Clinical Study Protocol

<table>
<tr><td colspan="2">Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.</td></tr>
<tr><td colspan="2">Test Product: Denosumab</td></tr>
<tr><td colspan="2">Brief Title: Denosumab biosimilar injection in postmenopausal women with osteoporosis.</td></tr>
<tr><td>Protocol Number: 0774-19</td><td>Version No: 2.0</td></tr>
<tr><td>Document Type: Clinical Study Protocol</td><td rowspan="3">Document Status: Final</td></tr>
<tr><td>Release Date: 14-Sep-2020</td></tr>
<tr><td>Study Phase: Phase 3</td></tr>
<tr><td>Sponsor Name: Intas Pharmaceutical Limited (Biopharma Division)

Legal Registered Address: Plot No. 423/P/A/GIDC, Sarkhej - Bavla Highway, Moraiya, Ahmedabad – 382213. Gujarat, India.

Tel No.: +91-2717-660921

Fax No.: +91-2717-660105</td><td>CRO Name: Lambda Therapeutic Research Limited, Ahmedabad

Legal Registered Address: Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad – 382481. Gujarat, India.

Tel. No.: +91-79-4020 2020

Fax No: +91-79-4020 2021/22</td></tr>
</table>

Protocol Signature

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.

Protocol Number: 0774-19

The information in the protocol is consistent with the current risk/benefit evaluation of the test preparation as well as with the moral, ethical and scientific principles governing clinical research as set out in the ICH E6 (R2) Guideline on Good Clinical Practice; New Drugs & Clinical Trial Rules, 2019 of CDSCO; Declaration of Helsinki (Fortaleza, 2013); as per any other applicable regulatory requirements.

Reviewed & Approved by:

Dr. Naman H. Shah	14-Sep-2020	
Name	**Date**	**Signature**

Reviewed by:

Head/Designee	Name	Signature and Date
Medical Monitor	Dr. Naman H. Shah	14-Sep-2020
Clinical Operations	Jitendra Soni	14-Sep-2020
Biostatistics and Programming	Ronak Patel	14/SEP/2020
Bioanalytical	PALLAVI HAJELA	14-Sep-2020
Quality Assurance	DR. CHAURI GATE2	14 Sep 2020

Sponsor's Approval Signature

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.

Protocol Number: 0774-19

I, on behalf of Intas Pharmaceutical Limited (Biopharma Division), have read, understood and approve this protocol.

Intas Pharmaceutical Limited (Biopharma Division) agree to comply with all requirements regarding the obligations of the Sponsor and all other pertinent requirements of ICH E6 (R2) Guideline on Good Clinical Practice; New Drugs & Clinical Trial Rules, 2019 of CDSCO; Declaration of Helsinki (Fortaleza, 2013); as per any other applicable regulatory requirements.

Authorized Signatory	**Date**

Name	**:**	Dr. Vinu Jose
Designation	**:**	Head – Clinical Development and Medical Affairs
Address	**:**	**Intas Pharmaceutical Limited (Biopharma Division)** Plot No: 423/P/A, Sarkhej-Bavla Highway, Moraiya, Sanand, Ahmedabad, Gujarat, India 382 213
Tel. No.	**:**	+91-2717-660921
Fax No.	**:**	+91-2717-660105
Email	**:**	Vinu_jose@intaspharma.com

List of Facilities

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.

Protocol Number: 0774-19

Contract Research Organization (CRO) Services

Clinical Laboratory, Pharmacy, Project Management, Bioanalytical services (Pharmacodynamic, Pharmacokinetic and Immunogenicity assessments), Monitoring, Data Management, Biostatistics and Programming, Medical Writing, and Quality Assurance.

Address **:** Lambda Therapeutic Research Limited, Ahmedabad
Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad – 382481. Gujarat, India
Tel. No. **:** +91-79-4020 2020
Fax No. **:** +91-79-4020 2021/22

Note: Clinical Laboratory will be utilized for all laboratory investigations. ECG and/or ECHO will be performed locally.

IMP Management

Address **:** Lambda Clinical Services Limited
Survey No. 530, Unit No. 22 to 31,
Silver Industrial Estate – 3.
Sarkhej-Bavla Road,
Changodar, Sanand, Ahmedabad 382213,
Gujarat, India.

Clinical Facilities

Clinical facilities will be of participating clinical investigators/ sites.

