Protocol Title:	A Randomised, Double Blind, Three Arm, Single Dose, Parallel Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity Profile of MB09 (Proposed Denosumab Biosimilar) and EU/US sourced Xgeva® in Healthy Male Volunteers.
NCT Number:	NCT05299073
Statistical Analysis Plan version date:	Version 1.0, 04 June 2022

mAbxience Research S.L.

MB09-A-01-19

A Randomised, Double-Blind, Three-Arm, Single-Dose, Parallel Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity Profile of MB09 (Proposed Denosumab Biosimilar) and EU/US-sourced Xgeva® in Healthy Male Volunteers

[redacted]

Final Statistical Analysis Plan

Version 1.0

Prepared by:

[redacted]

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List of Abbreviations

ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$\%AUC_{ext}$	percentage of $AUC_{0\text{-}\infty}$ due to extrapolation.
AUEC	area under the effect versus time curve
$AUEC_{0\text{-last}}$	area under the effect-time curve from time zero to the last quantifiable sCTX concentration time point using absolute data (without baseline-adjustment)
$AUEC_{0\text{-}253}$	area under the effect-time curve from time zero to Day 253 (ie, the last planned sampling time) using absolute data (without baseline-adjustment)
$AUIC_{0\text{-last}}$	area under the % inhibition curve from time zero to the last quantifiable sCTX concentration time point using percent change from baseline data
$AUIC_{0\text{-}253}$	area under the effect-time curve from time zero to Day 253 (ie, the last planned sampling time) using percent change from baseline data
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CK	creatine kinase
CL/F	apparent total body clearance following extravascular administration
C_{max}	maximum observed plasma concentration
C_{min}	minimum concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DHHS	Department of Health and Human Services
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate

HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
IgG	immunoglobulin G
I_{max}	maximum % inhibition
INR	international normalised ratio
IV	intravenous
K_{el}	elimination rate constant (λ_z) during terminal phase
mAb	monoclonal antibody
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MSD-ELC	Meso Scale Discovery-electrochemiluminescence
NA	not applicable
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANK	Receptor Activator of Nuclear Factor Kappa-B (NFκB)
RANKL	Receptor Activator of Nuclear Factor Kappa-B (NFκB) Ligand
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
sCTX	serum C-terminal telopeptide of Type 1 collagen
SOC	system organ class
SOE	schedule of events
TEAE	treatment emergent adverse event
TI_{max}	the time of occurrence of the maximum % inhibition
T_{max}	time to reach maximum observed plasma concentration
T_{min}	time of occurrence of the minimum concentration
$t_{1/2}$	terminal phase half-life
ULN	upper limit of normal
US	United States
V_z/F	Apparent volume of distribution during the terminal phase following extravascular administration

1. Introduction

Denosumab, the active substance of Xgeva® manufactured and marketed by Amgen in the EU and US, is a human monoclonal antibody (mAb) (IgG2) that targets and binds with high affinity and specificity to Receptor Activator of Nuclear Factor Kappa-B (NFκB) Ligand (RANKL). It prevents the RANKL/RANK interaction from occurring, thus resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

MB09 is a medicinal product containing mAb denosumab as the active substance, developed by mAbxience as a biosimilar product to Xgeva. mAbxience is using a similarity-by-design approach for development of the proposed biosimilar, MB09, and has designed an overall development program to establish similarity between MB09 and Xgeva, tailoring the design of the studies to focus on the molecule's mode of action and analytical similarity between reference medicinal product and MB09. This study in healthy male volunteers is part of the clinical development program for MB09 and is designed to assess the bioequivalence of MB09 compared with Xgeva.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on protocol aMB09-A-01-19, version 2.0, dated 30 November 2021.

