Alkem Laboratories Ltd.

ALK22/ENZ215-DEN2

A Phase 3, Randomized, Double-blind, Parallel-group, Active controlled Study to Compare the Efficacy, Safety, Pharmacodynamics, Pharmacokinetics, and Immunogenicity of Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis

Statistical Analysis Plan

Version: Final 2.0

Parexel Project Number: 254282

Sponsor Signature Page

This document has been approved and signed electronically on the final page by the following:

Approved by: _____ _____

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President & CMO

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Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

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Version History

SAP Version	Date	Change	Rationale
0.1	04 Apr 2024	Not applicable	New Document
0.2	28-May-2024	Updated based on sponsor team comments as follows: Change in ICE1 from "Missed First and Second study drug administration" to "BMD assessment deviation of more than 35 days"; Clarifications on missing baseline sCTX values and baseline sCTX value < BLQ considerations in the analysis; Update in model variables in primary endpoint analysis; Update in visit-window for LS-BMD analysis; Deleted visit-window for Visit 1 (Baseline) related to LS-BMD data in section 6.3.1	

1.0	07-Jun-2024	Clean & Final	
2.0	11-Jun-2024	To drop the sensitivity analysis for sCTX endpoint in section 4.2.2.2	This is done as we consider only the positive AUEC values (for log transformation) to use in the ANCOVA as part of the primary PD endpoint inferential analysis

1. Introduction

This is a Phase 3, randomized, double-blind, parallel group, active-controlled study to compare the efficacy, safety, pharmacodynamics, pharmacokinetics, and immunogenicity of Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data related to efficacy, immunogenicity, safety and tolerability and to describe the data reports to be provided for the final CSR.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (February 16, 2023)
- electronic Case Report Form (eCRF), Version 9.0 (September 06, 2023)

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints and/or Estimands
Co-Primary	
• To evaluate the efficacy of ENZ215 when compared to Prolia® in patients with postmenopausal osteoporosis, in terms of change in bone mineral density (BMD) at the lumbar spine from baseline to Month 12 • To compare the area under the effect curve (AUEC) of serum C-telopeptide of Type-1 collagen (sCTX) levels from baseline to Month 6	• Percentage change in BMD at Lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12 • AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)
Secondary Efficacy	
• To compare the change in sP1NP levels from baseline to Month 6 • To compare the change in BMD at lumbar spine from baseline to Month 6 • To compare the change in BMD at total hip and femoral neck from baseline to Month 6 and Month 12	• Percentage change in sP1NP concentrations from baseline to Month 1, Month 3, and Month 6 • Percentage change in BMD at lumbar spine measured by DXA from baseline to Month 6 • Percentage change in BMD at total hip and femoral neck measured by DXA from baseline to Month 6 and Month 12

Secondary Safety	
• To compare the immunogenicity potential of ENZ215 and Prolia® • To compare the safety and tolerability of ENZ215 and Prolia®	• ADAs incidence at baseline (Day 1) and Months 1,3,6,9, and 12 and during open-label switch-over period, i.e., Months 15 and 18 • Treatment-emergent serious and non-serious adverse events (TEAEs) during main treatment period and open-label switch-over period • Alteration in clinical laboratory parameters during main treatment period and open-label switch-over period
Secondary Pharmacokinetics	
• To compare the pharmacokinetics of ENZ215 and Prolia®	• PK parameters (C_{max}, T_{max}, partial $AUC_{(0\text{-}1\ month)}$, and $AUC_{(0\text{-}6\ month)}$ of denosumab measured at baseline (Day 1), Day 8, Day 15, Month 1, Month 3, Month 6 (prior to second dose), and Month 12

1.2. Study Design

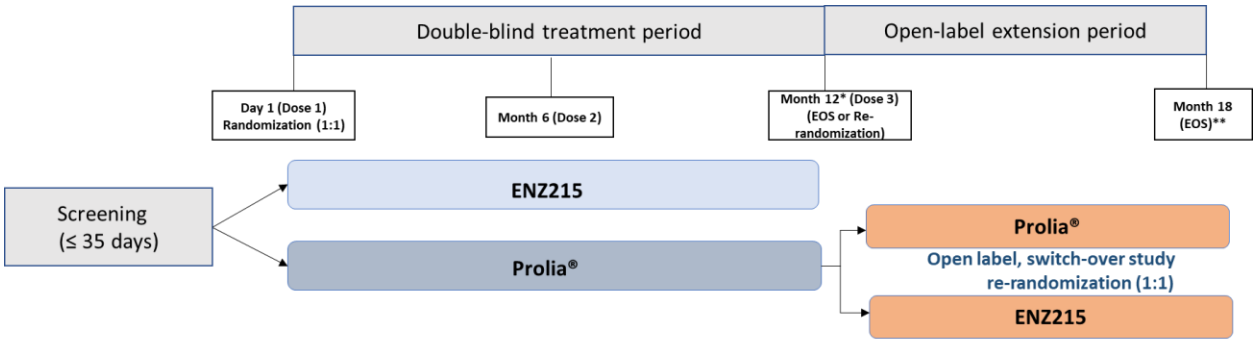
This is a Phase 3, randomized, double-blind, parallel-group, active-controlled study which aims to compare equivalence of the ENZ215 (test product) to Prolia® (reference product) in postmenopausal women with osteoporosis. The double-blind treatment period will be for 12 months followed by the open-label, switch-over study until Month 18.

Five hundred and four patients (252 patients in each treatment arm) will be enrolled in this study. All eligible patients will be randomized in the double-blind treatment period in a 1:1 ratio to receive either ENZ215 or Prolia® (60 mg) subcutaneously (SC) on Day 1 and Month 6. Patient allocation will be stratified by age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years) and based on prior use of bisphosphonate.

All patients randomized to the double-blind treatment period (except for a subset of 120 patients, as described hereafter) will complete the study at Month 12. A subset of 120 patients initially randomized to Prolia® arm will be re-randomized in a 1:1 ratio (i.e., 60 patients in each arm) in order to have 100 evaluable patients (i.e., 50 patients in each arm) in an open-label switch-over period to receive either ENZ215 or Prolia® (60 mg) SC at Month 12 in order to assess the impact

on immunogenicity and safety of switching patients from the Prolia® to ENZ215. These patients will complete the study at Month 18.

Figure 1–1 Study Design



EOS = end of study
*Month 12 will be EOS for patients randomized to ENZ215
**Month 18 will be EOS for subset of 120 patients re-randomized to receive Prolia® or ENZ215

Data Monitoring Committee:

A data monitoring committee (DMC) will periodically review all the available safety data and provide their recommendation to the sponsor. More details about the DMC analysis will be found in the DMC Charter.

2. Statistical Hypotheses

This study is designed to test for equivalence.

The test product (ENZ215 60 mg) and reference product (Prolia ® 60 mg) will be declared comparable if 95% CI of the treatment difference (test minus reference), the mean percentage change from baseline to Month 12 in LS-BMD is within the pre-defined equivalence margin of ± 1.45.

Symbolically, this is expressed as follows:

H_0: μ(% change ENZ215) - μ(% change Prolia ®) ≤ -1.45 or μ(% change ENZ215) - μ(% change Prolia ®) >= 1.45

H_1: -1.45< μ(% change ENZ215) - μ(% change Prolia ®) <1.45

2.1. Multiplicity Adjustment

No multiplicity adjustment will be required to test hypotheses for the co-primary endpoints.

3. Analysis Sets

The details of analysis set to be used for the study are described below:

Screened Set: The screened set will consist of all patients who have signed informed consent.

Intent-to-Treat (ITT) Set: The ITT analysis set consists of all randomized patients who received at least one dose of study intervention in the double-blinded treatment period. In the ITT analysis set, treatment is assigned based on the study intervention to which patients are randomized, regardless of which treatment they actually receive.

Modified ITT (mITT) Set: The mITT analysis set consists of all ITT patients who have baseline assessment and post-baseline LS-BMD value.

Per-Protocol (PP) Set: The PP set is a subset of the ITT set with the LS-BMD assessments at baseline and Month 12 and consists of all patients who do not have any major protocol deviations which would affect LS-BMD, receive the study intervention at baseline and Month 6, and have baseline and Month 12 LS-BMD data.

Safety Set: The safety set includes all randomized patients who receive at least one dose of study intervention. In the safety set, treatment is assigned based on the actual treatment that patients receive.

PD Set: The pharmacodynamic (PD) set consists of all patients in the safety set whose sCTX values are available in order to calculate pharmacodynamic parameter AUEC values for primary analysis and do not have any major protocol deviations which would affect sCTX or sP1NP measurement.

PK Set: The pharmacokinetic (PK) set is a subset of safety set with at least one evaluable PK endpoint (C_{max} or $AUC_{0\text{-}6\ month}$) and no major protocol deviations affecting the PK parameters up to Month 12. All the protocol deviations (irrespective of major / minor PDs) with action for analysis that leads to exclusion from PK Set will be considered for exclusion from PK Set in the PK analysis set derivation.

The ITT set will be the primary analysis set for all efficacy data related to BMD data. Efficacy data will also be analysed for the mITT and PP set to corroborate the results of the ITT analysis. All safety data will be analysed for the safety set.

PD Set will be used as the primary analysis set for PD Parameters data.

PK Set will be used as the main analysis set for PK Parameters data.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to Sponsor for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses.

Decisions made regarding the exclusion of patients and/or patient data from analyses will be made prior to database lock and will be documented and approved by Sponsor.

The number and percentage of patients included in each analysis set will be summarized on screened set by treatment and overall.

4. Statistical Analyses

4.1. General Considerations

Baseline will be taken as the last available assessment prior to first IP dosing in the study.