Sponsor's Safety Officer and Medical Monitor

Name	:	Dr. Dharma Rao Uppada
Address	:	Intas Pharmaceuticals Ltd. (Biopharma Division), Plot No: 423/P/A, Sarkhej-Bavla Highway, Moraiya, Sanand, Ahmedabad, Gujarat, India 382 213.
Tel. No.	:	02717-660948
Fax No	:	02717-660105
E-Mail:	:	Dharma_Uppada@intaspharma.com TrialBioDrugSafety@intaspharma.com

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Type**
Amendment 2.0	14-September-2020	Major [substantial]
Original Protocol	26-March-2020	

Amendment number 2.0 dated 14 September 2020

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Synopsis (Investigational Medicinal Product), Section 6.1	Bio analytical services (Pharmacodynamics, Pharmacokinetic and Immunogenicity assessments) has been kept at Lambda Therapeutic Research Limited, Ahmedabad only.	Change in facility
List of facilities: Sponsor's medical monitor	Updated the details of Sponsor's medical monitor.	Administrative change
Synopsis: and section 3.0 Objectives and Endpoints:	Addition of a secondary endpoint.	Regulatory advice related strategy change
Synopsis and Section 5.1	Update in upper age cut-off of participants for inclusion	Regulatory advice related strategy change
Synopsis and section 4.1 Overall Design	An additional PK, PD and Immunogenicity samples will be collected after third dose of denosumab in prespecified participants. However, analysis of PK and PD samples will be performed only if there is immunogenicity identified in a particular patient either clinically or by immunogenicity analysis.	Regulatory advice related strategy change
Section 1.3	Schedule of event has been updated based on changes in design.	Subsequent related changes
9.1. Sample Size Determination	Sample size justification has been added for the transition extension period, based on Immunogenicity assessment	Regulatory advice related strategy change
Section 9.2: Populations for Analyses	Updates in population set and addition of sensitivity analysis	Regulatory advice related strategy change
8. Study Assessments and Procedures	Blood loss has been revised due to additional PK and PD sample collections after third dose in applicable participants only.	Regulatory advice related strategy change
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized

Table of Contents

Abbreviations

λz	Terminal Rate Constant
AE	Adverse event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AUC_{0-t}	Area under the concentration versus time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the concentration versus time curve from time zero to infinity
AUC_%Extrap_obs	Residual area
$AUEC_{0-t}$	Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration
CI	Confidence Interval
Cl/F	Total body clearance
ClinRO	clinician-reported outcome
C_{max}	Maximum measured concentration
CRF	case report form(s) (paper or electronic as appropriate for this study)
DMC	Data Monitoring Committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
eDC	electronic data capture
E_{max}	Maximum % reduction from baseline
EMA	European Medicines Agency
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLM	General Linear Model
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IAC	Interim Analysis Committee
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
IWRS	interactive web response system
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

mITT	Modified Intent-To-Treat
MRU	Medical resource utilization
NIMP	Non-investigational medicinal product
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
Ref	Reference
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
T_{max}	Time of the maximum measured concentration/Time of the maximum % reduction from baseline
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
V_d/F	Volume of distribution

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.

Denosumab of Intas is biosimilar denosumab candidate under development by Intas Pharmaceutical Limited (Biopharma Division). Denosumab of Intas is already approved by Indian drug licensing authority- Drug Controller General (India) for marketing in Indian population since 2018.

Brief Title: Denosumab biosimilar injection in postmenopausal women with osteoporosis.

Rationale:
As per regulatory requirement, a comparative clinical study to establish Pharmacokinetic, Pharmacodynamic and Immunogenicity equivalence is required to conclude therapeutic equivalence to obtain marketing authorization of a biosimilar investigational product. This is a multicenter, randomized, double-blind, active-controlled study in approximately 552 postmenopausal women with osteoporosis.

An extension of the study is planned after completion of the initial 1 year of treatment. This extension is with the objective of submitting data on safety, and Immunogenicity, after switching of Prolia treatment arm to either Prolia or Intas denosumab for 6 months. This switching data is applicable only for FDA submission. Only patients who have undergone PK assessment will be eligible for the extension phase.