2. Objectives, Endpoints and Endpoints

2.1 Primary Objectives and Endpoints

Primary objective	**Endpoint description**
The primary objectives of this study are to assess the bioequivalence of single subcutaneous (SC) doses in healthy subjects of: • MB09 versus EU-sourced Xgeva • MB09 versus US-sourced Xgeva • EU-sourced Xgeva versus US-sourced Xgeva	• Pharmacokinetics: $AUC_{0\text{-last}}$ and C_{max}

2.2 Secondary Objectives and Endpoints

Secondary objective	**Endpoint description**
The secondary objectives of this study are: • To evaluate and compare the derived pharmacokinetics (PK) and pharmacodynamics (PD) of single SC doses of MB09 and EU-sourced Xgeva and MB09 and US-sourced Xgeva in healthy subjects • To evaluate the safety, tolerability, and immunogenicity of single SC doses of MB09, EU-sourced Xgeva, and US-sourced Xgeva in healthy subjects	• Pharmacokinetics: $AUC_{0\text{-}\infty}$, T_{max}, CL, $t_{1/2}$ • Pharmacodynamics: AUEC of sCTX • Safety: monitoring and recording of adverse events (AEs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and targeted physical examination findings. • Immunogenicity: Denosumab anti-drug antibodies (ADA) and neutralizing antibodies (NAb)

3. Study Design

This is a Phase 1, double-blind, randomized, single-dose, bioequivalence study to compare the PK, PD, safety, and immunogenicity of MB09 and EU/US-sourced Xgeva in 3 parallel arms.

Healthy male volunteers who meet all inclusion and none of the exclusion criteria will be randomly assigned to receive either 35 mg of MB09 SC (Study Arm 1) or 35 mg of EU-sourced Xgeva SC (Study Arm 2) or 35 mg of US-sourced Xgeva SC (Study Arm 3) in 1:1:1 ratio. The subjects will be stratified based on their body weight. Adequate number of healthy male subjects will be screened and enrolled at selected centers in Poland to have 204 evaluable subjects (68 subjects in each study arm).

The study will consist of a screening period (Days -30 to -2), check-in (Day -1), treatment period (Day 1), follow-up period (Days 2 to 252) and an EOS visit (Day 253).

The PK, PD, safety, and immunogenicity endpoints will be evaluated in this study.

Subjects will be confined to the clinical unit from Day -1 until discharge on Day 2. The duration of the study, excluding screening, is approximately 36 weeks.

Schedules of assessments can be found in Section 14.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures will be presented by treatment. The treatments below will be used for presentations:

- MB09
- EU Xgeva
- US Xgeva

All data listings will be sorted by treatment and subject number.

No algorithm for imputation of missing data will be employed.

Study days are calculated with respect to the first dose date as below:
If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1;
Otherwise, Study Day = Assessment/Observation Date – First Dose Date
Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug administration, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1 Sample Size

The sample size for this study is based on a statistical power calculation. A CV value of 33% was estimated for AUC parameter (which showed the highest variability) based on previous PK studies conducted at a dose of 60 mg or 1 mg/kg. Assuming a ratio of AUC and C_{max} between 0.95 and 1.05, 68 PK-evaluable subjects per arm would be required to provide at least 90% power to conclude bioequivalence of MB09 and Xgeva. Thus, 204 evaluable subjects will be required in all.

Assuming a 20% dropout rate, approximately 255 subjects are planned to be enrolled in this study. Enrollment could be stopped when the target of having 204 evaluable subjects is achieved. Subjects will be randomly assigned to 1 of 3 study arms in a 1:1:1 ratio.

4.2 Randomization, Stratification, and Blinding

PPD will generate the randomization schedule. Subjects who meet all inclusion and none of the exclusion criteria will be randomly assigned to 1 of the 3 study arms. Randomization numbers (in sequential order) will be assigned before the study drug is administered on Day 1. Randomization will be stratified based on the subject's body weight: 60 to <80 kg and 80 to 95 kg.

This study will employ a double-blind study design. MB09 and Xgeva will be packed in identical boxes. The unblinded pharmacists will be responsible for preparing and dispensing the study drug in a manner consistent with maintaining the blind.

The sites will be responsible for maintaining the blind throughout the study. If a subject becomes seriously ill during the study, the blind will be broken upon the investigator's approval only if knowledge of the administered study drug will affect that subject's available treatment options.

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 finalized for study closure.

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws for reasons other than those related to study treatment, before completing the study may be replaced to retain the target of 204 evaluable subjects. Any replacement subject will be assigned to receive the same treatment as the subject he is replacing.

4.3 Analysis Populations

The safety population will include all subjects who receive the study drug.

The PK population will include subjects who receive the study drug, who do not have major protocol deviations*, and have sufficient data to calculate primary PK endpoints.

The PD population will include subjects who receive the study drug, who do not have major protocol deviations*, and have sufficient data to calculate secondary PD endpoints.

