Protocol Title:	A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)
NCT Number:	NCT05338086
Statistical Analysis Plan version date:	Version 2.0, 18 January 2024

mAbxience Research S.L

MB09-C-01-19

A RANDOMISED, DOUBLE-BLIND, PARALLEL, MULTICENTRE, MULTINATIONAL STUDY TO COMPARE THE EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND IMMUNOGENICITY OF MB09 (PROPOSED DENOSUMAB BIOSIMILAR) VERSUS PROLIA® (EU-SOURCED) IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS (SIMBA STUDY)

18JAN2024

Statistical Analysis Plan

Version 2.0

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List of Abbreviations

%CfB	percentage change from baseline
25-OH vitamin D	25-hydroxy vitamin D
ADA	anti drug antibody
ANCOVA	analysis of covariance
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-}6\ months}$	area under the concentration-time curve from zero to 6 months
AUEC	area under the effect-time curve
$AUEC_{0\text{-}6\ months}$	area under the effect-time curve from zero to 6 months
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
C_{max}	observed maximum serum concentration
COVID-19	Coronavirus disease 19
CRF	case report form
C_{trough}	trough (predose) serum concentration
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EU	European Union
EU-Prolia	EU-Sourced Prolia
FAS	full analysis set
FAS-TP	full analysis set for the transition period
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1/HIV-2	human immunodeficiency virus subtype-1 and subtype-2
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
INR	International Normalised Ratio
IRT	interactive response technology
L1	first lumbar vertebra
L4	lumbar vertebra 4
MAR	missing at random

MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
mFAS-TP	modified full analysis set for the transition period
MI	multiple imputation
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
NYHA	New York Heart Association
PD	pharmacodynamic(s)
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PKCS	PK concentration set for the main treatment period
PKCS-TP	PK concentration set for the transition period
PKPS	PK parameter set for the main treatment period
PKPS-TP	PK parameter set for the transition period
PT	prothrombin time
RANK	receptor activator of nuclear factor-ΚB
RANKL	receptor activator of nuclear factor-ΚB ligand
REC	Research Ethics Committee
RMP	reference medicinal product
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAF	safety analysis set
SAF-TP	safety analysis set for the transition period
sCTX	serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	standard deviation
SI	International System of Units
SUSAR	suspected unexpected serious adverse reaction
TB-ADA	treatment-boosted anti drug antibody
TI-ADA	treatment-induced anti drug antibody
TP	transition period
ULN	upper limit of normal
US/USA	United States/United States of America
WHODRUG	World Health Organization Drug Dictionary

1. Introduction

MB09 is a medicinal product containing the mAb denosumab as the active substance and being developed by mAbxience as a biosimilar product to Prolia® (Prolia USPI 2020, Prolia SmPC 2020) which is used for the treatment of osteoporosis in postmenopausal women at increased risk of fractures 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 MB09-C-01-19 study (SIMBA Study) is to compare the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis. After collecting the totality of evidence proving its biosimilarity to Prolia®, MB09 may provide an opportunity to improve access to treatment while delivering substantial cost savings.

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 planned analyses for the Data and Safety Monitoring Board (DSMB). The DSMB charter and a DSMB 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 Guidelines.

2. Objectives, Endpoints and Estimands

Study objectives with estimands and endpoints that will be studied in the Main Treatment Period are presented in Tables 2-1, 2-2, and 2-3. The key secondary objectives and endpoints that will be studied in the Transition/Safety Follow-Up Period are presented in Table 2-4.

Table 2-1 Primary Objective, Estimands and Endpoints for the Main Treatment Period

Primary Objective	Endpoint and Estimand Descriptions
To demonstrate equivalent efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 12.	**Endpoint:** Percentage change from baseline (%CfB) in lumbar spine BMD after 52 weeks (12 months).
	Estimand 1a (Primary): Difference in means (MB09 minus EU-Prolia) in • *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.
	Estimand 1b (Supportive): Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.
Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; ICEs, intercurrent events.
Note that Estimands 1a and 1b take primarily hypothetical and treatment policy approaches, respectively, to handle ICEs and a composite strategy for death. The formation of antidrug antibodies and potential adjustments to calcium and vitamin D supplements are not explicitly mentioned in the estimand description summaries above but will be handled by a treatment policy approach in both estimands. Further details of ICEs and more detailed breakdown of the estimand attributes can be found in Section 4.3.
Note: The screening BMD assessment will be taken as the baseline BMD assessment.

Table 2-2 Secondary Objectives, Estimands and Endpoints for the Main Treatment Period

Secondary Objectives	Estimand Description (Including *Endpoint*)
To assess the efficacy of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of lumbar spine BMD at Month 6, and hip and femur neck BMD at Month 6 and Month 12.	**Estimand 2a\3a\4a:** Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB (zero is taken for anyone who dies) in* • *(2a) lumbar spine BMD after 6 months.* • *(3a) hip BMD after 6 and 12 months.* • *(4a) femur neck BMD after 6 and 12 months.* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive scheduled denosumab dose(s) without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications. **Estimand 2b\3b\4b:** Same as Estimand 1b for each endpoint above irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.
To assess the PD profile of MB09 to EU-Prolia in postmenopausal women with osteoporosis in terms of sCTX AUEC up to Month 6 and sCTX at Month 12.	**Estimand 5:** Ratio of geometric means (MB09/EU-Prolia) in *sCTX* $AUEC_{0\text{-}6\ months}$ in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming all women receive their first denosumab dose without any errors in dosing and without receipt of any prohibited therapies or other osteoporosis medications up to 6 months after first dose. **Additional summary:** Mean difference in sCTX at 11 days; 1, 3 and 6 months after the first dose; and 6 months after the second dose of study drug.

[1] Women will not have been previously treated with denosumab but may have had prior treatment with bisphosphonates and will be co-administered calcium and vitamin D supplements.
Abbreviations: %CfB, percentage change from baseline; AUEC, area under the effect curve; $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.
Note: The screening BMD assessment will be taken as the baseline BMD assessment.

Table 2-3 Secondary Objectives and Endpoints for the Main Treatment Period

Secondary Objectives	*Endpoints*
To assess the PK profile of MB09 compared with EU-Prolia.	• *$AUC_{0\text{-}6\ months}$ and C_{max} following the first dose.* • *C_{trough} of serum denosumab at Month 6 and Month 12.*
To evaluate the safety profile of MB09 compared with EU-Prolia.	• *Subject incidence of treatment-emergent adverse events up to and including Month 12.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture) up to and including Month 12.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from baseline and up to and including Month 12.* • *Subject incidence of deaths and serious adverse events up to Month 12.*
To assess the immunogenicity of MB09 compared with EU-Prolia assessed through antidrug antibodies.	• *Binding and neutralising serum denosumab antibodies from baseline and up to and including Month 12.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose) serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PK, pharmacokinetic.

Table 2-4 Secondary Objectives and Endpoints for the Transition/Follow-Up Period

Secondary Objectives	*Endpoints*
To assess the PK profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period $AUC_{0\text{-}6\ months}$ and C_{max} following the third dose at Month 12.* • *C_{trough} of serum denosumab at Transition Period Month 6.*
To assess the PD profile: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Transition Period sCTX AUEC up to Transition Period Month 6.* • *C_{trough} of sCTX at Month 12 and Transition Period Month 6.*
To assess the risk of hypersensitivity and adverse events: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Subject incidence of treatment-emergent adverse events from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of adverse events of special interest (injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction, and atypical femoral fracture) from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of clinically significant changes in physical examinations, laboratory safety tests, ECG and vital signs from third dose at Month 12 and up to and including Transition Period Month 6.* • *Subject incidence of deaths and serious adverse events from third dose at Month 12 and up to and including Transition Period Month 6.*
To assess the risk of immunogenicity through formation of antidrug antibodies: i. after the single transition from EU-Prolia to MB09 ii. on MB09 throughout each compared with those on EU-Prolia throughout.	• *Binding and neutralising serum denosumab antibodies from Month 12 and up to and including Transition Period Month 6.*

Abbreviations: $AUC_{0\text{-}6\ months}$, area under the concentration-time curve from zero to 6 months; AUEC, area under the effect curve; C_{max}, observed maximum serum concentration after administration; C_{trough}, trough (predose) serum concentration; ECG, electrocardiogram; EU-Prolia, EU-sourced Prolia; PD, pharmacodynamic; PK, pharmacokinetic; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, PK, PD, safety, and immunogenicity of MB09 (proposed denosumab biosimilar) and EU-Prolia in postmenopausal women with osteoporosis.

The study will randomise approximately 528 postmenopausal women with osteoporosis aged ≥ 55 and ≤ 80 years old with a bone mineral density (BMD) consistent with T-score of ≤ -2.5 and ≥ -4 at the lumbar spine or hip as measured by dual-energy X-ray absorptiometry (DXA) during the Screening Period. Screening evaluations will be completed within 28 days prior to randomisation.

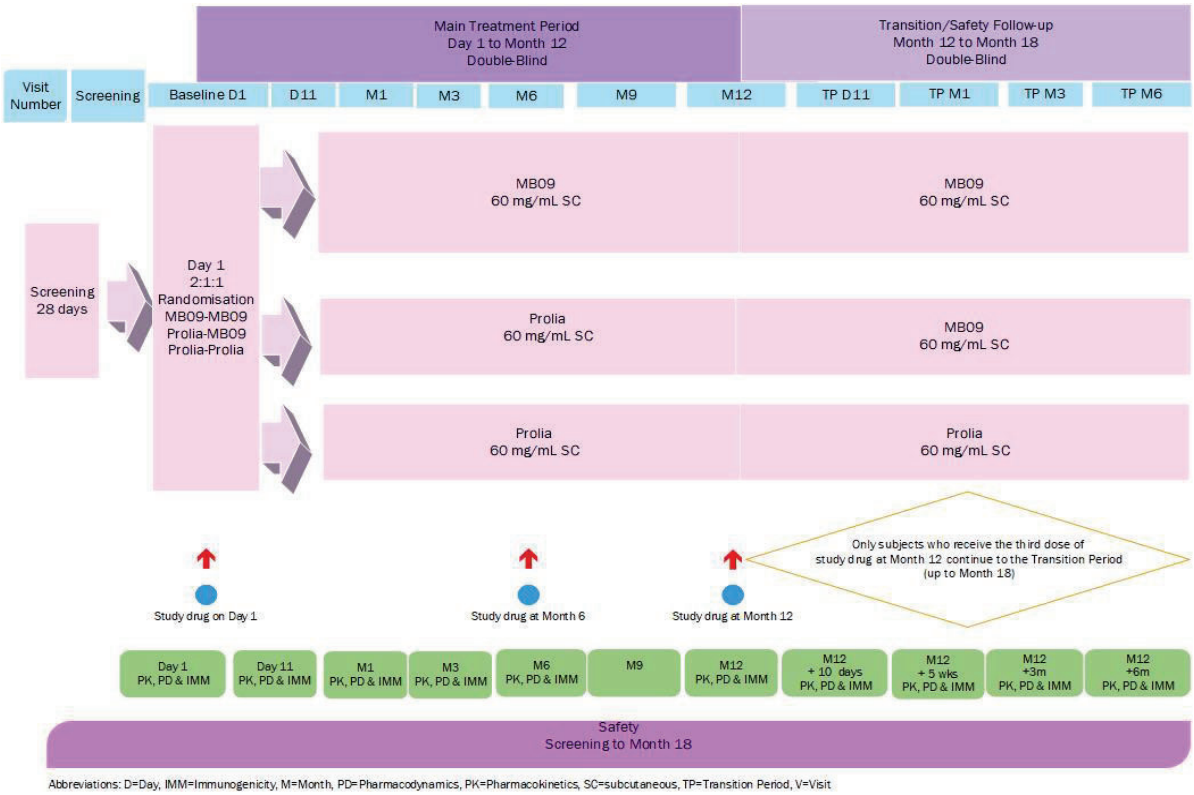
On Day 1, 528 eligible postmenopausal women with osteoporosis will be randomised in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2), or Prolia-Prolia (Arm 3) using an interactive response technology (IRT) system.