Objectives and Endpoints:

Objectives	Endpoint Comparison
Primary	
To compare the pharmacokinetic parameters of denosumab and denosumab-ref in postmenopausal women with osteoporosis.	• Pharmacokinetics: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ after first dose of denosumab and denosumab-ref
To compare the pharmacodynamic effect of treatment with denosumab and denosumab-ref on bone mineral density (BMD) and bone resorption marker in postmenopausal women with osteoporosis*	• Mean percentage change in BMD at lumbar spine from baseline to 12 months between denosumab and denosumab-ref • Pharmacodynamics: E_{max} and $AUEC_{0-t}$ of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab-ref* *To be considered as secondary endpoint for USFDA submission.
Secondary	
To compare the efficacy of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Incidence of clinical fracture between denosumab and denosumab-ref over 12 months.

To compare the pharmacodynamic effects of the treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 06 months between denosumab and denosumab-ref • Mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months between denosumab and denosumab-ref • Pharmacodynamics: T_{max} of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab-ref • Pharmacodynamics: $E_{max,}$ $AUEC_{0-t,}$ T_{max} of % reduction from baseline serum N-terminal propeptide of type 1 collagen (P1NP) after first dose of denosumab and denosumab-ref • Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref • Mean percentage reduction in CTX serum concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref
To compare the immunogenicity of denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Incidence of anti-denosumab antibody in denosumab and denosumab-ref arm over 12 months.
To compare the safety of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Monitoring of adverse events and lab parameters in denosumab and denosumab-ref arm
To evaluate the safety and immunogenicity of denosumab and denosumab-ref after single transition from denosumab-ref to denosumab and denosumab-ref in postmenopausal women with osteoporosis***** *****To be considered as secondary endpoint for USFDA submission.	• Incidence of anti-denosumab antibody in denosumab and denosumab-ref arms after single transition from denosumab-ref • Assessment for difference in PK or PD in patients who are found to be immunogenic • Monitoring of adverse events and lab parameters in denosumab and denosumab-ref arm arms after single transition from denosumab-ref

Overall Design

This is a randomized, double-blind, active-controlled, parallel-arm, multicenter study comparing the pharmacokinetics, pharmacodynamics, and immunogenicity of Denosumab of Intas (60 mg/ml) with Prolia, in postmenopausal women with osteoporosis aged 55 to 90 years, both inclusive.

After completion of 12 months of treatment period, participants who are (a) randomized in reference arm ***AND*** (b) undergone PK assessments during 12-month treatment period will be re-randomized in test and reference arm for additional follow up period of six months to assess the safety and immunogenicity. The PK, PD samples collected in these patients will be assessed for impact of immunogenicity on PK and PD only if there is immunogenicity identified in a particular patient either clinically or by immunogenicity analysis.

Brief Summary:
The purpose of this study is to compare and prove equivalence for the pharmacokinetic, pharmacodynamic parameters and Immunogenicity of denosumab against denosumab-ref.

Study Duration: 381 days (approx. 12 months) including screening period. For those patients who have been part of PK assessment and in Reference group and identified for single transition treatment the duration will be 541 days (approx. 18 months) for following up participants.

Condition/Disease: Postmenopausal women with osteoporosis.

Study Hypothesis: The primary clinical hypothesis is that in postmenopausal women with osteoporosis, the primary pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ after first dose of denosumab will be equivalent to denosumab-ref. Likewise, the primary pharmacodynamics parameter (Only for EMA) E_{max} and $AUEC_{0-t}$ of % reduction from baseline serum CTX after first dose of denosumab will be equivalent to that of those receiving denosumab-ref. It is further hypothesized that mean percentage change in BMD of lumbar spine from baseline to 12 months in participants receiving denosumab will be equivalent to that of those receiving denosumab-ref. The safety hypothesis is that the safety profile of denosumab will be similar to denosumab-ref in women with osteoporosis.

Investigational Medicinal Product, Dose and Mode of Administration: Denosumab of Intas Biopharmaceuticals Limited is the test product and EU-Prolia is the reference product. Study drugs will be administered at a dose of 60 mg as a subcutaneous injection once every 6 months into the thigh, abdomen or upper arm as per Prescribing Information.

IMP details

ARM Name	denosumab	denosumab-ref
Study IMP Name	Denosumab	Prolia®
Manufacturer	Intas Pharmaceuticals Ltd., India	Amgen Europe B.V. (EU-licensed product)
Dose Formulation	Solution for injection in single-use prefilled syringe	Solution for injection in single-use prefilled syringe
Unit Dose Strength(s)	60 mg/mL	60 mg/mL

Dosage Level(s)	60 mg once every 6 months	60 mg once every 6 months
Route of Administration	Subcutaneous injection	Subcutaneous injection

Other Protocol-Required Therapies
Other protocol-required drugs (ie, vitamin D and calcium supplements) that are commercially available will be provided by the Sponsor. The investigator will be responsible for obtaining supplies of these drugs.