* Each subject's data (e.g., dosing records, sample collection records, protocol deviations, concomitant medications, etc.) will be reviewed and assessed, and subjects may be excluded from the PK or PD populations on a case-by-case basis at the discretion of the Pharmacokineticist. It is assumed that such deviations are equally likely to occur in each of the 3 treatment groups.

5. Subject Disposition

5.1 Disposition

The following will be summarized overall for all subjects:

- The number of subjects who enrolled in the study
- The number of subjects who received each treatment
- The number of subjects who completed the study
- The number of subjects who did not complete the study (both overall and according to reasons for discontinuation from the study)
- The number of subjects in each analysis population

Subject disposition data will be presented in a data listing. Subjects who were unblinded by the site will be presented in a listing. Screen failure subjects and reasons for screen failure will be presented in a separate listing.

5.2 Protocol Deviations

Significant protocol deviations will be summarized by treatment. All protocol deviations will be presented in a data listing.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information collected at screening will be presented in a data listing.

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Race
- Ethnicity

The summaries will be presented by treatment and overall for the safety population.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0) and presented in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (WHODrug Global March 2022) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatment

The study drug administration and drug accountability data as collected on eCRF will be presented in the data listings.

8. Pharmacokinetics

8.1 Changes from Protocol

Only a PK population was defined in the protocol (Protocol Section 7.2). A PD population definition was therefore defined for the purposes of the PD analysis.

Rather than use an analysis of variance (ANOVA) approach to determine comparability for PD parameters (as specified in Protocol Section 7.3.2), given the parallel design it was deemed more appropriate to use an analysis of covariance (ANCOVA) to account for stratification factors (i. e. Body Weight) in the comparison of PD data, and to account for baseline sCTX levels when comparing PD data between treatments.

8.2 Data Handling

PK listings will be presented using the safety population; all summaries and analyses of PK data will be based on the PK population.

The following procedures will be used for plasma concentration data of denosumab below the limit of quantification (BLQ) and missing values:

- Concentration values that are BLQ will be reported as provided by the bioanalytical data in the PK data listings.

- Plasma concentration values that are BLQ will be treated as zero at individual time points for the calculation of summary statistics (e.g., mean, standard deviation [SD], etc.).
- Mean concentrations will be reported as BLQ if all concentration values are BLQ, and SD and CV will be reported as not applicable (NA).
- Missing concentration values will be excluded from the calculation of concentration summary statistics.
- For calculation of PK parameters, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.
- Missing concentrations will be treated as missing from the PK parameter calculations (no imputation will be performed).
- For graphical presentations, all BLQs will be set to missing.

8.3 Plasma Concentrations

Serial blood samples for plasma pharmacokinetic analysis of denosumab will be collected up to 2 hours before dosing (Predose) and at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), and on Days 6 (120 hours, ± 1 day), 8 (168 hours, ± 1 day), 11 (240 hours, ± 1 day), 15 (336 hours, ± 2 days), 22 (504 hours, ± 2 days), 29 (672 hours, ± 2 days), 43 (1008 hours, ± 3 days), 57 (1344 hours, ± 3 days), 71 (1680 hours, ± 3 days), 85 (2016 hours, ± 3 days), 99 (2352 hours, ± 3 days), 113 (2688 hours, ± 3 days), 141 (3360 hours, ± 3 days), 169 (4032 hours, ± 3 days), 197 (4704 hours, ± 3 days), 225 (5376 hours, ± 3 days), and 253 (6048 hours, ± 3 days) after dosing.

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be assessed by the Pharmacokineticist on a case-by-case basis for the potential of exclusion from the calculation of concentration summary statistics. PK collections identified for exclusion will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by scheduled time point for each treatment using the following descriptive statistics: number of subjects (n), arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Geometric mean will be reported as missing where any concentration is zero (BLQ). Individual plasma concentration versus actual time and mean plasma concentration versus scheduled time profiles by treatment will be presented in figures on both linear and semilogarithmic scales.

Plasma concentrations of denosumab will be displayed using the precision provided in the raw bioanalytical file received from the lab. Summary statistics for concentrations will be displayed to 2 decimal places, with the exception of n, which will be shown as an integer.

8.4 Pharmacokinetic Parameters

The PK parameters of denosumab will be analyzed based on the actual sampling times. In cases where an actual time is not recorded, the nominal time will be used. All pharmacokinetic parameters will be calculated using Phoenix® WinNonlin® [redacted] Version 8.0 or higher or SAS® [redacted] Version 9.4 or higher.