The EOS is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the schedule of activities (SoA) (Table 1-1 of the protocol) for the last patient in the study globally.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, quartiles and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

4.2. Primary Estimand(s) Analysis

4.2.1. Definition of Endpoint(s)

- Percentage change in BMD at Lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12
- AUEC of percentage change from baseline in sCTX (sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose))

4.2.2. Main Analytical Approach

4.2.2.1. Main Analytical Approach for co-primary endpoint of percentage change from baseline in LS-BMD at month 12

The co-primary efficacy variable of percentage change from baseline in LS-BMD at month 12 will be derived based on the data collected from the Dual Energy X-Ray Absorptiometry (DXA) scan using the parameter "IQC and XCAL Corrected BMD" at location "LUMBAR SPINE".

The co-primary endpoint of percentage change in LS-BMD will be analyzed following the framework of the estimand concept as detailed in the latest International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance. From this end, efficacy analysis will be defined with terms used for the estimand concept.

Table 4-1: Summary of the primary and secondary estimands for estimating percentage change from baseline in BMD at Lumbar spine at month 12

Estimands	**Primary: "Treatment Policy" estimand (TPE)**	**Secondary: "Principal Stratum" estimand (PSE)**
Clinical Question of Interest	Do ENZ215 and Prolia® have a similar efficacy and a similar effect on BMD at the lumbar spine at month 12 in females with postmenopausal osteoporosis regardless of the ICEs occurring during the Double-Blind treatment period?	Do ENZ215 and Prolia® have a similar efficacy and a similar effect on BMD at the lumbar spine at month 12 in females with postmenopausal osteoporosis in the Principal Stratum of patients who would not experience any ICEs on either treatment arms?
Variable	Percent change in LS-BMD from Baseline to month 12, i.e., %CfB, is the primary study endpoint and is defined as: %CfB = (Post Baseline – Baseline) / Baseline * 100	
Treatments	Test product: ENZ215 subcutaneous injection 60 mg Reference product: Prolia® subcutaneous injection 60 mg	
Study Population	Females with postmenopausal osteoporosis as defined in detail in eligibility criteria (ITT Set)	The principal stratum of females with postmenopausal osteoporosis who would not experience any ICEs on either treatment (PP Set)
Intercurrent Events	**Strategy for Primary Estimand**	**Strategy for Secondary Estimand**
ICE1: Significant BMD assessments delays for more than 35 days at visit 9 (M12)	ICE1: Treatment policy strategy (All obtained data points will be included in the analysis, in line with the ITT principle.)	Principal stratum causal estimand strategy will be used: Only patients who would not experience either ICE if exposed to either treatment are relevant to the clinical question.

ICE2: The patient received other medication alongside the IP, which affects the primary variable (prohibited medications)	ICE2: Composite variable strategy (Composite variable strategy will be applied: Intercurrent event is considered to be informative about the outcome, so that the responses obtained after ICE occurrence will be imputed under the null hypothesis. In other words, responses obtained after ICE occurrence will be imputed with multiple imputation techniques so that outcomes observed after ICE2 occurrence will be modelled under the null hypothesis.)	To control the validity of the estimand dropout and ICE rates and reasons will be monitored.
Study Population	Females with postmenopausal osteoporosis.	The principal stratum of females with postmenopausal osteoporosis who would not experience any ICEs on either treatment.
Population-level Summary	Difference of means between the test and reference arms in percentage change from baseline LS-BMD: $\delta = \mu_{ENZ215} - \mu_{Prolia}$ μ_{ENZ215}: LS-BMD mean %CfB in ENZ215 study arm μ_{Prolia}: LS-BMD mean %CfB in Prolia® study arm	
Analysed data points	All captured data points in the ITT Set are included to the analysis.	All captured data points in the PPS are included to the analysis, as far as ICE1 and ICE2 are not met.
Main estimator	δ will be estimated by using ANCOVA model with the following factors: 1. Randomized treatment 2. Baseline BMD value 3. Age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years) 4. Previous use of bisphosphonates	δ will be estimated by using ANCOVA model with the following factors: 1. Randomized treatment 2. Baseline BMD value 3. Age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years) 4. Previous use of bisphosphonates In the event of missing primary endpoint, to help alleviate the concern on the uncertainty introduced by missing data with potential impact on the integrity

		of randomization, the strategy analysis with MI will be followed.
Sensitivity estimator	Missing data will be assumed to be MCAR and will not be imputed and the δ will be estimated by using ANCOVA model with the following factors: 1. Randomised treatment 2. Baseline BMD value 3. Age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years) 4. Previous use of bisphosphonates	Due to the parallel design, robustness of the estimator will be assessed by tipping point analysis

Descriptive analysis of the number, proportion, reasons and timing of intercurrent events (ICEs) will be presented.

Primary efficacy analysis of primary endpoint of %CfB in LS-BMD at month 12

The primary efficacy analysis will be conducted to evaluate the primary endpoint of the study using a Treatment Policy Estimand. More in details, a model of Analysis of Covariance (ANCOVA) will be implemented to estimate the difference of means between the test (ENZ215) and reference (Prolia) arms in percentage change from baseline of BMD in lumbar spine at month 12. The observed %CfB in lumbar spine BMD at month 12 will be the dependent variable while the followings will be used as covariates:

- Treatment Arm (ENZ215 and Prolia, as planned (randomised) treatment)
- Stratification factors at randomisation:
  - Age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years)
  - Previous use of bisphosphonates (yes/no)
- Baseline BMD value in lumbar spine

As result from ANCOVA model, the effect $\hat{\delta}_{TPE}$ of the binary variable Treatment Arm will be estimated as regression coefficients. Wald's two-sided 95% Confidence Interval (CI) will be derived for the parameter estimate.

Handling of intercurrent events

ICE 1, significant BMD assessments delays for more than 35 days at visit 9 (M12), will be handled under treatment policy strategy: all obtained data points will be included in the analysis, in line with the ITT principle.

ICE 2 will consist of the participant receiving other medication alongside the IMP, which affects the primary variable, i.e., prohibited medications/therapies. Composite variable strategy will be applied; Intercurrent event is considered to be informative about the outcome, so that the responses obtained after ICE occurrence will be imputed under the null hypothesis.
Descriptive analysis of the number, proportion and timing of intercurrent events (ICEs) will be presented.

Analysis of Primary Estimand for percentage change from baseline (%CfB) in LS-BMD - Multiple Imputation Approach

To test the hypothesis of equivalence, the $\hat{\delta}_{TPE}$ 95% CIs, as obtained by the ANCOVA model described above will be studied. If the LCL of the two-sided 95% CI around $\hat{\delta}_{TPE}$ will be greater than -1.45 and the UCL will be less than 1.45, the null hypothesis will be rejected.

Missing data without experiencing ICE2 will be assumed to be MCAR and will not be imputed. Assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques.

Different assumptions will be made for handling of ICE2 in each of the two arms. Under Prolia® group, data artificially set as missing after ICE2 occurrence will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not taken prohibited medication. Under the ENZ215 group, Month 12 data artificially set as missing after ICE2 occurrence will be imputed using MNAR method 'Under the Null': after ICE2 primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin "delta". The equivalence margin of -1.45% will be used as the "delta" for the ICE2 in the ENZ215 group.

MI will be performed through SAS PROC MI, variables used to impute Month 12 missing values will be the dependent variables from ANCOVA model defined above; additionally, Month 6 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the post-ICE2 Moth 6 BMD will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.

Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

Step 1) In a copy of the whole original efficacy dataset, the Month 6 and Month 12 %CfB observed after ICE2 occurrence will be set as missing

Step 2) Two datasets, one including only Prolia® subject and another one including only ENZ215, will be filtered from the dataset resulting from Step 1

Step 3) In the Prolia® dataset created in Step 2, Month12 %CfB missing or assessed after ICE2 occurrence will be imputed as MAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 254282 will be used, variables used to impute missing values will be the stratification factors (age group and previous use of bisphosphonates), baseline BMD, and Month 6 lumbar spine BMD %CfB

Step 4) In the ENZ215 dataset created in Step 2, Month 12 %CfB missing or assessed after ICE2 occurrence will be imputed as MNAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 254282 will be used, variables used to impute missing values will be the stratification factors (age group and previous use of bisphosphonates), baseline BMD, and Month 6 lumbar spine BMD %CfB. MNAR statement will be used including ADJUST option with SHIFT as sub option, allowing a shift of -1.45 to be applied to the imputed Month 12 values

Step 5) From the dataset created at Steps 3 and 4, only data imputed because of ICE2 occurrence will be retained, while data that were originally missing will be reverted back as missing. The two resulting datasets will then be compiled in a unique dataset

Step 6) The primary efficacy ANCOVA model defined above will be executed by imputation on dataset obtained in Step 5

Step 7) Estimates from the Step 6 will then be combined through SAS MIANALYZE, alpha will be set at 5%. Combined estimation of the difference ENZ215 – Prolia will be examined together with the corresponding two-sided 95% CI. Equivalence of ENZ215 compared to Prolia® will be claimed if the LCL will be greater than -1.45 and the UCL will be less than 1.45.

As a title of example, a SAS code to implement the steps is provided in section 6.4.2.

As sensitivity analysis, missing data will be imputed in accordance with techniques proposed by Jakobsen et al (2017), which will be considered as described in this section for sensitivity analysis: if the proportion of non-complete cases is below 5%, sensitivity analysis will be not conducted.

Primary efficacy endpoint - Secondary Estimand

As described in Table 4-1, the secondary estimand analysis will be conducted to evaluate the primary endpoint of the study using a Principal Stratum Estimand (PSE).

PSE strategy relates to a target population of interest, taken as the principal stratum, in which both ICEs would not occur. The clinical question of interest relates to the treatment effect only within

the principal stratum. PSE is based on potential ICEs occurrence, i.e., subjects who would have ICE occurrence if assigned to either treatment arm.

