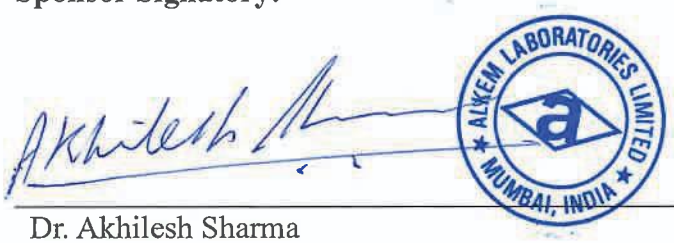
Title Page

Protocol Title:	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
Brief Title:	A Phase 3 Study to Compare Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis
Compound:	Enzene Denosumab (ENZ215)
Indication:	Postmenopausal Osteoporosis
Study Sponsor:	Alkem Laboratories Ltd. ALKEM HOUSE, "Devashish", Adjacent to Matulya centre, Senapati Bapat Marg, Lower Parel, Mumbai, India–400 013 Telephone: +91-22-39829999
Co-Sponsor	Enzene Biosciences Ltd. Plot No. A-22/A/1/2, MIDC Chakan Industrial Area, Phase II, Vill-Khalumbre, Taluka Khed, Pune-410 501, Maharashtra, India Phone: +91-20-30674622
Protocol Number:	ALK22/ENZ215-DEN2
Study Phase:	Phase 3
EUDRACT Number:	2021-004811-26
Version:	3.0
Approval Date:	Final: 16 February 2023

Sponsor Signatory:



16/02/2023

Dr. Akhilesh Sharma
President & Chief Medical Officer

Date

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY			
Document	**Amendment Scope**	**Protocol Version**	**Date**
Amendment 3	Global	Version 3.0	16 February 2023
Amendment 2	Global	Version 2.0	08 April 2022
Amendment 1	Global	Version 1.1	16 December 2021
Original Protocol	Not Applicable	1.0	22 October 2021

Amendment 3.0 (16 February 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The Global clinical study protocol (CSP) Amendment 3.0 was prepared to add clarifications and update typo errors noted in earlier version of the document.

Other improvements, such as updates to summary of protocol amendment are not presented in this summary.

Section	**Description of Change**	**Brief Rationale**
Section 1 Protocol Summary - Synopsis Section 3: Objectives and Endpoints	Secondary Pharmacokinetics Endpoint updated as: ~~Serum Concentrations~~ PK Parameters (C_{max}, T_{max}, partial $AUC_{(~~0-28 days~~ 0-1 month)}$, and $AUC_{(0-6 month)}$) ~~and $AUC_{(0-inf)}$~~)of denosumab measured at baseline (Day 1), Day 8, Day 15, Month 1, Month 3, Month 6	Typographic error: Replaced Serum Concentrations with PK parameters as these are PK parameters, not Serum concentrations. The $AUC_{(0-inf)}$) is removed from analysis as there are limited PK sample points in

	(prior to second dose), and Month 12.	Terminal phase and it is not possible to derive $AUC_{(0\text{-}inf)}$). $AUC_{(0\text{-}28\ days)}$ is made $AUC_{(0\text{–}1\ month)}$ to make it consistent with Protocol Schedule of assessment.
Table 1.1 Schedule of Activities, Section 8 Study Assessments and Procedures: Visit 2, Visit 7 and Visit 9 Section 8.2.3 Injection site reaction	Corrected Injection site reaction monitoring after IP administration as **at least for** ~~up to~~ one hour	Injection site reaction monitoring is required at least for one hour post dosing, the wording up to one hour was misleading thus the same was updated
Table 1.1 Schedule of Activities, Section 8: Study Assessments and Procedures	Added DXA at Early Termination visit if done after Month 6 and prior to Month 12	To have DXA assessments for subjects who have discontinued post Month 6 and prior to Month 12
Table 1.1 Schedule of Activities, Section 8 – Study Assessments and Procedures Screening (day -35 to day -1) Month 12 (±7 days) Month 18//EOS / Early Discontinuation Withdrawal (±7 days)	Lateral lumbar spine X-ray replaced with Lateral thoracic and lumbar spine X-ray	X-ray imaging site mentioned is corrected and made consistent with image acquisition guideline by Calyx.
Table 1.1 Schedule of Activities	Updated Instruction # 4 in footer as " A written, signed and dated re-consent form should be obtained from patients who volunteer to participant in the open-label, switch-over study until Month 18.	To clarify requirement of reconsenting at Month 12 for participation in Extension study.

	A written, signed and dated consent should also be obtained from those subjects who previously at visit 1 did not consent but now at visit 9 have shown interest to continue their participation in to the open-label, switch-over study."	
Table 1.1 Schedule of Activities	Deleted below instructions for "Blood sample collection for testing of TSH and iPTH should be done at early morning."	As there is no specific requirement or instruction for testing TSH and iPTH from the central lab.
Table 1.1 Schedule of Activities	Updated instruction # 21 as "**Only** Serum calcium levels will be tested on Day 15 for all patients". Updated Instruction # 24 as 'Serum calcium levels **can** ~~will~~ be tested locally prior to dosing at Month 6 and Month 12. This can either be done on the same day as the dosing visit or at a separate unscheduled visit if required per local standard of care. If hypocalcemia is identified, the patient should not be dosed until calcium levels are corrected. **In case the serum Calcium assessments are performed via the Central Lab, all lab samples required for the impending visit can be collected on the same day of Calcium assessment, provided the sample collection date is within the window period for the visit.**	To clarify the Lab Sample collection at Month 6 and Month 12
Section 5.1 Inclusion Criteria 7	Inclusion Criteria 7 updated as 'No other clinically significant medical history,	To add clarification

	vital signs, physical examination, laboratory profiles as deemed by the Investigator or designee **that would pose a risk to participant safety or interfere with the study evaluation, procedures or completion'**	
Section 5.2 Exclusion Criteria 5	Exclusion Criteria 5 updated as: Use of intravenous bisphosphonates within the past 5 years prior to screening. Added note **If used more than 5 years prior, patients will be excluded if cumulative use was > 3 years.**	To clarify subjects with cumulative use of bisphosphonates for more than 3 years to be excluded.
Section 5.2 Exclusion Criteria 6	Exclusion Criteria #6 updated as 'Use of parathyroid hormone or its derivatives, ~~systemic~~ hormone replacement therapy, **romosozumab**, selective estrogen-receptor modulators, or tibolone or calcitonin within 12 months prior to enrollment' **Added Note: occasional use of intravaginal estrogen treatment is not exclusionary**	Added romosozumab history as exclusion considering impact of its use on bone metabolism, To clarify continuous non systemic use of Hormone replacement therapy is also exclusion and occasional use of intravaginal estrogen treatment is not exclusion
Section 5.2 Exclusion Criteria 9	Exclusion Criteria updated as 'Other bone active drugs (i.e. drugs affecting bone metabolism) including heparin, anti-epileptics (except for benzodiazepines and pregabalin), **antidepressants such as SSRIs, SNRIs, antipsychotics,** systemic ketoconazole, adrenocorticotrophic	The criteria have been updated in order to make it consistent with section 6.11 – Prohibited Medications of the protocol.

	hormone (ACTH), lithium, protease inhibitors, gonadotropin releasing hormone (GnRH) agonists, or anabolic steroids within the past 3 months prior to screening **or requiring treatment with these agents during the study**. **Added Note: Please refer to Section 6.11 for a comprehensive list of prohibited medications**	
Section 5.2 Exclusion Criteria 20	Significantly impaired renal function (determined by glomerular filtration rate of ~~≤ 45 mL/min/1.73m^2~~ < **45 mL/min/1.73 m^2** by the Modification of Diet in Renal Disease (MDRD) formula, as calculated by the central laboratory) or receiving dialysis	corrected as it was typo error
Section 5.2 Exclusion Criteria 24	Updated exclusion criteria #24 as 1. Patient with an active infection or history of infection as follows: a. Any active infection for which systemic anti-infectives were used within 4 weeks prior to ~~screening~~ randomization b. A serious infection defined as requiring hospitalization or intravenous anti-infectives	Updated as it was typo error

	within 8 weeks prior to ~~screening~~ randomization c. Recurrent or chronic infections or other active infection that, in the opinion of the Investigator, might compromise the safety of the patient	
Section 6: Study Interventions and Concomitant Therapy	Updated Calcium as **elementary Calcium**	updated for better understanding
Section 6.11 Prohibited Medications	Deleted Raloxifen and Bazedoxifen Added Romosozumab to prohibited medications list Updated Antidepressants as selective serotonin reuptake inhibitors **(SSRIs) as well as Serotonin and norepinephrine reuptake inhibitors (SNRIs)** Antipsychotics made as a separate bullet, which was earlier specified under anti-depressants	As those are covered under class selective estrogen-receptor modulators listed as prohibited medication To Specify SNRIs are also prohibited along with SSRIs To specify antipsychotics as it is a different class of drug from antidepressants
Section 8.2.1 Physical Examinations	Updated Brief Physical Examination with below line: **Weight will also be measured and recorded at least 3 monthly i.e. at Visit 6, 7, 8, 9, 10, and 11.**	Added body weight under brief physical examination that was missed to mention earlier.
Section 8.2.2 Vital Signs	The following text: "**Oral temperature**, heart rate, respiratory rate, and blood pressure will be assessed"	This change is performed to allow other sites for body temperature measurement i.e., axillary, tympanic,

	has been updated to "**Body temperature**, heart rate, respiratory rate, and blood pressure will be assessed."	temporal artery, rectal etc inorder to avoid any potential risk of infection such as COVID-19 infection
Section 9.3.2 Primary Pharmacodynamic Analysis	The CI for Primary Pharmacodynamic analysis is updated as 90% instead of 95%. The assessment of equivalence for the co-primary endpoint will be assessed based upon the **90%** CI of the ratio of the geometric mean (test/reference) for the percentage change from baseline in AUEC sCTX over the initial 6 Months contained within the pre-specified acceptance limits of 80% to 125%.	sCTX is a highly variable parameter with a high inter subject variability hence 90% CI limits considered for assessment of equivalence instead of 95% CI
Section 10.2 Appendix	Deleted Instructions '~~Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.~~'	Deleted this point as it is a typo error

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1 Protocol Summary

1.1 Synopsis

Protocol Title: 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

Brief Title: A Phase 3 Study to Compare Enzene Denosumab (ENZ215) and Prolia® in Postmenopausal Women with Osteoporosis

Sponsor Protocol No.: ALK22/ENZ215-DEN2

Study Phase: Phase 3

Sponsor: Alkem Laboratories Ltd.

Co-Sponsor: Enzene Biosciences Ltd.

Rationale:

Biologics are relatively new and expensive drugs. Even though the use of biologics has enabled great advances in the treatment of numerous diseases, their high cost has a direct impact on their access and on healthcare budget around the world. Biosimilar medicines are similar to original biologics and are available at lower costs.

Denosumab (ENZ215), the proposed biosimilar to Prolia®, is a monoclonal antibody which is structurally and functionally similar to Prolia®. This study plans to compare equivalence of ENZ215 (test product) to Prolia® (reference product) in terms of efficacy, safety, and immunogenicity in postmenopausal women with osteoporosis.

Development of ENZ215 will involve extensive structural and functional characterization followed by non-clinical testing, human pharmacokinetics (PK), and pharmacodynamics (PD) studies, and clinical immunogenicity assessment. If there is residual uncertainty, additional comparative clinical studies will be required to support demonstration of biosimilarity.

Objectives and Endpoints:

Co-primary Efficacy Objectives	Co-Primary Efficacy Endpoints
• 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 lumbar spine from baseline to Month 12	• Percentage change in BMD at lumbar spine (L1-L4 region) measured by dual-energy X-ray absorptiometry (DXA) 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	• AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To compare the change in serum procollagen type 1 N-terminal propeptide (sP1NP) levels from baseline to Month 6	• Percentage change in sP1NP concentrations from baseline to Month 1, Month 3, and Month 6
• To compare the change in BMD at the lumbar spine from baseline to Month 6	• Percentage change in BMD at lumbar spine measured by DXA 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 BMD at total hip and femoral neck measured by DXA from baseline to Month 6 and 12
Secondary Safety Objectives	**Secondary Safety Endpoints**
• To compare the immunogenicity potential 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
• To compare the safety and tolerability of ENZ215 and Prolia®	• 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 Objective	**Secondary Pharmacokinetics Endpoint**
• 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

Overall Design:

This is a Phase 3, randomized, double-blind, parallel-group, active-controlled study 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 four (504) 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 Prolia® to ENZ215. Re-randomization will not be stratified. The subset of patients selected for re-randomization to the open-label, switch-over study will be patients who complete 12 months of the double-blind treatment period without any significant safety concerns as per the Investigator's discretion and who have re-consented for the open-label extension period. These patients will complete the study at Month 18.

For patients receiving ENZ215 or Prolia® and not continuing to the switch-over study, the study duration will be approximately 25 months, with a recruitment period of 12 months and a study period of 13 months (up to 5 weeks of screening period, 12 months of treatment period). For patients receiving Prolia® and who re-consent to continue to participate in the switch-over study, the study duration will be approximately 31 months (additional 6 months of open-label switch-over study, i.e. until Month 18).

