

- Baseline ADA positive subject: A subject with baseline ADA positive sample;
- Baseline ADA negative subject: A subject with baseline ADA negative sample;

- Overall ADA positive subject: A subject with at least one ADA positive sample at any time after initiation of treatment during double-blind period, irrespective of baseline result;
- ADA negative subject: A subject with only ADA negative samples at any time after initiation of treatment during double-blind period, irrespective of baseline result;
- Treatment-emergent ADA subject: A subject with at least one post-baseline positive result having a negative or non-evaluable baseline result;
- For ADA positive subjects, Nab positive subject: A subject with at least one ADA positive sample with neutralising antibodies detected post-baseline during double-blind period;
- For ADA positive subjects, Nab negative subject: A subject with only ADA positive samples with no neutralising antibodies at any time after initiation of treatment during double-blind period;

Similar definitions during transition period will only consider assessments after week 52 dose. For those, baseline will be considered as the last sample before week 52 dose:

- ADA positive subject in transition period: An ADA negative subject at week 52 (before dosing) with at least one ADA positive sample at any time [Time Frame: from Week 52 up to Week 78]
- ADA negative subject in transition period: An ADA negative subject at week 52 (before dosing) with only ADA negative samples at all time points [Time Frame: from Week 52 up to Week 78]

For the analyses through the study, initial baseline before first study drug administration will be consider, as well as all assessments performed during the study up to week 78 [Time Frame: Day 1 up to Week 78].

Incidence of ADAs to Bmab 1000 and Prolia and their neutralizing potential will be summarized for the SAF and SAF-TP using frequency of ADA positive and Nab positive samples for each timepoint and the following treatment periods: Double-blind Active-controlled Period, the Transition Period and Throughout study period. Frequencies of overall ADA positive patients plus treatment-emergent ADA patients will be also presented.

The titer of ADA positive will also be summarized by treatment group/regimen for each timepoint using descriptive statistics, including mean, SD, minimum [min], maximum [max], and median for the following treatment periods: Double-blind Active-controlled Period, the Transition Period and Throughout study period.

Effect of immunogenicity on efficacy will also be explored similarly. Summary of %CfB in lumbar spine BMD by visit and subject ADA status will be provided for baseline up to Week 78.

Additionally, percent change from baseline in BMD up to week 78 will be presented in a graph by ADA status and treatment based on FAS. If deemed appropoiate, the same graph will be presented by Nab status.

All ADA and NAb data will be listed.

12. COVID-19 Remote Visits

Visits and assessments completed remotely due to COVID-19 will be listed for the All Enrolled analysis set.

13. Blind Data Review Meeting

Prior to the database lock, the study data will be reviewed by Biocon Biologics UK Limited and appropriate Biocon team members during the blinded data review meeting (BDRM): this will include review of the protocol deviations and safety data, and their impact on analysis and populations assignment.

The protocol deviations and data will be used to decide if any subjects should be excluded from any of the populations and if there is any requirement for exclusions or special handling in the Efficacy and PK/PD analysis and/or reporting. All agreed decisions will be documented in the meeting minutes which will be finalized and signoff prior to the database lock.

14. Interim Analysis

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

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

- Double-blind Active-controlled Period: Analyses include data after all subjects have received the Week 52 assessments (prior to the third administration of study drug) 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 subjects have completed all final assessments and the complete database is locked.

15. Changes from Planned Analyses

Please refer to BDRM minutes for further details.