From screening to end of study, participants will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of at least 1000 mg calcium and at least 400 IU vitamin D. In addition, participants with a serum 25 (OH) Vitamin D level of < 20 ng/mL at screening will be repeated and retested during screening.

Where available, vitamin D3 preparations should be used; if vitamin D3 is not available, use of vitamin D2 preparations is acceptable.

If a participant develops hypercalcemia over the course of the study, the principal investigator may use his/her medical judgment and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range. If a participant develops hypocalcemia over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range. If a participant is unable to tolerate the daily calcium or vitamin D supplementation, the formulation may be changed, or the dose lowered. The intolerance as well as the resolution (i.e., change in formulation or dosage) should be documented in the source documents.

Visit Frequency: Visit have been scheduled at monthly frequency.

Number of Participants: A total of 552 patients (276 patients/arm) in the BMD and immunogenicity assessment, 296 patients (148 patients/arm) in the PK assessment and PD (Percentage reduction from baseline for serum CTX) assessment will be included for initial 1-year treatment. 136 patients (68 patients/arm) will be included in the immunogenicity assessment for extension 6-month phase of the study.

Inclusion criteria
Participants are eligible to be included in the study only if all of the following criteria are met:

1. Participant must sign an ICF to participate in the study indicating that she understands the purpose of, and procedures required for the study as described in this protocol and is willing to and will be able to adhere to requirement of the protocol.
2. Participant must be 55 to 90 years of age (both inclusive), at the time of signing the informed consent.
3. Participants who are medically/clinically stable on the basis of physical examination, medical history, vital signs, chest X-ray PA view, 12-lead ECG and clinical laboratory parameters performed at screening. Any abnormalities or deviation from normal, must be consistent with the underlying illness in the study population and judged by investigator to be not clinically significant. This determination must be recorded in the participant's source documents and initialed by the investigator.

4. Participants whose absolute bone mineral density T-score is ≤ -2.5 and ≥ -4.0 at the lumbar spine as measured by DXA (dual-energy x-ray absorptiometry), confirmed by the independent central imaging team.
5. At least two vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA, confirmed by the independent central imaging team.
6. Body weight between 50 kg and 90 kg (both inclusive) at screening.
7. Postmenopausal ambulatory female and not considered to be of child-bearing potential if:
    a. Women are considered post-menopausal and not of child-bearing potential if,
        i. They have had 12 months of natural (spontaneous) amenorrhea (no vaginal bleeding or spotting) with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) OR
        ii. Six months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL; OR
        iii. Have had surgical bilateral oophorectomy (with or without hysterectomy) at least six months ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment if she is considered not of child-bearing potential.

Exclusion criteria:
Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Documented medical history of clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances
2. Documented medical history of known allergies, hypersensitivity, or intolerance to denosumab or its excipients (sorbitol, acetate, polysorbate 20, and sodium hydroxide
3. History of any prior use of denosumab
4. Documented medical history of metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as Paget's disease, osteomalacia, osteogenesis imperfecta, osteopetrosis, rheumatoid arthritis, ankylosing spondylitis or any other joint disease limiting mobility, Cushing's disease, hyperprolactinemia, malabsorption syndrome
5. Documented medical history of latex or dry natural rubber allergy
6. Contraindications to the use of denosumab or Vitamin D and Calcium as per Investigator brochure/local prescribing information at screening and/or baseline
7. Documented medical history and/or current evidence of any of the following oral/dental conditions
    a) Prior history or current evidence of osteomyelitis or osteonecrosis of the jaw.
    b) Active dental or jaw condition which requires oral surgery.
    c) Planned invasive dental procedure expected during study period.
    d) Current evidence non-healed dental or oral surgery.
    e) Current evidence of poor oral hygiene
    f) Ill-fitting denture
8. Current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range at screening. Serum calcium levels may be retested once in case of an elevated/low serum calcium level as assessed by the clinical laboratory. Final decision to include the patient based on the risk of hypocalcemia to be taken by the Investigator.