Brief Summary:

Patients will be required to visit the site for the following visits: Visit 1/screening period (Day -35 to Day -1), Visit 2/Day 1, Visit 4/Month 1 (Day 15), Visit 5/Month 1 (Day 30), Visit 6/Month 3 (Day 90), Visit 7/Month 6 (Day 180), Visit 8/Month 9 (Day 270) and Visit 9/Month 12 (Day 360).

Visit 10/Month 15 (Day 450) and Visit 11/Month 18 (Day 540) will be additional visits to the above-mentioned visits for patients initially randomized to receive Prolia® and re-randomized in the switch-over study (subset of 120 patients).

Except on Visit 1 and Visit 2, a window period of ±3 days is allowed on Day 8, Day 15, Day 30 (Month 1), and Day 90 (Month 3). A window period of ± 7 days is allowed from Month 6 until EOS.

EOS assessment will be performed on Month 12 (±7 days) or Month 18 (±7 days) as applicable or at the time of early discontinuation or withdrawal of the patient.

Note: There will be an additional visit (Visit 3/Day 8) for those patients who provide consent for participation in PK sampling. 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.

Number of Patients:

Five hundred four (504) postmenopausal female patients with osteoporosis aged ≥ 55 years and ≤ 85 years fulfilling the study selection criteria will be enrolled from approximately 60 to 70 sites (centers) across the European Union.

Intervention Groups:

Based on the randomization schedule, the investigational product (IP, either ENZ215 or Prolia®) will be administered to the patients at a dose of 60 mg (multiple doses) SC at 6-month intervals into the upper thigh.

In addition, all patients will receive daily supplementation with at least 1 g of calcium and at least 400 IU of vitamin D till Month 12 or Month 18, as applicable. Calcium and vitamin D supplements will be dispensed to patients starting on Day 1 and at each subsequent study visit to be consumed at home daily till Month 12. Vitamin D supplements will be dispensed during the screening period, if required, for replenishment of vitamin D deposits. For patients initially

randomized to the Prolia® arm and who re-consent to participate in the open-label, switch-over study, calcium and vitamin D supplements will be dispensed again at Month 12 for daily supplementation until EOS. If a patient becomes hypercalcemic over the course of the study, the calcium and/or vitamin D supplementation may be reduced or temporarily discontinued per Investigators' medical judgment until the serum calcium concentration returns to the normal range. If a patient develops hypocalcemia over the course of the study, calcium and/or vitamin D supplementation may be adjusted per Investigators' medical judgment until the serum calcium concentration returns to the normal range.

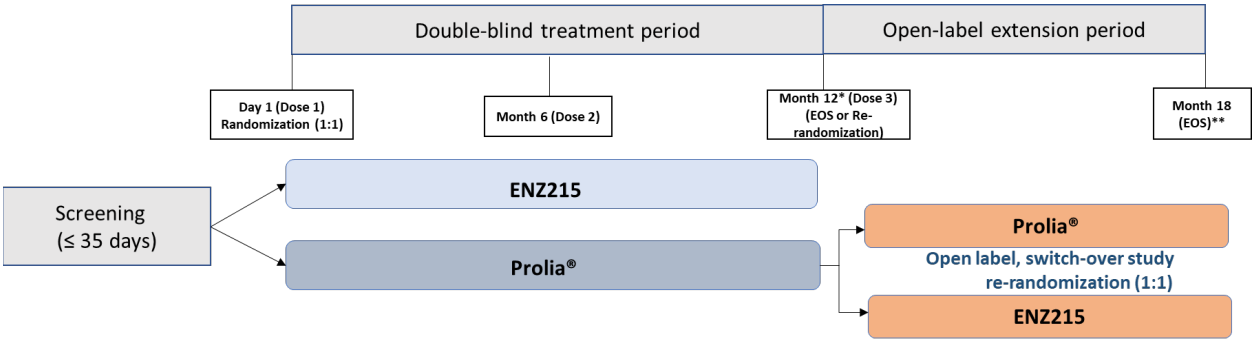
Data monitoring committee

A data monitoring committee (DMC) has been appointed for this study. The DMC is a group of independent scientists who are appointed to monitor the safety of a human research intervention. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring this particular study.

1.2 Schema

A complete study design is presented in Figure 1–1.

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

- Double-blind treatment period: The patients will be randomized in a 1:1 ratio to receive either ENZ215 or Prolia® (60 mg) administered as a SC injection (i.e. 252 patients in each treatment arm). All patients randomized to ENZ215 and all (except a subset of 120 patients) patients randomized to Prolia® will complete the study at Month 12.

- Open-label switch-over extension period: At Month 12, a subset of 120 patients initially randomized to Prolia® arm will be re-randomized to receive either ENZ215 or Prolia® (60 mg) 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) at Month 18.

1.3 Schedule of Activities

A complete study visit schedule (schedule of activities [SoA]) is presented in Table 1-1.

Table 1-1 Schedule of Activities

Assessments	Screening Period (D -35 to D -1)	Double-blind Randomized Main Study (Treatment) Period								Open label Switch over/ Extension period	EOS/ Early Discontinuation / Withdrawal[1]
		D1	M1			M3	M6	M9	M12*	M15	M12/M18
Days	**35 days**	**1**	**8[2]**	**15**	**30**	**90**	**180**	**270**	**360**	**450**	**540**
Visit window	**N/A**	**N/A**	**±3 days**				**± 7 days**				
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Informed consent PK consent, as applicable	X[3]								X[4]		
Inclusion and exclusion criteria	X	X									
Demographics	X										
Physical examination (including oro-dental examination)[5]	X[6]	X[6]	X	X	X	X	X[6]	X	X[6]	X	X
Medical/surgical history[7]	X										
Prior medication history	X										
Current medical conditions	X										
COVID-19 signs and symptoms[8]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[9]	X	X	X	X	X	X	X	X	X	X	X
Randomization		X							X[10]		
12-lead ECG	X						X		X		X
Patient diary review		X[11]	X	X	X	X	X	X	X	X	X[11]
Investigational product administration[12]		X					X		X		

Assessments	Screening Period (D -35 to D -1)	Double-blind Randomized Main Study (Treatment) Period								Open label Switch over/ Extension period	EOS/ Early Discontinuation / Withdrawal[1]
		D1	M1			M3	M6	M9	M12*	M15	M12/M18
Days	**35 days**	**1**	**8[2]**	**15**	**30**	**90**	**180**	**270**	**360**	**450**	**540**
Visit window	**N/A**	**N/A**	**±3 days**				**± 7 days**				
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Injection site reaction monitoring after IP administration (at least for one hour)		X					X		X		
Calcium and vitamin D supplementation[13]	X	X	X	X	X	X	X	X	X	X	
Lateral thoracic and lumbar spine X-ray for fracture/vertebral abnormality assessment	X								X		X
25 (OH) vitamin D level[14]	X						X[15]				
FSH	X										
Thyroid function test (T3, T4, TSH)	X						X[16]				
iPTH	X										
DXA lumbar spine, hip and femoral neck	X[17]						X		X		X[18]
Hematology[19]	X						X		X		X
HIV, HBsAg, HCV	X										
Serum chemistry[20]	X			X[21]		X	X[22]	X	X[22]		X
Urinalysis[23]	X					X	X	X	X		X

Assessments	Screening Period (D -35 to D -1)	Double-blind Randomized Main Study (Treatment) Period								Open label Switch over/ Extension period	EOS/ Early Discontinuation / Withdrawal[1]
		D1	M1			M3	M6	M9	M12*	M15	M12/M18
Days	**35 days**	**1**	**8[2]**	**15**	**30**	**90**	**180**	**270**	**360**	**450**	**540**
Visit window	**N/A**	**N/A**	**±3 days**				**± 7 days**				
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
sCTX[24]		X		X	X	X	X				
sP1NP[24]		X		X	X	X	X				
ADAs		X			X	X	X	X	X	X	X
PK assessment[25]		X	X[26]	X[26]	X	X	X		X		
AE/SAE recording[27]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-denosumab antibodies, ALP = alkaline phosphatase, ALT = alanine aminotransferase ALT, AST = aspartate aminotransferase, BP = blood pressure, BMD = bone mineral density, BUN = blood urea nitrogen, D = day, DXA = dual-energy X-ray absorptiometry, eGFR = estimated glomerular filtration rate, ECG = electrocardiogram, EOS = End of Study, FSH = follicle stimulating hormone, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, iPTH = intact parathyroid hormone, M = month, PA = posteroanterior, PK = pharmacokinetic, PR = pulse rate, RR = respiratory rate, RBC = red blood cells, sCTX = serum C-telopeptide of type 1 collagen, 25 (OH) vitamin D = 25-hydroxy vitamin D, WBC = white blood cells

1. EOS assessment will be performed at Month 12 (±7 days) or Month 18 (±7 days) based on the treatment arm in which the patients will be initially randomized. Information related to further management of patient is provided in Section 7.
2. Visit on Day 8 will only be applicable to patients participating in the PK sub-study.
3. While patient consent is being recorded for the main study, consent should also be obtained for continued participation into the open-label, switch-over study until Month 18. For patients volunteering to participate in PK sub-study, an additional written signed and dated consent should be obtained prior to PK assessments.
4. A written, signed and dated re-consent form should be obtained from patients who volunteer to participant in the open-label, switch-over study until Month 18. A written, signed and dated consent should also be obtained from those subjects who previously at visit 1 did not consent but now at visit 9 have shown interest to continue their participation in to the open-label, switch-over study.
5. A complete physical examination should be performed at screening and a brief physical examination will be performed at all other visits.

6. Oro-dental examination should be performed on screening as well as before IP administration on Day 1, Day 180 (Month 6) and Day 360 (Month 12). In case of any dental abnormality, the patient should be referred to a dental surgeon for further dental examination.
7. Includes fracture history and family history of premature cardiovascular disease.
8. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports.
9. Vital signs will be recorded in supine position after 5 minutes of rest: HR (beats/minute), BP measurement (mmHg), RR (breaths/minute), and body temperature (°F/°C).
10. 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) at Month 18.
11. Patient diary will be dispensed on Day 1, reviewed at each visit and will be collected at EOS assessment visit.
12. IP administration as mentioned in Section 6.1. IP administration at Month 12 is only applicable for patients who will continue into the open-label, switch over study.
13. Calcium and vitamin D supplements will be dispensed on Day 1 and at each subsequent visit to be consumed at home daily. Vitamin D supplements will be dispensed during the screening period, if required, for replenishment of vitamin D deposits.
14. During screening, if the 25 (OH) vitamin D level of a patient is < 20 ng/mL (<50 mmol/L), replenishment of vitamin D deposits can be attempted following sites standard of care (e.g., loading dose of Vitamin D). After replenishment, vitamin D should be retested to confirm value is within the eligibility range.
15. The 25 (OH) vitamin D level of all patients will be re-tested at Month 6.
16. Patients with thyroid dysfunction on L-thyroxine therapy should have thyroid function test (TSH) done at least at Month 6 visit or earlier per discretion of the Investigator.
17. DXA should be done and submitted as early as possible during the screening period to allow for enough time in case a repeat exam is requested by Medical Imaging.
18. Applicable only for early terminated/withdrawal subjects discontinued post 6 months and before Month 12. Not required for EOS in patients participating in OLE or if ET occurs during OLE.
19. Hematology includes total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, platelet count, and absolute neutrophil count.
20. Serum chemistry includes liver function tests (ALT, AST, ALP, total bilirubin, albumin and total proteins), kidney function tests (BUN, creatinine, and eGFR, electrolytes (sodium, potassium, and chloride), glucose, serum calcium, albumin-adjusted calcium, magnesium, and phosphorous.
21. Only Serum calcium levels will be tested on Day 15 for all patients.
22. Serum calcium levels can be tested locally in patients prior to dosing at Month 6 and Month 12. This can either be done on the same day as the dosing visit or at a separate unscheduled visit if required per local standard of care. If hypocalcemia is identified, the patient should not be dosed until calcium levels are corrected. In case the serum Calcium assessments are performed via the Central Lab, all lab samples required for the impending visit can be collected on the same day of Ca assessment, provided the sample collection date is within the window period for the visit.
23. Urine analysis includes: Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase, and microscopic examination including RBC, leukocytes, epithelial cells, bacteria, and crystals.
24. For sCTX and sP1NP, blood samples 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. Refer Section 8.5 for more details.

25. PK Parameters (C_{max}, T_{max}, AUC $_{(0\text{-}1\ month)}$ and $AUC_{(0\text{-}6\ months)}$ -) of denosumab will be measured at baseline (Day 1), Day 8, Day 15, Month 1, Months 3, and Month 6 (prior to second dose). PK parameters (C_{trough}) will be measured at Month 12. Refer Section 8.4 for more details.
26. 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.
27. Recording of adverse events will start after signing of informed consent up to EOS assessment.

*Month 12 visit will be the extension period baseline.

2 Introduction

Denosumab is a fully human monoclonal immunoglobulin G2 (IgG2) antibody that binds and inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL).

The term “study intervention(s)” throughout the protocol refers to the test product, ENZ215 or reference product, Prolia®.

2.1 Study Rationale

Biologics are relatively new and expensive drugs. Even though the use of biologics has enabled great advances in the treatment of numerous diseases, their high cost has a direct impact on their access and on healthcare budgets around the world. Biosimilar medicines are similar to original biologics and are available at lower costs.

Denosumab (ENZ215), the proposed biosimilar to Prolia®, is a monoclonal antibody which is structurally and functionally similar to Prolia®. This study plans to compare equivalence of the ENZ215 (test product) to Prolia® (reference product) in terms of efficacy, safety, and immunogenicity in postmenopausal women with osteoporosis.