Let U denote the principal stratum defined by the joint potential PPSC (Per-Protocol and Completer) and PSE (i.e., not having experienced the two ICEs as defined in Table 4-1) status had a subject been assigned to ENZ215 and Prolia®, U={S_1,S_0 }={ss,ss̄,s̄s,s̄s̄}.
There are four principal strata:

- "Always PPSC & PSE" ($U = ss$):($U = ss$): Participant who would comply with study (i.e., be PPSC & PSE) under both ENZ215 and Prolia®.
- "PPSC & PSE with ENZ215 only" ($U = s\bar{s}$):($U = s\bar{s}$): Participant who would be PPSC & PSE if assigned to ENZ215, but would not if assigned to Prolia®.
- "PPSC & PSE with Prolia® only" ($U = \bar{s}s$):($U = \bar{s}s$): Participant who would be PPSC & PSE if assigned to Prolia®, but would not if assigned to ENZ215.
- "Never PPSC & PSE" ($U = \bar{s}\bar{s}$):($U = \bar{s}\bar{s}$): Participant who would not be PPSC nor PSE regardless of the treatment group being assigned to.

Under the assumptions of Stable Unit Treatment Values Assumption (SUTVA) and random assignment of the current study, the Survivor Average Causal Effect (SACE) estimand of the difference of means between the ENZ215 and Prolia® arms in percentage change from baseline of BMD is composed of two parts, as follows

$$\delta_{SACE} = \delta_{PST} + \boldsymbol{BIAS} = \delta_{PST} + \frac{\boldsymbol{\pi_{\bar{s}s}}}{\boldsymbol{p_0}}\boldsymbol{\beta_0} - \frac{\boldsymbol{p_1 - p_0 + \pi_{\bar{s}s}}}{\boldsymbol{p_1}}\boldsymbol{\beta_1},$$

where:

- δ_{PST}: principal stratum estimate of the effect (difference) in mean (from ANCOVA).
- $\pi_{\bar{s}s}$: marginal proportion of PPSC & PSE with Prolia® only
- p_0: proportion of being observed PPSC & PSE subjects in the Prolia®
- p_1: proportion of being observed PPSC & PSE subjects in the ENZ215
- β_0: is the difference in average potential outcome under US-licenced Prolia® arm between the stratum "PPSC & PSE with Prolia® only" and the stratum "always PPSC & PSE"

- β_1: is the difference in average potential outcome under ENZ215 arm between the stratum "PPSC & PSE with ENZ215 only" and the stratum "always PPSC & PSE"

As for the secondary estimand analysis for this bioequivalence study, no deviations are expected in the two arms from the stratum of from "always PPSC & PSE", therefore $\beta_0 = 0$ and $\beta_1 = 0$ will be considered. In other words, $\delta_{SACE} = \delta_{PST}$ is assumed for secondary estimand analysis. Parameters β_0 and β_1 , as well as $\pi_{\bar{s}s}$, will be made to vary as part of the sensitivity tipping point as described under "Primary Efficacy Endpoint – Secondary estimand sensitivity tipping point analysis" of this SAP.

A model of Analysis of Covariance (ANCOVA) will be used to estimate δ_{PST}: the observed %CfB in lumbar spine BMD at Month12 will be the dependent variable while the followings will be model covariates:

- Treatment Arm (ENZ215 and Prolia®)
- Stratification factors for randomization:
  - Age (≥ 55 to < 70 years and ≥ 70 to ≤ 85 years)
  - Prior use of bisphosphonates (yes/no)
- Baseline BMD value in lumbar spine

As result from ANCOVA model, the estimated effect $\hat{\delta}_{\text{PSE}}$ of the binary variable Treatment Arm will be obtained as regression coefficients. Wald's 95% Confidence Interval will be derived for the parameter estimate.

As a title of example, a SAS code is provided in section 6.4.1.

To test the hypothesis of equivalence, the $\hat{\delta}_{\text{PSE}}$ 95% CIs will be studied. If the left side of the 95% CIs around $\hat{\delta}_{\text{PSE}}$ will be greater than -1.45 and the right side will be less than 1.45, the null hypothesis will be rejected.

Primary Efficacy Endpoint – Sensitivity Analyses for Primary estimand

Missing primary efficacy post baseline data will be imputed as a sensitivity estimation. As sensitivity analysis, missing data will be imputed in accordance with techniques proposed by Jakobsen et al (2017): if the proportion of non-complete cases is below 5%, sensitivity analysis will be not conducted.

Missing data will be assumed to be MAR and imputed using fully conditional specification (FCS) method via SAS PROC MI. Additionally, likewise for the primary endpoint primary estimand

analysis as outlined in section, assessments of the primary endpoints observed after occurrence of ICE2 will be disregarded, i.e., artificially set as missing, and will be replaced with MI techniques. Different assumptions will be made for handling of ICE2 in each of the two arms. Under Prolia® group, data artificially set as missing after ICE2 occurrence will be assumed to be MAR and imputed assuming they would have behaved like subjects in the same arm had they not taken prohibited medication. Under the ENZ215 group, Month 12 data artificially set as missing after ICE2 occurrence will be imputed using MNAR method 'Under the Null': after ICE2 primary efficacy data are assumed to worsen from "MAR" by an amount of equivalence margin "delta". The equivalence margin of -1.45% will be used as the "delta" for the ENZ215 group.

MI will be performed through SAS PROC MI, variables used to impute Month 12 missing values will be the dependent variables from ANCOVA model defined at section 4.2.2 under "Primary efficacy analysis of primary endpoint of %CfB in LS-BMD at month 12"; additionally, Month 6 data will be used as well in the SAS PROC MI as a post-randomization predictive variable; in that contest the missing Month 6 (originally or post-ICE2 assessments) will be imputed as well within the SAS PROC MI itself, with MAR approach for both the treatment arms.

Below steps will be followed (note: the steps below will be executed on a copy of the BMD %CfB column variable, while the original will be maintained as well):

Step 1) In a copy of the whole original efficacy dataset, the Month 6 and Month 12 %CfB observed after ICE2 occurrence will be set as missing

Step 2) Two datasets, one including only Prolia® subject and another one including only ENZ215, will be filtered from the dataset resulting from Step 1

Step 3) In the Prolia® dataset created in Step 2, Month 12 %CfB missing or assessed after ICE2 occurrence will be imputed as MAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 254282 will be used, variables used to impute missing values will be the stratification factors (age group and previous use of bisphosphonates), baseline BMD, and Month 6 lumbar spine BMD %CfB

Step 4) In the ENZ215 dataset created in Step 2, Week 52 %CfB missing or assessed after ICE2 occurrence will be imputed as MAR. SAS PROC MI will be executed with FCS method, 50 complete datasets will be created, seed 254282 will be used, variables used to impute missing values will be the stratification factors (age group and previous use of bisphosphonates), baseline BMD, and Month 6 lumbar spine BMD %CfB. To be able to impute 'Under the Null' the Month 12 post ICE2 occurrence values, the MNAR statement will be used including ADJUST option with SHIFT and ADJUSTOBS as sub options, allowing a shift of -1.45 to be applied to only the value imputed after occurrence of ICE2.

Step 5) MI datasets resulting from Steps 3 and 4 will be compiled in a unique dataset

Step 6) The primary efficacy ANCOVA model as defined at section 4.2.2 under "Primary efficacy analysis of primary endpoint of %CfB in LS-BMD at month 12" will be executed by imputation on complete dataset obtained in Step 5

Step 7) Estimates from the Step 6 will then be combined through SAS MIANALYZE, first type error alpha will be set at 5%. Combined estimation of the difference ENZ215 – Prolia will be examined together with the corresponding two-sided 95% CI. Equivalence of ENZ215 compared to Prolia® will be suggested if the LCL will be greater than -1.45 and the UCL will be less than 1.45.

As a title of example, a SAS code to implement the steps is provided in section 6.4.3.

Primary Efficacy Endpoint – Secondary estimand sensitivity tipping point analysis

Due to the nature of study design, robustness of the estimator will be assessed by implementing in a Causal Inference framework, as proposed by Lou et al. More in detail, principal stratification approach will be followed.

The BIAS component of the δ_{SACE} formula will be studied, please refer to formula and terminology presented in section 4.2.2 under "Primary efficacy endpoint - Secondary Estimand" of this SAP.

A tipping point sensitivity analysis will be conducted to evaluate the robustness of the conclusion based on the observed principal stratum [PST] estimator under different scenarios, by varying the values of β_0, β_1 and $\pi_{\bar{s}s}$ within clinically meaningful ranges. Boundaries for the range of $\pi_{\bar{s}s}$ can be easily derived as

$\pi_{\bar{s}s} \in [\max(0, p_0 - p_1), \min(p_0, 1 - p_1)]$.

The proportion of PST with US-licenced Prolia® only is bounded, but the selection effects (β_0, β_1) are not.