9. History of frequent occurrence of hypocalcemia, history of severe hypocalcemia or presence of diseases that can precipitate hypocalcemia frequently (like malabsorption syndromes (for example celiac disease, history of excision of small intestine etc.) and severe renal impairment)
10. Current, uncontrolled hyper- or hypoparathyroidism and history of hypoparathyroidism, per participant report or chart review. PTH outside the normal range (15-65 pg/mL) as assessed by central laboratory
11. Current, uncontrolled hyper- or hypothyroidism, defined as thyroid stimulating hormone outside of the normal range (TSH-0.465 to 4.68 mIU/L) at screening.
12. 25 (OH) Vitamin D lower than 20 ng/mL as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted, and participants may be rescreened once.
13. History of external beam or implant radiation therapy involving the skeleton.
14. History and /or presence of 1 severe fracture or 2 moderate vertebral fractures
15. Patients with bone metastases or a history of malignancies affecting bones.
16. Smokers or who have smoked within last 06 months prior to start of the study.
17. Documented medical history of major surgery, (e.g. requiring general anesthesia) within 12 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.
    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.
18. Documented medical history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.
19. Documented medical history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.
20. Documented medical history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 1 year before Screening
21. Lymphoma, leukemia, or any malignancy (current or suspected) within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years; carcinoma in situ of the cervix; or malignancy, which is considered cured with minimal risk of recurrence
22. QTc interval >470 msec or QT interval >480 msec in participants with bundle branch block.
    Note: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB). It is either machine-read or manually over-read.
23. Administration of bisphosphonate as follows: -
    a) IV Bisphosphonate in the past 3 years
    b) Oral bisphosphonates treatment for osteoporosis
        i. More than 3 years of cumulative use
        ii. Any dose received within 6 months prior to randomization
        iii. More than 1 month of cumulative use between 6 and 12 months prior to randomization
24. Teriparatide or any PTH analog treatment received within 12 months prior to randomization.
25. Systemic oral or transdermal estrogen, SERMs, or calcitonin treatment of more than 1 month of cumulative use within 6 months prior to randomization.
26. Androgen deprivation or hormonal ablation therapy of more than 1 month of cumulative use within 6 months prior to randomization.

27. Tibolone or cinacalcet treatment received within 3 months prior to randomization
28. Systemic glucocorticoids: ≥ 5 mg prednisone equivalent per day for more than 10 days within 3 months prior to randomization.
29. Abnormal laboratory values
    a. General: Any laboratory abnormality which, in the opinion of the Investigator, will prevent the patient from completing the study or interfere with the interpretation of the study results.
    b. Liver transaminases:
        i. Serum aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN)
        ii. Serum alanine aminotransferase (ALT) ≥3.0 × ULN
    c. Alkaline phosphatase and bilirubin ≥1.5 × ULN
    d. Creatinine clearance estimated using Cockcroft Gault formula is <30 mL/min
30. Taken any prohibited therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study IMP
31. Received any investigational IMP 30 days or 5 half-lives (whichever is longer) before the signing the consent or is currently enrolled in an investigational study
32. Unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. This includes but is not limited to hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the investigator.

    Note: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones) is acceptable if the participant otherwise meets entry criteria.
33. Any other clinical/social/ psychiatric condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
34. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study IMP is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Refer to Section 5.4 for further information.

Discontinuation of study IMP

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study IMP. If a participant discontinues study IMP for any reason before the end of the study, scheduled assessments of the study should be continued.

Subjects meeting the following criteria will be withdrawn from the study treatment. All withdrawn subjects from the study treatment will be followed up till the end of study as per schedule of activities.

- The participant withdraws consent to receive study IMP
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study IMP

- Concomitant medications: Consumption of co-medication / requirement to consume co-medication that can affect the safety of the participant continuing in the trial as per the investigator; Consumption of prohibited medication as mentioned in section 6.8

If a participant discontinues study IMP definitely for any reason before the end of the study visit but is still willing to collaborate in providing further data by continuing on study, the participant will remain in the study to be evaluated for further collection of information on primary endpoint as well as immunogenicity. These participants to be provided Standard of Care as per investigator and participants agreement.