2.2 Background

Osteoporosis is estimated to affect 200 million women worldwide, approximately one-tenth of women aged ≥ 60 years, one-fifth of women aged ≥ 70 years, and two-fifths of women aged ≥ 80 years. It is characterized by low bone mineral density (BMD), micro-architectural deterioration, and degradation of other determinants of bone strength, resulting in an increased risk of fractures. The United States Food and Drug Administration (US FDA) first approved denosumab in 2010 for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as having a history of osteoporotic fracture, multiple risk factors for fracture, or failure or intolerance to other available osteoporosis therapy.

By binding to RANKL on the surface of osteoclasts and their precursors, denosumab inhibits development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. For the treatment of osteoporosis, denosumab is administered at a dose of 60 mg subcutaneously (SC) once every 6 months (Q6M) and is thus associated with greater compliance than medications requiring daily administration. Its efficacy in reducing the risk of vertebral, hip, and nonvertebral fractures has been demonstrated in a large prospective, randomized multicenter study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months [FREEDOM]) involving 7808 postmenopausal women with osteoporosis with Q6M administration of 60 mg denosumab for 36 months.

Another 2-year randomized, double-blind, placebo-controlled study involving 332 postmenopausal women also showed that Q6M denosumab increased BMD and decreased bone turnover markers.

Biosimilar medicines are similar to original biologics and are available at lower costs. The regulatory pathway uses a stepwise totality-of-evidence approach as the basis for approval of biosimilars, which is required to be similar to the reference product with respect to quality, safety, and efficacy. For demonstration of biosimilarity between the innovator product (Prolia®) and proposed biosimilar (ENZ215), the stepwise approach starts with an extensive structural and functional characterization followed by nonclinical testing, human pharmacokinetic (PK) and PD studies, and the clinical immunogenicity assessment. If there is residual uncertainty, additional comparative clinical studies will be required to support demonstration of biosimilarity.[1]

2.2.1 Non-clinical Data of Innovator Denosumab

The carcinogenic and genotoxic potential of denosumab has not been evaluated in long-term animal studies. Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL. In ovariectomized monkeys, once-a-month treatment with denosumab suppressed bone turnover and increased BMD and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered Q6M, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone. As the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered ("knockout") mice or use of other biological inhibitors of the RANK/RANKL pathway, namely OPG-Fc, provided additional information on the PD properties of denosumab. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats that were administered the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model upon discontinuation of dosing with the RANKL inhibitors.[2,3]

2.2.2 Clinical Data of Prolia®

The efficacy and safety of Prolia® in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled study. Enrolled women had a baseline BMD T-score between -2.5 and -4.0, either at the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled

women were aged between 60 and 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD (LS-BMD) T-score was -2.8. Approximately 23% of women had a vertebral fracture at baseline. Women were randomized to receive SC injections of either placebo (N = 3906) or Prolia® 60 mg (N = 3902) Q6M. All women received at least 1 g calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.[2,3]

2.2.2.1 Effect on Vertebral Fractures

Prolia® significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 2-1. The incidence of new vertebral fractures at Year 3 was 7.2% in the placebo-treated women compared with 2.3% in the Prolia®-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at Year 3 (Table 2-1).

Table 2-1 Effect of Prolia® on the Incidence of New Vertebral Fractures in Postmenopausal Women

Years	Proportion of Women with Fracture (%)+		Absolute Risk Reduction (%)* (95% CI)	Relative Risk Reduction (%)* (95% CI)
	Placebo N = 3691 (%)	Prolia® N = 3702 (%)		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

CI = confidence interval

+ Event rates based on crude rates in each interval.

*Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

Prolia® was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.[2,3]

2.2.2.2 Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia®-treated women at Year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years (p-value = 0.04).[2,3]

2.2.2.3 Effect on Nonvertebral Fractures

Treatment with Prolia® resulted in a significant reduction in the incidence of nonvertebral fractures as seen in Table 2-2.[2,3]

Table 2-2 The Effect of Prolia® on the Incidence of Nonvertebral Fractures at Year 3 in Postmenopausal Women

	Proportion of Women with Fracture (%)+		Absolute Risk Reduction (%)	Relative Risk Reduction (%)
	Placebo N = 3906 (%)	Prolia® N = 3902 (%)	(95% CI)	(95% CI)
Nonvertebral fracture[1]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)*

+ Event rates based on Kaplan-Meier estimates at 3 years.

[1] Excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges.

* p-value = 0.01.

2.2.2.4 Effect on Bone Mineral Density

Treatment with Prolia® significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index, baseline BMD, and level of bone turnover. After Prolia® discontinuation, BMD returned to approximately baseline levels within 12 months.[2,3]

2.2.2.5 Bone Histology and Histomorphometry

A total of 115 trans-iliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either Month 24 and/or Month 36 (53 specimens in the Prolia® group, 62 specimens in the placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia®.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling while the absence of tetracycline label suggests suppressed bone formation. In patients treated with Prolia®, 35% had no tetracycline label present at the Month 24 biopsy and 38% had no tetracycline label present at the Month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo,

treatment with Prolia® resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.[2,3]

2.2.3 SARS-CoV-2

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This new virus has rapidly spread across the globe causing the World Health Organization to declare a pandemic situation on March 11, 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect patients, site staff, and society as a whole.

Both European Medicines Agency (EMA)[4] and FDA[5] as well as national health authorities in Europe have issued guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regards to the spread of COVID-19 in future, special attention will be paid to protect patients in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of denosumab may be found in the Summary of Product Characteristics.[2]

2.3.1 Risk Assessment

ENZ215 has been developed as a similar biological medicinal product to Prolia® (denosumab, Amgen Inc.). ENZ215 and Prolia® have identical primary, secondary ,and tertiary structures and the active substance for both products is denosumab (a novel antiresorptive agent that inhibits osteoclast-mediated bone resorption through a different pathway). Thus, the risk assessment of the ENZ215 is expected to be similar to the innovator denosumab (Prolia®).

Table 2-3 Risk Assessment

Potential Risk of Clinical Significance[2]	Summary of Data/Rationale for Risk[2]	Mitigation Strategy[2]
Study Intervention (Innovator denosumab, Prolia®)		
Hypocalcemia	• In two phase 3 placebo-controlled clinical studies in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4050) of patients had decline in serum calcium levels (< 1.88 mmol/L) following Prolia® administration. • Rare cases of severe symptomatic hypocalcemia with most cases occurring in the first weeks of initiating therapy leading to symptoms such as QT interval prolongation, tetany, seizures, altered mental status, paresthesias or muscle stiffness, twitching, spasms and muscle cramps. • Patients with severe renal impairment (creatinine clearance < 30mL/min) or undergoing dialysis have an increased risk of hypocalcemia and increase in parathyroid hormone levels.	• Adequate intake of calcium and vitamin D. • Monitoring of calcium and vitamin D levels for the duration of the study.
Serious infections	Patients receiving denosumab may develop serious infections including skin infections (predominantly cellulitis).	Prompt medical attention if a patient develops signs or symptoms of cellulitis or other severe infections.
Osteonecrosis of the jaw (ONJ)	The risk of ONJ increased with duration of exposure to denosumab. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of denosumab treatment in a Phase 3 study in postmenopausal women with osteoporosis.	• Discontinuation of treatment should be considered after evaluation of individual benefit-risk assessment.

Potential Risk of Clinical Significance[2]	Summary of Data/Rationale for Risk[2]	Mitigation Strategy[2]
Study Intervention (Innovator denosumab, Prolia®)		
		• Mitigation of risk factors such as comorbid oral conditions or concomitant medications (corticosteroids, chemotherapy, head and neck radiotherapy, angiogenesis inhibitors)
Atypical femur fractures	Atypical femoral fractures have been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors) and also without antiresorptive therapy.	Discontinuation of study intervention in patients suspected to have an atypical femur fracture after evaluation of individual benefit-risk assessment.
Fertility, pregnancy and lactation	Limited clinical data available about use of denosumab in pregnant women. However, animal studies have shown reproductive toxicity.	Only postmenopausal women aged ≥ 55 and ≤ 85 years will be enrolled in the study.
Study Procedures		
Dry natural rubber of the needle cover of the pre-filled syringe	The dry natural rubber may cause allergic reactions	Site staff to monitor patient for allergic manifestation after administration of study intervention.

2.3.2 Benefit Assessment

The study of biosimilars such as ENZ215 may help in contributing to the process of developing therapies that are as effective as their innovative drugs with access to a wider patient population.

Appropriate medical measures have been implemented into this protocol to detect COVID-19 disease to confirm eligibility of patients and to safely conduct the study.

2.3.3 Risk Assessment for COVID-19 Pandemic

As with Prolia®, ENZ215 is a RANKL inhibitor and can increase the risk of infection although there is no evidence to date that denosumab treatment can be associated with increased risk of severe COVID-19. Since risk of exposure to infected people cannot be completely excluded as the patients may need to expose themselves to public areas (e.g., commute to the site) and have additional human contact (e.g., with site staff and other patients of the clinical study), adequate precautionary measures should be taken by patients to prevent accidental exposure and patients should seek prompt medical attention in case of any signs and symptoms of COVID-19.

Measures to mitigate the potential additional risks caused by COVID-19 are as follows:

- Study enrollment will begin only when the Sponsor and Parexel in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Patients will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat, and fatigue throughout the study. Once clinical signs of infection are reported by patients, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during outpatient visits will be implemented.
- The study intervention will not be administered to patients upon identification of any signs of COVID-19 infection.
- The probability of virus transmission will be controlled as much as possible by:
    - Advice for patient to adhere to local requirements for reduction of the public exposure while ambulatory.

- All patients may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports. In addition, patients will be asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, patients will be referred to the local healthcare system for further follow-up and treatment.
- Physical distancing and person-to-person contact restrictions will be applied during site visits.
- Where physical distancing is not possible, personal protective equipment will be used by patient (surgical face mask, gloves) and staff (e.g., but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
- Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

2.3.4 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ENZ215 are justified by the anticipated benefits that may be afforded to postmenopausal women with osteoporosis.

3 Objectives and Endpoints

The study objectives and endpoints are provided in Table 3-1.

Table 3-1 Objectives and Endpoints

Co-primary Efficacy Objectives	Co-primary Efficacy Endpoints
• To evaluate the efficacy of ENZ215 when compared to Prolia® in patients with postmenopausal osteoporosis, in terms of change in BMD at the lumbar spine from baseline to Month 12	• Percentage change in BMD at lumbar spine (L1-L4 region) measured by DXA from baseline to Month 12
• To compare the AUEC of sCTX levels from baseline to Month 6	• AUEC of sCTX over the initial 6 months (from Day 1 pre-dose to Month 6 pre-dose)

Secondary Efficacy Objectives	Secondary Efficacy Endpoints
• To compare the change in sP1NP levels from baseline to Month 6	• Percentage change in sP1NP concentrations from baseline to Month 1, Month 3, and Month 6
• To compare the change in BMD at lumbar spine from baseline to Month 6	• Percentage change in BMD at lumbar spine measured by DXA 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 BMD at total hip and femoral neck measured by DXA from baseline to Month 6 and Month 12
Secondary Safety Objectives	**Secondary Safety Endpoints**
• To compare the immunogenicity potential 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
• To compare the safety and tolerability of ENZ215 and Prolia®	• 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 Objective	**Secondary Pharmacokinetics Endpoint**
• To compare the pharmacokinetics of ENZ215 and Prolia®	• PK Parameters (C_{max}, T_{max}, partial $AUC_{(0\text{-}1\ month)}$, $AUC_{(0\text{-}6\ month)}$) of denosumab measured at baseline (Day 1), Day 8, Day 15, Month 1, Month 3, Month 6 (prior to second dose), and Month 12

4 Study Design

Environmental sanitization procedures will be implemented in the study site and where study procedures are conducted. The study design and associated safety measures are deemed appropriate for conduct during COVID-19 pandemic.

4.1 Overall Design

This is a Phase 3, randomized, double-blind, parallel-group, active-controlled study 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 four (504) 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) 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.

PK sub-study will be conducted in a subset of the patients, i.e. 60 patients in each arm in order to have 50 evaluable patients in each arm. For patients participating in PK sub-study, PK samples will be collected as mentioned in the PK sample collection (Section 8.4).

In addition, all patients will receive daily supplementation with at least 1 g of calcium and at least 400 IU of vitamin D till Month 12 or Month 18 as applicable. Calcium and vitamin D supplements will be dispensed to patients starting on Day 1 and at each subsequent visit to be consumed at home daily till Month 12. Vitamin D supplements will be dispensed during the screening period, if required, for replenishment of vitamin D deposits. For patients initially randomized to the Prolia® arm and who re-consent to participate in the open-label, switch-over study, calcium and vitamin D supplements will be dispensed again at Month 12 for daily supplementation until EOS. If a patient becomes hypercalcemic over the course of the study, the calcium and/or vitamin D supplementation may be reduced or temporarily discontinued per Investigators' medical judgment until the serum calcium concentration returns to the normal range. If a patient develops hypocalcemia over the course of the study, calcium and/or vitamin D supplementation may be adjusted per Investigators' medical judgment until the serum calcium concentration returns to the normal range.