16. References

B1000-PMO-03-G-02 Protocol Version 3.0, 31Aug 2022

17. Appendices

17.1. Schedule of Events

Table 4 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	Doub]e-Blind Active-Controlled Period (Part 1)									Transition Period (1[1]art 2)			Early tudy Withdrawal"/ EoS
Visit	1	2	3	4	5	6	7	7a	8	9	10	11	12	13
Study Week	-28to-l	**Wk0/ 01**	**Wk0/ 03**	**Wk2/ D15**	**Wk4/ D29**	**Wkl2, D85**	**Wk20 D141**	**1Wk23/ Dl62**	**Wk26/ Dl83**	**Wk38/ D267**	**Wk52/ D365**	**Wk56/ D393**	**Wk64/ D449**	**Wk78/ D547**
Allowed Window			**:1D**	:1,2D	**:SD**	**:50**	**:SD**	:1,71!)	**:7D**	**:7D**	:1,70	:1,70	**:7D**	:1,70
Study Month	-1				1	3	5	5	6	9	12	13	15	18
Safety/laboratory te.sti	X	X				X			X	X	X			X
Albumin-adjusted total serum calci1m	X	X		X		X			X	X	X			X
Hepatitis B, C and HfV testk	X													
SARS-CoV-2i	X	As required												
Serum FT3/FT4rrSH	X													
Lateral spine X-ra.ym	X								X		X			
Radiography"		As required												
DXAscan°	X								X		X			X
Smdy treatment (Bmab I000 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 reactionP, injection site reaction mon.itoringq		X							X		X			
Calci1.1m and vitamin D supplement'		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: Subjects who early discontinue study treatment will be followed as described in Section 4.2.1 of protocol.

a. For subjects who discontinue the study early and do not wish to attend Week 26 and/or Week 52 as described in Section 4.2.1 of protocol, all procedures specified for EoS visit will 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. Subjects 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. Subjects who are initially randomized to Bmab 1000 on Day 1 will continue to receive Bmab 1000. Subjects 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/symptomdirected 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 subject 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 of protocol 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 subjects. If a subject has HBsAg positive, the subject will be excluded from the study. If a subject has HBsAg negative and HBcAb positive, an HBV DNA test will be performed at screening. If the HBV DNA test result is positive, the subject will be excluded from the study. At screening, hepatitis C antibody will be assessed in all subjects. 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 subject will be excluded from the study; If the HCV RNA test result is negative, the subject can be included in the study at the investigator's discretion. HIV test will be assessed in all subjects at screening. If the HIV test result is positive, the subject 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. Subjects 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 of protocol. 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 subject 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 subject-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 subject experiences any hypersensitivity signs and symptoms outside the study site, the subject 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 subjects will be instructed to take daily supplementation containing calcium and vitamin D as described in Section 5.2.2 of protocol.
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 subjects will be required to refrain from intense physical activity in the 48-hour period prior to sample collection.
v. Includes PFS related issues.

17.2. Imputation Algorithm for Partial and Missing Dates and Time for Safety Analysis

Medications and Procedures

Impute partial/missing start date with earliest possible date, and end date with latest possible date.

If start date is completely missing in which the day, month, and year are all unknown, then the start date will not be imputed.

For the partial start date,

- If the year is present and the month and day are missing, set month and day to January 1st.
- If the year and month are present and the day is missing and year and month are equal to year and month of first dose, set day to the first dose day.
- If the year and month are present and the day is missing and year and month are not equal to year and month of first dose, set to 1st day of month.

If the end date is completely missing, in which the day, month, and year are all unknown, then the end date will not be imputed.

For the partial end date,

- If the year is present and the month and day are missing, set month and day to December 31st.
- If the year and month are present and the day is missing, set day to last day of the month.

Medications/Procedures with both missing start and end date after imputation will be considered as concomitant.

AEs

If onset date is completely missing, onset date is set to date of first dose.

If year is present and month and day are missing:

- If year = year of first dose, then set month and day to month and day of first dose
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

- If year = year of first dose and

- If month = month of first dose then set day to day of first dose
- If month < month of first dose then set day to last day of month
- If month > month of first dose then set day to first day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

If the end date is completely missing, in which the day, month, and year are all unknown, then the end date will not be imputed.

For the partial end date,

- If the year is present and the month and day are missing, set month and day to December 31st.
- If the year and month are present and the day is missing, set day to last day of the month.

For AEs with completely missing onset date and end date; and for AEs with completely missing onset date and the end date is on or after the first dose of study drug will be considered TEAE.