Participant withdrawal
A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Investigator must determine the primary reason for a participant's premature withdrawal from the study and record this information on the eCRF and in the source document. If premature withdrawal from the study occurs for any reason, if possible, End of Study visit as described in Section 1.3 (SoA) should be conducted. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

A participant will be withdrawn from the study for any of the following reasons:

- Consent is withdrawn: Subjects have the right to withdraw from the trial at any time for any reason. If withdrawal occurs, the subject will be requested to come for a complete follow-up examination.
- Non-compliance: The subject may be withdrawn from the trial at the discretion of the Investigator if it is judged that participant is non-compliant to study assessment and schedule and it can cause safety concerns.
- Protocol deviation:
  - Subject entered in the study in violation of the protocol.
  - Any deviations from the protocol-prescribed dose regimen and/or dose delay for the study drug.
  - Participant can be withdrawn from trial after consultation with the sponsor, if participant's continued participation in trial affects his/her safety due to protocol deviation
- Pregnancy: A female participant with pregnancy will be withdrawn from the trial.
- Lost to follow-up
- Death

If the participant withdraws consent for disclosure of future information, the sponsor can retain and continue to use any data collected before such a withdrawal of consent.

The Investigator will discuss the appropriate therapy with each participant who withdraws early from this study. Determination of the appropriate follow-up therapy will be left to the discretion of the Investigator.

Study Assessments:
Various assessment related to PK, PD, safety, immunogenicity and efficacy will be performed at time points mentioned in SoA.

Efficacy assessment includes DXA, lateral spine X-ray, and clinical fractures.

Safety assessment includes physical examination with vital signs, ECGs, clinical safety laboratory assessment, periodontal examination and immunogenicity. Denosumab levels will be assessed by validated method. Serum CTX and Serum P1NP will be the pharmacodynamic biomarker for denosumab.

Sampling Schedule for PK and PD evaluation
Sample collection after first dose and prior to second dose:

The venous blood samples will be withdrawn at pre-dose (0.000 hour) and at 4.000, 12.000 (Day 1), 24.000 (Day 2), 48.000 (Day 3), 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 168.000 (Day 8), 216.000 (Day 10), 240.000 (Day 11), 264.000 (Day 12), 312.000 (Day 14), 360.000 (Day 16), 408.000 (Day 18), 504.000 (Day 22), 624.000 (Day 27), 792.000 (Day 34), 1008.000 (Day 43), 1344.000 (Day 57), 1680.000 (Day 71), 2016.000 (Day 85), 2352.000 (Day 99), 2688.000 (Day 113), 3024.000 (Day 127), 3360.000 (Day 141), 3840.000 (Day 161), 4320.000 (Day 181) hours post dose following first dose administration.

Sample collection after second dose: The venous blood samples will be withdrawn at 5040.000 (Day 211; Month 7), 5760.000 (Day 241; Month 8), 6480.000 (Day 271; Month 9), 7200.000 (Day 301; Month 10), 7920.000 (Day 331; Month 11), and 8640.000 (Day 361; Month 12) hours post dose following first dose administration.

Sample collection after third dose: The venous blood samples will be withdrawn at pre third dose, 24.000 (Day 2), 720.000 (Day 31), 1440.000 (Day 61), 2160.000 (Day 91), 2880.000 (Day 121), 3600.000 (Day 151) and 4320.000 (Day 181) hours post dose following third dose administration.

Sampling Schedule for Immunogenicity evaluation
8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre-dose (baseline), at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361 with respect to first dosing.

8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre- third dose (baseline), at day 2, 31, 61, 91 and 181 with respect to third dosing.*Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration and day 361 before 3rd dose administration respectively.

Bioanalytical Procedure:
The PK measurement, PD analysis and Immunogenicity assessment will be performed by using validated bioanalytical methods and according to the bioanalytical laboratory's standard operating procedures and applicable regulatory requirements.

Note: Samples for PD evaluation [CTX and P1NP] should be collected in the morning under fasting condition.

Pharmacokinetic Parameters

The following pharmacokinetic parameters will be computed for denosumab.

- Primary PK Parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first-dose
- Secondary PK Parameters: T_{max}, AUC_%Extrap_obs, λ_z, V_d/F, Cl/F, and $t_{1/2}$ of denosumab after first dose; T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_z, and $t_{1/2}$ of denosumab after second and individual patient's PK parameters after third dose

Pharmacodynamic Parameters

For Serum C-terminal telopeptide (CTX):

- Primary PD Parameters: E_{max} and $AUEC_{0-t}$ after first dose (These will be primary parameters for EMA Submission only)
- Secondary PD Parameters: T_{max} after first dose; T_{max}, E_{max} and $AUEC_{0-t}$ after second and individual patient's PD parameters after third dose

For Serum N-terminal propeptide of type 1 collagen (P1NP):

- Secondary PD Parameters: T_{max}, E_{max} and $AUEC_{0-t}$ after first, second and individual patient's PD parameters after third dose

Note: Pharmacodynamic effect for Serum C-terminal telopeptide (CTX) and Serum N-terminal propeptide of type 1 collagen (P1NP) will be assessed as decrease from the baseline.