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. This open-label, switch-over study will assess the impact on immunogenicity and safety of switching patients from Prolia® to ENZ215. Re-randomization will not be stratified. The subset of patients selected for re-randomization to the open-label, switch-over study will be patients who complete 12 months of the double-blind treatment period without any significant safety concerns as per the Investigator's discretion and who have re-consented for the open-label extension period. These patients will complete the study at Month 18.

For patients receiving ENZ215 or Prolia® and not continuing to the switch-over study, the study duration will be approximately 25 months with a recruitment period of 12 months and a study period of 13 months (up to 5 weeks of screening period, 12 months of treatment period). For patients receiving Prolia® and who re-consent to continue to participate in the switch-over study, the study duration will be approximately 31 months (additional 6 months of open-label switch-over study, i.e. until Month 18).

Patients will be required to visit the site for the following visits: Visit 1/screening period (Day -35 to Day -1), Visit 2/Day 1, Visit 4/Month 1 (Day 15), Visit 5/Month 1 (Day 30), Visit 6/Month 3 (Day 90), Visit 7/Month 6 (Day 180), Visit 8/Month 9 (Day 270) and Visit 9/Month 12 (Day 360).

Visit 10/Month 15 (Day 450) and Visit 11/Month 18 (Day 540) will be additional visits to the above-mentioned visits for patients initially randomized to receive Prolia® and re-randomized in the switch-over study (subset of 120 patients).

Except on Visit 1 and Visit 2, a window period of ±3 days is allowed on Day 8, Day 15, Day 30 (Month 1), and Day 90 (Month 3). A window period of ± 7 days is allowed from Month 6 until EOS.

EOS assessment will be performed at Month 12 (±7 days) or Month 18 (±7 days) as applicable or at the time of early discontinuation or withdrawal of the patient.

Note: There will be an additional visit (Visit 3/Day 8) for those patients who provide consent for participation in PK sampling. 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. Details of the study visit schedule is provided in Section 1.3.

During the study, blood and urine samples will be collected for eligibility and safety assessments (hematology, serology, routine serum chemistry, urine analysis, PK analysis, PD assessments, and ADA).

4.2 Scientific Rationale for Study Design

This study forms part of the clinical development program and is aimed to assess the efficacy and safety of ENZ215 compared to Prolia® in women with postmenopausal osteoporosis as a randomized, double-blind, multicenter phase 3 study. The concept study design has been discussed and agreed with FDA and EMA. Of all therapeutic indications of Prolia®, postmenopausal osteoporosis is considered to be the most sensitive indication as postmenopausal osteoporotic females are exempt from underlying disease conditions and concomitant medications that might influence the efficacy and the safety of the study intervention. Consequently, they represent the most homogenous study population. The safety assessments for the study are accepted measures for ensuring safety of patients during a clinical study. The sample size is considered adequate and sufficient to allow for a meaningful comparison between ENZ215 and Prolia®. The rationale for dose selection is discussed in Section 4.3. The study design is deemed appropriate for conduct during the COVID-19 pandemic.

4.3 Justification for Dose

Dose, frequency, and route of administration of the study intervention are chosen according to the current Prolia® label for the treatment of postmenopausal women with osteoporosis. This is the dose approved in postmenopausal women.

4.4 End of Study Definition

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) for the last patient in the study globally.

A patient is considered to have completed the study if she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Table 1-1).

5 Study Population

Five hundred four (504) postmenopausal women with osteoporosis aged ≥ 55 and ≤ 85 years, fulfilling the study selection criteria will be enrolled in approximately 60 to 70 sites (centers) across the European Union.

Patient selection will be established by reviewing all inclusion/exclusion criteria at screening and at baseline (Day 1). The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria (all the inclusion and none of the exclusion):

5.1 Inclusion Criteria

The patients will be included in the study if they meet all the following criteria:

1. Willing to provide voluntary written informed consent and able to comply with the protocol requirements
2. Postmenopausal women aged ≥ 55 and ≤ 85 years globally, except for Spain. In Spain specifically refer to the below criteria:

    a. Postmenopausal women aged ≥ 75 and ≤ 85 years with LS T-score ≤ -2.5 or

    b. Postmenopausal women aged ≥ 65 and < 75 years with LS T-score is ≤ -2.5 and a prior fragility fracture (except for hip fracture), including non-exclusionary vertebral fractures

    c. In both cases (i.e. criteria a and b), it must also be that these are women who present a contraindication for the use of bisphosphonates or who do not tolerate the oral route.
3. Body weight ≥ 50 kg and ≤ 90 kg
4. Diagnosed with osteoporosis, with absolute BMD consistent with T-scores of ≤ -2.5 and ≥ - 4.0 at the lumbar spine (L1-L4 region) as measured by dual-energy X ray absorptiometry (DXA) at screening
5. At least 5 years of postmenopausal status confirmed by follicle-stimulating hormone (FSH) levels at screening
6. At least one hip joint and two vertebrae in L1-L4 region evaluable by DXA
7. No other clinically significant medical history, vital signs, physical examination, laboratory profiles as deemed by the Investigator or designee that would pose a risk to participant safety or interfere with the study evaluation, procedures or completion

5.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

1. Known hypersensitivity to denosumab or any of the excipients of the study drug
2. Known intolerance to, or malabsorption of calcium or vitamin D supplements
3. Previous exposure to Prolia® or any other denosumab biosimilar
4. Previous use of oral bisphosphonates:
    a. Used for 3 or more years cumulatively
    b. If used for < 3 years, use within the past 12 months prior to screening
5. Use of intravenous bisphosphonates within the past 5 years prior to screening. If used more than 5 years prior, patients will be excluded if cumulative use was > 3 years.
6. Use of parathyroid hormone or its derivatives, hormone replacement therapy, romosozumab, selective estrogen-receptor modulators, or tibolone or calcitonin within 12 months prior to enrollment

    Note: occasional use of intravaginal estrogen treatment is not exclusionary
7. Any prior use of fluoride or strontium
8. Systemic glucocorticoids (≥ 5 mg prednisone equivalent per day or cumulative dose ≥ 50 mg) for more than 10 days within 3 months prior to enrollment (topical and inhaled corticosteroids are allowed)
9. Other bone active drugs (i.e. drugs affecting bone metabolism) including heparin, anti-epileptics (except for benzodiazepines and pregabalin), antidepressants such as SSRIs, SNRIs, antipsychotics, systemic ketoconazole, adrenocorticotrophic hormone (ACTH), lithium, protease inhibitors, gonadotropin-releasing hormone (GnRH) agonists, or anabolic steroids within the past 3 months prior to screening or requiring treatment with these agents during the study.

    Note: Please refer to Section 6.11 for a comprehensive list of prohibited medications
10. Known sensitivity to drug products derived from mammalian cell lines such as hormones, enzymes, cytokines, bone morphogenic proteins, clotting factors, antibodies, and fusion protein therapeutics. Patients with any known hypersensitivity to complex proteins such as monoclonal antibodies will be excluded.
11. History of one severe or more than two moderate vertebral fractures per Genant classification as determined by the central reading center
12. History of hip fracture or bilateral hip replacement
13. Total hip or femoral neck T-score <−4.0
14. History and/or presence of atypical femoral fracture

15. Presence of any active healing fracture according to the Investigator's assessment
16. History of any transplant or chronic immunosuppression (including patients on immunosuppressive therapy)
17. Severe liver dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 times upper limit of normal)
18. Positive testing for hepatitis B (hepatitis B virus surface antigen [HbsAg]) or hepatitis C (hepatitis C virus antibody [HCV Ab]) virology
19. Known history of human immunodeficiency virus (HIV) infection or positive serology for HIV at screening
20. Significantly impaired renal function (determined by glomerular filtration rate of < 45 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) formula, as calculated by the central laboratory) or receiving dialysis
21. Oral or dental conditions:
    a. Osteomyelitis or history and/or presence of osteonecrosis of the jaw (ONJ)
    b. Presence of risk factors for ONJ (e.g., periodontal disease, poorly fitting dentures, poor oral hygiene, invasive dental procedures such as tooth extractions within 6 months prior to screening)
    c. Active dental or jaw condition which requires oral surgery
    d. Planned invasive dental procedure
22. Major surgery within 8 weeks prior to screening or anticipated major surgery during the study
23. Clinically significant leukopenia, neutropenia, or anemia as determined by the Investigator or any other clinically significant medical condition or laboratory abnormality that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with adherence to study procedures, study completion, or the interpretation of study results

    Note: In case of an abnormal laboratory result which in the opinion of the investigator may be an error, is borderline, or indeterminate for inclusion in the study, the investigator may consider repeating the test once in order to rule out laboratory error.
24. Patient with an active infection or history of infection as follows:
    a. Any active infection for which systemic anti-infectives were used within 4 weeks prior to randomization
    b. A serious infection defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to randomization

c. Recurrent or chronic infections or other active infection that, in the opinion of the Investigator, might compromise the safety of the patient

25. Evidence of any of the following conditions per laboratory test results, medical history, electrocardiogram (ECG), DXA, or X-ray review:

a. Uncontrolled hyperthyroidism or hypothyroidism

Note: Clinical significance of abnormal TSH values in patients on stable replacement therapy due to hypothyroidism or on anti-thyroid medication should be assessed and discussed with the Medical Monitor.

b. History or current hyperparathyroidism or hypoparathyroidism (intact parathyroid hormone levels not within normal range)

Note: Mild secondary hyperparathyroidism in the context of vitamin D deficiency may be acceptable upon discussion with the Medical Monitor.

c. Vitamin D deficiency defined as 25 (OH) vitamin D level < 20 ng/mL (< 50 nmol/L)

Note: Patients can be enrolled if a repeat test (post supplementation) prior to enrollment shows corrected 25 (OH) vitamin D level ≥ 20 ng/mL (≥ 50 nmol/L).

d. Current hypocalcemia (albumin-adjusted serum calcium < 8.0 mg/dL [< 2.0 mmol/L]) or hypercalcemia (albumin-adjusted serum calcium > 10.6 mg/dL [> 2.62 mmol/L])
e. History of parathyroid surgery
f. Any bone or metabolic disease which may affect BMD or interfere with the interpretation of the findings, e.g., osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, Cushing's disease, hyperprolactinemia, or malabsorption syndrome
g. Any malignancy, including solid tumors, and hematologic malignancies (except basal cell carcinoma and squamous cell carcinomas of the skin, cervical, or breast ductal carcinoma in situ, that have been completely excised and are considered cured) within the last 5 years
h. Known or suspected history of alcoholism (including heavy drinking defined as consuming more than 3 drinks on one day or more than 7 drinks per week) or substance abuse within the past 12 months prior to the first dosing that the Investigator believes would interfere with understanding or completing the study
i. Current heavy smoking, defined as smoking 20 or more cigarettes per day.
j. Participated in any other clinical study in last 30 days prior to screening
k. History and/or presence of significant cardiac disease as per Investigator's discretion, including but not restricted to:

i. History of cardiac arrhythmia or long QT syndrome or ECG abnormalities at screening indicating significant risk for safety (e.g., that required hospitalization, emergency cardioversion, or defibrillation)
ii. History and/or presence of myocardial infarction within 6 months before screening
iii. History and/or presence of New York Heart Association (NYHA) class III or IV heart failure

26. Suspected signs and symptoms of COVID-19/confirmed COVID-19 or with recent history of travel/contact (less than 2 weeks from screening) with any COVID-19 positive patient/isolation/quarantine

5.3 Lifestyle Considerations

5.3.1 Activity

Patients will be allowed to do normal routine activity avoiding strenuous physical activity 24 hours prior to all study visits.

5.4 Screen Failures

A screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomly assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and documentation of any medical occurrences that qualify as serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, after discussion with the Medical Monitor. Patients that are screen-failed due to hypocalcemia are not eligible for rescreening. Rescreened patients will be assigned a new patient number. All screening procedures will be repeated except for:

- DXA, if performed within 5 weeks from the date of rescreening
- Spine X-ray, if performed within 3 months from the date of rescreening

5.4.1 Screening and Enrollment Log and Patient Identification Numbers

The patient's enrollment will be recorded in the Screening and Enrollment Log. Upon enrollment, each patient will receive a unique patient identification number. Patient numbers must not be re-used for different patients.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6 Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a patient according to the study protocol. An Investigator manual will be prepared to describe the procedure for handling of IPs.

6.1 Study Interventions Administered

Based on the randomization schedule, either ENZ215 or Prolia® will be administered to the patients at a dose of 60 mg (multiple-dose) SC in 6-month intervals into the upper thigh.

In addition, all patients will receive daily supplementation with at least 1 g of elementary calcium and at least 400 IU of vitamin D till Month 12 or Month 18, as applicable. Calcium and vitamin D supplements will be dispensed to patients starting on Day 1 and at each subsequent visit to be consumed at home daily till Month 12. Vitamin D supplements will be dispensed during the screening period, if required, for replenishment of vitamin D deposits. For patients initially randomized to the Prolia® arm and who re-consent to participate in the open-label, switch-over study, calcium and vitamin D supplements will be dispensed again at Month 12 for daily supplementation until EOS. If a patient becomes hypercalcemic over the course of the study, the calcium and/or vitamin D supplementation may be adjusted or temporarily discontinued per Investigator's medical judgement until the serum calcium concentration returns to the normal range. If a patient develops hypocalcemia over the course of the study, calcium and/or vitamin D supplementation may be adjusted per Investigator's medical judgment until the serum calcium concentration returns to the normal range. For further details, refer to Section 6.1.1.