The following plasma PK parameters will be calculated for denosumab:

$AUC_{0\text{-last}}$	Area under the plasma concentration versus time curve from time zero to the last quantifiable concentration time point, calculated using the linear up log down trapezoidal rule.
$AUC_{0\text{-}\infty}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity calculated per the formula: $AUC_{0\text{-}\infty} = AUC_{0\text{-last}} + C_{last} / K_{el,,}$ where C_{last} is the concentration of the last quantifiable concentration timepoint sample and K_{el} is the first order rate constant of the terminal phase.
C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach maximum observed plasma concentration.
K_{el}	Elimination rate constant (λ_z) during terminal phase
$t_{1/2}$	Terminal phase half-life, calculated as $t_{1/2} = \ln 2/K_{el}$
CL/F	Apparent total body clearance following extravascular administration, calculated as $CL/F = Dose/AUC_{0\text{-}\infty}$
V_z/F	Apparent volume of distribution during the terminal phase following extravascular administration, calculated as $V_z/F = (CL/F)/K_{el}$

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

Number points	Number of data points used to estimate K_{el}; a minimum of 3 data points must be used, and C_{max} must not be included.
K_{el} lower	Lower bound used for the estimation of K_{el}.
K_{el} upper	Upper bound used for the estimation of K_{el}.
Span	Number of elapsed half-lives over which K_{el} is estimated, calculated as (K_{el} upper – K_{el} lower) / $t_{½}$.
Rsq	r^2, the coefficient of determination (goodness of fit statistic); K_{el} and all associated parameters ($AUC_{0\text{-}\infty}$, $t_{1/2}$, CL/F, V_z/F) will only be reported where $r^2 \geq 0.80$.

$\%AUC_{ext}$	Percentage of $AUC_{0-\infty}$ due to extrapolation.

Additional parameters may be calculated as required.

The individual PK parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects (n), arithmetic mean, SD, CV, median, minimum, and maximum. T_{max} will be summarized by number of subjects, median, minimum, and maximum only. Geometric means will be included for C_{max}, $AUC_{0-last,}$ and $AUC_{0-\infty}$.Plasma pharmacokinetic parameters and summary statistics will be rounded to 3 significant figures, with the exception of n, which will be shown as an integer, and K_{el} lower, K_{el} upper, and T_{max}, which will be rounded to 2 decimal places.

8.5 Statistical Analysis for Relative Bioequivalence

An analysis of variance (ANOVA) model with treatment and stratification factors (i.e., Body Weight) as fixed effects will be performed on the natural log-transformed values of C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ to assess the relative bioequivalence between MB09 (test) versus EU-sourced or US-sourced Xgeva (reference), as well as comparing EU-sourced Xgeva (test) to US-sourced Xgeva (reference). The geometric least squares means, ratios of the geometric least squares means, and corresponding 90% confidence intervals (CIs) for the ratios will be computed for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ by taking the antilog of the least squares means from the ANOVA model on the natural logarithms of the corresponding PK parameters for the following comparisons:

- MB09 / EU-sourced Xgeva
- MB09 / US-sourced Xgeva
- EU-sourced Xgeva / US-sourced Xgeva

A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity.

Biosimilarity will be concluded if the 90% CIs for the test to reference ratios of the geometric least square means for C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ are entirely contained within the [80.00%, 125.00%] interval.

Forest plots will also be presented for C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$.

Nonparametric methods (Wilcoxon signed-rank test) will be performed to examine median differences in T_{max} for MB09 vs EU-sourced Xgeva, MB09 vs US-sourced Xgeva, and EU-sourced Xgeva vs US-sourced Xgeva comparisons. The Hodges-Lehmann estimate, and its 90% CI will be calculated for the median difference between treatments, and a p-value will be generated by the Wilcoxon signed-rank test.

Additional sensitivity analyses may also be performed excluding body weight from the model and/or including additional covariates that may affect the PK e.g., subject demographic, protein concentration of the vials, batch of test material etc. Results by site may also be presented separately.