Populations for Analyses

Analysis populations are defined as below.

- Safety set: The safety set is defined as all randomized patients who will receive at least one dose of study medication.
- Pharmacokinetic (PK) set: The PK set is defined as all patients who will complete the study and has no major protocol deviation which can significantly influence the pharmacokinetic parameter estimation.
- Pharmacodynamic (PD) set: The PD set is defined as all patients who will complete the study and has no major protocol deviation which can significantly influence the pharmacodynamic parameter estimation.
- Intent-To-Treat (ITT) set: The ITT set is defined as all randomized patients who will receive at least one dose of study medication.

  Sensitivity analysis will be performed on patients in ITT set for primary endpoint mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months. For this analysis, missing values of individual BMD of lumbar spine at 12 months will be imputed with value as baseline value ± 0.73 (i.e. half of equivalence limit 1.45 considered in the study). Imputation will be done with value as (baseline value - 0.73) for test and (baseline value + 0.73) for reference product. Additionally, imputation will be done with value as (baseline value + 0.73) for test and (baseline value - 0.73) for reference product.
- Modified Intent-To-Treat (mITT) set: The mITT set is defined as all randomized patients who will receive at least one dose of study medication and will undergo at least one post-dose efficacy evaluation. Missing data will be imputed using last observation carried forward (LOCF) and other techniques if requested by the regulatory agency.
- Per-protocol (PP) set: The PP set is defined as all randomized patients who will complete the study with no major protocol deviations.

Statistical Analysis

Descriptive statistics will be reported for pharmacokinetic and pharmacodynamic parameters.

Baseline and demographic characteristics will be summarized using descriptive statistics by treatment. Categorical variable will be summarized with frequency distribution. Continuous variables will be summarized with mean, standard deviation, median, minimum and maximum.

ANOVA, 90% confidence interval, power and ratio analysis will be computed for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose.

ANOVA, 90 & 95% confidence interval, power and ratio analysis will be computed for ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Bioequivalence criteria (PK and PD)

For USFDA:

Based on the statistical results of 90% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for denosumab after first dose, conclusion will be drawn for Test Product-T vs. Reference Product-R.

Bioequivalence of the test product with that of the reference product will be concluded, if 90% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose.

For EMA:

Based on the statistical results of 90% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for denosumab after first dose and 95% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ for % reduction from baseline Serum C-terminal telopeptide (Serum CTX) after first dose, conclusion will be drawn for Test Product-T vs. Reference Product-R.

Bioequivalence of the test product with that of the reference product will be concluded, if 90% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose and 95% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) after first dose.

Efficacy/ Pharmacodynamic Analysis

The primary endpoint is mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months. A point estimate and a two-sided 95% confidence interval will be computed for the treatment groups and their differences. 95% CI will be calculated using ANCOVA considering baseline as a covariate. Descriptive statistics for mean percentage change in BMD at lumber spine from baseline to 12 months will be calculated. Independent t-test will be used to evaluate the between-treatment comparison.

Acceptance criteria: Therapeutic equivalence of the test with the reference treatment will be concluded if the 95% CI of the difference between test and reference for mean percentage change in BMD at lumber spine from baseline to 12 months is within the range of ± 1.45.

Note: Therapeutic equivalence of the test with the reference treatment will be claimed on ITT set for USFDA and on PP set for EMA.

Secondary endpoints of the study will be analyzed as below:

Descriptive statistics for mean percentage change in BMD of lumber spine from baseline to 06 months and mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months will be calculated presented. Independent t-test will be used to evaluate the between treatment comparison.

Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) and in serum CTX concentrations from baseline to 06 and 12 months will be calculated and reported.

Fracture incidence rate will be provided and compared. Incidence of anti-denosumab antibody at respective visits will be presented.

Safety data collected after 12 months will be presented in separate tables and listings.

Ethical Issues
The trial will be conducted in accordance with this protocol and will comply with all requirements regarding the obligations of investigators and all other pertinent requirements of the ICH E6 (R2) Guideline on Good Clinical Practice; New Drugs & Clinical Trial Rules, 2019 of Central Drugs Standard Control Organization (CDSCO); Declaration of Helsinki (Fortaleza, 2013); as per any other applicable regulatory requirements.