IP administration, disposal and other handling information will be included in the Investigator manual. Retention samples will be maintained as per local regulations.

The study interventions are presented in Table 6-1.

Table 6-1 Study Interventions Administered

Intervention Label	ENZ215	Prolia®	Vitamin D	Calcium
Intervention Name	ENZ215	Prolia®	N/A	N/A
Type	Biologic	Biologic	Drug	Drug
Dosage Formulation	PFS	PFS	Tablet	Tablet
Unit Dose Strength(s)	60 mg/mL	60 mg/mL	400 IU daily	1 g daily
Dosage Level(s)	60 mg	60 mg	At least 400 IU	At least 1 g
Route of Administration	SC injection	SC injection	Oral	Oral
Use	Experimental	Active comparator	Supplement	Supplement
IP/NIP	IP	IP	NIP	NIP
Sourcing	EU Manufactured by: Enzene Biosciences Ltd. India	EU marketing authorization holder: Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, The Netherlands.	Locally sourced	Locally sourced
Packaging and Labeling	Study intervention will be provided in a PFS. Each PFS will be labeled as required per country requirement.	Study Intervention will be provided in a PFS. Each PFS will be labeled as required per country requirement.	Per local labelling requirement	Per local labelling requirement
Current Name	ENZ215 (denosumab)	Prolia® (denosumab)	N/A	N/A

EU = European Union, IP = Investigational product, NIP = Non-investigational product PFS = Prefilled syringe, SC = Subcutaneous

6.1.1 Calcium and Vitamin D supplementation

Compliance with daily calcium and vitamin D intake will be monitored and assessed throughout the study. If hypercalcemia or hypocalcemia occurs, the Investigator can modify the dietary intake of calcium and adjust the calcium and/or vitamin D dosage if needed, according to local practice. The change should be reported in the eCRF and hypercalcemia or hypocalcemia should be reported as an AE if clinically significant.

Intolerance to non-IMP may occur, especially for calcium. Calcium intolerance can manifest as bloating or constipation. The formulation and/or dose frequency (e.g., dose divided twice daily) can be changed to reduce intolerance and increase compliance at the Investigator's discretion. If intolerance continues after lowering the dose, temporary discontinuation may be considered. Permanent discontinuation of calcium and/or vitamin D should be discussed with the Medical Monitor and should be documented in the source data. Further participation of these patients in the study should be reconsidered after discussion with Medical Monitor.

6.2 Preparation, Handling, Storage, and Accountability

Clinical supplies (both test and reference product) will be packed, labeled, handled, and stored in accordance with current Good Manufacturing Practice of IPs.

IP (test and reference products) will be supplied by Enzene Biosciences Ltd./Alkem Laboratories Ltd. in sufficient quantities as required by the study. Individual patient containers as required will be shipped to the sites (centers). The received IPs will be verified with certificates of analysis for the sealed condition of packs and adequacy of the label, including product name, strength, number of dosage units, lot number or batch number, expiry date/retest date, and storage condition mentioned clearly.

It is the Investigator's responsibility to perform the accountability check and verify that the shipment contains all the items noted in the shipment inventory including a check for any damages or unusable IP. A record of the inventory received should be documented in the drug accountability form. The Investigator or the Investigator's designated personnel should verify the IP, sign and date the drug receipt, and maintain a copy of the receipt at the study center.

Investigational product labels will be prepared in compliance to the applicable regulatory requirements and will have the following information:

- Name, address, and telephone number of Sponsor
- Pharmaceutical dosage form, route of administration, quantity of dosage units

- Directions for use (reference may be made to a leaflet or other explanatory document intended for the patient or staff administering the product)
- Study number
- Randomization ID
- Investigator and site details
- Patient details
- Lot/batch number
- Storage conditions
- Manufacturing date
- Expiry/Retest date
- Statement: 'For clinical trial use only"

Temperature will be monitored on a daily basis during the conduct of the study. The IPs will be stored as per the product requirements.

The Investigator, site pharmacist, or other Investigator's assigned personnel allowed to receive, store, issue, and dispense the IPs will be responsible for ensuring that the IPs to be used in the clinical study are securely maintained as specified by the Sponsor and in accordance with the current Good Clinical Practice.

All IPs shall be issued and used in accordance with the protocol and it is the Investigator's responsibility to ensure that an accurate record of the IPs issued and returned is maintained.

Under no circumstances will the Investigator supply the IP to a third party, allow the IP to be used other than as directed by this clinical study protocol, or dispose the IP in any other manner.

Further guidance and information for the final disposition of unused study intervention are provided in the Investigator manual.

6.3 Retrieval of Study Interventions

As the IP is an injectable, IP (test or reference) will be administered to the patient at the site during the applicable visit.

At the completion of the study, there will be a final reconciliation of IP shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form. Any discrepancies noted will be investigated, resolved, and documented prior to return of unused IP.

6.4 Unused Study Interventions

Units of IPs that have not been dispensed will be retained in their original containers. Any product that were dispensed but not used will be labeled as "unused" and returned, along with other unused products to the Sponsor at the end of the study.

Note: If IPs are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for disposal and written authorization has been granted by the Sponsor, and the procedures for proper disposal have been established according to applicable regulations, guidelines, Sponsor's instructions, and institutional procedures. Appropriate records of the disposal must be maintained. The unused study products can only be destroyed after being inspected and reconciled by the responsible study monitor.

6.5 Measures to Minimize Bias: Randomization and Blinding

6.5.1 Randomization

Patients will be randomized in a 1:1 ratio to receive either ENZ215 or Prolia® (60 mg SC injection) at baseline and Month 6. 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) at Month 12.

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 will be centrally randomized using an Interactive Response Technology (IRT). Each patient will be assigned a unique number (randomization number) that encodes the patient's assignment to one of the 2 arms of the study, according to the randomization schedule. The randomization schedule will be generated by the IRT vendor.

6.5.2 Blinding

This is a double-blind study (till Month 12) in which patients and Investigators are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's study intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's study intervention assignment unless this could delay emergency treatment for the patient. If a patient's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The duration of the double-blind study is 12 months after which study analysis will be carried out and the study report will be submitted to the EMA. The further study period, i.e. open-label switch-over period till Month 18, is part of the safety study for US FDA regulatory submission. Primary analysis will be performed once all patients complete Month 12 (including early-drop outs) and after partial lock of Month 12 data.

Data will be frozen at patient level before patient transition from the double-blind treatment period to the open-label extension study. Further details of transition of patients to the open-label extension study will be outlined in the Data Management Plan.

6.6 Study Intervention Compliance

The Investigator or his/her designated and qualified representatives will administer IP only to patients who are eligible to participate in the study in accordance with the protocol. The IP must not be used for reasons other than that described in the protocol.

If there are any significant irregularities in compliance in the opinion of the Investigator, the patient should be discontinued from the study.

The Investigator or Investigator's designated personnel will maintain a careful record of the inventory and disposition of all agents received for study using a drug accountability form or log. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received
- Amount currently in place
- Label ID number or batch number and use by date or expiry date
- Dates and initials of person responsible for IP inventory
- Amount dispensed, including unique patient identifiers
- Non-study disposition (e.g., lost, wasted, broken)
- Amount returned to Sponsor
- Amount destroyed at study site, if applicable

6.7 Dose Modification

Not applicable.

6.8 Continued Access to Study Intervention After the End of the Study

Not applicable as standard of care is approved and available.

6.9 Treatment of Overdose

Incidences of overdose are not expected as ENZ215 and Prolia® are supplied in pre-filled syringes and patients will not self-administer the IP. Any overdose must be recorded in the AE section of the eCRF and the source documents. Any case of overdose leading to SAEs must be reported in an expedited manner using the SAE reporting form. Overdose (with associated symptoms or without any associated symptoms) should be reported as an AE using the Preferred Term "overdose".

For this study, any dose of ENZ215 or Prolia® (60 mg) SC greater than indicated in this protocol will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose as up to 180 mg of ENZ215 is tolerated without any significant events. However, patients should be followed-up specifically for hypocalcemia and any other adverse events for safety purposes.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and follow-up until planned study completion or until 3 half-lives, i.e. 90 days.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.10 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient receives during her participation in the study should be reported in the eCRF. In addition, any diagnostic, therapeutic or surgical procedure performed during the study period (from screening to EOS assessment) should be recorded. The Investigator should be contacted if there are any questions regarding concomitant or prior therapy(ies). At screening visit, all relevant prior medication history must be recorded while concomitant medication details will be recorded throughout the study i.e. from screening visit to safety EOS assessment visit. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Patients will receive daily supplementation with at least 1 g of elementary calcium and at least 400 IU of vitamin D. Patients with thyroid dysfunction on L-thyroxine therapy should have thyroid function test (TSH) done at least at Month 6 or earlier per discretion of the Investigator.

6.11 Prohibited Medications

- Patients are not allowed to take Xgeva during the study as ENZ215 and Prolia® contain the same active ingredient as in Xgeva® (denosumab).
- Use of the following medications is also prohibited during the study:

Any osteoporosis treatment (other than calcium and vitamin D supplements) such as:

- Intravenous or oral bisphosphonates
- Teriparatide
- Romosozumab
- Strontium ranelate or fluoride
- Calcitonin or its derivates and calcimimetics (such as cinacalcet or etelcalcetide)
- Parathyroid hormone or its derivatives, hormone replacement therapy (oral or transdermal oestrogen; exceptionally, occasional non-systemic vaginal oestrogen treatment is permitted), selective estrogen-receptor modulators, or tibolone

Drugs affecting bone metabolism:

- ACTH
- Anabolic steroids
- Androgens
- Anti-epileptics (except for benzodiazepines and pregabalin)
- Aromatase inhibitors
- Barbiturates
- Calcimimetics
- Systemic glucocorticoids (Topical and inhaled glucocorticosteroids are allowed).
- Growth hormone-releasing hormone
- GnRH agonists
- Heparin (including unfractionated heparin and low molecular weight heparins)
- Immunosuppressants, e.g., cyclosporine A, tacrolimus, methotrexate
- Lithium
- Protease inhibitors
- Systemic ketoconazole
- Tamoxifen
- Thiazolidinediones
- Warfarin

- Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) as well as Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Antipsychotics

If, in addition to the above, any medication(s) in the opinion of the Investigator is likely to affect the study outcome, the use of these medications should be prohibited.

This prohibition must continue until EOS assessment. All such instances in which prohibited therapies are administered or required to be administered, should be notified to the Sponsor.

For any concomitant therapy given as a treatment for a new AE or a worsening of an existing AE, the condition must be documented on the AE page in the eCRF.

Invasive dental procedures (e.g., dental implants or oral surgery) and major surgeries or bone surgeries (unless required for AE/SAE management) should be avoided during the study period as far as possible.

7 Discontinuation of Study Intervention and Patient Discontinuation

Discontinuation of specific sites or of the study as a whole are handled as part of the appendix on Governance, Appendix 1, Section 10.1.13.

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue study intervention. However, following discontinuation of IP administration, increased fracture risk can be expected, including the risk of multiple vertebral fractures. Patients should be informed of this risk and Investigators should ensure prescription of appropriate follow-up osteoporosis treatment per their medical judgement and according to local guidelines.

Delay in administering the study intervention for not longer than 28 days is allowed in exceptional cases such as patients diagnosed with any transient disease/SAE/reversible hypocalcemic condition where IP administration would not be possible or would be contraindicated.

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. The patients will be permanently discontinued from the study intervention and the study at that time. A patient may be withdrawn / discontinued from the study due to the following reasons:

- A patient suffers from significant inter-current illness or undergoes surgery during the course of the study that warrants withdrawal in the Investigator's or Sponsor's judgment.
- Patient's voluntary withdrawal of consent
- Protocol violation that may affect the patient's safety seriously and/or the integrity of data (including ineligibility) agreed by the Investigator (e.g., IP dosing out of visit window, non-compliance with calcium/vitamin D supplementation, or using prohibited medication during the study period)
- In Investigator's opinion, it is not in the patient's best interest to continue
- Patient develops the risk of ONJ during the study duration
- Patient is found to conceal important medical history which in opinion of Investigator may compromise her safety during participation in this study.
- Any AE or SAE which requires discontinuation of patient in the opinion of Investigator
- Potential Hy's law (ALT or AST ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT or AST ≥ 3 × ULN and INR > 1.5 (if INR measured)
- Study termination by the Sponsor
- Unblinding of treatment arm to patient or Investigator during the double-blind study period
- Any other justifiable reason, which should be adequately documented

Investigator should try to obtain the reason from the patient for withdrawing consent. Reason for withdrawal from the study shall be documented, whenever possible.

If a patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a patient withdraws from the study, she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

EOS assessments (as per Table 1-1) shall be performed for all prematurely discontinued and withdrawn patients. For all discontinued patients, data collected till the time of discontinuation shall be reported in eCRF.

In case of discontinuation for safety reason, the patient should be followed-up for safety purpose for 6 months and all the protocol specific assessment should be performed as planned. At the last visit, all the assessments planned for EOS visit shall be performed. See the SoA (Table 1-1) for

data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Safety data shall be collected for all discontinued patients, who are discontinued due to an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If the patient is discontinued due to an event, patient should be given appropriate care under medical supervision until the symptoms of any AE resolve or the patient's condition becomes stable. Fifteen percent dropout rate has been considered while estimating the sample size, hence patients who withdraw or are withdrawn from the study will not be replaced.