The randomisation will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 standard deviation [SD]), body mass index (< 25 and ≥ 25 kg/m^2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

This study will involve a screening period, a Main Treatment Period, and a Transition/Safety Follow-Up Period. During the Main Treatment Period, subjects will receive one subcutaneous injection (60 mg/mL) of study drug on Day 1 and at Month 6. At Month 12, after all efficacy and safety assessments have been performed, the subject will enter the Transition/Safety Follow-Up Period and will receive the third dose of study drug. Subjects assigned to the MB09-MB09 arm (Arm 1) will receive MB09 on Day 1, at Month 6, and at Month 12. Subjects assigned to the Prolia-MB09 arm (Arm 2) will receive EU-Prolia on Day 1 and at Month 6, and MB09 at Month 12. Subjects assigned to the Prolia-Prolia arm (Arm 3) will receive EU-Prolia on Day 1, at Month 6, and at Month 12. All subjects will be followed up to Transition Period Month 6. Of note, only subjects who tolerated the initial two doses and are willing to take the third dose will proceed to the Transition/Safety Follow-up Period.

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

Figure 1 Study Scheme



Abbreviations: D=Day, IMM=Immunogenicity, M=Month, PD=Pharmacodynamics, PK=Pharmacokinetics, SC=subcutaneous, TP=Transition Period, V=Visit

The maximum study duration for a subject will be approximately 19 months: 28 days for screening, a Main Treatment Period of 12 months, and a Transition/Safety Follow-Up Period of 6 months. There will be two analyses after each study period is complete: primary efficacy analysis after all subjects have received the Month 12 assessments (prior to the third administration of study drug) or have terminated the study before Month 12 and a safety addendum at month 18 when the last subject completes the End of Study (EOS) visit or withdraws early from the study.

If the subject has known SARS-CoV-2 exposure (even without symptoms related to COVID-19), the study visit for the administration of study drug will be rescheduled at the discretion of the investigator according to local regulations. Treatment with study drug can be re-introduced if the subject has tested negative for COVID-19 or after two weeks of symptom-free observation.

Administration of study drug should be interrupted if the subject has documented a presumptive COVID-19 infection and until the subject is recovered. Treatment with study drug can be re-introduced in line with local practice following the recovery of the subject and following discussion with the medical monitor and with his/her agreement.

An independent radiology review committee will assess the BMD using DXA at Month 6 and Month 12. The central reading and analysis of imaging data will be used to evaluate drug efficacy, including estimation of the primary Estimand 1a, i.e. difference in means (MB09 minus EU-Prolia) in composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies) in postmenopausal women with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications of the trial.

A DSMB will assess the safety data periodically and will recommend to mAbxience 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 summarised in the schedule of events provided in the Appendix 16.1.

4. General Statistical Considerations

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

As stratification factors are known to be incorrect for some subjects (due to errors in stratification) the actual/corrected stratification covariates will be used whenever a stratified analysis is specified. This is to reduce variability and increase precision of analysis as well as to attain a power at a level similar to the case where there are no errors. The source data for the corrected stratification covariates is presented in Table 4-1.

Table 4-1 Source Data for the Corrected Stratification Covariates

Stratification Covariate	Source Data
Baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD)	Clario
Baseline BMI (< 25 and ≥ 25 kg/m^2)	CRF
Age at randomisation date (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years)	CRF
Prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use)	CRF

Abbreviations: BMD, bone mineral density; BMI, body mass index; CRF, case report form; IRT, interactive response technology; SD, standard deviation.

Data collected in this study will be presented using summary tables, subject data listings and figures. Continuous variables will be summarised using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. 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 N of the analysis set and number of subjects with missing data will also be included.

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. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

All confidence intervals (CIs) presented will be 95% (two-sided) CIs. For primary efficacy, therapeutic equivalence is demonstrated if the 95% CI falls entirely within predefined margins; this approach is equivalent to two one-sided tests at the 2.5% significance level.

Unless otherwise specified, baseline will be defined as the last non-missing assessment prior to the study drug administration including both scheduled and unscheduled visits and assessments.

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

- In the Main Treatment Period, subjects will be summarised by treatment (MB09 versus Prolia) up to Month 12 (predose). The Prolia group will pool subjects from Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia.

- In the Transition /Safety Follow-Up Period, subjects will be summarised by treatment arm (Prolia-MB09, Prolia-Prolia) up to Transition Period Month 6.

- In the whole study period (cumulative safety data analysis), subjects that started MB09 at randomisation will be compared to subjects that started Prolia at randomisation and did not switch to MB09 in the transition period.

Study day will be calculated relative to the first dosing date as:

- If assessment date is on or after the first dosing date, then Study Day = Assessment Date – First Dosing Date + 1

- Otherwise, Study Day = Assessment Date – First Dosing Date

All analyses will be conducted using SAS Version 9.4 or higher.

All data are summarised based on the visit name collected on the CRF page.

Missing Start and Stop Dates

For the purpose of inclusion in prior and/or concomitant medication and AE tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-UKN-YYYY:
  - If the year of the start date is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug or the end date is missing, then the start date is imputed as the date of first dose of study drug.
  - If the year of the start date is the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
  - If the year of the start date is different from the year of the date of first dose of study drug, then 01 January will be assigned to the missing fields.
  - If missing only the month of the start date, then the day will be treated as missing and both month and day will be replaced according to the missing day and month logic above.

- UK-MMM-YYYY:
  - If the month and year of the start date are different from the month and year of the date of first dose of study drug, then the first day of the month will be assigned to the missing day.
  - If month and year of the start date are the same as the month and year of the first dose of study drug, and the end date (after any imputation) is on or after the date of first dose of study drug or the end date is missing, then assume the date of the first dose of study drug.
  - If the month and year of the start date are the same as the date first dose of study drug month and year, and the end date (after any imputation) is prior to the date of first dose of study drug, then assume the end date for the start date.

If the start date is not recorded on CRF then no date imputation will be performed.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.
- If missing only the month of the end date, then the day will be treated as missing and both month and day will be replaced according to the missing day and month logic above.
- After imputation, if end date is after date of death, then end date is assumed to be date of death.

If the end date is not recorded on CRF then no date imputation will be performed.

4.1. Sample Size

A sample size of 448 subjects (224 subjects on each of MB09 and EU-Prolia [Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia pooled] at Month 12) will approximately achieve 85% statistical power for the demonstration of equivalence in the %CfB lumbar spine BMD at Month 12, based on the two one-sided 2.5% significance level and an equivalence margin of ± 1.45%. In this sample size calculation, the common SD is assumed to be 4.5% and the true mean difference of %CfB is assumed to be zero. Therefore, allowing for a 15% dropout, 528 subjects will be randomised 2:1:1 to the MB09-MB09, Prolia-MB09 and Prolia-Prolia treatment arms.

A meta-analysis of three studies (Bone et al 2008, Cummings et al 2009, and McClung et al 2006) 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%). Please refer to Appendix 16.2 for further documentation on sample size assumptions.

4.2. Randomisation, Stratification, and Blinding

Interactive response technology will be used to administer the randomisation schedule. Biostatistics will generate the randomisation schedule using SAS® software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina) for IRT, which will link sequential subject randomisation numbers to treatment codes. The randomisation schedule will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m^2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use). IRT system will dynamically allocate stratification combination of the stratification factors in order to allocate a subject to a treatment arm in a blinded manner.

Eligible subjects will be randomised in a 2:1:1 ratio to receive MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2), or Prolia-Prolia (Arm 3).

Subjects who withdraw the study will not be replaced.

Stratification

The randomisation will be stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m^2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

Blinding

This study will remain double-blinded until the end of all follow-up procedures. The randomisation codes will not be revealed to study subjects, investigators, or study site

personnel, except for delegated unblinded staff who will handle the study drug, and predefined unblinded mAbxience and PPD personnel, until all final clinical data have been entered into the database and the database is locked and released for analysis.

The overall randomisation code will be broken only for reporting purposes. This will occur after database lock for data up to the end of Month 12 for all subjects. The unblinded personnel will be predefined and documented before breaking the study blinding. The study will remain blinded to the investigators, subjects, and predefined mAbxience and PPD blinded personnel until all subjects have completed the study and the database has been finalised for study closure.

A separate unblinded project team at PPD will be unblinded after the database is locked up to Month 12 for the primary efficacy analysis. Datasets (and related Table, Listing, Figure [TLFs]) containing unblinding data will be exclusively handled by unblinded project team members at PPD. However, for the blinded Clinical Study Report for the primary efficacy analysis only cumulative summary results (Tables and Figures) that do not contain information about individual study treatment assignments or other unblinding data for individual subjects will be provided to unblinded and blinded project teams at PPD and mAbxience. An unblinding plan will give full details.

Breaking the Blind Methods for Unblinding a Subject

Under normal circumstances, the blind will not be broken. The blind will be broken only if specific emergency treatment that will be dictated by knowing the study drug assignment is required for medical management. In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IRT. In case the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation.

The date, time, and reason for the unblinding must be documented in the appropriate field of the electronic case report form (eCRF), and the medical monitor must be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IRT to the medical monitor and mAbxience personnel. Any subject for whom the blind is broken may continue in the study and receive the further study drug (per protocol) at the investigator's discretion.

mAbxience's Pharmacovigilance Department will have access to the randomisation code, if SUSARs, which are subject to expedited reporting and will be unblinded before submission to the regulatory authorities.

4.3. Intercurrent Events and Estimands

Intercurrent Events

The following intercurrent events (ICEs) are relevant in the treatment of postmenopausal women with osteoporosis by subcutaneous injection of study drug (MB09 or EU-Prolia every 6 months):

- Discontinuation of study drug due to any reason.
- Errors or deviations in dosing: this would include incorrect dose, incorrect study drug, incorrect route, or a deviation in timing of the Month 6 dose (defined as being outside of the window (181 ± 28 days). Of note, study drug will be administered by the clinical staff to minimise the chance of error.
- Administration of any prohibited therapies or other osteoporosis medications.
- Adjustments to vitamin D or calcium supplements.
- Formation of antidrug antibodies.
- Death.

Estimands

Table 4-1 presents the primary objective with its estimands and rationale for strategies to address ICEs.

Table 4-1 Primary Objective and Estimands With Rationale for Strategies to Address Intercurrent Events

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

	Estimand 1a (Primary)	Estimand 1b (Supportive)
Endpoint	Percentage change from baseline in lumbar spine bone mineral density (*%CfB* lumbar spine BMD) to Month 12 and taking *%CfB* value of zero for someone who dies.	
Population Level Summary	Difference between treatments in population mean *%CfB* BMD at Month 12.	
ICEs and Strategies to Handle ICEs	**Hypothetical strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. **Treatment policy strategy** for: • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.	**Treatment policy strategy** for: • Discontinuation of study drug due to any reason (related or unrelated to study drug or osteoporosis). • Errors or deviations in dosing. • Administration of any prohibited therapies or other osteoporosis medications. • Formation of antidrug antibodies. • Adjustments to calcium and vitamin D. **Composite strategy** for death.
Rationale	It is anticipated that the occurrence of each ICE will be balanced between groups since the biosimilar, MB09, should have similar properties to the EU-Prolia. Note that the treatment policy approach in the primary Estimand 1b requires **follow-up of subjects to measure BMD at Month 12 irrespective of whether they have taken any prohibited therapies or other osteoporosis medication or not received both doses.** It should be noted that Prolia has a good safety profile, and it is anticipated that < 1% of subjects will have tolerability issues or die during the year after first dose. The hypothetical strategy of Estimand 1a will require statistical modelling to estimate the difference that might exist in the scenario that those ICEs do not occur. Note: The formation of antidrug antibodies against EU-Prolia in the first year of treatment is not particularly common (< 1%) and thus this ICE has not been specifically mentioned in the estimand and will be ignored in estimation approaches.	

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

Abbreviations: %CfB, percentage change from baseline; BMD, bone mineral density; EU-Prolia, EU-sourced Prolia; ICE, intercurrent event.

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

4.4. Analysis Sets

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

4.4.1. All Enrolled Analysis Set

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

4.4.2. All Randomised Analysis Set

The all randomised analysis set will include all (consenting) subjects who were randomised regardless of whether they actually received any study drug. Analysis will be based on treatment allocated at randomisation.

4.4.3. Safety Analysis Set

The safety analysis set (SAF) will consist of all randomised subjects who received at least one administration of study drug. The SAF will be used for all safety and immunogenicity analyses. In the SAF, subjects will be analysed per the actual treatment received.