8.6 Assessment of Impact of Immunogenicity on Pharmacokinetics

Each subject's overall ADA status will be included in all PK data listings: subjects will be assigned an overall ADA negative status where all ADA assessments are negative throughout the duration of the study or were only positive at baseline and negative after; if a subject has at least one treatment-induced (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA) their overall ADA status will be assigned as positive. All PK tables (concentration summaries, parameter summaries, and statistical analyses) and summary plots (mean concentrations and Forest plots) will include 3 separate populations:

- Overall (all subjects in the PK population, irrespective of ADA status)
- ADA Negative (all ADA assessments are negative throughout the duration of the study and subjects which were only positive at baseline and negative after)
- ADA Positive (at least one treatment-induced ADA positive assessment observed)

In case of Treatment-boosted ADA: Pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a scientifically reasonable margin such as fourfold, similar analysis would be run.

If there are an insufficient number of ADA positive subjects, statistical analyses will not be performed, and a descriptive analysis will be generated on this population..

9. Pharmacodynamics

9.1 Data Handling

The following procedures will be used for sCTX concentrations below the limit of quantification (BLQ) and missing values:

- Concentration values that are BLQ will be reported as provided by the bioanalytical data in the PD data listings.
- Concentration values that are BLQ will be treated as missing at individual time points for the calculation of summary statistics (e.g., mean, standard deviation [SD], etc.).
- Mean concentrations will be reported as BLQ if all concentration values are BLQ, and SD and CV will be reported as not applicable (NA).
- Missing concentration values will be excluded from the calculation of concentration summary statistics.
- For calculation of PD parameters, BLQ values will be treated as ½ lower limit of quantification (LLOQ).
- Missing concentration values will be treated as missing (no imputations will be performed).

Serum PD concentrations will be displayed using the precision provided in the raw bioanalytical file received from the lab. Summary statistics for PD concentrations will be rounded to 3 significant figures, with the exception of n, which will be shown as an integer.

9.2 PD Biomarker Concentrations

Serial blood samples for serum PD analysis will be collected before up to 2 hours before dosing (Predose) and at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), and on Days 6 (120 hours, ± 1 day), 8 (168 hours, ± 1 day), 11 (240 hours, ± 1 day), 15 (336 hours, ± 2 days), 22 (504 hours, ± 2 days), 29 (672 hours, ± 2 days), 43 (1008 hours, ± 3 days), 57 (1344 hours, ± 3 days), 71 (1680 hours, ± 3 days), 85 (2016 hours, ± 3 days), 99 (2352 hours, ± 3 days), 113 (2688 hours, ± 3 days), 141 (3360 hours, ± 3 days), 169 (4032 hours, ± 3 days), 197 (4704 hours, ± 3 days), 225 (5376 hours, ± 3 days), and 253 (6048 hours, ± 3 days) after dosing.

PD collections that have an actual sampling time that deviates from the predefined collection time windows will be assessed by the Pharmacokineticist on a case-by-case basis for the potential of exclusion from the calculation of concentration summary statistics. PK collections identified for exclusion will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Serum PD concentration and time deviation data will be presented in a data listing along with change from baseline (CFB) and percentage change from baseline (%CFB). Serum PD concentration data (absolute and %CFB) will be summarized by scheduled time point for each treatment using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Individual absolute and %CFB serum concentration versus actual time and mean absolute and %CFB serum concentration versus scheduled time profiles by treatment will be presented in figures on both linear and semilogarithmic scales.

9.3 Pharmacodynamic Parameters

The PD parameters will be analyzed based on the actual sampling times. In cases where an actual time is not recorded, the nominal time will be used. All PD parameters will be calculated using Phoenix® WinNonlin® [redacted] Version 8.0 or higher or SAS® [redacted]) Version 9.4 or higher.

The following PD parameters will be estimated for sCTX using absolute (without baseline-adjustment) sCTX concentrations:

C_{min}	The minimum concentration (which represents the maximum PD effect)
T_{min}	The time of occurrence of the minimum concentration
$AUEC_{0\text{-last}}$	Area under the effect-time curve from time zero to the last quantifiable sCTX concentration time point using absolute data (without baseline-adjustment) and the linear trapezoidal rule.

$AUEC_{0-253}$	Area under the effect-time curve from time zero to Day 253 (ie, the last planned sampling time) using absolute data (without baseline-adjustment), and the linear trapezoidal rule. Where the last observation is observed before Day 253, the AUEC until Day 253 will be extrapolated from $AUEC_{0-last}$, where possible. If extrapolation is not possible, $AUEC_{0-253}$ will be set to missing. Where the last observation is observed after Day 253, the AUEC until Day 253 will be interpolated.