7.3 Loss to Follow-up

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

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

- The site must attempt to contact the patients and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record/eCRF.
- Should the patient continue to be unreachable, she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

All reasonable measures will be taken to decrease potential transmission of COVID-19; for example, clinic staff and physicians will wear surgical masks and gloves while meeting with patients and will wash their hands per the Center for Disease Control[5] guidelines before, between, and after meeting each participant.

The study procedures described below will be carried out at the study visits:

Visit 1 / Screening Period (Day -35 to Day -1)

The screening procedures will be completed within up to 35 days (5 weeks) from the signing of the ICF.

- Written informed consent will be taken from the patients. No study related procedure will be conducted prior to obtaining informed consent.
- While patient consent is being recorded for the main study, consent should also be obtained for continued participation into the open-label, switch-over study until Month 18. For patients volunteering to participate in PK sub-study, an additional written signed and dated consent will be obtained prior to randomization.
- Assessment of patient eligibility as per inclusion and exclusion criteria
- Demographics (age, sex, body weight [in kg], height, race, ethnicity) will be noted
- Complete physical examination (including oro-dental examination)
- Medical/Surgical 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)
- Prior medication/surgical history
- Current medical conditions

- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in the Section 8.2.2.
- 12-lead ECG
- Vitamin D supplements will be dispensed during the screening period, if required, for replenishment of vitamin D deposits.
- Lateral thoracic and lumbar spine X-ray for fracture/vertebral abnormality assessment
- DXA for lumbar spine, total hip, and femoral neck assessment
- Blood sample collection:
    - Hematology: total leukocyte count (white blood cell [WBC] count), total erythrocyte count (red blood cell [RBC] count), hemoglobin, platelet count and absolute neutrophil count (ANC)
    - Serology: HIV, HBsAg, HCV assessment
    - Serum chemistry: liver function tests (ALT, ASP, ALP, total bilirubin, albumin and total proteins), kidney function tests (blood urea nitrogen [BUN], creatinine, and estimated glomerular filtration rate [eGFR]), electrolytes (sodium, potassium, and chloride), glucose, serum calcium, albumin-adjusted calcium, magnesium, and phosphorus.
    - 25 (OH) vitamin D level assessment.
      Note: During screening, if the 25 (OH) vitamin D level of a patient is < 20 ng/mL (<50 mmol/L), replenishment of vitamin D deposits can be attempted following sites standard of care (e.g., loading dose of Vitamin D). After replenishment, vitamin D should be retested to confirm value is within the eligibility range.
    - FSH assessment
    - Thyroid function tests (T3, T4, TSH)
    - Intact Parathyroid hormone test (iPTH)
- Urine sample collection for routine urine analysis: Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase, and microscopic examination including RBC, leucocytes, epithelial cell, bacteria, and crystals

- AE/SAE recording and reporting
- Concomitant medications assessment

Visit 2/Day 1

- Assessment of patient eligibility as per inclusion and exclusion criteria
- Brief physical examination including oro-dental examination which should be performed before IP administration
- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2
- Randomization
- Patient diary will be dispensed and patients will be instructed on how to fill the diary
- IP administration
- Monitoring of injection site reaction at least for - one hour
- Dispensing of calcium and vitamin D supplements for daily dosing
- Blood sample collection
    - Anti-denosumab antibodies (ADA) assessment
    - PK assessment (only for patients participating in the PK sub-study)
    - sCTX and sP1NP
- AE/SAE recording and reporting
- Concomitant medication assessment

Visit 3 / Day 8 (Month 1) and Visit 4 / Day 15 (Month 1): ± 3 Days

Day 8 will be an additional visit for patients participating in the PK sub-study. Details pertaining to sampling time points are provided in Section 8.4.

- Brief physical examination
- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2
- Patient diary will be reviewed
- Dispensing of calcium and vitamin D supplements for daily dosing
- Serum calcium levels will be monitored for all patients on Day 15
- Blood sample will be collected for PK assessment on Day 8 and Day 15
- Blood sample collection for assessment of sCTX and sP1NP
- AE/SAE recording and reporting
- Concomitant medication assessment

Visit 5 /Month 1 (Day 30) and Visit 6/Month 3 (Day 90): ± 3 days;
Visit 7 / Month 6 (Day 180), Visit 8/Month 9 (Day 270): ±7 days

- Brief physical examination on all visits: This examination will also include oro-dental examination before IP administration only on Month 6
- Signs and symptoms of COVID-19 on all visits (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2 on all visits
- 12-lead ECG at Month 6

- Patient diary review on all visits
- IP will be administered at Month 6
- Monitoring of injection site reaction at least for - one hour at Month 6
- Dispensing of calcium and vitamin D supplements for daily dosing
- The 25 (OH) vitamin D level of all patients will be re-tested at Month 6
- TSH at Month 6
- DXA for lumbar spine, total hip and femoral neck assessment at Month 6
- Blood sample collection for the following:
    - Hematology: total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, platelet count and absolute ANC at Month 6
    - Serum chemistry: liver function tests (ALT, AST, ALP, total bilirubin, albumin and total proteins), kidney function tests (BUN, creatinine, and eGFR, electrolytes [sodium, potassium, and chloride]), glucose, serum calcium, albumin-adjusted calcium, magnesium, and phosphorus at Months 3, 6, and 9
    - sCTX and sP1NP at Months 1 (Day 30), Month 3 and Month 6
    - ADA assessment at Month 1, Month 3, Month 6, and Month 9
    - PK assessment will be measured at Month 1 (Day 30), Month 3 and Month 6 (prior to second dose) (only for patients consenting to participate in the PK sub-study)
- Urine sample collection for routine urine analysis: Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase, and microscopic examination including RBC, leukocytes, epithelial cells and bacteria, crystals at Month 3, Month 6, and Month 9.
- AE/SAE recording and reporting
- Concomitant medications assessment

Visit 9/Month 12 (Day 360) [±7 days]

- Re-consent on Month 12 from patients initially randomized to Prolia® arm who volunteer to continue to participate in the open-label, switch-over study.
- Brief physical examination including oro-dental examination before IP administration

- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2
- Re-randomization of patients initially randomized to Prolia® arm who volunteer to continue to participate in the open-label, switch-over study
- 12-lead ECG
- Patient diary review
- IP administration
- Monitoring of injection site reaction at least for - one hour
- Dispensing of calcium and vitamin D supplements for daily dosing
- Lateral thoracic and lumbar spine X-ray for fracture/vertebral abnormality assessment
- DXA for lumbar spine, total hip and femoral neck assessment
- Blood sample collection for the following:
    - Hematology: total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, platelet count and absolute ANC
    - Serum chemistry: liver function tests (ALT, AST, ALP, total bilirubin, albumin and total proteins), kidney function tests (BUN, creatinine, and eGFR, electrolytes [sodium, potassium, and chloride]), glucose, serum calcium, albumin-adjusted calcium, magnesium, and phosphorus
    - PK assessment
    - ADA assessment
- Urine sample collection for routine urine analysis: Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase, and microscopic examination including RBC, leukocytes, epithelial cells and bacteria, crystals
- AE/SAE recording and reporting
- Concomitant medications assessment

Visit 10 / Month 15 (Day 450) [±7 days]

This visit is applicable only for those patients participating in the open-label switch-over period.

- Brief physical examination
- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2
- Patient diary review
- Dispensing of calcium and vitamin D supplements for daily dosing
- Blood sample will be collected for ADA assessment
- AE/SAE recording and reporting
- Concomitant medication assessment

End of Study assessment at Month 18 (Day 540) or Month 12 or Early Discontinuation/Withdrawal

EOS will be conducted at Month 12 for patients initially randomized to receive ENZ215.

- Brief physical examination
- Signs and symptoms of COVID-19 (especially fever, cough, difficulty in breathing, loss of taste and smell) along with recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine shall be evaluated. Patients having signs and symptoms of COVID-19 or recent history of travel/contact with any COVID-19 positive patient/isolation/quarantine will be further evaluated for SARS-CoV-2 infection as per the local guidelines. Patient may be contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected reports
- Vital signs will be recorded as described in Section 8.2.2

- 12-lead ECG
- Patient diary review and collection
- Lateral thoracic and lumbar spine X-ray for fracture/vertebral abnormality assessment
- Blood sample collection for the following:
    - Hematology: total leukocyte count (WBC count), total erythrocyte count (RBC count), hemoglobin, platelet count and ANC
    - Serum chemistry: liver function tests (ALT, AST, ALP, total bilirubin, albumin and total proteins), kidney function tests (BUN, creatinine, and eGFR), electrolytes (sodium, potassium, and chloride), glucose, serum calcium, albumin-adjusted calcium, magnesium, and phosphorus
    - ADA assessment at Month 18
- Urine sample collection for routine urine analysis: Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase, and microscopic examination including RBC, leukocytes, epithelial cells, bacteria, and crystals
- AE/SAE recording and reporting
- Concomitant medications assessment

Unscheduled Visit

During the study, patients are free to contact the Investigator. Patient can come for unscheduled visits anytime during the study duration in case of AEs or aggravation of an existing disorder. During an Unscheduled Visit, laboratory tests and other investigations, if required, will be done at the Investigator's discretion.

Serum calcium levels will be tested locally in patients prior to dosing at Month 6 and Month 12. However, this can either be done on the same day as the dosing visit or at a separate unscheduled visit if required per local standard of care. If hypocalcemia is identified, the patient should not be dosed until calcium levels are corrected.

PK sample collection

A total of seven (7) PK blood samples will be collected from each patient in the study. Blood samples of about 3.5 mL each will be collected at baseline (Day 1), Day 8, Day 15, Month 1, Month 3, Month 6 (prior to second dose) and Month 12. For PK sampling on Day 8 and Day 15, a window period of ± 2 hours is allowed in relation to the time of IP administration on Day 1.

8.1 Efficacy Assessments

The efficacy assessments will be performed as per timing summarized in the SoA (Table 1-1).
BMD: DXA Spine and hip and femoral neck: All patients will undergo BMD assessments of the lumbar spine, total hip, and femoral neck performed by DXA at baseline (screening/Day 1), Month 6, and Month 12 and ET visit (if after Month 6 and prior to Month 12).

DXA should be done and submitted as early as possible during the screening period to allow for enough time in case a repeat exam is requested by Medical Imaging. In addition, as far as possible, DXA should be done during the applicable study visits and before dosing. Exceptionally, in case DXA cannot be done before dosing and/or on the same day as the rest of the visit procedures at Month 6 and Month 12, it can be performed within the allowed window period of ±7 days (refer Section 1.3). The results will be evaluated by a central assessor. The same DXA machine will be used for all study procedures for a particular patient. Detailed instructions on DXA scan acquisition are provided separately in the Image Acquisition Guideline.

Instrument quality control (IQC) is carried out in order to allow for correction of any DXA instrument calibration shifts or drift that may occur during the course of the study. Local spine phantom data will be obtained regularly from each DXA machine in the course of the study and this will be analyzed by cumulative sum analysis (CUSUM; analysis done by the software) to identify significant shifts or drifts in calibration and generate IQC corrections accordingly. These IQC corrections can then be applied to patient DXA BMD results accordingly. IQC BMD corrections are scanner and time-specific and are applied where necessary to the final DXA data set. Further information is provided in the BMD charter document.[7]

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1-1).

8.2.1 Physical Examinations

The physical examination will be performed as per timing summarized in the SoA (Table 1-1).

- A complete physical examination will be performed at screening only and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, and oro-dental examination. Height and weight will also be measured and recorded.

- A brief physical examination will be performed at all other visits and will include, at a minimum, general appearance, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will also be measured and recorded at least 3 monthly i.e. at Visit 6, 7, 8, 9, 10, and 11. Oro-dental examination should be done at dosing visits prior to administration of study intervention. However, a complete physical examination may be done at other visits at the Investigator's discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs will be performed as per timing summarized in the SoA (Table 1-1). -Body temperature, heart rate, respiratory rate, and blood pressure will be assessed. 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 (°F/°C).

8.2.3 Injection site reaction

Patients will be observed at least for one hour for any injection site reaction after administration of the study intervention. An injection site reaction will be reported as AE. The intensity will be recorded as mild, moderate, or severe per CTCAE definitions:

Intensity Grade	Definition
Grade 1	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)
Grade 2	Pain; lipodystrophy; edema; phlebitis
Grade 3	Ulceration or necrosis; severe tissue damage; operative intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated

8.2.4 Electrocardiograms

Twelve-lead ECG(s) will be obtained as outlined in the SoA (Table 1-1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval (QTc) intervals.

8.2.5 Clinical Safety Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1-1) for the timing and frequency. Laboratory samples for all patients will be assessed

using an accredited central laboratory and if required by a certified local laboratory. ADA assessment will be done at a bioanalytical laboratory.

Qualified medical staff at the site will review, initial, and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be reported as AE and followed as appropriate. Reports from the central laboratory should be filed with the source documents for each patient.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Laboratory abnormalities that are considered clinically significant by the Investigator constitute an AE and should be recorded on the AE eCRF. Sample collection date and time shall be considered as AE onset date and time. Abnormal laboratory values or abnormal clinical findings at the time of screening will be considered as medical history and not AE. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

All laboratory tests with values considered clinically abnormal during participation in the study or within 90 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Table 1-1).
- If laboratory values from laboratory tests not specified in the protocol and performed at the institution’s local laboratory result in the need for a change in patient management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 4.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or a legally authorized representative [LAR]), investigator, or designated medically qualified staff.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

All AEs regardless of seriousness or relationship to IP, spanning from the first visit planned in the Clinical Study Protocol/signature of the ICF (i.e. occurring during the screening period even in the absence of any administration of IP), up to EOS are to be recorded on the corresponding page of the CRF, i.e. AE/SAE form.