4.4.4. Safety Analysis Set for the Transition Period

The SAF-TP will consist of all subjects in the SAF who progressed to receive a dose of study drug at Month 12, and so thereby enter the Transition Period. The SAF-TP will be used for all safety and immunogenicity analyses of the Transition Period (per the actual treatment received).

4.4.5. Full Analysis Set

The Full Analysis Set (FAS) will consist of all (consenting) randomised subjects who receive at least one dose of study drug. Subjects from the FAS will be analysed under the treatment as randomised and will be used for supportive analyses for efficacy endpoints.

4.4.6. Modified Full Analysis Set

The Modified Full Analysis set (mFAS) will consist of the subset of subjects in FAS who meet all eligibility criteria. Furthermore, the mFAS term will define a set at the data point level which includes a data record at each time point for all eligible subjects in the FAS but excludes data observed after the first occurrence of those ICEs where a hypothetical strategy is taken (e.g., missing a dose, errors or deviations in dosing, or receipt of any prohibited therapies or other osteoporosis medication). Data in the mFAS will be analysed under the treatment as randomised and used as the primary analysis set for efficacy and PD.

4.4.7. Full Analysis Set for the Transition Period

The Full Analysis Set for the Transition Period (FAS-TP) will consist of all randomised subjects in the safety analysis set for the transition period (SAF-TP) who progressed to receive a dose of study drug at Month 12.

4.4.8. Modified Full Analysis Set for the Transition Period

The term mFAS-TP will be used to define the analysis data set with a data record at each time for subjects in the FAS-TP but excludes subjects who failed eligibility criteria and data observed after the first occurrence of ICE.

4.4.9. Pharmacokinetic Analysis Sets

The PK Concentration Sets for the Main Treatment Period (PKCS) and for the

Transition Period (PKCS-TP) are concentration observation-level sets which comprise all subjects who received at least one full dose of study drug (MB09 or EU-Prolia) in the respective period and exclude observations after relevant ICEs which impact PK (e.g., missing a dose, errors or deviations in dosing or receipt of other therapies which also contain denosumab). These sets will be used for summaries of concentrations and troughs.

The PK Parameter Set (PKPS) for the Main Treatment Period comprises all subjects who have at least three measurable concentrations in PKCS which must include Day 11 to allow for reliable estimation of both C_{max} and $AUC_{0\text{-}6\ months}$. The PK Parameter Set for the Transition Period (PKPS-TP) is defined similarly.

5. Subject Disposition

5.1. Disposition

Subject disposition in the Main Treatment Period will be summarised for each treatment group and overall for the All Enrolled Analysis Set. Similarly, subject's disposition in the Transition Period will be summarised for each treatment arm and overall for the FAS-TP. The number of enrolled subjects and screen failures (including re-screened subject IDs), and subjects who are randomised in the study to each treatment group and the count and percentage of subjects who completed the Main Treatment Period and the Transition Period (i.e., study participation until the Month 12 or Month 18/EOS visit respectively without early termination) will be presented. Count and percentage of subjects who are on ongoing treatment at data cut-off date, who discontinue study treatment with the primary reason, completed the study or discontinued study early, as well as the primary reason for study discontinuation, will also be summarised.

The count and percentage of subjects in each analysis set will be presented in a summary table, separately for the Main Treatment Period and the Transition Period analysis sets. Percentages will be calculated out of the number of subjects in the All Randomised and FAS-TP for the Main Treatment Period and the Transition Period, respectively.

Subject disposition data including reason for individual unblinding, analysis sets, and randomisation data will be presented in data listings. Screen failure data will be summarised and will be presented in data listings.

5.2. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations deemed to impact critical data and lead to exclusion from efficacy analyses (based on Modified Full Analysis Set). Major protocol deviations rules associated with eligibility criteria will be developed, documented in the study deviation rules document, and finalised in a blinded manner before database lock.

The number and percentages of subjects with each major protocol deviation type will be provided separately for the Main Treatment Period and the Transition Period by treatment (arm) and overall, using the SAF and SAF-TP, respectively.

A listing of major protocol deviations and a separate listing for COVID-19 related protocol deviations will be provided for two periods (Main treatment period and Transition period), using the SAF analysis set.

6. Demographics and Baseline Characteristics

6.1. Demographics

The following demographic and baseline disease characteristics will be summarised separately for the Main Treatment Period and the Transition Period, using the SAF and SAF-TP analysis sets, respectively:

- Age (years)
- Age group (age 55 to 67, 68 to 80) as per eCRF
- Sex (female)
- Smoking status (Current Smoker, Former Smoker, Never-smoker)
- Race (White, Black or African American, Asian, American Indian Or Alaska Native, Native Hawaiian Or Other Pacific Islander, Not to be collected as per regulations, Other, Multiple [if more than one race category is selected])
- Ethnicity (Hispanic or Latino, Not Hispanic Or Latino)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI Group (>= 25 kg/m^2, < 25 kg/m^2) as per eCRF
- BMD T-score at the lumbar spine (<= -3 SD, > -3 SD) as per eCRF
- Lumbar spine BMD (g/cm^2)
- Total hip BMD (g/cm^2)
- Femur neck BMD (g/cm^2)
- Menopause duration (years) defined as (randomization date-date of menopause +1)/365. In case date of menopause is incomplete, only the year will be used for calculation.
- Osteoporosis duration (years) defined as (randomization date-osteoporosis diagnosis date +1) /365. In case date of menopause is incomplete, only the year will be used for calculation.

- Prior use of bisphosphonates (yes, no) as per eCRF
- Fracture history (yes, no)
- History of vertebrae fractures (yes, no)

Summaries for the mFAS analysis set will be also provided if SAF and mFAS are not concordant for more than 5% of the subjects. 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 All Randomised analysis set.

Demographic and baseline characteristics data will be listed for two periods (Main treatment period and Transition period) using the All Randomised analysis set.

6.2. Medical History

Medical history will be classified by system organ class (SOC) and preferred term (PT) using MedDRA (Version 24.1 or higher) and summarised by SOC and PT for each treatment group and overall for the Main Treatment Period and Transition Period using the SAF analysis set. Medical history will be presented in a data listing for subjects in the All Randomised analysis set.

6.3. Inclusion and Exclusion Criteria

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

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using WHODRUG (Version B3 dated September 2021 or higher). Summaries of all medications by drug class (ATC Level 4 coding) and PT will be provided separately for prior medications and concomitant medications.

For the Main Treatment Period, prior medications are those with the stop date prior to the first dose of the Main Treatment Period. Concomitant medications are those with start dates prior to the first dose of the Main Treatment Period and continuing after the first dose of the Main Treatment Period or with start dates between the first dose of the Main Treatment Period and the first dose of the Transition Period.

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 summarised and listed for both the Main Treatment Period and the Transition Period. For the Main Treatment Period, prior and concomitant medications will be summarised separately using the SAF analysis set. For the Transition Period, concomitant medications will be summarised using the SAF-TP analysis set.

For the purpose of inclusion in prior and concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 4.

If start date is completely missing and end date is after the first study drug dose or completely missing, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing and the start date is after first study drug dose, then the medication will be considered as ongoing and classified as concomitant. If the end date is missing and the start date is before first study drug dose, then the medication will be considered as ongoing and classified as both prior and concomitant.

Prior and concomitant medications for two periods (Main treatment period and Transition period) will be presented in a listing for the SAF analysis set presenting information collected under the “Prior and Concomitant Medications” and “Bisphosphonates” eCRF forms.

For concomitant medications only, any that are reporting Vitamin D or Calcium will not be summarised or listed.

7.2. Prohibited Concomitant Medications

Prohibited concomitant therapy will be summarised separately for the Main Treatment Period and the Transition Period using the SAF and SAF-TP, respectively.

For this study, prohibited concomitant therapy will be defined as the bundle of medication compound, indication, dose, frequency and duration of the therapy, or any other consideration which impacts on bone metabolism, BMD and/or denosumab mechanism of action. To select the prohibited therapies, the same medication compounds that were considered to have an impact on bone metabolism for eligibility were analysed. After flagging them in an excel file report taken from CM SDTM, medical assessment was performed to conclude whether that therapy was to be prohibited or not. The medical assessment was performed case by case considering therapy as a bundle of factors including dose, frequency, indication and duration of medication. In cases where applies, also cumulative dose was considered, as well as any other potential impact on bone metabolism, BMD or denosumab mechanism of action.

Before primary and final data cut-off date, mAbxience team will flag prohibited medications in an excel file report taken from CM SDTM. Prohibited medications flagged will be loaded back in CM SDTM to be used in the statistical analysis. This process is documented in a

Data Import Agreement document.

In addition, time to first prohibited or other osteoporosis medication will be presented by treatment (MB09 or Prolia) using a Kaplan-Meier curve on the SAF whereby the first dose date of prohibited or other osteoporosis medication will be the event date. Subjects who have not had an event will be censored at the earliest of data cut-off date and EOS visit date.

7.3. Vitamin D and Calcium Supplementation

Vitamin D and calcium supplementation compliance will be summarised separately for the Main Treatment Period using the SAF and for the Transition Period and throughout the study using the SAF-TP and SAF respectively.

Compliance (%) = (total number of scheduled visits when supplement was taken/total number of scheduled visits performed) × 100.

Summary statistics for vitamin D and calcium supplementation compliance percentages and compliance categories (<25, ≥25 - <50, ≥50 - <75, ≥75 - <100, 100) will be summarised.

All vitamin D and calcium supplementation administration data for two periods (Main Treatment Period and Transition Period) will be presented in a data listing using the SAF analysis set.

7.4. Study Treatments

Study treatments will be summarised separately for the Main Treatment 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.

In addition, time to treatment discontinuation will be presented by treatment (MB09 or Prolia) using a Kaplan-Meier curve on the SAF whereby the last visit date will be the event date for those subjects who are off study treatment. Subjects who have not had an event will be censored at the earliest of data cut-off date and EOS visit date.

All study drug administration data for two periods (Main treatment period and Transition period) will be presented in a data listing using the SAF analysis set.

8. Efficacy Analysis

8.1. Overview of Statistical Methods: Estimation of Estimands and Sensitivity Analyses

Table 8-1 presents a summary of statistical methods including sensitivity analyses.

Table 8-1 Summary of Statistical Methods, Including Sensitivity Analyses

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1a (Primary)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive two denosumab doses without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications.	mFAS	The composite endpoint defines any deaths as zero. mFAS removes data occurring after ICEs for which the hypothetical strategy is used (keeping all eligible subjects in the FAS). For sensitivity [i], MI under MAR [ii] delta applied to imputation in the tipping point approach.	MMRM of *%CfB* BMD at Month 6 and Month 12 including terms for visit by treatment, baseline BMD (as a covariate), and classification variables for: age, body mass index and prior use of bisphosphonates. The estimated mean difference in *%CfB* will be presented with 95% CI at each time point. The 95% CI for the mean difference at Month 12 in *%CfB* BMD will be compared to margins of [-1.45, 1.45]. (See Section 8.2.1 for further details).	[i] MI under MAR approach will be applied to the mFAS (see Section 8.2.2.1 for further details). %CfB BMD at Month 12 from each multiple imputed data set will be analysed by MMRM and results pooled using Rubin's method. [ii] A tipping point analyses will be performed. First, MI under MAR will be used to impute missing data where a penalty will be added to the imputed %CfB values. The same penalty (delta) will be applied to anyone who dies. The tipping point will consider delta1 and delta2 for the Prolia and MB09, respectively in a matrix of delta so that tipping points for both the upper and lower margins are considered (see Section 8.2.2.2 for further details). **Supplementary:** MMRM analysis of log transformed data (see Section 8.2.5 for further details).