Biocon Biologics UK Limited

B1000-PMO-03-G-02

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

05th July 2024

Statistical Analysis Plan Addendum

SAP Addendum 1.0

Prepared by:

[redacted]

[redacted]

TABLE OF CONTENTS

1. Introduction

The purpose of this SAP addendum is to provide summary of changes to SAP version 1.0 prior to the final database lock of the study and study unblinding.
Reference document is the SAP Final Version 1.0 dated 24th of January 2024, from now onwards called the "SAP".

2. Changes to SAP Version 1.0

After the review of dry-run blinded outputs for final analysis, changes to planned analysis were proposed and agreed with Biocon as part of the final blinded data review meeting (BDRM).

2.1 Analysis sets in Transition Period

In SAP section 4.4.7, Modified Full Analysis Set for Transition Period was defined. This analysis set is finally not used for any statistical analysis, so it is removed from the analysis sets definition.

2.2 Analysis periods

In SAP Section 4 the analysis periods are specified, and current SAP addendum adds clarity on how study assessments/events are associated to the different periods:

- *In the Double-blind Active-controlled Period, subjects will be summarized by treatment (Bmab 1000 versus Prolia) up to week 52 (predose).*
- *In the Transition Period from week 52 (post dose) up to week 78/EOS, subjects will be summarized by treatment schedule (Bmab 1000-Bmab 1000 (Arm 1), Prolia-Bmab 1000 (Arm 2) and Prolia-Prolia (Arm 3)).*
- *Through the study including all data up to week 78/EOS, subjects will be summarized by treatment schedule (Bmab 1000-Bmab 1000 (Arm 1), and Prolia-Prolia (Arm 3)).*

Study assessments/events will be associated to double-blind period (period 1) or to transition period (period 2) based on their assessment date and time or event start date and time, compared to the treatment start date and time of first and third dose respectively.

For the cases where time is not collected, it is assumed that the assessment/event occurred in period 1 in case assessment/even start date is equal to the third dose date (except for injection site reactions). Those assessments are used as baseline for period 2.

For protocol deviations, concomitant medications, and adverse events with missing start time we assign the events to the period 2 in case event date is equal to third dose date.

2.3 Efficacy analyses in Transition Period

SAP Section 8.6.2 describes the bone mineral density (BMD) endpoints for transition period. The present SAP addendum adds clarity around the multiple imputation methodology for those statistical analyses.

Data Pre-processing

Data for subjects in FAS-TP will be transposed to give a single record per subject at each relevant scheduled timepoint (Screening, or Baseline, Week 26, Week 52 and Week 78)

Imputation Model Step 1
Multiple imputation (MI) will be used with 30 imputations so that 30 complete multiply imputed data sets are produced using SAS 9.4 (or higher) PROC MI by treatment arm (3 groups) and including continuous terms for age, BMI at screening, BMD data at screening, Week 26, Week 52 and Week 78, so that any intermittent missing data at Week 26 or Week 52 will be imputed under MAR using a Markov Chain Monte Carlo approach, with single chain, non-informative prior, 200 burn-in iterations, 30 iterations between imputations in a chain and Expected-Maximization algorithm (using mcmc chain=single, the impute = monotone prior=Jeffreys options) and a non-informative prior with seed of 907876).

Imputation Model Step 2
The output data set from Imputation Model Step 1 (MI1) will be the input for Step 2 using Monotone Regression. The second imputation model will generate one imputation for each of the previous multiply imputed datasets of MI1 (i.e., by _Imputation_) and a seed of 293654.

The MI model will include continuous terms for age, BMI at screening, BMD at Screening, Week 26, Week 52 and Week 78.

Data Post-Processing
The output dataset from the multiple imputation model requires post-processing. In particular, the composite endpoint of %CfB lumbar spine BMD will be derived. In this case, two BMD percentage change for:

- % change at Week 78 from baseline Day 1
- % change at Week 78 from baseline Week 52

will be derived and analyzed.

Statistical analyses similar to the ones presented in section 8.5.1 (ANCOVA) will be performed on Week 78 lumbar spine BMD based on FAS-TP in 2 separate analyses which will be considering either original baseline or Week 52 baseline as a covariate.