Whenever possible, diagnosis or single syndrome should be reported instead of individual, separate symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IP, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the Investigational Product.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

The outcome of the AEs will be assessed and recorded as per the following categories:

- Recovered/resolved
- Ongoing (Not resolved or stabilized on follow-up)
- Recovered with sequelae
- Unknown
- Death

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of informed consent until the end of study at the timepoints specified in the SoA (Table 1-1).

In addition, AE questioning will include specific questions regarding symptoms of COVID-19: fever, cough, dry throat, difficulty breathing, and potential exposure in the past 2 weeks.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded as an AE/SAE.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AESI will be followed until resolution, stabilization, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, see Appendix 4) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Package insert and will notify the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), if appropriate according to local requirements.

All SAEs that occur during the study, and all SAEs occurring up to 90 days after receiving the last dose of study intervention, whether considered to be associated with the study intervention or not, must be reported within 24 hours to the Parexel Safety Contact using the numbers in the List of Study Personnel.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 AEs of Special Interest

AEs of special interest (AESI) include hypocalcemia, ONJ, atypical femoral fracture, fracture healing complications, severe infection (including skin infection) not leading to hospitalization, hypersensitivity leading to emergency room visit, and potential Hy's law. Any AESI should be reported within 24 hours to Parexel. Clinical monitoring of calcium levels will be done at each pre-defined visit. If any patient presents with suspected symptoms of hypocalcemia during the study, calcium levels should be measured. If a patient develops hypocalcemia over the course of the study, calcium and/or vitamin D supplementation may be adjusted per Investigator's medical judgment until the serum calcium concentration returns to the normal range. In addition, patients will be encouraged to report symptoms indicative of hypocalcemia.

8.4 Pharmacokinetics

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 of PK concentration will be provided.

A total of seven (7) PK blood samples will be collected from each patient in the study. Blood sample of 3.5 mL each will be collected at baseline (Day 1), Day 8, Day 15, Month 1, Month 3 Month 6 (prior to second dose), and Month 12. 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.

8.5 Pharmacodynamics

sCTX and sP1NP concentrations will be measured as specified in Table 1-1. All blood samples for a given patient should be collected prior to IP administration (if applicable for the visit) at

approximately 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.

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity Assessments

A total of eight (8) blood samples will be collected from each patient in the study at baseline (Day 1), Month 1, Month 3, Month 6, Month 9, Month 12, Month 15, and Month 18.

Antibodies to the study intervention will be evaluated in serum samples collected from all patients according to the SoA (Table 1-1). Additionally, blood samples should also be collected at the final visit from patients who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Blood samples will be screened for antibodies binding to denosumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to denosumab and/or further characterize the immunogenicity of denosumab.

The detection and characterization of antibodies to denosumab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study intervention will also be evaluated for denosumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s).

Samples may be stored for a maximum of 15 years following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to denosumab.

9 Statistical Considerations

The statistical analysis plan (SAP) will be developed and finalized prior to database lock and unblinding. The SAP will include a detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses including primary and secondary endpoints.

9.1 Statistical Hypotheses

9.1.1 Multiplicity Adjustment

Percentage change in BMD at lumbar spine (LS-BMD) from baseline to Month 12 and AUEC of sCTX over the initial 6 months [$sCTX_{0\text{-}6m}$] (from Day 1 pre-dose to Month 6 pre-dose) are defined as co-primary endpoints. No multiplicity adjustment will be required to test hypotheses for the co-primary endpoints.

9.2 Analysis Sets

Intent-to-Treat (ITT) population: The ITT analysis population consists of all randomized patients who received at least one dose of study intervention in the double-blind 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) population: The mITT analysis population consists of all ITT patients who have baseline assessment and post-baseline LS-BMD value.

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

Safety population: The safety population includes all randomized patients who receive at least one dose of study intervention. Patients will be analyzed according to treatment received.

PD Population: The PD population consists of all patients in the safety population 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 Population: The PK population is a subset of safety population with at least one evaluable PK endpoint (C_{max} or $AUC_{0\text{-}6\ months}$) and no major protocol deviations affecting the PK parameters up to Month 12.

9.3 Statistical Analyses

9.3.1 General Considerations

All data will be listed and descriptive analysis along with appropriate graphs will be provided by treatment. Categorical data shall be summarized by means of absolute and relative frequencies (counts and percentages) and continuous data by means of the number of observations, the arithmetic mean, standard deviation, minimum, median, maximum, confidence interval (CI), geometric mean and coefficient of variation as appropriate.

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

9.3.2 Primary Endpoint Analysis

The primary analyses will be performed at Month 12 for this study.

The main objective of this study is to demonstrate similar efficacy and PD of ENZ215 and Prolia® in postmenopausal women with osteoporosis. This will be performed by comparing percentage change from baseline to Month 12 in LS-BMD as well as AUEC of percentage change from baseline in $sCTX_{0\text{-}6m}$.

The mean percentage change from baseline to Month 12 in LS-BMD will be analyzed using an analysis of covariance (ANCOVA) model including treatment, age strata, previous treatment with bisphosphonate and baseline BMD value as covariates.

Summary statistics for the results include least-squares means (LSM) point estimates of the mean percentage change from baseline for each treatment group at Month 12. The point estimate of the difference in LSM between the groups as well as its two-sided 95% CI and associated p-value will be provided.

The test product and reference product 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.

The primary analysis population for LS-BMD analyses will be the ITT population. Sensitivity analyses will be performed on the mITT and PP population.

For the ITT analysis of LS-BMD, missing data in the reference arm will be assumed to be missing at random (MAR) and imputed assuming they would have behaved like patients in the same arm with complete data. Missing data in the treatment arm will be imputed using the "impute under the null" method by conducting two separate one-sided tests (for non-inferiority and non-superiority) at alpha=0.05 using a suitable multiple imputation technique. A sensitivity analysis will be performed to assess the robustness of the primary results by imputation under the MNAR (missing not at random) assumption using the tipping-point approach.

Missing data in the secondary efficacy endpoints will be imputed using a suitable multiple imputation technique such as completer case missing value (CCMV) imputation.

Primary Pharmacodynamic Analysis

The individual serum concentration of sCTX will be listed and summarized by treatment group at each planned sampling time using descriptive statistics. Percent change from baseline derived from sCTX concentrations will be listed and summarized.

The assessment of equivalence for the co-primary endpoint will be assessed based upon the 90% CI of the ratio of the geometric mean (test/reference) for the percentage change from baseline in AUEC sCTX over the initial 6 Months contained within the pre-specified acceptance limits of 80% to 125%.

ANCOVA will be performed on the log-transformed AUEC. The ANCOVA model will include 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 on the PD population.

Descriptive statistics of AUEC of percentage change from baseline in sCTX after the first dose will be provided by treatment group.

9.3.3 Secondary Endpoint(s) Analysis

9.3.3.1 Efficacy Endpoints

The individual serum concentration of P1NP will be summarized by treatment group at each planned sampling time using descriptive statistics. Percent change from baseline of P1NP will be summarized in tabular and graphical format using PD population.

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

- 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

9.3.3.2 Safety Endpoints

The incidence of patients who develop binding and neutralizing anti-drug antibodies (ADAs) will be summarized by treatment descriptively for safety population.

9.3.3.3 Pharmacokinetics Endpoints

Descriptive summary statistics of drug serum concentrations will be provided by treatment group and visit/sampling time points.

Concentrations below the lower limit of quantification (LLOQ) will be considered as zero in summary statistics. Geometric means will not be reported if there are values below LLOQ. 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, as well as summary figures of mean concentrations over time by treatment. The analysis will be carried out on the PK population.

More detail will be provided in the SAP.

9.3.4 Safety Analyses

Safety parameters such as incidence of AEs, clinically significant changes in physical examination findings, safety laboratory analytes (serum chemistry, hematology, and urinalysis), vital signs, and ECG will be descriptively summarized, for the treatment groups as appropriate. All safety analyses will be performed on the safety population.

9.3.5 Other Analyses

Analysis methodologies for other efficacy, immunogenicity, PK, and safety endpoints will be elaborated in the SAP.

9.4 Interim Analyses

Not applicable.

9.5 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.[7]

Considering the PD co-primary endpoint (percentage change from baseline in AUEC $sCTX_{0\text{-}6m}$), healthy volunteer data[8] were used for the sample size calculations due to the lack of information on AUEC $sCTX_{0\text{-}m6}$ 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[8], the inter-subject CV of AUEC $sCTX_{0\text{-}m6}$ 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 $sCTX_{0\text{-}6m}$ 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.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

The clinical study will be conducted as per the principles and requirements of Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, 2013) and are consistent with the ICH-GCP E6 (R2) guidelines, relevant United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) guidelines and applicable local regulatory requirements.

Sponsor or each participating institution/hospital must provide this protocol (protocol amendment, if applicable) and associated documents for the review and approval to Ethics Committee registered with US FDA and EMA, for the formal approval of the study conduct. The decision of the EC signed by its chairman with EC composition, concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. If requested, a progress report during the study and a summary of the study at the end of the clinical study will be sent to the EC. The study will not commence until the committee has approved the final version of the protocol.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and

accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Deviation from the study Protocol, especially the prescription of a dose other than that scheduled in the study Protocol, other modes of administration, other indication, and longer treatment periods, is not permitted and shall not be covered by the statutory patient Insurance scheme.

10.1.3 Responsibilities of Investigators

The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Study in accordance with this Clinical Study Protocol, guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator must maintain confidentiality of all study related documents and take measures to prevent accidental or premature destruction of these documents.

The Investigator is required to ensure compliance with all procedures required by the Clinical Study Protocol and with all study procedures provided by the Sponsor (including security rules).

The Investigator agrees to provide reliable data and all information requested by the Clinical Study Protocol in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data, particular attention should be paid to the confidentiality of the patient’s data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Study in accordance with the Clinical Study Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and will work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Study Protocol and all necessary information.

10.1.4 Responsibilities of Sponsor and Study Management

The Sponsor of this clinical study shall take all reasonable steps to ensure proper conduct of the Clinical Study Protocol as regards ethics, Clinical Study Protocol compliance, integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor in maintaining a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical study.

At regular intervals during the clinical study, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance with Clinical Study Protocol requirements, and any emergent problems. These monitoring visits will include, but not be limited to, review of the following aspects: patient informed consent, patient recruitment and follow-up, source data verification, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, IP allocation, patient compliance with the IP regimen, IP accountability, concomitant therapy use, and quality of data.

10.1.5 Informed Consent Process

The Investigator or a person designated by the Investigator, and under the Investigator's responsibility, should completely inform the patients and/or their families describing this study and providing sufficient information to them for making an informed decision about their participation in this study.

All the patients should be informed to the complete extent possible about the study, in language and terms they are able to understand. Consent form must be IRB/IEC approved and the patient will be provided the same in local language(s).

Prior to patient's participation in this study, the written informed consent form must be signed, name filled in and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Patients must be informed that their participation is voluntary. Patients or the patient's LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, an international Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and

signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.6 Patient and Data Confidentiality

Patient confidentiality along with the information disclosed/provided/produced by the Sponsor during the clinical study, including, but not limited to, the clinical study protocol, the eCRF, ICFs and results are strictly held in trust by the Sponsor, Sponsor's authorized personnel, Investigator and their staff members. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

However, the submission of this clinical study protocol and other necessary documentation to the ethics committee is expressly permitted, the EC members having the same obligation of confidentiality. The European Union (EU) General Data Protection Regulation (GDPR) will be followed for data protection and privacy for EU submission.

10.1.7 Committees Structure

10.1.7.1 Data Monitoring Committee

A data monitoring committee (DMC) has been appointed for this study. The DMC is a group of independent scientists who are appointed to monitor the safety of a human research intervention. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

10.1.8 Dissemination of Clinical Study Data

After completion of study at 12 months, a report will be prepared for submitting it to EMA regulatory agency. Another report will be prepared for further study, i.e. the extension period of 6 months (Month 18) and this report will be submitted to the US FDA and EMA regulatory agency.

A final clinical study report will be prepared in accordance with the ICH E3 guideline on structure and content of Clinical Study Report, regardless of whether the study is completed or prematurely terminated. The final report will be prepared according to the electronic Common Technical Document (eCTD) format. Deviations from the protocol will be documented as protocol deviations and presented in the final report.

10.1.9 Auditing and Inspection

The Investigator will permit study-related monitoring, audits and inspections by the EC, the Sponsor, government regulatory bodies, and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Investigator agrees to allow the auditors or inspectors to have direct access to patient's study records for review being understood that these personnel are bound by professional secrecy and as such will not disclose any personal identity or personal medical information. The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

The Investigator will ensure the capacity for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, study documents, etc.). Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and quality assurance offices. As soon as the Investigator is notified of a future inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in these inspections. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

10.1.10 Data Quality Assurance

The Investigator by careful planning, assigning responsibilities to well qualified study personnel, and through continuous review, verifies and maintains desired level of quality in the study process.

The Sponsor or Sponsor's designee will serve as the statistical and data coordinating center for the present study and will be responsible for data management, quality review, analysis, and reporting of the study data.