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 2a	Similarly for lumbar spine BMD at 6 months	mFAS	As above	As above	As above for [i] MI under MAR, and supplementary MMRM on log data.
Estimand 1b (Supportive)	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB in lumbar spine BMD after 52 weeks/12 months (where %CfB of zero is taken for anyone who dies)* in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months irrespective of discontinuation of treatment for any reason, errors or deviation in dosing and whether any prohibited therapies or other osteoporosis medications are taken.	FAS	The composite endpoint defines *%CfB* of zero for anyone who dies. For the main analysis, MI under MAR with offset applied to "treatment failures" (not receiving the 2nd dose) to be centred around baseline. *%CfB-TF* will define *%CfB* after applying offset for treatment failures (see Section 8.2.3.1).	ANCOVA of *%CfB-TF* BMD at Month 12 for each multiply imputed dataset and including terms for treatment, baseline BMD (as a covariate), and classification variables for: age, body mass index and prior use of bisphosphonates. Results will be pooled using Rubin's method The estimated mean difference in *%CfB* BMD will be presented with 95% CI (see Section 8.2.3 for further details).	The same tipping point approach used for Estimand 1a will be performed. A penalty will be added to the imputed %CfB-TF values. The tipping point will consider delta1 and delta2 for the Prolia and MB09, respectively in a matrix of delta so that tipping points for both the upper and lower margins are considered (Section 8.2.2.2 and 8.2.4). **Supplementary:** ANCOVA analysis of untransformed and log transformed data in FAS without imputation (see Section 8.2.5 for further details).
Estimand 2b (Supportive)	Similarly for lumbar spine BMD at 6 months.	FAS	The composite endpoint defines any deaths as zero. Observed data will be analysed without any imputation.	ANCOVA of *%CfB* BMD at Month 6 as above.	**Supplementary:** ANCOVA analysis of log transformed data (see Section 8.2.5 for further details).

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 3a-4a	Difference in means (MB09 minus EU-Prolia) in *composite endpoint of %CfB (zero is taken for anyone who dies) in* • *(3a) hip BMD after 6 and 12 months.* • *(4a) femur neck BMD after 6 and 12 months.* In postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming that all women receive scheduled denosumab dose(s) without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications are taken.	mFAS	The composite endpoint defines *%CfB* of zero for anyone who dies. The mFAS removes data occurring after ICEs for which the hypothetical strategy is used (keeping all subjects in the mFAS).	As per Estimand 1a and 2a for lumbar spine BMD, MMRMs will be fitted to hip BMD and to femur neck *%CfB* BMD at Month 6 and Month 12 and these will be of the same form including terms for visit by treatment, baseline BMD and strata as classification variables. (See Section 8.3.1 for further details).	None.
Estimand 3b-4b	Difference in means (MB09 minus EU-Prolia) in • *(3b) hip BMD after 6 and 12 months.* • *(4b) femur neck BMD after 6 and 12 months.* (where *%CfB* of zero is taken for anyone who dies) in postmenopausal women[1] with osteoporosis treated with scheduled denosumab	FAS	The composite endpoint defines any deaths as zero. Observed data will be analysed without any imputation.	ANCOVA of *%CfB* BMD for each endpoint by time point and including terms for treatment, baseline BMD, and strata as classification variables. The estimated mean difference in *%CfB* will be presented with 95% CI. (See Section 8.3.2 for further details).	None.

Estimand Label	Estimand Description	Main Estimation			Sensitivity Analysis
		Analysis Set	Imputation/Data/ Censoring Rules	Analysis Model/Method	
	dose(s) every 6 months irrespective of discontinuation of treatment for any reason, errors or deviations in dosing and whether any prohibited therapies or other osteoporosis medications are taken.				
Estimand 5	Ratio of geometric means (MB09/EU-Prolia) in *sCTX* $AUEC_{0\text{-}6\ months}$ in postmenopausal women[1] with osteoporosis treated with subcutaneous denosumab injections every 6 months assuming all women receive their first denosumab dose without any errors in dosing and without receipt if any prohibited therapies or other osteoporosis medications up to 6 months after the first dose. Additional summary: Mean difference in *sCTX* at 11 days; 1, 3 and 6 months after the first dose; and 6 months after the second dose of study drug.	mFAS	Interpolation/extrapolation will be used to calculate AUEC but will require at least baseline and three post-dose time points.	ANCOVA model on log transformed data including log transformed baseline *sCTX* as a continuous covariate with stratification variables included as classification factors. Back transformation of mean differences will give the ratio of geometric means (MB09/EU-Prolia) with 95% CI. (See Section 10.1 for further details).	**Supplementary:** MMRM on the unlogged *sCTX* allowing for different variability at each time point up to Month 12. The least square means and differences with 95% CI will be plotted over time. An estimate statement will be used to calculate a weighted average across the scheduled time points where the weights correspond to the weights used in calculating AUEC. Thus this will give an estimate of mean AUEC and difference between mean AUEC with 95% CI. (See Section 10.1 for further details).

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

Abbreviations: %CfB, percentage change from baseline; %CfB-TF, percentage change from baseline for treatment failure; ANCOVA, analysis of covariance; AUEC, area under the effect curve; $AUEC_{0\text{-}6\ months}$, area under the effect curve from zero to 6 months; BMD, bone mineral density; CI, confidence interval; EU-Prolia, EU-sourced Prolia; FAS, Full Analysis Set; ICE, intercurrent event; MAR, missing at random; mFAS, Modified Full Analysis Set; MI, multiple imputation; MMRM, mixed model for repeated measures; sCTX, serum carboxy-terminal cross-linking telopeptide of type I collagen.
Note: The screening BMD assessment will be taken as the baseline BMD assessment.

8.2. Primary Efficacy Endpoint

8.2.1. Main Estimation of Estimand 1a (Primary)

The centralized independent and blinded reading and analysis of DXA scans will be used to assess BMD. Uncorrected subject BMD results will be sent to PPD, and if and when corrections are determined as they are all retrospective, the corrected data will be sent as well. These are corrections for longitudinal drift, cross-calibration, and machine equivalence (scanner upgrades). Efficacy analysis will be based on the corrected data if corrections are applied.

Unadjusted total lumbar spine BMD results will include lumbar vertebrae from L1 to L4 and will be sent to PPD. Due to fracture, artifact such as hardware or other issues individual vertebral levels may be excluded retrospectively from all visits with the total spine BMD calculated based on the evaluable vertebral levels. If and when adjustment in vertebral levels occurs, the adjusted data will be sent as well. Efficacy analysis will be based on the adjusted total spine BMD results.

The statistical hypothesis associated with the difference in treatments for the primary efficacy analysis of %CfB in lumbar spine BMD at Month 12 is:

H0: $(\mu_{MB09} - \mu_{Prolia} \leq -1.45\%)$ or $(\mu_{MB09} - \mu_{Prolia} \geq +1.45\%)$

H1: $-1.45\% < \mu_{MB09} - \mu_{Prolia} < +1.45\%$

where μ_{MB09} and μ_{Prolia} denotes the true mean %CfB in lumbar spine BMD at Month 12 for MB09 and EU-Prolia, respectively.

For the primary efficacy analysis, a MMRM will be fitted to the composite %CfB lumbar spine BMD at Month 6 and Month 12 on the mFAS. The MMRM will include terms for visit by treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. Note: Baseline BMD at the lumbar spine is included as a covariate rather than including BMD T-score as a classification factor. Subject will be included as a random effect.

The estimated treatment LS means will be presented at each time point. Due to potential imbalances in stratification covariates treatment LS means will be computed for the two weighting schemes:

1. The standard weighting scheme with equal coefficients across stratification covariates.
2. Weighting scheme with coefficients that are proportional to those found in the data (using SAS OM option).

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

The estimated mean difference in %CfB lumbar spine BMD at Month 12 will be presented with 95% CI and equivalence will be concluded if this falls within the predefined equivalence margins of [-1.45%, 1.45%].

Of note, the main analysis method is on the mFAS and, therefore, does not use data after any errors or deviation in dosing and without receipt of any prohibited therapies or other osteoporosis medications.

All efficacy data will be presented in listings.

8.2.2. Sensitivity Analysis of Primary Efficacy Endpoint

Two sensitivity approaches will be performed:

1. A multiple imputed data set produced under MAR, as explained below in Section 8.2.2.1, will be applied to the mFAS. In each multiple imputed data set, all eligible subjects in the FAS (i.e. mFAS) will have complete data and an indicator variable will be derived to indicate if data are observed or imputed. The composite %CfB lumbar spine BMD will be calculated as a post processing step from BMD values.

2. "Sensitivity using tipping point" will assess the robustness of results in both of the one-sided hypotheses by adding penalties in both directions to all missing data (see Section 8.2.2.2).

8.2.2.1. Multiple Imputation Model Under Missing at Random

The multiple imputation approach will be tested on blinded data and thus should be confirmed, and any changes documented before database lock in the blinded review. 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 Clinical Study Report.

Data Pre-processing

Data will be transposed to give a single record per subject (FAS or mFAS) at each relevant scheduled timepoint (Screening, 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

The multiple imputation process will be used with 30 imputations so that 30 complete multiple imputed datasets are produced using SAS 9.4 (or higher) PROC MI.

The first step is to impute any intermittent missing data at Month 6 (i.e., where Screening and Month 12 data are available) using a Markov Chain Monte Carlo (MCMC) method with single chain, non-informative prior, 200 burn-in iterations, 30 iterations between imputations in a chain and Expectation-Maximization algorithm (using mcmc chain=single impute=monotone prior = jeffreys options) and seed of 8749102 (this seed has been randomly generated).

The imputation model will be fitted by treatment (MB09 or Prolia) and analysis set (mFAS or FAS) and include the following terms in this specific order with terms included in chronological order (i.e. all baseline terms are first and all Month 12 terms are last):

- Age (continuous)
- BMI at baseline (continuous)
- Total number of doses received
- Prior use of bisphosphonates (0, 1)
- Baseline sCTX
- Lumbar spine BMD at Baseline
- sCTX at Day 11, Month 1, Month 3, Month 6
- Lumbar spine, hip, femur BMD at Month 6
- sCTX at Month 12
- Lumbar spine, hip, femur BMD at Month 12

In the event that the model does not converge then removal of some of the later sCTX terms will be considered first.

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 multiple imputed datasets of MI1 (i.e., by *_Imputation_* and analysis set) and a seed of 293654.

The model will include the same variables and in the same specific order as above with the additional first term for Randomised treatment (MB09 or Prolia).

In the event that the model does not converge then removal of some of the later sCTX terms will be considered first.

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 the %CfB lumbar spine BMD is defined as zero for anyone who dies, and any imputed values will be replaced at this step.

Additionally, %CfB-TF will be calculated for FAS as defined in Section 8.2.3.1 to achieve a return to baseline imputation at Month 12 of those who only received a single dose.

Multiple Imputation: Analysis Phase

For Estimands 1a and 2a (mFAS) a MMRM model of %CfB lumbar spine BMD at Month 6 and Month 12 will be run on each of the 30 multiple imputed datasets. The MMRM model (as per Estimand 1a) will comprise terms for visit by treatment, baseline lumbar spine BMD (as a covariate), and classification variables for: age, body mass index and prior use of bisphosphonates.

For Estimands 1b and 2b (FAS) an ANCOVA model of %CfB (%CfB-TF for Month 12 FAS) lumbar spine BMD at Month 6 and Month 12 will be run on each of the 30 multiple imputed datasets. The ANCOVA model (as per Estimand 1b) will comprise terms for treatment, baseline lumbar spine BMD (as a covariate), and classification variables for: age, body mass index and prior use of bisphosphonates.

Datasets will be produced comprising a record for each imputation of the difference in means (MB09 minus EU-Prolia) with corresponding 95% CI.

Multiple Imputation: Combining Phase

Difference in means with corresponding 95% CI from MMRM (for Estimand 1a) and ANCOVA (for Estimand 1b) 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 95% CI.

8.2.2.2. Sensitivity Using Tipping Point

Multiple imputation under MAR should produce results close to MMRM and ANCOVA analysis of observed data. The tipping point approach tests the robustness of results from MI assuming MAR by adding a penalty.

A tipping point penalty will be added to the Month 12 imputed %CfB lumbar spine BMD values (but not to data observed). The same penalty (delta) will be applied to anyone who dies for related reasons. The tipping point will add penalties of delta1 and delta2 to %CfB BMD values for EU-Prolia and MB09, respectively, in a matrix of values (delta1 = -6 to 6 by delta2 = -6 to 6 in steps of 1.5). For each combination of delta values, ANCOVA is performed for each multiply imputed dataset and then result pooled using Rubin's method. Of note, both positive and negative values of delta will be tested in order to evaluate the

tipping point of where the 95% CI for the mean difference in %CfB BMD fails to meet each of the lower and upper bounds of the equivalence margins of [-1.45, 1.45].

8.2.3. Main Estimation of Estimand 1b (Supportive)

The supportive Estimand 1b requires that study conduct has made a good effort to follow-up on subjects particularly after ICEs.