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

I_{max}	The maximum % inhibition
TI_{max}	The time of occurrence of the maximum % inhibition
$AUIC_{0-last}$	Area under the % inhibition curve from time zero to the last quantifiable sCTX concentration time point using percent change from baseline data and the linear trapezoidal rule.
$AUIC_{0-253}$	Area under the effect-time curve from time zero to Day 253 (ie, the last planned sampling time) using percent change from baseline data and the linear trapezoidal rule. Where the last observation is observed before Day 253, the AUIC until Day 253 will be extrapolated from $AUIC_{0-last}$, where possible. If extrapolation is not possible, $AUIC_{0-253}$ will be set to missing. Where the last observation is observed after Day 253, the AUIC until Day 253 will be interpolated.

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

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, and maximum. Geometric means will be included for C_{min}, I_{max}, $AUEC_{0-last}$, $AUIC_{0-last}$, $AUEC_{0-253}$, and $AUIC_{0-253}$. T_{min} and TI_{max} will be summarized by number of subjects, median, minimum, and maximum only.

PD parameters and summary statistics will be rounded to 3 significant figures, with the exception of n, which will be shown as an integer, and T_{min} and TI_{max}, which will be rounded to 2 decimal places.

9.4 Statistical Analysis for Relative Bioequivalence

An analysis of covariance (ANCOVA) model with treatment and stratification factors (i.e. body weight) as fixed effects and logged pre-dose sCTX concentrations (baseline) fitted as a covariate will be performed on the natural log-transformed values of $AUEC_{0-253}$ and $AUIC_{0-253}$ to assess the relative bioequivalence between MB09 (test) versus EU-sourced or US-sourced Xgeva (reference), as well as comparing EU-sourced Xgeva (test) to US-sourced Xgeva (reference). The geometric least squares means, ratios of the geometric least squares means, and corresponding 90% confidence intervals (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 for the following comparisons:

- MB09 / EU-sourced Xgeva
- MB09 / US-sourced Xgeva
- EU-sourced Xgeva / US-sourced Xgeva

A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference. No adjustment will be made for multiplicity. Biosimilarity in PD biomarker will be reported as the test to reference ratio of geometric means and its corresponding 90% CI for $AUEC_{0-253}$ and $AUIC_{0-253}$ PD parameters.

Forest plots will also be presented for $AUEC_{0-253}$ and $AUIC_{0-253}$.

9.5 Assessment of Impact of Immunogenicity on Pharmacodynamics

Select analyses may be performed for subsets with or without ADA as appropriate.

10. Safety Analysis

All safety summaries and analyses will be based upon the safety population.

10.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A serious AE (SAE) is defined as any AE that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: related, or not related.

All AEs will be graded for intensity according to the CTCAE, Version 5.0 – November 2017 (DHHS 2017). All other laboratory and clinical AEs not outlined in the CTCAE that occur in a

subject will be assessed (graded) for intensity and then classified into 1 of 5 clearly defined categories as follows:

- 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; limits age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limits self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 (Life-threatening): Urgent intervention indicated.
- Grade 5 (Death).

An overall AE summary will be generated presenting the frequency and percentage of subjects and the number of AEs by treatment for the following:

- Any AE
- Any TEAE
- Any treatment-related TEAE
- Any moderate TEAE
- Any treatment-related moderate TEAE
- Any treatment-related severe TEAE
- Any SAE
- Any treatment-related SAE
- Any TEAE leading to early discontinuation
- Any death

All AEs will be coded using MedDRA (version 24.0). The TEAEs will be summarized by treatment, severity, and relationship to the study drug. The frequency of TEAEs (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) will be summarised by treatment, severity grade, and by Medical Dictionary for Regulatory Activities system organ class and preferred term.

The proportion of subjects experiencing at least one TEAE will be compared among the treatments using Fisher's exact test at 0.05 significance level. As adverse events from the same body system may be correlated and there may also be correlations between adverse events from different body

systems, to control the family-wise error rate, Bonferroni correction will be applied to resulting p-values from Fisher´s test.

Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A Subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in each treatment in the safety population.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, and AEs leading to study discontinuation.