The robustness analysis will be conducted, below steps will be followed:

Step 1) Compute $\hat{p}_0$ and $\hat{p}_1$ and compute the $\hat{\delta}_p = \hat{p}_1 - \hat{p}_0$ and derive the two-sided 90% confidence interval of $\hat{\delta}_p$ using Yates's continuity correction. If the 90% CI is included in the specific equivalence margin, tipping point analysis can be performed. For this study, the specific equivalence margin for the difference of proportion of PSE subjects is set as ± 15%

Step 2) Estimate $\hat{\delta}_{PST}$ and Wald's 95% CI by ANCOVA model (δ_{PST} as estimated by the secondary estimand analysis described in section 4.2.2 under "Primary efficacy endpoint - Secondary Estimand" of this SAP)

Step 3) Compute the boundaries for $\pi_{\bar{s}s}$ as previously defined and identify a few cut point inside the range to perform tipping point analysis (for example if the range of $\pi_{\bar{s}s}$ is between 0 and 15%, it is suggested to cover the interval with 0%, 5%, 10% and 15%). Furthermore, derive $\hat{\pi}_{s\bar{s}}$ as:

$$\pi_{s\bar{s}} = \hat{p}_1 - \hat{p}_0 + \pi_{\bar{s}s}$$

Step 4) For each value of $\pi_{\bar{s}s}$, a clinical meaningful range is set for β_0 and β_1 (for example, between ±35%)

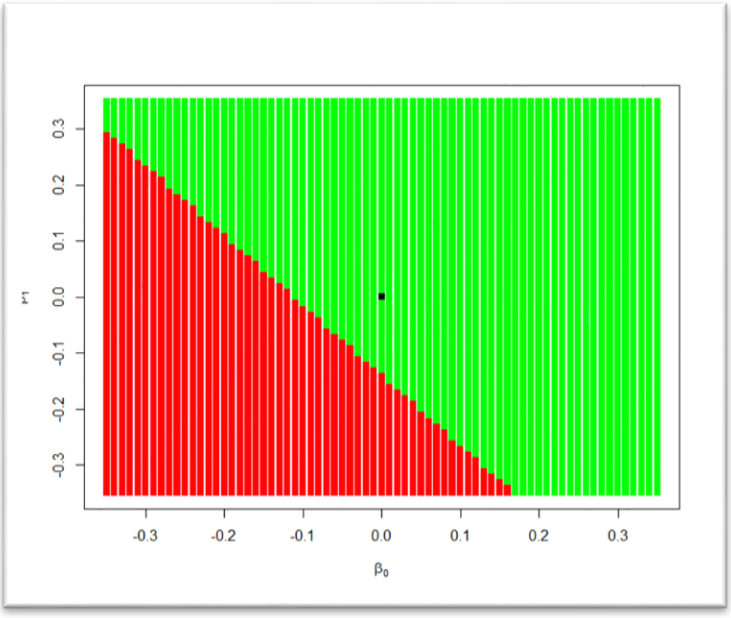
Step 5) Compute $\hat{\delta}_{SACE}$ as defined below with its 95% CI: because the sensitivity parameters are considered as "fixed," the 90% CI for an estimator of the SACE can simply be constructed by shifting the CI of the observed δ_{PST} (as estimated by the secondary estimand analysis described in section 4.2.2 under "Primary efficacy endpoint - Secondary Estimand" of this SAP) by the BIAS

Step 6) Figure 3 shows an example of tipping point plot. A plot will be produced for each value of a series that cover the whole $\pi_{\bar{s}s}$. Horizontal and vertical axes respectively represent values for β_0 and β_1. Considering the value of $\pi_{\bar{s}s}$ and for each value of β_0 and β_1, $\hat{\delta}_{SACE}$ and its 95% are derived. If the LCL for the set of β_0, β_1 and $\hat{\pi}_{\bar{s}s}$ is greater than -1.45 and UCL is less than 1.45, the point is plotted as green, while red otherwise. The black point is $\hat{\delta}_{PST}$ where the BIAS quantity is zero due to $\beta_0 = \beta_1 = 0$

Step 7) If most of the multiple plots, which cover the range of variation of $\pi_{\bar{s}s}$, will not show large red areas close to the PST estimate black point, the equivalence conclusion would be considered robust. The equivalence conclusion reverses only if the selection effects under ENZ215 and Prolia® are very unbalanced (i.e., if the absolute value of $\beta_0 - \beta_1$ is large). This will happen if ENZ215 and Prolia® have very different safety and efficacy profiles

Step 8) The associated green/red value related to any $\hat{\delta}_{SACE}$ values will be listed and quantitative summaries will be provided

Figure 3 – Example of Tipping Point Plot



4.2.2.2. Primary Pharmacodynamic (PD) Endpoint Analysis - Main Analytical Approach for co-primary endpoint of AUEC of sCTX

The individual observed serum concentration of sCTX, change from baseline (CfB) in sCTX concentration, and %CfB of sCTX will be listed and summarized by treatment group, visit at each planned sampling time using descriptive statistics. AUEC of sCTX, will be calculated from %CfB of sCTX as described in Section 4.6.4 and will be listed and summarized in tabular and graphical format. Analysis will be performed on the PD set.

To evaluate the AUEC of sCTX, the treatment comparison will be made using the ANCOVA on log-transformed data of AUEC of sCTX with treatment group as fixed effect, and baseline sCTX value as a covariate. The ANCOVA will include calculation of LSM for the treatment groups. The ratios of LSM will be calculated using the exponentiation of the LSM from the analyses on the corresponding log-transformed AUEC of sCTX on the PD set.

Pharmacodynamic equivalence will be concluded if the 90% CI of the treatment ratio is contained within the acceptance limits of 80% to 125%. 95% CIs of geometric mean ratio between the treatment groups will also be provided as an exploratory analysis.

As an example, SAS code is provided in section 6.4.5.

In the primary PD analysis, patients with missing sCTX sampling at Baseline will not be included in the analysis of the AUEC of sCTX. Additionally, to be included in the analysis of the AUEC of sCTX, patients will need to have the results from the visits of Day 1, Day 15, Day 30 (M1), and Day 180 (M6). Serum sCTX concentration below the limit of quantification (BLQ) will be considered as BLQ in summary tables.

sCTX values < BLQ will be considered as zero (0) value in the analysis. sCTX values missing at baseline visit and sCTX value of zero (0) or < BLQ at baseline will not be considered in the primary PD endpoint analysis and also in the summary statistics analysis.

4.2.3. Sensitivity Analyses

Please refer Section 4.2.2.1 for the sensitivity analysis for co-primary endpoint of LS-BMD.

4.2.4. Supplementary Analyses for primary efficacy endpoint of LS-BMD

The supplementary estimand of BMD %CfB at Month 12 will utilize a hypothetical ICE handling strategy as if the ICE did not occur, as a further, sensitive, investigation into whether differences in outcomes would emerge if the whole study population were fully compliant with treatment.

Data points captured after the ICE will be left out from the ITT analysis. The same ICEs will be applied as for the primary and secondary estimands.

Primary endpoint will be analyzed by using MMRM with the following factors:

- Treatment (ENZ215 and Prolia®, as planned treatment)
- Stratification factors for randomization:
  - Age group
  - Previous use of bisphosphonates (yes/no)
- Baseline BMD value
- Visit (Month 6 and Month 12 data will be included in the model)
- Visit (Month 6 and Month 12) * Treatment interaction

Unstructured covariance matrix will be used. In case of convergence issues, alternative structures will be considered in the following order: Autoregressive(1), Compound Symmetry, Toeplitz; until convergence is met.

Missing data will be assumed to be MCAR and will not be imputed.

As a title of example, a SAS code to implement the steps is provided in section 6.4.4.

4.3. Secondary Endpoint(s) Analysis

4.3.1. Secondary Efficacy Endpoint(s)

The individual serum concentrations of sCTX and sP1NP will be summarized by treatment group at each planned sampling time using descriptive statistics. Percent change from baseline in sP1NP will be summarized in tabular and graphical format using PD set. A by-patient listing will be provided for sCTX and sP1NP concentrations data.

The following secondary endpoints will be analyzed descriptively by treatment group using ITT set and sensitivity analyses will also be performed on the mITT and PP set:

- Percentage change in LS-BMD from baseline to Month 6
- Percentage change in BMD at total hip and femoral neck from baseline to Month 6 and Month 12

Instrument Quality Control (IQC) and DXA Inter-scanner cross-calibration (XCAL) Corrected BMD measurement at the required location will be used in the above secondary efficacy endpoints descriptive analyses related to BMD data.
Missing total hip and femoral neck BMD will not be imputed and will thus result in missing %CfB.

A by-patient listing will be provided for all the BMD parameters data.

4.4. Exploratory Analysis

Not Applicable

4.5. Safety Analyses

Safety set will be used for all safety analysis unless any other specific analysis set is mentioned.

4.5.1. Extent of Exposure

Extent of exposure will be assessed with the exposure duration (days) and the total dose of study treatment. A summary of the exposure duration (days), and the total dose of study treatment will be provided using the descriptive statistics.

The exposure duration (days) and treatment compliance (%) for IP administration will be calculated as follows:

Exposure Duration (days) = [Date of last injection + 180 (days)] – [Date of 1st injection] + 1.

Treatment compliance (%) will also be summarized descriptively and will be calculated as follows:

Treatment compliance (%) = [(Number of Injections Administered) / (Number of Injections supposed to be administered)]*100.

Study duration will also be summarized descriptively and will be calculated as follows:

Study duration (days) = (Date of termination/completion – Date of 1st injection) +1.

Exposure duration for Non-IP administration will be summarized descriptively and will be calculated as follows:

Exposure Duration (days) = [Date of last dose of Non-IP administration - Date of 1st Non-IP administration] + 1.

A by-patient listing of study treatment, and a by-patient listing of extent of exposure including exposure duration, and the total dose of study drug treatment along with dose administered date, time and study duration will be provided.

Summary of treatment exposure will be provided in terms of number of injections administered and treatment duration by treatment group and overall, based on Safety set for the IP administration. A by-patient listing will also be provided.

Summary of Non-IP administration of Calcium and Vitamin D will be provided by treatment group and overall, based on safety set. A by-patient listing for non-IP administration of Calcium and Vitamin D will be provided separately.

Patient diary review data will be summarized and a by-patient listing for patient diary review data will be prepared, based on safety set.

4.5.2. Injection site reactions

Injection site reactions (number and intensity) will be summarized and listed appropriately by treatment group and overall, based on safety set.

4.5.3. Adverse Events

Assessment of safety will be done by determining the number of patients with any AE, including SAE.
Reported AE terms will be mapped to latest available version of Medical Dictionary for Regulatory Activities (MedDRA)-preferred terminology. All reported events will appear in AE listings; however, only treatment-emergent adverse events (TEAEs) will be summarized. A TEAE is an AE that starts or increases in severity on or after the first administration of study treatment up to the End-of-Study/Early Termination Visit following the last administration of study treatment.