Analysis Phase
2 separate ANCOVA models of %CfB lumbar spine BMD at Week 78 will be run on each of the 30 multiply imputed datasets considering original baseline or baseline at week 52 and with initial randomization stratification variables (region, age and prior use of bisphosphonates) included as classification factors, original baseline or baseline at week 52 BMD included as a continuous covariate and treatment, respectively. Datasets will be produced comprising a record for each imputation of the difference in means (relative to Prolia arm) with corresponding 90% CI.

Combining Phase
Difference in means with corresponding 90% CI from 2 separate ANCOVA of the multiply imputed datasets will be pooled using PROC MIANALYZE to produce an overall estimate (the mean of the 30 estimates) based on Rubin's formula with corresponding 90% CI.

- The least-squares (LS) mean percentage change from baseline in BMD at *Week 78* will be presented for each treatment group, as well as the LS mean difference in change from original baseline or baseline at week 52 in BMD across treatment groups (relative to Prolia arm).

- No penalty will be added and no sensitivity or supplementary analysis will be conducted for other secondary objectives in Transition period.

2.4 Immunogenicity Assessments

In the SAP section 11, the following additional definitions were considered and presented in the incidence table for Double-blind Active-controlled Period:

- Baseline Nab positive subject: A subject with baseline ADA positive sample with neutralising antibodies detected.
- Baseline Nab negative subject: A subject with baseline ADA positive sample with no neutralising antibodies detected.
- Overall ADA negative: A subject with only ADA negative samples at any time after initiation of treatment during double-blind period, irrespective of baseline result.
- Overall Nab Positive (for ADA positive subjects): subjects with at least one ADA positive sample with neutralising antibodies detected post-baseline during double-blind period.
- Overall Nab Negative (for ADA positive subjects): subjects with only ADA positive samples with no neutralising antibodies at any time after initiation of treatment during double-blind period.

Similar additional definitions were considered and presented in the incidence table for Transition Period:

- Baseline Nab positive subject: A subject with baseline (week 52) ADA positive sample with neutralising antibodies detected.
- Baseline Nab negative subject: A subject with baseline (week 52) ADA positive sample with no neutralising antibodies detected.
- Overall ADA Positive: subjects with at least ADA positive sample at any time after initiation of treatment during transition period, irrespective of baseline (week 52) result.
- Overall ADA Negative: subjects with only ADA negative samples at any time after initiation of treatment during transition period, irrespective of baseline (week 52) result.
- Overall Nab Positive (for ADA positive subjects): subjects with at least one ADA positive sample with neutralising antibodies detected post-baseline during transition period.
- Overall Nab Negative (for ADA positive subjects): subjects with only ADA positive samples with no neutralising antibodies at any time after initiation of treatment during transition period

Similar additional definitions were considered and presented in the incidence table for Throughout the Study:

- Baseline Nab positive subject: A subject with baseline (Day 1) ADA positive sample with neutralising antibodies detected.
- Baseline Nab negative subject: A subject with baseline (Day 1) ADA positive sample with no neutralising antibodies detected.
- Overall ADA Positive: subjects with at least ADA positive sample at any time after initiation of treatment, irrespective of baseline result.
- Overall ADA Negative: subjects with only ADA negative samples at any time after initiation of treatment, irrespective of baseline result.

- Overall Nab Positive (for ADA positive subjects): subjects with at least one ADA positive sample with neutralising antibodies detected post-baseline.
- Overall Nab Negative (for ADA positive subjects): subjects with only ADA positive samples with no neutralising antibodies at any time after initiation of treatment.

2.3. Compliance calculation for Vitamin D and Calcium supplements

Per SAP Section 7.1.3, compliance for Vitamin D and Calcium supplements is summarized for Double-blind Active-controlled Period and Transition Period. Following discussion on summarizing intake of supplements, it was decided that summary table will present percentage of subjects who took the supplements at each visit and recorded CRF compliance will only be displayed in corresponding listing.

2.4 Intercurrent event for Transition period

Per current methodology described in section 8 of SAP, intercurrent events are ignored in the Transition period analysis and applicable only for Double-blind Active-controlled Period analyses. Therefore, respective table summarizing the distribution of the intercurrent events will only be created for the double-blind period and not for transition period.