10.2 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

Hematology	Leukocyte count and percentage and absolute differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils), hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and red blood cell distribution width
Coagulation	INR, prothrombin time, aPTT
Serum Chemistry	ALT, albumin, ALP, AST, bilirubin (total, direct, indirect), BUN, calcium, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), CK, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, triglycerides, uric acid, creatinine, and GFR. GFR will be calculated by the MDRD equation: 175 × (standardized serum creatinine/88.4)-1.154 × (age)-0.203 × (1.212 if black)
Urinalysis	Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis B DNA test (optional), HCV antibody, and HIV antibody types 1 and 2 (screening only)

Other tests	All subjects: COVID-19 test, alcohol test (breath/urine), urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, tricyclic antidepressants, and opiates)

The hematology, coagulation, serum chemistry, and urinalysis tests will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 14).

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Actual results and change from baseline for hematology, coagulation, serum chemistry and urinalysis at each time point will be summarized for the safety population. Shift from baseline in terms of low/normal/high for hematology and serum chemistry tests, and in terms of normal/abnormal for urinalysis tests will be summarized for the safety population.

10.3 Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, respiratory rate, and tympanic temperature, and will be measured at the timepoints indicated in the schedule of assessments after the subject has been in the supine position for at least 5 minutes (schedules of assessments can be found in Section 14).

All vital sign, body weight, and height measurements will be presented in a data listing. The actual values and change from baseline values at each time point will be summarized for the safety population.

10.4 Physical Examination

A full physical examination will be performed at screening (at minimum, assessment of skin, head, oral cavity, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination will be performed at check-in, Day 225, and EOS (at minimum, assessment of oral cavity, skin, lungs, cardiovascular system, and abdomen [liver and spleen]). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

All physical examination results will be presented in a data listing. Dental and otolaryngological examinations will be done at screening and will be presented in a separate data listing.

10.5 Electrocardiograms

Single 12-lead ECG recordings will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening for eligibility determination. Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and QTcF. Assessments should include comments on whether the tracings are normal or abnormal; rhythm; presence of arrhythmia or conduction defects; morphology; any evidence of myocardial infarction; or ST-segment, T-wave, and U-wave abnormalities.

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 14).

Actual values and changes from baseline for numeric ECG data will be summarized by visit and treatment for subjects in the safety population.

All ECG data will be presented in a data listing.

10.6 Immunogenicity analysis

Denosumab ADA and NAb will be assessed by a validated MSD-ELC assay at the following time points (seven samples in total): at baseline, prior to study drug administration, which is Day -1 (check-in) and on Days: 11, 43, 99, 169, 225 and 253 after the single SC administration. The analysis will involve both a screening, confirmatory, and titer assay to confirm positive results. Assay results and validation details will be provided in a separate bioanalytical report.

Proportion of subjects positive and negative for antidrug antibodies to denosumab will be summarized by treatment and visit for subjects in the safety population. The neutralizing potential and titre of positive ADAs will be summarized by treatment and visit for the safety population. Two positive ADA subsets will be considered for immunogenicity analysis:

- Overall ADA positive: includes all subjects with any positive ADA result at any time
- Treatment-induced ADA positive: includes subjects with only post-treatment positive ADA results

In case of Treatment-boosted ADA: Pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a scientifically reasonable margin such as fourfold, will be summarized accordingly.
All immunogenicity data will be presented in a data listing and tables

10.7 COVID-19 Impact

The clinic will follow standard procedures and/or local guidelines with respect to COVID-19 testing at screening and any other timepoints during the study, if deemed necessary by the investigator. COVID-19 impact data will be presented in a data listing.

11. Changes in the Planned Analysis

Any changes from this statistical analysis plan will be documented in the CSR for this study.

12. References

[redacted]