Severity

TEAEs will be summarized by SOC, PT, and severity, including the number and percentage of patients experiencing events. If a patient reports the same TEAE more than once within that SOC and PT, the TEAE with the highest severity will be used in the corresponding severity summaries.

In summaries including severity, the following intensity categories will be summarized: ‘Mild’, ‘Moderate’, ‘Severe’. Events with missing intensity will be considered as ‘Severe’ events for summary purposes but recorded as missing in the listings.

If severity is reported by Common Terminology Criteria for Adverse Events (CTCAE) grade, then summary of severity will be presented using CTCAE grade.

Relationship (Causality)

TEAEs will be summarized by SOC, PT, and causality, including the number and percentage of patients experiencing events. Relationship to study drug will be tabulated respectively. If a patient reports the same TEAE more than once within that SOC and PT, the TEAE with the worst-case relationship to study drug will be considered. Patients who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as 'Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Following Summary tables will be prepared for Adverse Events (Safety Set):

- Overall Summary of Adverse Events
- Overall summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship
- TEAEs by SOC, PT and action taken
- TEAEs by SOC, PT and outcome
- TEAEs of special interest by SOC and PT

Adverse event summaries will be ordered in terms of ascending order of SOC code, and sorted by decreasing frequency of PT within SOC, and then sorted by ascending order of PT code for the PTs with the same frequency.

A by-patient listing of all adverse events experienced consisting of start/end date, severity, seriousness, relationship to study treatment, action taken, and outcome information will be prepared. It will also consist if the AE is of Special Interest or not.

4.5.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Other significant adverse events are those adverse events reported as leading to an intervention e.g., death, hospitalization, life threatening events, Congenital Anomaly or Birth Defect, disability or permanent damage etc.

The following summary tables will be provided:

- A summary of the number and percentage of deaths during the study, by treatment group (if numbers allow)
- A summary of the number and percentage of patients reporting a serious treatment-emergent adverse event, by treatment group, SOC and PT
- A summary of the number and percentage of patients with adverse events leading to discontinuation of study treatment, by treatment group, SOC and PT

The following listings will be prepared:

- A by-patient listing of all deaths that occurred during the study
- A by-patient listing of all serious adverse events
- A by-patient listing of all other significant adverse events
- A by-patient listing of all adverse events leading to discontinuation of study treatment

4.5.5. Additional Safety Assessments

4.5.5.1. Clinical Laboratory Evaluation

Clinical laboratory values (hematology, serum chemistry, urinalysis, pregnancy and other blood test parameters) will be presented descriptively.

The baseline for the laboratory values is defined as the last evaluable measurement before first dose, including any unscheduled assessment.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. If visit windows are to be used, the latest non-missing assessment in the visit will be summarized (including repeat and unscheduled assessments). For across visit summaries (e.g., maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

A patient will be defined as having a treatment-emergent laboratory abnormality if any of the following conditions are satisfied for a specific laboratory parameter:

- Laboratory result within the normal range at Baseline and either a result below the lower limit of the normal range or above the upper limit of the normal range at any post-baseline time point.
- Laboratory result below the lower limit of the normal range at Baseline and a laboratory result above the upper limit of the normal range at any post-baseline time point.
- Laboratory result above the upper limit of the normal range at Baseline and a laboratory result below the lower limit of the normal range at any post-baseline time point.

The following summaries will be provided:

- A summary of absolute value and change from baseline for each laboratory parameter at all collection points with the descriptive statistics
- Shift tables by overall and treatment group and visit by laboratory parameter.

By-patient listing will be provided for all treated patients by visit, including changes from baseline and reference range. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings.

4.5.5.2. Vital Signs, Physical Findings and Other Observations Related to Safety

4.5.5.2.1. Vital Signs

Vital signs will be performed as per timing summarized in the SoA. The following vital signs will be measured:

- Weight
- Height
- Temperature
- Heart rate
- Respiratory rate
- Blood Pressure (SBP, DBP)

Vital signs will be recorded in supine position after 5 minutes of rest: heart rate (beats/minute), blood pressure measurement (mmHg), respiratory rate (breaths/minute), and body temperature (°C).

The summary of the absolute value and its change from baseline in each vital sign parameter by treatment group and time point will be provided in addition to a by-patient listing of vital sign data.

4.5.5.2.2. Physical examinations

Physical examination will be performed according to the schedule of activities from the protocol. A summary of the physical examination by treatment group over time will be provided along with a by-patient listing of physical examinations data.

- A summary of the number and percentage of patients with normal/abnormal physical examination findings, by body system, treatment group and time point.

4.5.5.2.3. 12-lead ECG

A 12-Lead ECG will be performed as described in the schedule of activities from the protocol.

A summary of absolute value and change from baseline for each ECG parameter at all collection points with the descriptive statistics will be provided for the treatment groups in the summary table.

Number and percentage of patients by overall evaluation (Normal, Abnormal NCS and Abnormal CS) will be provided by treatment group over time in a separate summary table.

A by-patient listing of ECG data will be provided.

4.5.5.2.4. COVID-19 Signs and Symptoms

COVID-19 signs and symptoms will be collected as described in the schedule of activities from the protocol. A summary of COVID-19 signs and symptoms data will be provided by treatment group over time along with a by-patient listing.

4.5.6. Secondary Safety Endpoint(s)

- The incidence of patients who develop binding and neutralizing anti-drug antibodies (ADAs) will be summarized by treatment descriptively for safety set.
- Treatment-emergent serious and non-serious adverse events (TEAEs) during main treatment period and open-label switch-over period will be summarized.
- Alteration in clinical laboratory parameters during main treatment period and open-label switch-over period will be summarized.

4.6. Other Analyses

4.6.1. Other Variables and/or Parameters

4.6.1.1. Lumbar and Post Lateral Spine X-ray

Lumbar and post lateral spine X-ray will be performed as described in the schedule of activities from the protocol. A summary of lumbar and post lateral spine X-ray data in terms of number and percentage of patients by overall evaluation (Normal, Abnormal NCS, Abnormal CS, Other) will be provided by treatment group over time along with a by-patient listing.

4.6.1.2. Immunogenicity

All immunogenicity results (ADA confirmed positive or negative, ADA titers and neutralizing activity) will be listed and summarized by treatment group, assay type and sampling point. The incidence of patients who develop binding ADAs and NAbs will be summarized by visit and treatment group appropriately. This analysis will be carried out based on the safety set.
A by-patient listing will be provided for the immunogenicity results.

4.6.1.3. Patient Reported Outcome (PRO) Measures

Not Applicable

4.6.2. Subgroup Analyses

Not Applicable

4.6.3. Pharmacokinetic Endpoints

PK study will be conducted in a subset of the population, i.e. 60 patients in each arm in order to have 50 evaluable patients in each arm. Summary statistics for ENZ215 or Prolia® serum concentrations will be provided by treatment group and visit.

Pharmacokinetic concentration data will be obtained at time point(s) described in the protocol amendment 3.0 as follows:

A total of seven (7) PK blood samples (3.5 mL/sample) will be collected from each patient at the following nominal times: Baseline (Day 1, up to 2 hours prior to dosing), Day 8 (collect within ± 1 day i.e. Day 7, 8, or 9 after Dose 1), Day 15 (collect within ± 3), Month 1 (collect within ± 3 days of Day 30 after Dose 1), Month 3 (collect within ± 3 days of Day 90 after Dose 1), Month 6 (collect within ± 7 days of Day 180 after Dose 1, prior to second dose), and Month 12 (collect within ± 7 days of Day 180 after Dose 2). For PK sampling on Day 8 and Day 15, the visit window is ±3 days but a window period of ± 2 hours is allowed in relation to the time of IP administration on Day 1.

Unless otherwise stated, derivation of PK parameters will be the responsibility of CPMS group, Parexel. The PK analyses will be conducted using Phoenix® WinNonlin (WNL) version 8.3 or later in a secure and validated environment.

If calculable, the following PK parameters listed in Table 4-2 will be determined for ENZ215 or Prolia® in serum following First SC dose administration.

Table 4-2 Serum Pharmacokinetic Parameters After First Dose Administration of Multiple Dose Study

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration
t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
AUC_{0-1M}	AUC0-1M	AUCINT	AUC from time zero to 1 month
AUC_{0-3M}	AUC3M	AUCINT	AUC from time zero to 3 month
AUC_{0-6M}	AUC6M	AUCINT	AUC from time zero to 6 month

If calculable, the following PK parameters listed in Table 4-3 will be determined for ENZ215 or Prolia® in serum following multiple dose administration via SC administration:

Table 4-3 Serum Pharmacokinetic Parameters after Multiple Dose Administration

Parameter	WNL Name	CDISC Name	Definition
$C_{trough,6m}$	Ctrough,6M	CTROUGH	Concentration at the end of a dosing interval at 6 month [taken directly before next administration]
$C_{trough,\ 12m}$	Ctrough,12M	CTROUGH	Concentration at the end of a dosing interval at 12 month [taken directly before next administration]
AUC_{6M-12M}	AUC12M	AUCINT	AUC from time 6 month to 12 month

4.6.3.1. Pharmacokinetic concentrations

Concentration Listings:

Pharmacokinetic concentration data for ENZ215 or Prolia®, will be listed by treatment group, visit and subject for the Safety Set. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR), as appropriate and considered excluded from PK analysis.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Summary statistics will be presented at baseline (Day 1), Day 8, Day 15, Month 1, Month 3, Month 6 (prior to second dose), and Month 12. Tabular summaries for concentration-time data will report N (number of subjects who received treatment), n (number of subjects with non-missing values), and n(BLQ) (the number of subjects with BLQ samples).