In order to estimate Estimand 1b an ANCOVA will be fitted to the composite %CfB lumbar spine BMD at Month 12 to each multiple imputed data set on the FAS where a treatment failure offset penalty is applied to missing values of those not receiving the 2nd dose (see Section 8.2.3.1 for details). The ANCOVA will include terms for treatment, with stratification variables (age, body mass index and prior use of bisphosphonates) included as classification factors and baseline BMD included as a continuous covariate. Of note, baseline BMD at the lumbar spine is included as a covariate rather than including BMD T-score as a classification factor.

The estimated mean difference in %CfB lumbar spine BMD results will be pooled using Rubin's method and will be presented with 95% CI.

8.2.3.1. Return to Baseline Multiple Imputation using Treatment-Failure Penalty

MI under MAR approach will be applied to the FAS (see Section 8.2.2.1) and then an offset penalty applied where Month 6 doses was not received. Subjects will be assumed "treatment-failure" if they have missing data at Month 12 and only received the baseline dose (did not receive Month 6 treatment for any reason). It is assumed that these "treatment failure" subjects would return to around baseline levels rather than benefit from any improvement that may have been expected following Month 6 dose administration. In order to allow for a reasonable level of uncertainty in the Month 12 imputed values, the Month 12 imputed BMD data from the MI under MAR will be adjusted by an individual offset so that %CfB BMD values for a subject considered as treatment failure will be centred around zero. Thus, an alternative %CfB-TF will be calculated defined as %CfB minus offset where offset is calculated for each individual as the mean of that individual's %CfB values (imputed under MAR) for subjects classified as treatment failures. No offset (i.e. offset = 0) is applied to:

- any observed data (treatment policy approach uses data as observed);
- any missing Month 6 BMD data (since at Month 6 everyone will have only received a single dose)
- deaths (deaths have composite %CfB BMD defined as zero);
- subjects who receive both baseline and Month 6 treatment.

An ANCOVA is performed on %CfB-TF for each multiply imputed dataset and then results pooled using Rubin's method in order to present the difference in mean %CfB with 95% CI.

8.2.4. Tipping Point Sensitivity Analysis of Estimand 1b (Supportive)

The main estimation method for Estimand 1b is ANCOVA on Month 12 imputed %CfB lumbar spine BMD values where a multiple imputation approach with treatment failure offset is used and thus the dependent variable is defined as %CfB-TF (see Section 8.2.3.1).

The same approach will be taken as for the primary estimand tipping point (see Section 8.2.2.2). A tipping-point penalty (delta) will be added to all imputed %CfB-TF above (but not to data observed). This penalty will be applied regardless of the reason for missingness and even if the treatment failure offset penalty has already been applied. In the case of any deaths, the penalty will be applied to anyone who dies for related reasons but for unrelated deaths zero change from baseline is assumed (the same approach as per Section 8.2.2.2).

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

8.2.5. Supplementary Analysis of Primary Efficacy Endpoint

In order to investigate assumptions of normality, the log transformed BMD as a ratio of baseline will be analysed in a similar MMRM model to the main analysis but with baseline covariate as the log BMD (using the mFAS). The least squares means and difference will be back-transformed to present geometric mean ratios of baseline, and 95% CI for the ratio of geometric means (MB09/EU-Prolia). Note: For anyone who dies, no change from baseline will be assumed (BMD ratio of baseline of 1). Residual plots will be produced and compared to the main analysis.

Similarly, the ANCOVA analysis on the FAS (without multiple imputation) will be performed on non-transformed and log transformed data as supplementary analysis for Estimand 1b. Geometric mean ratios of baseline at Month 12, and 95% CI for the ratio of geometric means (MB09/EU-Prolia) will be presented.

Residual plots from these analyses on untransformed and log-transformed data will be visually inspected.

8.3. Analysis of Key Secondary Efficacy Endpoints

8.3.1. Main Estimation of Hypothetical Estimand 2a-4a

MMRM as per the main analysis of the primary endpoint (see Section 8.2.1) will be used to analyse composite endpoint of %CfB (zero is taken for anyone who dies) on the mFAS in:

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

- Femur neck BMD after 6 and 12 months.

8.3.2. Main Estimation of Treatment Policy Estimand 2b-4b

An ANCOVA (see Section 8.2.3) on the FAS (without any multiple imputation methods) will be used to analyse the composite endpoint of %CfB (zero is taken for anyone who dies) in:

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

8.4. Subgroup Analyses

Subgroup analyses will be conducted for the primary estimand 1a and the secondary estimand 2a in the mFAS 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 (MB09 minus EU-Prolia) will be estimated using the same analysis model as described in Section 8.1.

- Baseline lumbar spine BMD T-score (as per Clario) (≤ -3.0 versus > -3.0 SD).
- Body mass index at baseline (< 25 versus ≥ 25 kg/m^2).
- Age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years).
- Prior bisphosphonate medication use at study entry
  (prior use of bisphosphonates versus no prior bisphosphonate use).
- Body weight at baseline (≥ 50 to < 70 kg versus ≥ 70 to ≤ 99.9 kg).
- Smoker (Yes/No).
- Region (Latin America/Europe)

A forest plot of difference in means at Month 6 and 12 will be produced. The number and percentage of subjects in each subgroup level, difference in means and corresponding 95% CI will be provided.

9. Safety Analysis

Safety assessments include vital sign assessments, ECG, physical examination, clinical laboratory analyses, adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and deaths.

All safety measurements will use all available data for analyses (listings only), including data from unscheduled visits.

Main Treatment Period and the Transition Period will be analysed on SAF and SAF-TP, respectively. Analysis in the Main Treatment Period will be tabulated by MB09-MB09 (Arm 1) and combined treatment group of Prolia-MB09 (Arm 2) and Prolia-Prolia (Arm 3). Analysis in the Transition Period will be tabulated by Prolia-MB09 (Arm 2) and Prolia-Prolia (Arm 3). Additionally, cumulative safety data throughout the study (Baseline to the end of Transition Period [Month 18]) will be analysed for MB09-MB09 (Arm 1) and Prolia-Prolia (Arm 3) as described in section 4.

In the Transition Period, changes from Month 12 and changes from baseline (Day 1) in selected laboratory parameters will be of interest (see Section 9.2).

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 drug.

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.

Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen are not considered AE. Laboratory results of disease/disorders being studied, medical/surgical procedures are not an AE but rather the condition/event that leads to it are defined as an AE.

Any abnormal laboratory test results (haematology, clinical chemistry, coagulation 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 clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, will not be reported as AE or SAE. Disease progression of postmenopausal osteoporosis will not be recorded as an AE or SAE; however, any new fractures confirmed by the central imaging vendor will be recorded as AE or SAE.

Medical intervention such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They will be recorded as

treatment(s) of the AEs. The event term of primary cause will be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

AEs experienced by the subjects will be collected throughout the entire study and will be all listed and coded using the MedDRA (version 24.1 or higher).

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 the Main Treatment Period, TEAE is an event observed after first administration of study drug on Day 1 until Month 12 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 Month 12 until Month 18.

For the cumulative safety data analysis at Month 18, TEAE is an event that is classified as either Main Treatment Period TEAE or Transition Period TEAE.

Imputed AE data will be summarised, 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 summarised.

In the case of missing or partially missing AE onset dates, the rules described in Section 4 will be applied.

9.1.2. Incidence of Adverse Events

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 number and percentage of subjects and the number of events will also be presented by SOC and PT. At each level of subject summarisation, a subject will be counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the SAF and SAF-TP for the Main Treatment Period and the Transition Period respectively. Cumulative safety data analysis will be calculated out of the number of subjects in the SAF.

. The number of events at each level of SOC and PT will also be summarised.

The summary of TEAEs will be presented in descending order of frequency of SOC and PT in the specified treatment (arm) (that is, MB09-MB09 arm (Arm 1) for the Main Treatment Period, Prolia-MB09 arm (Arm 2) for the Transition Period, and MB09-MB09 arm (Arm 1) and Prolia- Prolia (Arm 3) for cumulative safety data analysis. If the incidence for two or more SOCs (PTs) is equal, the SOCs (PTs) will be presented in alphabetical order.

The number and percentage of subjects and the number of events will also be categorised by PT only and will be presented in descending order of incidence.

9.1.3. Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Unrelated”, “Possibly Related”, “Probably Related” and “Definitely Related”. "Unrelated” AEs will be categorised as “Not Related”. All other AEs: “Possibly Related”, “Probably Related” and “Definitely Related” will be categorised as “Related”. TEAEs that are missing a relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship. The TEAE data will be categorised 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 Main Treatment Period and the Transition Period respectively. Cumulative safety data analysis will be calculated out of the number of subjects in the SAF.

9.1.4. Severity of Adverse Event

The assessment of severity, or intensity, of an TEAE will be made using the following CTCAE grading criteria Version 5.0:

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; hospitalisation or prolongation of hospitalisation indicated; disabling; limited self-care activities of daily living.

Grade 4: Life-threatening consequences: urgent intervention indicated.

Grade 5: Death related to adverse event.

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 TEAE, only the most severe will be presented. TEAEs that are missing severity will be presented in table as “Grade 3” 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 Main Treatment Period and the Transition Period respectively. Cumulative safety data analysis will be calculated out of the number of subjects in the SAF.

The TEAE data will be categorised 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 9.1.3.

9.1.5. Serious Adverse Events

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 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect. Medical and scientific judgement will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

AEs to be treated as SAEs by the investigator are AEs associated with hospitalisation (over 24 hours) or prolongation of hospitalisation. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalisation or prolongation of hospitalisation 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 categorised presented by SOC and PT in a manner similar to that described in Section 9.1.2. The number and percentage of subjects and the number of events will also be categorised 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 9.1.4.

All SAEs will be presented in a listing.

9.1.6. Serious Adverse Events, Related to Study Drug

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

9.1.7. Adverse Events of Special Interest

Adverse events of special interests (AESIs) are defined as AEs of scientific or medical concern.

The following AEs are considered as AESIs: injection site reaction, drug-related hypersensitivity/allergic reaction, infection, hypocalcaemia, osteonecrosis of the jaw, dermatologic reaction and atypical femoral fracture.

A summary of AESIs will be presented by severity, SOC and PT similar to that described in Section 9.1.4.

All AESIs will be presented in a listing.

9.1.8. Serious Adverse Events of Special Interest

A summary of serious AESIs will be categorised and presented by SOC, PT, in a manner similar to that described in Section 9.1.2.

9.1.9. Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs with a study drug action taken of "Drug Withdrawn" will be presented in a table in a similar manner to that described in Section 9.1.2.

All TEAEs leading to treatment discontinuation will be presented in a listing.

9.1.10. Adverse Events Leading to Death

A summary of TEAEs where the answer to "Outcome" is "Fatal" will be presented in a table in a similar manner to that described in Section 9.1.2.
All subjects who have an AE with an outcome of "Fatal" will be presented in a listing.

9.1.11. Death

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

9.1.12. 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, AE leading to death, and all deaths will be provided by treatment (arm).

9.1.13. Summary of Non-Traumatic Fractures

A summary of non-traumatic fractures will be presented in a table in a similar manner to that described in Section 9.1.2.

9.2. Clinical Laboratory Evaluations

All summaries will be based on SI units. Blood and urine samples collected for clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis) will be analysed by the central laboratory.

Clinical chemistry and haematology are collected at screening, baseline (Day 1), Day 11, Month 1, Month 3, Month 6, Month 9, Month 12 (End of Treatment), Transition Period Day 11, Transition Period Month 3, and Transition Period Month 6 (End of Study) visits. Coagulation and urinalysis are collected at screening, baseline (Day 1), Month 6, Month 12 (End of Treatment), and Transition Period Month 3.

In the Main Treatment Period, a summary table presenting observed values and changes from baseline will be presented for clinical chemistry (PTH parameter) only with numeric values. Change from baseline to each scheduled post-baseline visit will be presented.

The following graphics will also be provided for selected clinical laboratory tests (albumin-corrected calcium only):

- A plot showing baseline and worst post-baseline in clinical laboratory values.
- A boxplot of values per visit.
- A spaghetti plot of values per visit.

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.

A summary table presenting the worst post-baseline CTCAE grade for the albumin-adjusted total serum calcium will be provided. Results will be programmatically graded according to CTCAE v5.0.