13. Schedule of Assessments

	Screening	Check-in	Treatment				Follow-up																		EOS
Day	-30 to -2	-1	1				2	3	4	6	8	11	15	22	29	43	57	71	85	99	113	141	169	197	225	253
Procedure[a] Time Postdose	—	—	Pre dose	H0	H8	H16	H24	H48	H72						M1	M1.5	M2	M2.5	M3	M3.5	M4	M5	M6	M7	M8	M9
Admission to clinic		X																								
Discharge from clinic[b]							X																			
Outpatient visit[c]	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X																									
Demographics	X																									
Serology[d]	X																									
Inclusion/exclusion criteria	X	X																								
Medical history	X	X																								
Urine drug screen/alcohol test[e]	X	X																								
Height, weight, and BMI[f]	X	X																								X
Physical examination[g]	X	X																							X	X
Dental and otolaryngological examination[h]	X																									
Vital sign measurements[i]	X	X	X		X		X			X				X				X				X			X	X
12-lead ECG[j]	X	X	X		X		X			X																X
Clinical laboratory testing[k]	X	X					X			X				X		X		X		X		X			X	X
COVID-19 test[l]	X																									
Randomisation[m]		X																								
Study drug administration[n]				X																						
PK sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sample collection[p]			X									X				X				X			X		X	X
AEs[q]	◄ X ►																									
Prior/concomitant medications	◄ X ►																									

Abbreviations: AEs, adverse events; BMI, body mass index; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EOS, end of study; H, hour; ICF, informed consent form; M, month, PD, pharmacodynamic; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SC, subcutaneous.
Notes:
(a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time point as possible.
(b) Discharge following 24-hour PK/PD sample collection.
(c) Follow-up visits will occur from Day 3 through EOS visit on Day 253.
(d) Serology testing will include hepatitis B surface antigen, anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis C virus antibodies, and human immunodeficiency virus types 1 and 2 antibodies. Hepatitis B DNA test can be done as a confirmatory test in exceptional cases, if needed.
(e) Urine drug screen/alcohol test (urine/breath) will occur at screening and check-in per the clinic's standard procedures.

(f) The BMI (kg/m2) will be calculated at check-in using the following formula: weight (kg)/height (m2). Height will be measured at screening only. Only weight will be measured at EOS visit.
(g) A full physical examination will be performed at screening (at minimum, assessment of skin, head, oral cavity, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination will be performed at check-in, Day 225, and EOS (at minimum, assessment of oral cavity, skin, lungs, cardiovascular system, and abdomen [liver and spleen]). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.
(h) To be performed by dentist and otolaryngologist, respectively at screening only.
(i) Vital signs will include systolic and diastolic blood pressure, respiratory rate, pulse rate, and tympanic temperature and will be measured after the subject has been in the supine position for at least 5 minutes. Tympanic temperature will be measured at screening, Days 2, 22, 225, and EOS. Vital signs will be measured within 15 minutes prior to study drug dosing on Day 1.
(j) Single 12-lead ECG recordings will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening for eligibility determination. Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and QTcF. Assessments should include comments on whether the tracings are normal or abnormal; rhythm; presence of arrhythmia or conduction defects; morphology; any evidence of myocardial infarction; or ST-segment, T-wave, and U-wave abnormalities.
(k) A complete list of assessments is provided in Section 6.4.2. Blood and urine samples will be collected after overnight fasting for 10 hours and prepared per the clinic's standard procedures. The same visit windows will apply for safety laboratory sample collection as for PK (refer to footnote (o)).
(l) The clinic will follow standard procedures and/or local guidelines with respect to COVID-19 testing at screening and any other timepoints during the study, if deemed necessary by the investigator.
(m) Randomisation should be done on Day -1 or Day 1 prior to initiating any study procedures.
(n) The time of study drug dosing will be called "0" hour and is denoted with grey shading. A single SC dose of 35 mg of the study drug will be administered in the upper arm to each subject. Subjects will remain semi-supine for the first 4 hours after administration unless moving is medically necessary, requires procedures, or means going to the washroom.
(o) Blood samples for PK analysis of the study drug (MB09 or Xgeva) in plasma and PD analysis of area under the effect curve will be collected up to 2 hours prior to study drug dosing and after dosing at 8 and 16 hours (± 2 hours), 24, 48, and 72 hours (± 4 hours), Days 6, 8, and 11 (± 1 day), Days 15, 22, and 29 (± 2 days), Days 43, 57, 71, 85, 99, 113, 141, 169, 197, 225, and 253 (± 3 days). At each time point, blood samples will be collected after overnight fasting of at least 10 hours.
(p) Samples for immunogenicity analysis will be obtained prior to study drug dosing and at the timepoints indicated in the schedule of events. If hypersensitivity occurs after the study drug dosing, additional samples for immunogenicity testing may be obtained at the discretion of the investigator to determine serum sickness.
(q) Adverse events and SAEs will be assessed from the time of signing the ICF until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.