2.5 Ongoing adverse events

Patients with ongoing adverse events at the time of double-blind period end will be added to the summary AE table during double-blind period.

2.6 Prohibited Concomitant Medications

In SAP section 7.1.2, final list of ATC codes considered as prohibited is specified here:

Drug name	**ATC codes**
DENOSUMAB	M05BX Other drugs affecting bone structure and mineralization
ROMOSOZUMAB	M05BX Other drugs affecting bone structure and mineralization
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES	L01FX, L01FA, L04AB, L04AA, L01FD, J06BD. L01FE, Other monoclonal antibodies and antibody drug conjugates
BISPHOSPHONATES	M05BA Bisphosphonates used after randomization
FLUORIDE [SODIUM FLUORIDE]	A12CD Alimentary Tract and Metabolism-Mineral Supplements-Other Mineral Supplements]
STRONTIUM	V03AX Other therapeutic products umc-assigned ,
TERIPARATIDE	H05AA, Parathyroid hormones and analogues official
PARATHYROID HORMONES AND ANALOGUES	H05A - Parathyroid Hormones and Analogues
TIBOLONE	G03CX - Other estrogens

ESTROGEN	G03CA - Natural and semisynthetic estrogens, plain official L02AA - Estrogens official
SELECTIVE ESTROGEN RECEPTOR MODULATORS	G03XC - Selective estrogen receptor modulators
CALCITONIN	H05BA, Calcitonin preparations
CALCITRIOL	A11CC04.
ANTICOAGULANTS: WARFARIN, HEPARIN,	B01AA Vitamin K Antagonists [Blood and Blood Forming Organs-Antithrombotic Agents-Antithrombotic Agents] B01AB-Heparin Group
ANTIPLATELET	B01AC - Platelet aggregation inhibitors excl. heparin (excluding Aspirin or Acetylsalicylic Acid).
ANTICONVULSANTS	N03AX, ANTIEPILEPTICS official N03AB, N03AA, N03AF, N03AD, N03AG, N02BF
SYSTEMIC KETOCONAZOLE	J02AB02 - Ketoconazole
ADRENOCORTICOTROPIC HORMONE	H01AA - ACTH
LITHIUM	N05AN, Lithium official
GONADOTROPIN RELEASING HORMONE AGONISTS	L02AE - Gonadotropin Releasing Hormone Analogues; H01CA – Gonadotropin-Releasing Hormones
ANABOLIC STEROIDS	A14AA - Androstan Derivatives [Alimentary Tract and Metabolism-Anabolic Agents For Systemic Use-Anabolic Steroids] G03XA-Antigonadotropins And Similar Agents G03BA - 3-Oxoandrosten (4) Derivatives G03BB - 5-Androstanon (3) Derivatives
SYSTEMIC GLUCOCORTICOSTEROIDS	H02AB, Glucocorticoids official (≥ 5 mg prednisone equivalent per day for ≥ 10 days).
INVESTIGATIONAL DRUGS	V98 Investigational drug
PROTON PUMP INHIBITORS	A02BC used for Longer than a Year (> 365 days)
COVID-19**	JO7BN (an interval of 7 days is advised between the COVID-19 vaccine and study drug administration)

** Excluded for ICE5 definition.

Following updates are added to existing list of prohibited medications:

BISPHOSPHONATES	M05BB Bisphosphonates used after randomization
ESTROGEN	L02BA- ANTI-ESTROGENS
SYSTEMIC GLUCOCORTICOSTEROIDS	H02AB, Glucocorticoids official (≥ 5 mg prednisone equivalent per day for ≥ 10 days total duration overall).

3. Changes to the study protocol

In study protocol Version 3.0 dated 31Aug2022 section 7.6.4.2, we find the description of the analyses of BMD After Transition. There it is mentioned that 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. However, Transition period analyses using FAS-TP population present 90% CIs instead of 95% CIs for consistency with analysis in Double blind period (Estimand 1a-US FDA).

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