In the Transition Period, summary tables and graphics will be presented for all laboratory parameters described in sections 9.2.1 to 9.2.4, except changes will be presented from Month 12 instead of baseline (Day 1). Additionally, changes from baseline (Day 1) to each scheduled visit in the Transition Period will be presented for selected clinical laboratory tests: albumin-corrected calcium.

For the cumulative safety data analysis at Month 18, summary tables and graphics will be presented for all laboratory parameters described in sections 9.2.1 to 9.2.4, except data will be analysed for armMB09-MB09 (Arm 1) and Prolia-Prolia (Arm 3) and all assessments up to Month 18 will be included.

Listings of clinical laboratory data will be provided separately for two periods (Main treatment period and Transition period) using the SAF analysis set.

9.2.1. Haematology

The following laboratory tests will be included: haemoglobin, haematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, absolute lymphocyte count, and platelet count. Summary tables and listings will be presented as described in Section 9.2.

9.2.2. Clinical Chemistry

The following laboratory tests will be included: albumin-adjusted total serum calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total cholesterol, creatinine, creatine clearance estimation, gamma-glutamyl transferase, glucose, triglycerides, magnesium, phosphorus, PTH, potassium, sodium, total bilirubin direct bilirubin, protein, thyroid-stimulating hormone and serum 25-OH vitamin D. Summary tables and listings will be presented as described in Section 9.2.

Albumin-adjusted total serum calcium level will be calculated using the following formula: Corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]), where 4.0 represents the average albumin level.

If the albumin-adjusted total serum calcium level is calculated using mg/dL unit, it will be adjusted for SI units using the following formula: Corrected calcium (mmol/L) = total calcium (mmol/L) + 0.02 (40 – serum albumin [g/L]).

9.2.3. Coagulation

The following laboratory tests will be included: INR, aPTT and PT. Summary tables and listings will be presented as described in Section 9.2.

9.2.4. Urinalysis

The following laboratory tests will be included: colour, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination (only if urinalysis dipstick results are abnormal). Summary tables and listings will be presented as described in Section 9.2.

9.3. Vital Sign Measurements

Vital signs (including systolic and diastolic blood pressures, heart and respiratory rates, and body temperature) will be measured once at pre-dose and once at post-dose for Day 1, Month 6, and Month 12 visits; and once for all other visits. Actual values, and changes from Month 12 in the Transition Period for systolic and diastolic blood pressures will be summarised by scheduled visit, timepoint (pre-dose and post-dose) on days of study drug administration, and by treatment (arm), for the Transition Period.

The following graphics will also be provided for systolic and diastolic blood pressures, separately for the Transition Period.

- A plot showing baseline and worst post-baseline in vital signs.
- A boxplot of values per visit.

For the cumulative safety data analysis at Month 18, summary tables and graphics will be presented as described for the Transition Period, except data will be analysed for arm MB09-MB09 (Arm 1) and Prolia-Prolia (Arm 3) and all assessments up to Month 18 will be included.

All vital signs measurements for two periods (Main treatment 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), Month 6, Month 12 and Transition Period Month

6 (End of Study) visits. A symptom-specific physical examination will be collected for other visits.

Both complete and symptom-specific physical examination results will be presented in a listing together with abnormality specification when provided for two periods (Main treatment 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 screening, baseline (Day 1), Month 3, Month 6, Month 12, and Transition Period Month 3 visits. Each scheduled visit captures ECG interpretation results as Normal, Abnormal NCS, Abnormal CS.

In the Main Treatment 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 Month 12 will be presented by visit.

For the cumulative safety data analysis at Month 18, summary tables will be presented as described for the Main Treatment Period, except data will be analysed for arm MB09-MB09 (Arm 1) and Prolia-Prolia (Arm 3) and all assessments up to Month 18 will be included.

All ECG interpretation results will be presented in a listing together with abnormality specification when provided for two periods (Main treatment period and Transition period) using the SAF analysis set.

9.6. Other Safety Data

9.6.1. Injection Site Reaction

Injection site reactions will be assessed up to 1 hour (± 10 minutes) after the End of Study drug administration, as specified in the Schedule of Events (Appendix 16.1). Injection site reactions will be graded per FDA guidance (DHHS 2007) as shown in Table 9-1.

Table 9-1 Local Reactions to Injected Study Drug

Local Reaction to Injected Study Drug	None (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalisation
Erythema/Redness*	None	2.5 to 5 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	None	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

**Indurations/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

All injection site reactions data will be presented in a data listing for two periods (Main treatment period and Transition period) using the SAF analysis set.

9.6.2. Hypersensitivity/Allergic Reaction

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), Month 6, and Month 12 (End of Treatment) visits.

All hypersensitivity/allergic reactions data will be presented in a data listing for two periods (Main treatment period and Transition period) using the SAF analysis set.

10. Pharmacokinetics and Pharmacodynamics

10.1. Pharmacokinetics

Blood samples for the determination of serum concentrations of denosumab will be collected from subjects in the Main Treatment Period and Transition/Safety Follow-Up Period at the time points specified in the Schedule of Events (Appendix 16.1) and as follows: during the main treatment period, PK samples will be collected on Day 1 (0 pre-dose), Day 11 and at Month 1 (Day 36), Month 3 (Day 90), Month 6 (Day 182, pre-dose) and Month 12 (Day 365) (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug). During the Transition/Safety Follow-Up Period, additional PK samples will be taken at 10 days, 5 weeks, 3 months and 6 months after the administration of the third dose of study drug (i.e., Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

The serum concentration-time data for denosumab will be listed and summarised by treatment, treatment-induced ADA (TI-ADA) status (where data permits), and time point using the PK Concentration Set (PKCS) for the Main Treatment Period and by arm, TI-ADA status (where data permits), and time point using the PK Concentration Set for the Transition Period (PKCS-TP). Samples whose concentrations are assessed as BLQs (Below Limit of Quantification) will be treated as half of LLOQ (lower limit of quantification) value for summary statistics. Individual serum denosumab concentration versus actual time data will be presented graphically on linear and semilogarithmic scales. Mean serum concentration versus nominal time of denosumab data on linear and semilogarithmic scales will also be provided.

If baseline predose concentrations are above the lower limit of quantification, the subject's data (without any adjustments) will be included in all PK tables and statistical evaluations where the pre-dose concentration is < 5% of Cmax for the affected subject profile. If the pre-dose value is > 5% of Cmax, the subject will be flagged in all associated data listings and the affected profile will be excluded from all PK summaries and statistical evaluation.

The pharmacokinetic parameters including C_{max}, $AUC_{0\text{-}6\ months}$ and C_{trough} as defined below will be generated for each individual subject if data permit by the non-compartmental analysis using Phoenix® Win-Nonlin® software Version 8.3 (Certara USA, Inc, Princeton, NJ) or SAS software Version 9.4. Actual dose and collection time will be used in the calculation of PK parameters. For non-compartmental analysis the following conventions will be utilized for BLQ samples: for time points prior to first measurable concentration, concentrations BLQs will be treated as zero whereas, embedded BLQ concentrations will be treated as missing and terminal BLQ concentrations will be treated as half of LLOQ. Individual PK parameters will be listed and summarised by treatment, arm, and TI-ADA status.

Parameter	Definition
C_{max}	Observed maximum serum concentration after administration
$AUC_{0\text{-}6\ months}$	Area under the concentration-time curve from time zero to 6 months, calculated using the linear trapezoidal linear interpolation method
C_{trough}	Trough (pre-dose) serum concentration

Additional PK parameters, such as truncated AUCs or AUCs over a common time period across all subjects, may be calculated as required.

To assess the denosumab PK profile of MB09 compared with EU-Prolia, C_{max} and $AUC_{0\text{-}6\ months}$ will be analysed on the log scale by ANCOVA. The model will include treatment and stratification variables (baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use as fixed effects. The estimated mean difference with 95% CI will be back-transformed to give the ratio of geometric means (MB09/EU-Prolia) with 95% CI following the first dose in the Main Treatment Period. Similarly, parameters derived in the Transition Period will be analysed and comparisons will be made (Arm 2 Prolia-MB09/Arm 3 Prolia-Prolia and Arm 1 MB09 MB09/Arm 3 Prolia-Prolia). C_{trough} may also be compared at Month 6 and Month 12 in the Main Treatment Period and at Month 6 in the Transition Period.

10.2. Pharmacodynamics

Concentrations of the bone turnover marker (sCTX) will be measured from fasting serum samples in the Main Treatment Period and Transition/Safety Follow-Up Period at the time points specified in the Schedule of Events (Appendix 16.1). The sCTX concentration and percent change from baseline (% CFB) data will be listed and summarised by treatment, ADA status (where data permits), and time point using the Modified Full Analysis Set (mFAS) for the Main Treatment Period, and by arm, ADA status (where data permits), and time point using the Modified Full Analysis Set for Transition Period (mFAS-TP). Samples whose concentrations are assessed as BLQs will be treated as half of LLOQ (lower limit of quantification) value for summary statistics. Individual original sCTX concentration and %CFB in sCTX concentration versus actual time data will be presented graphically on linear scale. Mean original sCTX concentration and %CFB in sCTX concentration versus nominal time data on linear scale by study period, treatment or arm, and ADA status (where data permits) will also be provided. The %CFB will be determined by subtracting each postdose sCTX concentration from the D1 predose concentration divided by the D1 predose concentration X 100.

All PD parameters will be calculated for each individual subject if data permit by the non-compartmental analysis using Phoenix® Win-Nonlin® software Version 8.3 (Certara USA,

Inc, Princeton, NJ). $AUEC_{0\text{-}6months}$ will be estimated for sCTX using absolute sCTX concentrations. The following PD parameters will be estimated for sCTX using %CFB in sCTX values: Imax (the maximum % inhibition), TImax (the time of occurrence of the maximum % inhibition) and $AUIC_{0\text{-}6months}$ (area under the % inhibition curve from time zero to month 6 using %CFB data).

$AUEC_{0\text{-}6\ months}$ and $AUIC_{0\text{-}6months}$ will be calculated by the linear trapezoidal method provided there are at least baseline, and three post-dose time points between Day 11 and Month 6, inclusive. Interpolation or extrapolation will be used if the last time point is not at exactly Day 182 whereby concentrations are estimated based on the slope of elimination.If the slope cannot be characterized and the Month 6 sample is missing the AUEC0-6 months or AUIC0-6 months will not be reported. In such cases, additional PD parameters, such as truncated AUECs or AUICs over a common time period across all subjects, may be calculated as required. Individual sCTX $AUIC_{0\text{-}6\ months}$ will be listed and summarised by treatment, arm, period, and ADA status (as data permits).

As sCTX is highly variable and can be influenced by many factors (food, circadian rhythm, sample handling and processing etc.) (Szulc et al 2017) which might affect in particular the baseline CTX values, in order to standardise the PD analysis of equivalence will be conducted using the %CFB.

If sCTX baseline values are close to the LLOQ of the sCTX assay the effect of denosumab on sCTX in terms of %CFB cannot be measured and will lead to unreliable %CFB values (ie, within the assay precision of 16.3% for LLOQ level). Therefore, for baseline PD values of <1.163 fold the LLOQ, the AUIC of %CFB in serum CTX will still be calculated, but excluded from further analysis.

The individual PD parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean and geometric CV.
To assess the denosumab sCTX PD profile of MB09 compared with EU-Prolia, $AUEC_{0\text{-}6\ months}$ and $AUIC_{0\text{-}6\ months}$ will be analysed on the log scale by ANCOVA. The geometric least squares means, ratios of the geometric least squares means (MB09 compared with EU-Prolia), and corresponding 90% CIs for the ratios will be computed by taking the antilog of the least squares means from the ANCOVA model on the natural logarithms of the corresponding PD parameters including log transformed baseline sCTX as a continuous covariate with treatment and stratification variables (baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 SD), body mass index (< 25 and ≥ 25 kg/m2), age at study entry (≥ 55 to < 68 years versus ≥ 68 to ≤ 80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use) as fixed effects. Biosimilarity will be concluded if the 90% CIs for the test (MB09) to reference (EU-Prolia) ratios of the geometric least square means is entirely contained within the [80.00%, 125.00%] interval for AUEC and AUIC.