Concentration for ENZ215 or Prolia® will be summarized by treatment group, visit and nominal timepoint for the PK Set. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(es^2-1)*100; where s is the SD of the log transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).
For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero (except for intravenous administration when these BLQs should not be displayed). When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to zero.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing.
- Measurable concentrations after consecutive BLQs will be set to missing.

To visualize subject-level concentrations and the comparison by treatment group, visit for each treatment, the descriptive PK graphs listed below will be generated. Include LLOQ line in individual plots.

- Figure: Individual subject profiles for ENZ215 serum Concentration-Time Data (Linear Scale and Semi-Logarithmic Scale) (PK Set) (from time 0 to M12)
- Figure: Individual subject profiles for Prolia® serum Concentration-Time Data (Linear Scale and Semi-Logarithmic Scale) (PK Set) (from time 0 to M12)
- Figure: Overlaid individual subject profiles for ENZ215 serum Concentration-Time Data (Linear Scale and Semi-Logarithmic Scale) (PK Set) (spaghetti plots) (from time 0 to M12)
- Figure: Overlaid individual subject profiles for Prolia® serum Concentration-Time Data (Linear Scale and Semi-Logarithmic Scale) (PK Set) (spaghetti plots) (from time 0 to M12)
- Figure: Arithmetic Mean (± SD) ENZ215 and Prolia® serum Concentration-Nominal Time Data (Linear Scale and Semi-Logarithmic Scale) (PK Set) (from time 0 to M6)

Figures will be generated in black and white (or color) using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.6.3.2. Pharmacokinetic parameters

PK parameters will be provided by CPMS group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin Version <8.3> or higher following these guidelines:

- Actual sampling times relative to dosing will be used in the calculation of all derived pharmacokinetic parameters.
- There will be no imputation of missing data.

- Handling of BLQ samples for derivation of serum PK parameters after single dose administration
    - BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to zero.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing.
    - Measurable concentrations after consecutive BLQs will also be set to missing.

• Handling of BLQ samples for derivation of plasma PK parameters after multiple dose administration

- BLQs for Day 1 at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
- BLQs on subsequent dosing days and not separated by a washout: pre-dose values, BLQs in the absorption phase, and BLQs between evaluable concentrations, will be substituted by zero before the calculation of the PK variables.
- Terminal BLQs (at the end of participant profile) will be set to zero.

Pharmacokinetic parameters will be estimated according to the guidelines presented in 4-4.

Table 4-4 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max}, $C_{trough,}$	Obtained directly from the observed concentration-time data
AUC_{0-x}	The AUC from zero time (pre-dose) to the time of specific time x will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The AUC from zero time to the specific time x is the sum of areas up to the specific time x sample: $AUC_{0-x}=AUC_{0-x} = \int_0^x Cx * dx$

PK Parameters Listings:

PK parameters will be listed by subject for the PK Set. If PK parameters need to be excluded from summary tables and statistical analyses, they will be flagged and footnoted with the reason for exclusion.

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary table and statistical analysis. PK parameters will be summarized by treatment for the PK Set.

Tabular summaries for PK parameters will report N (number of subjects who received treatment) and n (number of subjects with non-missing values).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For t_{max}, only N, n, median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of participant level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g. ratios)	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s.f = significant figures, d.p. = decimal place

4.6.4. Pharmacodynamic Endpoints

Blood samples will be collected for measurement of serum concentrations of sCTX and sP1NP as per SoA (Table 1-1 of the protocol). Baseline is defined as the concentration values of P1NP and sCTX derived by serum sampling collected pre-dose at Day 1. Change from Baseline will be calculated by subtracting observed concentration by baseline concentration.

%CfB in serum sP1NP will be computed as follows,

$$\%\text{CfB} = \frac{sP1NP_{timepoint} - sP1NP_{baseline}}{sP1NP_{baseline}} * 100$$

where $sP1NP_{baseline}$ and $sP1NP_{timepoint}$ respectively are concentration value at baseline (pre-dose at Day 1) and at post-baseline timepoint CfB.

%CfB in serum sCTX will be computed as follows,

$$\%\text{CfB} = \frac{sCTX_{baseline} - sCTX_{timepoint}}{sCTX_{baseline}} * 100$$

where $sCTX_{baseline}$ and $sCTX_{timepoint}$ respectively are concentration value at baseline (pre-dose at Day 1) and at post-baseline timepoint CfB.

The area under the effect curve (AUEC) after first dose until month 6 (Day 180) will be calculated using percent change from Baseline (%CfB) in sCTX and will be estimated as key PD parameter for the co-primary endpoint.

Serum samples for determination for sCTX should be collected prior to IP administration (if applicable for the visit) at the same time (in the morning between 07:30 and 10:00 am) and after a minimum of 8 hours of fasting. Patients should refrain from strenuous physical exercise 24 hours prior to each blood collection for PD analysis.

Drug effect model will be used to derive the sCTX PD parameter listed in table below using Phoenix version 8.3 or higher. Derivation of this PD parameter will be the responsibility of CPMS, Parexel. The details of sCTX PD parameter is provided in Table 4-5.

Table 4-5 Serum Pharmacodynamic Parameter of sCTX

Protocol Parameter	WNL Name	Definition
AUEC	AUC_NET_B	Area under the effect curve of sCTX, from time zero to month 6 of sCTX (percentage change from baseline)

Percent change from baseline of sCTX and P1NP will be summarized in tabular and graphical format using PD set. AUEC of sCTX will be summarized in tabular and graphical format using PD set. A by-patient listing will be provided for of sCTX and P1NP data. The individual serum concentration of change from baseline sCTX will be listed and summarized by treatment group, visit at each planned sampling time using descriptive statistics (number, arithmetic mean, SD, CV%, geometric mean, gCV%, minimum, median, and maximum) by treatment for observed, absolute, and percentage change from baseline, where appropriate.

Listings will include actual sampling times relative to dose administration, observed sCTX value, change from baseline value, and percentage change from baseline. Baseline will be taken as the last measurement prior to dosing. Descriptive statistics (number, mean, SD, CV%, minimum, median, and maximum) will be presented by treatment for observed, absolute, and percentage change from baseline sCTX assessment.

The following descriptive statistics will be presented for serum sCTX concentrations obtained at each nominal time point: N, n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(es^2-1)*100; where s is the SD of the log transformed values), median, minimum, and maximum values.

For summary tables, the number at each scheduled time point will be reported.
The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:
To visualize subject-level sCTX concentrations and the comparison by treatment group, visit for each treatment, the descriptive PD graphs listed below will be generated.

- Figure: Individual subject profiles for sCTX serum Concentration of ENZ215- Time Data – (Linear Scale) (PD Set) (change from Baseline)
- Figure: Individual subject profiles for sCTX serum Concentration of Prolia®- Time Data – (Linear Scale) (PD Set) (change from Baseline)
- Figure: Overlaid individual subject profiles for sCTX serum Concentration of ENZ215- Time Data (Linear Scale and Semi-Logarithmic Scale) (PD Set) (change from Baseline)
- Figure: Overlaid individual subject profiles for sCTX serum Concentration of ENZ215- Time Data (Linear Scale and Semi-Logarithmic Scale) (PD Set) (change from Baseline)
- Figure: Arithmetic Mean (± SD) for sCTX serum Concentration of ENZ215 and Prolia® groups- Nominal Time Data –(Linear Scale) (PD Set) (percentage change from Baseline)

Figures will be generated in black and white (or color) using unique line style and marker for each plot in the graph. For all sCTX concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.6.4.1. Pharmacodynamic Parameters (AUEC of sCTX)

AUEC of % change from baseline in sCTX until 6 months will be calculated using drug effect model from the sCTX- time data using Phoenix® WinNonlin® <8.3> or higher. The AUEC for sCTX adjusted for baseline will be estimated by treatment groups.

The AUEC will be listed and summarized by treatment groups. Descriptive statistics will be presented. Descriptive statistics (number, mean, SD, CV%, minimum, median, and maximum) will be presented by treatment groups (ENZ215 vs Prolia®) for percentage change from baseline sCTX assessment.

Pharmacodynamic parameters will be estimated according to the guidelines presented in Table 4-6.

Table 4-6 Pharmacodynamic Parameter and Estimation

Parameter	Guideline for Derivation
AUEC	The AUEC from zero time (pre-dose) to the time of specific time x will be calculated by a combination of linear-linear methods. The AUEC from zero time to the specific time x is the sum of areas up to the specific time x sample: $AUEC_{0\text{-}x}=AUEC_{0-x} = \int_0^x Cx * dx$

PD Parameter Listings:

AUEC of sCTX will be listed by subject for the PD Set by treatment groups.

PD Parameter Summary Tables:

Biostatistics group will consider the AUEC of sCTX parameter as source data and will use this data without rounding for calculation of PD parameter summary statistics tables. AUEC of sCTX will be summarized by treatment for the PD Set.

Tabular summaries for AUEC of sCTX will report N (number of subjects who received treatment) and n (number of subjects with non-missing values). Descriptive statistics for calculated AUEC of sCTX will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. No descriptive statistics will be determined when fewer than three individual AUEC of sCTX are available.

The rules followed for presentation of AUEC of sCTX data with regards to the number of decimal places/significant digits for the listings of subject level PD parameters and summary tables of PD parameters are as follows:

PD Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.

Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g. ratios)	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

To evaluate the AUEC of sCTX, the treatment comparison will be made using the ANCOVA on log-transformed data of AUEC of sCTX with treatment group as fixed effect, and baseline sCTX value as a covariate. The ANCOVA will include calculation of LSM for the treatment groups. The ratios of LSM will be calculated using the exponentiation of the LSM from the analyses on the corresponding log-transformed AUEC of sCTX on the PD set.