Sponsor or the Sponsor's designee will monitor the study and site activity while ongoing, to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of the patients are being protected
- Study is conducted in accordance with the currently approved protocol and amendments and any other study agreements, GCP, and all applicable regulatory requirements

The pharmacokinetic and bioanalytical site will be responsible for quality assurance audit of pharmacokinetic and bioanalytical data respectively.

The electronic Case Report/Record Form (eCRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. The electronic data capture (EDC) system maintains an audit trail on entries, changes, or corrections in the eCRF. All the data entries on the eCRF will be authenticated by the Investigator.

Authorized site personnel will record the data (consistent with the source documents) in the provided study (e)CRF, accurately and in a timely manner. The Investigator is responsible for confirming data entries are complete and accurate by physically or electronically signing the eCRF. Study monitors will perform ongoing source data verification to ensure that data entered into the eCRF by authorized site personnel are consistent with the source documents.

Data cleaning and processing will be managed through the electronic data capture (EDC) and data management system. The database development process will include the production of a code book containing annotated eCRF screens detailing the variable names used in the database. The EDC system will be programmed to capture all data in a dedicated database through the specified eCRF screens in a secure manner. Clinical Data will be recorded directly into an eCRF by assigned site personnel.

All data should be recorded as early as possible within the eCRF. Access via the internet to the eCRF is defined through permission based roles, for example data entry or read-only. All changes to the eCRF are recorded, along with a reason for change, in the system audit trail. Username, password, and web-address will be provided to study personnel.

When the database is complete and accurate, it will be locked. After the data have been entered and verified, various edit checks will be performed by Data Management Team for the purpose of ensuring the accuracy, integrity, and validity of the database against the eCRF. These should include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Probabilistic checks and
- Protocol adherence checks

It is the responsibility of the Investigator to resolve all data queries that arise during data management in a timely manner.

10.1.11 Record Retention

It is the responsibility of Sponsor to plan for safe and secure custody of all study related documents and material for a period of 5 years after the completion of the study or submission of the data to the regulatory authority(ies) whichever is later. These documents should be retained for a longer period of time, if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The PK and bioanalytical data will be archived at the laboratories performing these tests.

10.1.12 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.13 Study and Site Start and Closure

First Act of Recruitment

The study start date and first act of recruitment is the date when the first patient is screened for the study.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator.
- Total number of patients included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.14 Publication Policy

It is the responsibility of Parexel to register this study on an applicable trial registry. On the basis of the statistical and clinical evaluation of the pooled results across the study centers, a clinical study report will be prepared. This can form the basis of a manuscript for publication in a peer-reviewed journal. The Sponsor will hold the right to publish the results of present study at any time. An Investigator may seek permission to publish results of the study from the Sponsor.

10.1.15 Protocol Approval and Amendment

Any change or addition to the protocol, other than administrative ones (i.e. typographical or logistical), can only be made in a written protocol amendment that must be approved by Sponsor, EMA where required, and the EC. Only amendments that are required for patient safety may be implemented prior to EC approval.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a violation of the protocol. In such cases, Sponsor should be notified of this action and the EC should be informed immediately.

Changes to the protocol affecting only administrative aspects of the study do not require formal protocol amendments or EC approval but the EC must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and EC approval include:

- Changes in the staff used to monitor studies
- Changes in shipping address for eCRF

10.1.16 Protocol Deviations and Violations

A protocol deviation/violation that is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A deviation or violation is any noncompliance with the requirements of clinical study protocol, Standard Operating Procedures (SOPs), and ICH-GCP-E6 (R2) guidelines. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations or violation, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to observe vigilance to identify and report deviations immediately upon identification of the protocol deviation. All deviations must be promptly reported to Sponsor through written communication. All deviations from the protocol must be addressed in study patient source documents. A completed copy of the protocol deviation form must be maintained in the regulatory file as well as in the patient's source document. Protocol deviations must be sent to the local EC, if required, per guidelines. The site Investigator/study staff is responsible for adhering to EC requirements.

10.1.17 Liability and Insurance

Sponsor undertakes to maintain an appropriate clinical study insurance and indemnity policy. The insurance policy is in accordance with local laws and requirements. A copy of the insurance certificate will be provided to the EC. In the case of an injury occurring to the patient during the study, free medical management will be provided to the patients as long as required or till such time it is established that the injury is not related to the clinical study, whichever is earlier.

10.1.18 Property Rights and Data Protection

All information, documents, and IP provided by the Sponsor or its assignee are and remain the sole property of the Sponsor. The Investigator shall not mention any information or the product name in any application for a patent or for any other intellectual property rights. All the results, documents and inventions, which arise directly or indirectly from the clinical study in any form, shall be the exclusive property of the Sponsor. Any Investigator involved with this study is obliged to provide the Sponsor with complete test results and all data derived from the study. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical study.

The data collected during the entire study will be included in the Sponsor database and shall be treated in compliance with the SOPs prepared according to applicable laws and regulations. When archiving or processing the data, Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred. The patient must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent. The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by the central laboratory.

All patients will have the laboratory samples drawn as outlined in Table 1-1. Laboratory samples for all patients will be assessed using a certified central laboratory. PK and anti-denosumab antibody assessment will be done at bioanalytical laboratory.

Qualified medical staff at the site will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be reported as AE and followed as appropriate. Reports from the central laboratory should be filed with the source documents for each patient.

Additional tests or safety assessments may be performed at any time in a certified local laboratory during the study as determined necessary by the Investigator or as required by local regulations.

Investigators must document their review of each laboratory safety report.

All samples collected for PK, PD, and immunogenicity assessment will be analyzed using validated bioanalytical methods. The details of collection, processing and shipment of biological samples will be outlined in a laboratory manual.

Table 10-1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	Leukocyte count (WBC count) Total erythrocyte count (RBC count), Hemoglobin Platelet count Absolute neutrophil count (ANC)
Serum chemistry	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP) Total bilirubin Albumin Total proteins Kidney function tests: (Blood urea nitrogen [BUN], Creatinine, Glomerular filtration rate [eGFR]) Electrolytes (sodium, potassium, chloride) Glucose

	Serum calcium, Albumin-adjusted calcium Magnesium Phosphorus
Routine urinalysis	Routine examination (Color, transparency, pH, specific gravity, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocyte esterase) Microscopic examination if blood, protein, leukocyte esterase or Nitrite is positive or if deemed necessary by the Investigator.
Other blood tests	Anti-Denosumab antibody sCTX sP1NP Serology: HIV, HBV, HCV 25 (OH) vitamin D level Follicle stimulating hormone (FSH) Thyroid function test (T3, T4, TSH) Parathyroid hormone test (iPTH)
NOTES: Liver chemistry stopping criteria: All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and INR >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to Parexel in an expedited manner. If alkaline phosphatase is elevated, consider fractionating. For further investigations such as USG, gastroenterologist or hepatologist should be consulted to rule out any other cause of deranged LFTs. Only if there is confirmed DILI should the patient be withdrawn from the study and should be followed-up until resolution or until the event has stabilized.	

10.3 Appendix 3: Total blood loss

Total volume of blood drawn for study will not exceed 166.5 mL+ 10 mL (if required) per patient during the entire study.

Blood samples not collected at the scheduled time will be documented as sampling deviations. The actual time of collection of each blood sample will be used for statistical analysis.

Details of Blood Withdrawal	Amount of blood required
Blood withdrawn for screening procedures	20.0 mL
Blood withdrawn for Hematology on M6, M12, and M18 (03 samples of 3.0 ml each)	09.0 mL
Blood withdrawn for serum chemistry on D15, M3, M6, M9, M12 and M18 (06 samples of 5.0 ml each)	30.0 mL
Blood volume for sCTX and sP1NP on D1, D15, M1, M3 and M6 (05 samples of 3.5 mL each)	17.5 mL
Blood volume for Denosumab Antibody Assay (ADAs) on D1, M1, M3, M6, M9, M12, M15 and M18 (08 samples of 10.0 mL each)	80.0 mL
Blood withdrawn for end of study safety assessment	10.0 mL
Total amount of blood required for each patient	166.5 mL + 10 mL (If required)

If patients are willing to participate in the PK assessment sub-study, an additional 24.5 mL + 5 mL (if required) blood will be drawn from each patient as part of the PK assessment.

Details of Blood Withdrawal	Amount of Blood required
Blood withdrawn for PK assessment on D1, D8, D15, M1, M3, M6, and M12 (07 samples of 3.5 mL each)	24.5 mL
Total amount of blood required from each patient	24.5 mL + 5 mL (if required)

10.4 Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE Definition
As per ICH-GCP E6 (R2) guidelines, adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product regardless of its causal relationship to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IP.

Events Meeting the AE Definition
Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease) should be recorded as an AE. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2 Definition of SAE

An SAE is an AE that:
a. Results in death
b. Is life-threatening The term *life-threatening* in the definition of *serious* refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect

f. Malignancy

g. Other situations

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.4.3 Recording and Follow-up of AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the eCRF/SAE reporting form.

There may be instances when copies of medical records for certain cases are requested by the Ethic committee. In this case, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records before submission to the Ethic committee.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the electronic data collection tool.**

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following "binary" decision choice will be used by the Investigator to describe the initial causality assessment:

- Related: Reasonable possibility of a relatedness
- Not related: No reasonable possibility of relatedness.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
Any follow-up information received for the SAE should be analyzed and reported as per the process and timelines mentioned for initial SAE reporting. The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE (clinical signs, laboratory values or other, etc.) until the patient returns to normal or consolidation of the patient's condition. In case of any SAE, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the clinical study. New or updated information will be recorded in the originally completed form. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.4 Reporting of SAE

SAE Reporting via Electronic/Paper Data Collection Tool
For all sites: If any SAE occurs in the course of the study, then Investigators or other site personnel inform the Parexel Global Safety Processing Group within 1 day, i.e. immediately but no later than 24 hours of when he or she becomes aware of the event. The Parexel Global Safety Processing Group works with the Investigator to ensure that all the necessary information is provided. Any AE considered serious by the Investigator or sub-investigator or which meets the aforementioned criteria is subjected for expedited reporting. All the SAEs will be reported as applicable to the local regulatory requirement. All serious and unexpected AEs will be followed until a satisfactory resolution or until the Investigator deems the event to be chronic or the patient to be stable. The further course of action for all SAEs; shall be observed as per current applicable rules and regulations. The primary mechanism for reporting an SAE will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to Parexel Global Safety Processing Group mailbox (NorthAmerica_Medical@Parexel.com). If the EDC system is not available, then the Investigator or other study site staff reports a SAE to Parexel Global Safety Processing Group by email by completing the SAE report form and faxing the documents to Parexel Global Safety Processing Group, using the appropriate regional Parexel SAE fax number: NA (Billerica): +1 781 434 5957. The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/Parexel will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (Investigator Brochure or

Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form.

10.5 Appendix 7: Abbreviations

Abbreviation	Description
ACTH	Adrenocorticotrophic Hormone
ADAs	Anti denosumab antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUEC	Area Under the Effect Curve
BMD	Bone Mineral Density
CDSCO	Central Drugs Standard Control Organization
CI	Confidence Interval
COA	Certificates of Analysis
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organization
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENZ215	Proposed biosimilar to Prolia®
EOS	End of Study
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin-Releasing Hormone
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	Investigational Product
iPTH	Intact Parathyroid Hormone
IQC	Instrument Quality Control

Abbreviation	Description
ITT	Intent-to-Treat
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally Authorized Representative
LS-BMD	Bone Mineral Density at Lumbar Spine
LSM	Least-Squares Means
MVF	Multiple Vertebral Fractures
ONJ	Osteonecrosis of the Jaw
PA	Posteroanterior
P1NP	Procollagen Type 1 N-terminal Propeptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
Q6M	Once Every 6 months
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
SC	Subcutaneously
sCTX	Serum C-Telopeptide of Type 1 Collagen
SD	Standard Deviation
SOA	Schedule of Activities
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
USA	United States of America
USFDA	United States Food and Drug Administration
WBC	White Blood Cell

10.6 Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 2: (8 April 2022)

Section	Description of Change	Brief Rationale
Section 2.3.1 Risk Assessment	Table 2-3 Risk Assessment: Fertility, pregnancy and lactation mitigation was changed from "Pregnant women and women of child-bearing potential not using contraception will not be enrolled in the study" to "Only postmenopausal women aged ≥ 55 and ≤ 85 years will be enrolled in the study".	For consistency with inclusion criteria
Section 5.2 Exclusion Criteria	Exclusion criteria #10 language has been updated.	Clarify

Amendment 1: (16 December 2021)

Summary of Changes

Section	Description of Change	Brief Rationale
Title Page	Updated the address of Co-Sponsor, Enzene Biosciences Ltd	Change in address of the Co-Sponsor
Section 5.2 Exclusion Criteria	Exclusion criteria #13 was changed from "Total hip or femoral neck T-score <4.0" to "Total hip or femoral neck T-score <−4.0"	Clarify

11 References

1. United States Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. April 2015. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product | FDA. Accessed September 2021
2. Summary of Product Characteristics (SmPC): Prolia® 60 mg solution for injection in pre-filled syringe; Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands, Updated 22 July 2021
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Investigator Agreement Page

Declaration of the Principal or Global Coordinating Investigator

Title: 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

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the IP as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, 2013) and the guidelines on Good Clinical Practice.

Principal or Global Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

Title: 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

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, EDCs/eCRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number