If deemed necessary by the sponsor, a supplementary analysis may be performed to assess the impact of missing data. A mixed model for repeated measures (MMRM) will be fitted to the unlogged sCTX (mFAS) allowing for different variability at each time point (up to Month 12). The model will include fixed effect terms for visit by treatment, baseline sCTX and classification factors for each stratum. The least squares means and differences with 95% CI will be plotted over time. An estimate statement will be used to calculate a weighted average across the scheduled visits where the weights correspond to the weights used in calculating AUEC. Thus, this will give an estimate of mean AUEC and difference between mean AUEC with 95% CI.

Descriptive statistics of sCTX concentrations for TP will be presented.

11. Immunogenicity Assessments

The immunogenicity of MB09 and EU-Prolia will be analysed in the Main Treatment Period by treatment (i.e MB09-MB09 (Arm 1) and combined treatment group of Prolia-MB09 (Arm 2) and Prolia-Prolia (Arm 3)), in the Transition Period by treatment arms: MB09-MB09 (Arm 1), Prolia-MB09 (Arm 2), and Prolia-Prolia (Arm 3). Additionally, immunogenicity data throughout the study (Baseline to the end of Transition Period (Month 18)) will be analysed for MB09-MB09 (Arm 1) and Prolia-Prolia (Arm 3).

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 Main Treatment Period or the Transition Period/whole study period, respectively.

The formation of ADAs against MB09 or EU-Prolia will be assessed in blood samples (Day 1, Month 6 and Month 12) up to 30 minutes before the study drug administration. All other samples will be collected as close as possible to the scheduled time point within windows as specified in the schedule of events (Appendix 16.1).

ADA test methods enable characterization of samples into ADA positive vs. ADA negative. Each sample is categorized based on the following definitions:

- Baseline ADA positive: ADA is detected in the sample before initiation of treatment
- Baseline ADA negative: ADA is not detected in the sample before initiation of treatment or no evaluable ADA assessment before initiation of treatment
- ADA positive sample during main treatment period: treatment induced or treatment boosted ADA positive sample
    - Treatment induced ADA (TI-ADA) positive sample: After initiation of treatment and during main treatment period, an ADA detected sample in a

subject for whom ADA is not detected at baseline (ADA negative or no evaluable ADA assessment at baseline)

  - Treatment boosted ADA (TB-ADA) positive sample: After initiation of treatment and during main treatment period, an ADA detected sample with ADA titer to be at least n-fold or greater than baseline positive titer, where n represents twice the dilution level applied for titration (i.e., at least 4-fold increase in ADA titer is considered a positive TB-ADA sample when a 2-fold serial dilution is applied for titration).

- ADA negative sample: After initiation of treatment and during main treatment period, ADA not positive sample relative to baseline

Subject ADA status 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
- ADA positive subject: A subject with at least one ADA positive sample relative to baseline during main treatment period after initiation of treatment
- Nab positive subject: At least one ADA positive sample with neutralising antibodies detected post-baseline during main treatment period.
- ADA negative subject: A subject with no ADA positive sample after initiation of treatment during main treatment period.

For analyses based on transition period, ADA positive and ADA negative will consider all data after initiation of treatment at week 52 for all three arms. For the analyses thought the study, definitions will consider all data after initiation of treatment at Day 1.

Number and percentage of subjects by subject ADA status will be provided.

Number and percentage of subjects at each timepoint with positive sample ADA status and positive Nab status will be provided. ADA titre data at each timepoint will be summarised using summary statistics.

Effect of immunogenicity on safety will be explored by examining the frequency of AEs. Overall AE summary table by subject ADA status will be provided.

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.

Association between PK parameters CL and AUC0-6m and TI-ADA status may be explored, as needed.

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 Randomized analysis set.

13. Interim Analysis

There will be no formal interim analysis. Safety data will be generated for approximately seven DSMB review meetings. In accordance with the protocol, the first formal data review meeting will be conducted 3 months after first subject in. After the first data review meeting has occurred meetings will be held regularly to evaluate safety during main treatment period.

14. Changes in the Analysis

14.1. Changes from the Protocol in the Planned Analysis

The following changes in methods or additional details to those given in Protocol Amendment 1 (07 November 2022) are listed below. Note that these are all made prior to data base lock and breaking the study blind.

FAS Definition (Section 4.4.1). The requirement to strictly meet all eligibility criteria has been removed from FAS. Thus, FAS will be used to compare treatments using an intent-to-treat philosophy and including all randomised subjects receiving at least one dose. However, it should be noted that some ineligible subjects dosed in error were discontinued from the study at W26 as per the original protocol. After Protocol Amendment 1 (07 November 2022), at the investigator discretion, subjects who did not meet all eligibility criteria were allowed to remain in the study when there was considered to be a potential clinical benefit without safety concerns.

mFAS Definition (Section 4.4.6).
Note that the text of the mFAS definition has been updated due to the change above in the FAS but the intent of mFAS remains unchanged from the protocol. This comprises the subset of subjects in FAS who are in the target population of interest defined as meeting all eligibility criteria. This set is used for the primary estimation of Estimand 1a in order to achieve a sensitive comparison to test equivalence of the groups for the primary analysis.

FAS-TP Definition (Section 4.4.7). Similar to FAS above, eligibility criteria have been removed so that set is as wide as possible to give information on the 3rd transition dose.

Multiple Imputation Model Terms (Section 8.2.2.1)
The protocol specified full details of terms in the MI model would be specified in the SAP. sCTX has been included as a term in the MI model since this is an important PD biomarker which may provide useful information to inform the imputation and data may be available at Day 11, Month 1 and Month 3 even if missing at Month 6.

The number of doses has been removed as a term; it is not required for the hypothetical Estimand 1a (mFAS) as imputation should be as though both doses received. For estimation of the treatment policy Estimand 1b (FAS), there is only a small amount of Month 12 observed data available for those receiving 1 administration only and so rather than build this term into the imputation model and risk convergence issues and inflated variability, the treatment failure offset will be applied to resulting imputations (Section 8.2.3.1) to achieve a return to baseline imputation.

Main Estimation of Estimand 1b (Section 8.2.3). This main estimation approach will use multiple imputation and a return to baseline assumption on those who only received a single dose so as to not over-estimate the benefit of treatment.
The original ANCOVA without imputation on FAS is retained as a supportive approach (Section 8.2.5).

Return to Baseline Multiple Imputation using Treatment Failure Penalty (Section 8.2.3.1). This approach to achieve a return to baseline level MI on those who only have received a single dose is moved from sensitivity to be the main estimation method of Estimand 1b (treatment policy). An offset penalty to shift imputations to return to baseline levels will apply to withdrawn subjects who only received a single dose administration and discontinued treatment **for any reason** (not just those related to study drug or osteoporosis). %CfB-TF is defined as the endpoint with treatment failure offset applied where applicable. This is aligned to the assumption that we are interested in the treatment policy estimand and any benefit of the initial dose of treatment will be gone by Month 12. The requirement to also apply a penalty for those who take any prohibited therapies or other osteoporosis medication is removed as the assumption that they would have returned to baseline does not seem reasonable.

Tipping Point Sensitivity Analysis of Estimand 1b (Section 8.2.4) A tipping point approach will be used for Estimand 1b (not just Estimand 1a) to explore the robustness of conclusions to missing data imputations. MI under MAR is used as the initial step of the main imputation process and removed as a standalone sensitivity.

ICE – dosing window (Section 4.3) As part of blinded data review meeting, an ICE definition in Section 4.3 was relaxed slightly so that a window of 28 days rather than 10 days around the Month 6 dose would be used as cut off. This cut off was chosen based on clinical evidence that a dosing deviation of up to 4 weeks was considered to not clinically impact either the primary endpoint of BMD (Lyu, Zhau et al 2020) or fracture risk (Lyu, Yoshida et al 2020) and thus by definition, such minor deviations should not be considered an ICE. The impact of this extended window is that in the primary analysis method, it will allow for the use of observed Month 12 BMD data for approximately 29 patients who have a Month 6 dosing deviation above 10 and up to 28 days that would otherwise be removed and imputed. The inclusion of these data may benefit study power.

14.2. Changes from the Prior SAP version

The following changes were made in V2.0 of the SAP compared to V1.0:

1. Implementation of the changes from the planned analyses in the protocol as detailed in the section above.
2. Updates based on the mAbxience review of TLFs as part of dry-run delivery.
3. Inclusion of relevant documentation for sample size estimation, in Appendix 16.2, and prohibited medications, in Section 7.2.
4. PK/PD updates based on latest agreements as specified in Section 10.
5. IMM analysis is updated including the descriptive analysis of the Prolia-MB09 (Arm 2).

15. References

Clinical study protocol MB09-C-01-19 v1.0 EudraCT 2021-003609-24

Clinical study protocol MB09-C-01-19 Version 2.0 (Amendment 1) EudraCT 2021-003609-24

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16. Appendices

16.1. Schedule of Events

Study Period		**Main Treatment Period**							**Transition/Safety Follow-Up Period**			
Visit Number*	1	**2**	3	4	5	**6**	7	**8**	9	10	11	12
Visit Label	Screening	**Baseline**	D11	M1	M3	**M6**	M9	**M12 EOT**	TP D11	TP M1	TP M3	TP M6 EOS
Visit Day	-28 to -1	1	11	36	90	182	270	365	M12 +10 days	M12 +5 weeks	456	547
Window (±days)			±3	±5	±7	±10	±10	±10	±3	±5	±10	±10
Written informed consent[a]	X											
Eligibility[b]	X	X										
Demography data	X											
Medical history	X	X[c]										
NYHA Functional Classification	X											
Lateral spine X-ray[d]	X											
HBV, HCV and HIV-1/HIV-2[e]	X											
SARS-CoV-2[f]	X	As required										
Follicle-stimulating hormone	X											
Randomisation[g]		X										
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs weight, height, and body mass index[i]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X	X			X	X		X			X	
Haematology[k]	X	X	X	X	X	X	X	X	X		X	X
Coagulation[l]	X	X				X		X			X	
Clinical chemistry[m]	X	X	X	X	X	X	X	X	X		X	X
Urinalysis[n]	X	X				X		X			X	
Drug administration[g]		X				X		X				
Hypersensitivity, allergic reaction, injection site reaction monitoring[o]		X				X		X				

Study Period		**Main Treatment Period**							**Transition/Safety Follow-Up Period**			
Visit Number*	1	**2**	3	4	5	**6**	7	**8**	9	10	11	12
Visit Label	Screening	**Baseline**	D11	M1	M3	**M6**	M9	**M12 EOT**	TP D11	TP M1	TP M3	TP M6 EOS
Visit Day	-28 to -1	1	11	36	90	182	270	365	M12 +10 days	M12 +5 weeks	456	547
Vitamin D and calcium supplement administration		Daily										
Review of vitamin D and calcium intake			X	X	X	X	X	X	X	X	X	X
BMD assessed with DXA[p]	X					X		X				
Pharmacodynamics sCTX[q]		X	X	X	X	X		X	X	X	X	X
Pharmacokinetics[r]		X	X	X	X	X		X	X	X	X	X
Immunogenicity[s]		X	X	X	X	X		X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[t]	X	X	X	X	X	X	X	X	X	X	X	X
Radiography[u]	As required											

Abbreviations: 25-OH vitamin D, 25-hydroxy vitamin D; aPTT, activated partial thromboplastin time; BMD, bone mineral density; COVID-19, coronavirus disease 19; D, Day; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; HBV, hepatitis virus B; HCV, hepatitis virus C; HIV-1/HIV-2, human immunodeficiency virus subtypes 1 and 2; ICF, informed consent form; INR, International Normalised Ratio; M, month; NYHA, New York Heart Association; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PT, prothrombin time; SARS-CoV-2, severe acute respiratory coronavirus 2; sCTX, serum carboxy-terminal telopeptide cross-linked type 1 collagen; TP, Transition Period.