Pharmacodynamic equivalence will be assessed if the 90% CI of the treatment ratio is contained within the acceptance limits of 80% to 125%. 95% CIs of geometric mean ratio between the treatment groups will also be provided as an exploratory analysis.

In the primary PD analysis patients with missing sCTX sampling at Baseline will not be included in the analysis of the AUEC of sCTX, additionally to be included in the analysis of the AUEC of sCTX, patients will need to have the results from the visits of Day 1, Day 15, Day 30 (M1), and Day 180 (M6). Serum sCTX concentration below the limit of quantification (BLQ) will be considered as zero (0) in summary tables.

4.7. Interim Analysis

Interim analysis is not Applicable in this study.

There will be two analyses performed and two CSRs will be prepared, one at month 12 primary endpoint analysis and second one at the final database lock at end of open label phase, month 18.

4.8. Changes to Protocol-planned Analyses

Not Applicable

5. Sample Size Determination

The sample size for study is computed to demonstrate equivalence of ENZ215 and Prolia® in the percent change from baseline in LS-BMD at 12 months. The equivalence margin is pre-defined at ±1.45%. Assuming a standard deviation (SD) of 4.16%, the study will have 90% power to demonstrate equivalence at the (2-sided) 2.5% level of significance with 214 evaluable patients in each treatment group. Allowing for a 15% dropout rate, 504 patients (252 per treatment group) will be required to be randomized in the study.

Considering the PD co-primary endpoint (percentage change from baseline in AUEC of $sCTX_{0\text{-}6m}$), healthy volunteer data were used for the sample size calculations due to the lack of information on AUEC of $sCTX_{0\text{-}6m}$ derived from the patient population. The expected variability to the proposed PD endpoint is considered to be significantly lower than that of the proposed efficacy endpoint (in the NCT2053753 study, the inter-patient CV of AUEC of $sCTX_{0\text{-}6m}$ was approximately 28%).

The correlation between the sCTX and LS-BMD is assumed to be zero. Most likely there will be a correlation between percentage change from baseline in LS-BMD and log (AUEC). It is difficult to estimate the value a-priori and the correlation of zero will provide a conservative estimate of the power.

A total sample size of 428 patients will have >99.9% power for the co-primary endpoint percentage change from baseline in AUEC of $sCTX_{0\text{-}6m}$ considering the CV of 28%. The overall power of the study will be approximately 90% to succeed on both the equivalence tests for co-primary endpoints.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

Abbreviation / Acronym	Definition / Expansion
ADAs	Anti denosumab antibodies
AE	Adverse event
ANCOVA	Analysis of Covariance
AUC	Area under the curve
AUEC	Area Under the Effect Curve
BLQ	Below the limit of quantification
BMD	Bone Mineral Density
CfB	Change from Baseline
CI	Confidence interval
CRF	Case Report Form
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
COVID-19	Corona Virus Disease 2019
CV	Coefficient of variation
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
ENZ215	Enzene Denosumab (Proposed biosimilar to Prolia®)
EOS	End-of-study
ICE	Intercurrent Event
IP	Investigational Product
ITT	Intent-to-Treat
LLOQ	Lower limit of quantification
LS-BMD	Bone Mineral Density at Lumbar Spine
LSM	Least Mean Square
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
MNAR	Missing not at random
NCS	Not clinically significant
NK	Not known
P1NP	Procollagen Type 1 N-terminal Propeptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol

Abbreviation / Acronym	Definition / Expansion
ADAs	Anti denosumab antibodies
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SC	Subcutaneously
sCTX	Serum C-Telopeptide of Type 1 Collagen
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization - Drug Dictionary

6.2. Appendix 2: Supporting Study Information

6.2.1. Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

Disposition of Patients for treatment completion and study completion will be summarized by overall and/or by treatment group. Number and percentage will be provided for:

- Patients screened
- Patients failed screening
- Patients randomized
- Patients randomized but not treated
- Patients treated
- Patients completed the study (Month 12)
- Patients discontinued from study, showing reasons for study discontinuation
- Patients completed the study (Month 18)
- Patients discontinued from study, showing reasons for study discontinuation

A by-patient listing of patients' disposition with their withdrawal/study completion details (including reason for discontinuation) will be provided.

This analysis will be carried out based on the Screened Set.

6.2.2. Demographics

All demographic summaries will be provided based upon the ITT set. The summaries provided will include the following:

- A summary of demographic variables, Age, Age group, Sex, Years since menopause, Ethnicity, Race, height, and weight by treatment group and overall
- A listing of all the demographic variables and other possible relevant variables

6.2.3. Fracture or X-Ray finding History

Fracture or X-Ray finding history will be provided by treatment group and overall, based on the Safety set.

A by-patient listing will also be provided.

6.2.4. Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the different analysis sets for the study. Prior to database lock, protocol deviation and analysis set outputs will be produced and will be sent to Sponsor for review. Analysis set classifications will be discussed in Data Review Meeting to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses.

The following summaries and listings will be prepared:

A summary of the number and percentage of patients with a major protocol deviation by treatment group and overall and by type of deviation based on ITT set.

A summary of the number and percentage of patients with a major protocol deviation leading to exclusion from different analysis sets by treatment group and overall and by type of deviation based on ITT set.

A by-patient listing of major protocol deviations with reason for exclusion from the analysis set(s) will be provided.

Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

6.2.5. Medical History

Relevant medical history will be collected including prior and ongoing medical illnesses, conditions, and surgical procedures (including fracture history and family history of premature cardiovascular disease)

Medical history will be coded using the most recent version of the MedDRA and will be summarized by system organ class and preferred term. Missing coding terms will be listed and summarized as ‘Not Coded’ based on ITT set. A by-patient listing will be provided for medical history data.

6.2.6. Prior/Concomitant Medications

For summaries of medications, entries will be classified as either “prior only”, “both prior and concomitant”, or “concomitant only”. To help with the correct identification, the concomitant medication start date and end date will be used from eCRF data comparing these dates with the

first dose date/time of study treatment to classify the record correctly. The overview in Table 6-1 below shows the rules for classification.

Table 6-1: Classification of medications

Was the concomitant medication given / taken prior to first study treatment?	Was the medication stopped prior to first study treatment?	Classification
yes	Yes	"prior only"
yes	no	"both prior and concomitant"
no	Yes	This combination is not plausible. Use dates to classify. If the dates do not allow to clearly classify then assign as "both prior and concomitant".
no	No	"concomitant only"
yes	Missing	Use dates to classify as either "prior only" or "both prior and concomitant". If the dates do not allow to clearly classify then assign as "both prior and concomitant".
no	Missing	"concomitant only"
missing	Yes	"prior only"
missing	No	Use dates to classify as either "both prior and concomitant" or "concomitant only". If the dates do not allow to clearly classify then assign as "both prior and concomitant".
Missing	missing	Use dates to classify. If the dates do not allow to clearly classify then assign as "both prior and concomitant".

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest

that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Medications will be coded using the latest World Health Organization-Drug Dictionary (WHO-DD) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Summaries will be provided for Prior medications, prior and concomitant medications, and concomitant medications by ATC level 3 and preferred name, treatment group and overall based on ITT set. A by-patient listing will also be provided.

6.3. Appendix 3: Data Handling Conventions

6.3.1. Analysis Visit Windows

6.3.1.1. Effectiveness and Safety

The following analysis visit-windowing will be used for the BMD data analysis as part of the primary efficacy endpoint analyses.

Visit	Minimum	Target Day	Maximum
7	145	180	215
9	325	360	395

For all other analyses (including the primary pharmacodynamic endpoint of sCTX, secondary efficacy endpoints and safety endpoints), nominal visits will be used in the analysis tables. Unscheduled visit assessments will not be considered in the tables and those unscheduled assessments will be displayed in the listings along with the scheduled visit assessments.

6.3.2. Missing Date Imputation

To account for missing time in date/time when deriving duration variables, the following approaches will be used:

- Time points with unknown start times (where the date is known) will be imputed with a time of 00:00 h or treatment administration time
- Time points with unknown end times (where the date is known) will be imputed with a time of 23:59 h
- Unknown time part will be shown as NK in the listings (where NK = Not Known).

6.3.2.1. Missing/Incomplete TEAE Start/End Date

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.

Start/Increase Severity Date	Stop Date	Action
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.
	Partial	The last day of the month and the last month (i.e., December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE
	Missing	Considered as a TEAE

6.3.2.2. Missing/Incomplete Prior/Concomitant Medications Start/End Date

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.

Start Date	Stop Date	Action
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.

6.4. Appendix 4: Sample SAS Code

In this appendix, examples of SAS codes are provided; these are intended to guide programmers and it is expected these will be adapted in phase of analysis.