* In the case when site visits are not possible or the subject does not wish to visit the site, remote visits (by means of phone calls or video calls) or home visits (as a last option) may be allowed for visits that do not include study drug administration or BMD assessments. Even if a study visit cannot be made, possible data will be continuously collected via a telephone call and during the next visit, if applicable. The investigator will keep following up with subjects regarding any safety issues (adverse events, concomitant medication) by telephone call before the subjects visit the study site. Note: All remote activities depend on site- and country-specific requirements.

a. Informed consent must be obtained before any study-related procedures are performed.
b. The inclusion and exclusion criteria will be checked at screening and confirmed at baseline.
c. Review medical history and ensure that the subject remains qualified for the study.
d. An X-ray of the lateral spine will be performed at screening. This assessment may be also performed as required for confirmation of suspected new vertebral fractures. Radiographs will be assessed by quantitative grading at a central imaging centre.

e. At the screening visit, subjects will be screened for HBV surface antigen, HCV antibody and HIV-1/HIV-2 antibody. If a positive surface antigen test result is obtained for hepatitis B, a confirmatory test is required. In the case of a positive HCV test, an HCV viral RNA load test will be performed as a confirmatory test. In the case of a positive HIV-1/HIV-2 test result, a confirmatory test will be performed. Hepatitis B virus, HCV and HIV-1/HIV-2 analyses will be performed at the central laboratory.
f. At the screening visit, a COVID-19 test will be performed. Subjects who have a COVID-19 infection will be allowed to be rescreened on the basis that they have a confirmatory negative COVID-19 test result and have completely recovered from COVID-19 before being entered into the study. In the case that a subject is required to be rescreened within 28 days of the initial screening no additional tests are required to be performed. In the case that the subject is required to be rescreened after 28 days from the initial screening, all screening procedures/tests are required to be repeated (with the exception of DXA scans performed at screening, which will have a validity period of 3 months, provided the investigator considers the data from the DXA scan to be relevant [ie, the same DXA instrument will be used for the study and data on total hip, femoral neck and lumbar spine are available]). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined. 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 randomisation, the investigator will discuss case-by-case with mAbxience and the medical monitor. If the subject has contact with COVID-19 infected patients within 14 days following any site visit, the investigator will re-assess the visit schedule following the site and/or local regulatory guidelines.
g. On Day 1, during the Main Treatment Period, all subjects will be randomised in a 2:1:1 ratio to receive MB09-MB09, Prolia-MB09 or Prolia-Prolia. Subjects will receive one subcutaneous injection (60 mg/mL) of study drug on Day 1 and at Month 6, and Month 12. At Month 12, after all efficacy and safety assessments have been performed, the subject will enter the Transition/Safety Follow-Up Period and will receive the third dose of study drug. Subjects assigned to the MB09-MB09 arm (Arm 1) will receive MB09 on Day 1, and at Month 6, and at Month 12. Subjects assigned to the Prolia-MB09 arm (Arm 2) will receive EU-Prolia on Day 1 and at Month 6, and MB09 at Month 12. Subjects assigned to the Prolia-Prolia arm (Arm 3) will receive EU-Prolia on Day 1, at Month 6, and at Month 12. All subjects will be followed up to Transition Period Month 6.
h. A complete physical examination will be performed at the screening, baseline (Day 1), Month 6, Month 12, and Transition Period Month 6 (End of Study) visits. A symptom-specific physical examination will be completed for other visits.
i. Vital signs (including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature) will be measured after 5 minutes of rest (sitting) (once at pre-dose and once at post-dose for Day 1, Month 6 and Month 12 visits, and once for all other visits).
j. Subjects are required to rest in a supine position for at least 5 minutes prior to recording of 12-lead ECG.
k. Haematology tests include haemoglobin, haematocrit, red blood cell count, white blood cell count with differential count, absolute neutrophil count, lymphocyte count, and platelet count.
l. Coagulation tests include INR and aPTT.
m. Clinical chemistry tests include albumin, albumin-adjusted total serum calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, total cholesterol, high-density lipoprotein cholesterol, creatine kinase, creatine kinase-myocardial band isoenzyme, creatine phosphokinase, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, triglycerides, magnesium, phosphate, potassium, sodium, total bilirubin, direct bilirubin, total protein, uric acid, troponin I, thyroid-stimulating hormone, parathyroid hormone (intact) and serum 25-OH vitamin D. Clinical monitoring of albumin-adjusted total serum calcium, serum 25-OH vitamin D and mineral levels (magnesium, phosphate) will be performed. Any sign and symptoms of hypocalcaemia will be closely sought and adequately treated at the investigator's discretion. Serum 25-OH vitamin D will be re-tested within the Screening Period. Clinical monitoring of albumin-adjusted total serum calcium levels is recommended before each dose of study drug and in subjects predisposed to hypocalcaemia within

two weeks after the initial dose of study drug. If any subject presents with suspected symptoms of hypocalcaemia during study drug treatment, albumin-adjusted total serum calcium levels should be measured during an unscheduled visit. After each administration of study drug at Day 1 and Month 12, albumin-adjusted total serum calcium levels will be monitored as part of the clinical chemistry panel on Day 11 and Transition Period Day 11, respectively. Note: Serum 25-OH vitamin D levels will also be measured at the unscheduled visit, if required.

n. Urinalysis tests include colour, pH, specific gravity, glucose, ketones, leukocytes, nitrite, protein, bilirubin, urobilinogen, occult blood, and microscopic examination (only if urinalysis dipstick results are abnormal).

o. Subjects will be closely monitored by the investigator and/or subinvestigator for signs of injection site reactions or hypersensitivity/allergic reactions during the administration of the study drug and up to 1 hour (± 10 minutes) after the administration of study drug. Vital signs including blood pressure, heart and respiratory rates and temperature (within 15 minutes prior to and at 1 hour ± 10 minutes after every injection) to monitor for possible hypersensitivity reactions. Hypersensitivity/allergic reactions will be also monitored by routine continuous clinical monitoring, including subject-reported signs and symptoms. Study drug will be administered at a location with immediate access to emergency support. The clinical team at the site facility should be prepared and qualified to conduct emergency care. In the case of anaphylaxis, the investigator must follow national and/or international recommendations of the specific treatment. Anaphylaxis with necessary therapeutic interventions will be reported as serious adverse events. In case of hypersensitivity, emergency 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. Injection site reactions will be assessed 1 hour (± 10 minutes) after the end of administration of the study drug. In the case that the subject experiences an adverse event on the day of study drug administration, they are to call the site or get immediate help.

p. Bone mineral density will be assessed by DXA at screening, and at Month 6 and Month 12, 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. Note: The screening BMD assessment will be taken as the baseline BMD assessment. Note: A DXA scan taken up to 3 months of the screening DXA scan will be accepted as a rescreening DXA scan, provided the investigator considers the data from the DXA scan to be relevant (ie, the same DXA instrument will be used for the study and that data on total hip, femoral neck and lumbar spine are available). In the event the investigator deems the DXA scan invalid, a repeat DXA scan should be performed for the subject who has been re-examined.

q. Samples for PD testing (sCTX) will be taken in the morning after fasting overnight for 8 hours prior to assessment, and the subjects have to refrain from intense exercise the day prior to PD assessment. During the Main Treatment Period, PD assessments will be performed on Day 1 (0 pre-dose), Day 11 and at Month 1, Month 3, Month 6 (pre-dose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug). During the Transition/Safety Follow-Up Period, PD assessments will be performed at Month 12 (pre-dose) and 10 days, 5 weeks, 3 months, and 6 months after the administration of the third dose of study drug (i.e., Transition Period Day 11, Transition Period Month 1, Transition Period Month 3 and Transition Period Month 6).

r. Samples for PK testing will be collected up to 30 minutes prior to dosing of the study drug if study drug is administered on the same visit. Other samples may be taken at any time during a scheduled visit. During the Main Treatment Period, PK assessments will be performed on Day 1 (0 pre-dose), Day 11 and at Month 1, Month 3, Month 6 (pre-dose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the third dose of the study drug). During the Transition/Safety Follow-Up Period, PK assessments will be performed at Month 12 (pre-dose) and 10 days, 5 weeks, 3 months, and 6 months after the administration of the third dose of study drug (i.e., Transition Period Day 11, Transition Period Month 1, Transition Period Month 3, and Transition Period Month 6).

s. Samples for immunogenicity testing will be collected up to 30 minutes prior to dosing of the study drug. Other samples may be taken at any time during a scheduled visit. Immunogenicity (antidrug antibody and neutralising antibody) will be performed on Day 1 (0 predose), Day 11 and at Month 1, Month 3, Month 6 (predose) and Month 12 (for those subjects entering the Transition Period, this sample should be taken prior to the

third dose of the study drug) during the Main Treatment Period. During the Transition/Safety Follow-Up Period, immunogenicity assessments will be performed at Month 12 (predose) and 10 days, 5 weeks, 3 months, and 6 months after the administration of the third dose of study drug (ie, Transition Period Day 11, Transition Period Month 1, Transition Period Month 3, and Transition Period Month 6). If any additional immunogenicity samples are required to be taken if immune-related adverse events occur, the investigator is to seek prior advice from PPD medical monitor and mAbxience before performing the additional sampling.

t. Adverse events will be assessed from the date that the ICF is signed until the End of Study visit (Transition Period Month 6 visit), regardless of the relationship to the study drug. The related adverse events will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure.

u. Lateral spine radiographs will be performed at screening only (per footnote d). Radiographs will be performed only as required for confirmation of suspected new clinical fractures. Radiographs will be assessed by quantitative grading at a central imaging centre.

16.2. Sample size assumptions and calculation MB09

In order to gain an understanding of the clinical effect of the reference treatment, Prolia®, a meta-analysis has been conducted to ascertain the expected %CFB for the reference arm, including the following references: (Bone et al 2008, Cummings et al 2009, and McClung et al 2006).

a) Standard deviation selection

A standard deviation of 4.5% was chosen based on the publication McClung et al 2006.

Table A-1: Percentage Change From Baseline in Bone Mineral Density, Mean (SE)*

		Denosumab 3-monthly			Denosumab 6-monthly				
	Placebo (n = 46)	6 mg (n = 40)	14 mg (n = 43)	30 mg (n = 40)	14 mg (n = 53)	60 mg (n = 46)	100 mg (n = 41)	210 mg (n = 46)	ALN (n = 46)
Lumbar spine, 1 month, n	43	37	40	38	49	44	41	43	45
Mean (SE)	-0.2 (0.4)	1.2 (0.5)	1.8 (0.4)[b]	2.4 (0.5)[c,d]	1.2 (0.4)	1.6 (0.4)[a]	0.9 (0.4)	1.2 (0.4)	1.0 (0.4)
Lumbar spine, 12 months, n	40	36	35	32	48	41	37	41	45
Mean (SE)	-0.8 (0.5)	4.4 (0.5)[d,c]	4.7 (0.5)[d,c]	6.7 (0.5)[c,e]	3.0 (0.4)[c,d]	4.6 (0.5)[c]	5.5 (0.5)[c]	5.1 (0.5)[c]	4.6 (0.5)[c]

Based on 60 mg Denosumab 6-monthly BMD to M12 in Lumbar Spine, SE was 0.5 and so SD based on this paper is approximately 3.4. However, the calculated sample size based on this estimated SD value to 4.5 for the calculation of sample size to increase the chance of demonstrating equivalence.

b) Margin derivation of %CfB in LS-BMD

These references were chosen due to achieving the following criteria:

- Study of denosumab 60mg vs Placebo;
- Evaluation using BMD, with results available at 12-month (52-week) timepoint (weighted mean difference);
- PMO indication;
- Lumbar spine outcome.

The results of this meta-analysis, StatsDirect3 software, are as follows:

Study	Mean difference	Variance of mean difference	Weight
FREEDOM (Cummings et al 2009)	5.5	0.1308	7.6479
McClung et al 2006	5.35	0.4519	2.2131
DEFEND (Bone et al 2008)	5.1	0.2209	4.5269
Overall weighted average	**5.35**	**0.0695**	

Therefore, the point estimate of the difference in treatment effects is 5.35% with 95% CI (4.83%, 5.87%).

The lower bound of the 95% CI is used to justify an appropriate margin. A margin of 1.45% retains at least 70% of the minimum treatment effect.

A meta-analysis of three studies (Bone et al 2008, Cummings et al 2009, and McClung et al 2006) 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%).

As state in the clinical study protocol, Section 7.3, a sample size of 448 subjects (224 subjects on each of MB09 and EU-Prolia (Arm 2 Prolia-MB09 and Arm 3 Prolia-Prolia pooled) at Month 12) will achieve 85% statistical power for the demonstration of equivalence in the %CfB lumbar spine BMD at Month 12, based on the two one-sided 2.5% significance level and an equivalence margin of ± 1.45%. In this sample size calculation, the common SD is assumed to be 4.5% and the true mean difference of %CfB is assumed to be zero. Therefore, allowing for a 15% dropout, 528 subjects will be randomised 2:1:1 to the MB09-MB09, Prolia-MB09 and Prolia-Prolia treatment arms.