Primary efficacy analysis for % CfB in LS-BMD at Month 12:

```
ODS OUTPUT PARAMETERESTIMATES=COEFFICIENTS;
PROC GLM DATA=GEDEON PLOTS=NONE;
      CLASS ARM(REF="PROLIA") Age_group BISPHOSPHONATES;
```

```
      MODEL BMD_PC_M12 = ARM BMD_BASELINE Age_group BISPHOSPHONATES /
SOLUTION;
<Add /modify "lsmeans" and "estimate" statements as needed preserving the
model>
RUN;
```

6.4.1. Secondary Estimand – ANCOVA sample SAS (code is provided as general example and will be adapted in phase of analysis)

```
ODS OUTPUT PARAMETERESTIMATES=COEFFICIENTS;
PROC GLM DATA=GEDEON PLOTS=NONE;
      CLASS ARM(REF="PROLIA") Age_group BISPHOSPHONATES;
      MODEL BMD_PC_M12 = ARM BMD_BASELINE Age_group BISPHOSPHONATES /
SOLUTION;
<Add /modify "lsmeans" and "estimate" statements as needed preserving the
model>
RUN;

DATA TEST_P_VALUE_NONINF_COEFFICIENTS;
SET COEFFICIENTS;
IF PARAMETER = "ARM     ENZ215";
STAT_TEST = (ESTIMATE - (-1.45))/STDERR;
P_VALUE_TEST_NON_INF = 1-CDF('NORMAL', STAT_TEST);
RUN;

DATA TEST_P_VALUE_NONSUP_COEFFICIENTS;
SET COEFFICIENTS;
IF PARAMETER = "ARM     ENZ215";
STAT_TEST = (ESTIMATE - (1.45))/STDERR;
P_VALUE_TEST_NON_SUP = CDF('NORMAL', STAT_TEST);
RUN;
```

6.4.2. ICE2 Multiple Imputation – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

```
*STEP (1) WEEK 52 BMD COLLECTED AFTER ICE 2 ARE SET TO MISSING;
data BMD_primeff_ICE2;
set BMD_primeff;
if ICE2='1' then CFBperc_M12_IMP=.; *ICE2 date to be taken into
account;
run;

*STEP (2) PROLIA & ENZ215 SUBJECTS FILTERED TO SUBSET DATASETS;
data BMD_primeff_PRO; set BMD_primeff_ICE2; if trt_main='b_Prolia';
run;
data BMD_primeff_ENZ215; set BMD_primeff_ICE2; if trt_main='a_ENZ215';
run;

*STEP (3) PROLIA MULTIPLE IMPUTATION MAR;
PROC MI DATA=BMD_primeff_PRO NIMPUTE=50 OUT=MI_MVN_PRO SEED=254282;
CLASS Age_group Bisphosphonates;
VAR Age_group Bisphosphonates BMD_SCR CFBperc_M6_IMP CFBperc_M12_IMP;
FCS REG (CFBperc_M6_IMP = Age_group Bisphosphonates BMD_SCR  /
details);
FCS REG (CFBperc_M12_IMP = Age_group Bisphosphonates BMD_SCR
CFBperc_M6_IMP / details);
RUN;

*STEP (4) ENZ215 MULTIPLE IMPUTATION MNAR;
PROC MI DATA=BMD_primeff_ENZ215 NIMPUTE=50 OUT=MI_MVN_ENZ215
SEED=254282;
CLASS Age_group Bisphosphonates;
VAR Age_group Bisphosphonates BMD_SCR  CFBperc_M6_IMP CFBperc_M12_IMP;
FCS REG (CFBperc_M6_IMP = Age_group Bisphosphonates BMD_SCR / details);
FCS REG (CFBperc_M12_IMP = Age_group Bisphosphonates BMD_SCR
CFBperc_M6_IMP / details);
mnar adjust (CFBperc_M12_IMP / shift=-1.45);
RUN;
```

```
*STEP (5) MULTIPLE IMPUTED VALUES ARE RETAINED ONLY FOR THE POST-ICE2
EFFICACY;
data MI_MVN_ICE2PRO; set MI_MVN_PRO; if trt_main='b_Prolia';
*below, values originally missing are reverted back to missing so that
the MI is retained only for post ICE2 assessemnts;
if CFBperc_M6=. then CFBperc_M6_IMP=.;
if CFBperc_M12=. then CFBperc_M12_IMP=.;
run;
data MI_MVN_ICE2ENZ215; set MI_MVN_ENZ215; if trt_main='a_ENZ215';
*below, values originally missing are reverted back to missing so that
the MI is retained only for post ICE2 assessemnts;
if CFBperc_M6=. then CFBperc_M6_IMP=.;
if CFBperc_M12=. then CFBperc_M12_IMP=.;
run;
*imputed Prolia and ENZ215 are compiled in unique dataset;
data MI_MVN_ICE2; set MI_MVN_ICE2PRO MI_MVN_ICE2ENZ215; run;

*Step (6) ANCOVA MODEL EXECUTED ON THE 50 IMPUTED DATASETS;
proc sort data=MI_MVN_ICE2; by _IMPUTATION_ PatID; run;
PROC GLM DATA=MI_MVN_ICE2;
  BY _IMPUTATION_;
  id PatID;
  CLASS trt_main Age_group Bisphosphonates;
  MODEL CFBperc_M12_IMP=trt_main Age_group Bisphosphonates BMD_SCR
   /SOLUTION CLM;
  LSMEANS trt_main / PDIFF CL;
  ESTIMATE "ENZ215-PROLIA" trt_main 1 -1;
  OUTPUT OUT=ANEW P=PREDY;
  ODS OUTPUT PARAMETERESTIMATES=PE;
  ODS OUTPUT PREDICTEDVALUES=RRR;
  ODS OUTPUT ESTIMATES=DIFFERENCE;
  ODS OUTPUT LSMeanDiffCL=LSMeanDiffCL;
RUN; QUIT;

*Step (7) PROC MIANALYZE EXECUTED TO OBTAIN POOLED EFFECT ESTIMATE;
PROC MIANALYZE DATA=DIFFERENCE ALPHA=0.05;
ODS OUTPUT PARAMETERESTIMATES=TEST_COMBINED;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
RUN;
```

6.4.3. Multiple Imputation for Sensitivity analysis – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

```
*STEP (1) WEEK 52 BMD COLLECTED AFTER ICE 2 ARE SET TO MISSING;
data BMD_primeff_ICE2;
set BMD_primeff;
if ICE2='1' then CFBperc_M12_IMP=.; *ICE2 date to be taken into
account;
run;

*STEP (2) PROLIA & ENZ215 SUBJECTS FILTERED TO SUBSET DATASETS;
data BMD_primeff_PRO; set BMD_primeff_ICE2; if trt_main='b_Prolia';
run;
data BMD_primeff_ENZ215; set BMD_primeff_ICE2; if trt_main='a_ENZ215';
run;

*STEP (3) PROLIA MULTIPLE IMPUTATION MAR;
PROC MI DATA=BMD_primeff_PRO NIMPUTE=50 OUT=MI_MVN_PRO SEED=254282;
CLASS Age_group Bisphosphonates;
VAR Age_group Bisphosphonates BMD_SCR CFBperc_M6_IMP CFBperc_M12_IMP;
FCS REG (CFBperc_M6_IMP = Age_group Bisphosphonates BMD_SCR / details);
FCS REG (CFBperc_M12_IMP = Age_group Bisphosphonates BMD_SCR
CFBperc_M6_IMP  / details);
RUN;

*STEP (4) ENZ215 MULTIPLE IMPUTATION MAR (MNAR post ICE2);
PROC MI DATA=BMD_primeff_ENZ215 NIMPUTE=50 OUT=MI_MVN_ENZ215
SEED=254282;
CLASS Age_group Bisphosphonates ICE2;
VAR Age_group Bisphosphonates BMD_SCR CFBperc_M6_IMP CFBperc_M12_IMP;
FCS REG (CFBperc_W26_IMP = Age_group Bisphosphonates BMD_SCR e  /
details);
FCS REG (CFBperc_M12_IMP = Age_group Bisphosphonates BMD_SCR
CFBperc_M6_IMP  / details);
mnar adjust (CFBperc_M12_IMP / shift=-1.45 adjustobs=(ICE2='1'));
RUN;
```

```
*Step (5) IMPUTED PROLIA AND ENZ215 ARE COMPILED IN UNIQUE DATASET;
data MI_MVN_ICE2; set MI_MVN_PRO MI_MVN_ENZ215; run;

*Step (6) ANCOVA MODEL EXECUTED ON THE 50 IMPUTED DATASETS;
proc sort data=MI_MVN_ICE2; by _IMPUTATION_ PatID; run;
PROC GLM DATA=MI_MVN_ICE2;
  BY _IMPUTATION_;
  id PatID;
  CLASS trt_main Age_group Bisphosphonates;
  MODEL CFBperc_W52_IMP=trt_main Age_group Bisphosphonates BMD_SCR
   /SOLUTION CLM;
  LSMEANS trt_main / PDIFF CL;
  ESTIMATE "ENZ215-PROLIA" trt_main 1 -1;
  OUTPUT OUT=ANEW P=PREDY;
  ODS OUTPUT PARAMETERESTIMATES=PE;
  ODS OUTPUT PREDICTEDVALUES=RRR;
  ODS OUTPUT ESTIMATES=DIFFERENCE;
  ODS OUTPUT LSMeanDiffCL=LSMeanDiffCL;
RUN;
QUIT;

*Step (7) PROC MIANALYZE EXECUTED TO OBTAIN POOLED EFFECT ESTIMATE;
PROC MIANALYZE DATA=DIFFERENCE ALPHA=0.05;
ODS OUTPUT PARAMETERESTIMATES=TEST_COMBINED;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
RUN;
```

6.4.4. Supplementary Estimand – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

```
PROC MIXED DATA=GEDEON method=ml;
      CLASS ARM(REF="PROLIA") Age_group BISPHOSPHONATES AVISIT;
      MODEL BMD_PC = ARM BMD_BASELINE Age_group BISPHOSPHONATES AVISIT
        AVISIT *TREATMENT/ SOLUTION;
      REPEATED / TYPE=UN SUBJECT=USUBJID R;
<Add /modify "lsmeans" and "estimate" statements as needed preserving the
model>
RUN;
```

6.4.5. Primary Pharmacodynamic Endpoint ANCOVA model and GMR derivation – sample SAS code (code is provided as general example and will be adapted in phase of analysis)

```
ods trace on;
ods output LSMeans=geomean Diffs=geomean_diff;
proc mixed data=ancova;
class trt Age_group BISPHOSPHONATES;
model logAUC = trt Age_group BISPHOSPHONATES logbase;
lsmeans trt / cl diff=control pdiff=control tdiff;
estimate 'ENZ215 - Prolia' trt -1 1 / e cl;
run;
ods trace off;
```

7. References

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