1.2. Schema

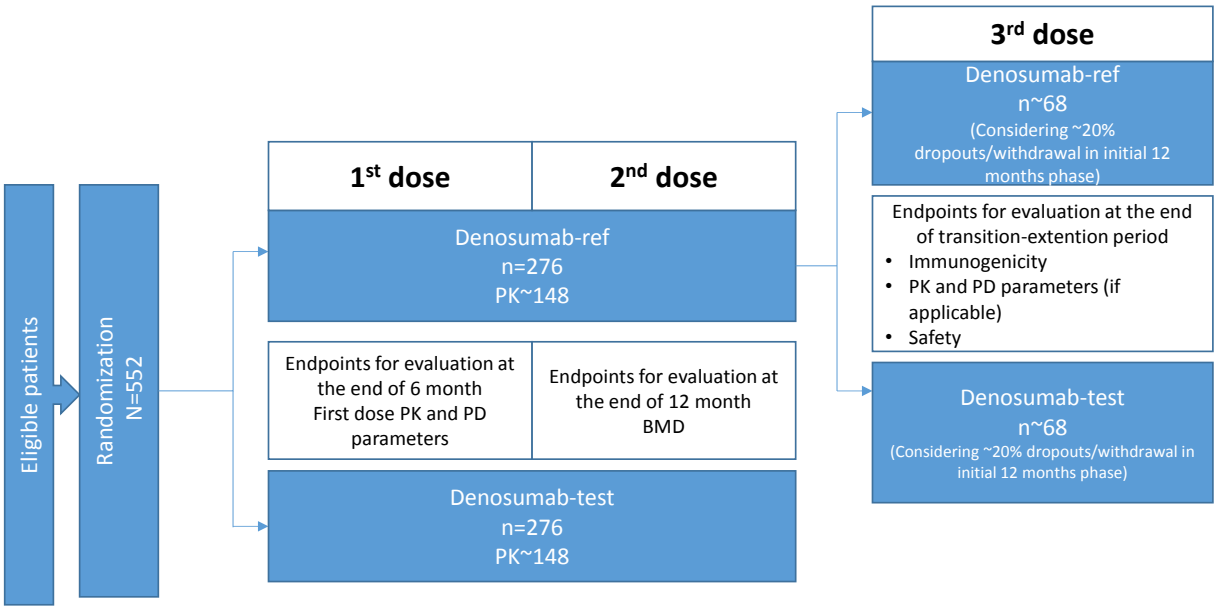

Figure 1. Study Schema

1.3. Schedule of Activities (SoA)

Table 1. Schedule of Activities

Phase	Screening	Treatment Period														Transition-extension period*				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOS)**	**16**	**17**	**18**	**19**	**20 (ET)**
End of Month	**-**	**-**	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**-**	**-**	**-**	**-**	**-**
Days	**-21 to -1**	**1**	**14**	**31**	**61**	**91**	**121**	**151**	**181**	**211**	**241**	**271**	**301**	**331**	**361**	Any day within 21 days after EOS visit	Day 31 after last visit	Day 61 after last visit	Day 91 after last visit	Day 181 after last visit
Window period for visit (± days)	**0**	**0**	**0**	**1**	**3**	**3**	**3**	**3**	**14**	**3**	**3**	**3**	**3**	**3**	**3**	**5**	**5**	**5**	**5**	**5**
General / administrative																				
Informed consent (ICF)[a]	X																			
Inclusion and exclusion criteria[b]	X	X[c]																		
Demography	X																			
Medical history[d]	X																			
Past treatment history	X	X																		
Instruction for daily vitamin D and calcium supplementation	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests																				
Hepatitis B and C, HIV	X																			
Hematology, Biochemistry	X					X			X			X			X	X				X
Urine analysis	X					X			X			X			X	X				X
Serum PTH 1-84	X																			
Serum TSH	X																			
Albumin-adjusted calcium	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum FSH (if required)	X																			
25 (OH) Vitamin D	X					X			X			X			X	X				X
Serum pregnancy	X																			
Safety Assessments																				
Full physical examination	X	←==========Targeted physical examination driven by signs and symptoms==========→																		

Phase	**Screening**	**Treatment Period**														**Transition-extension period***				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOS)**	**16**	**17**	**18**	**19**	**20 (ET)**
End of Month	**-**	**-**	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**-**	**-**	**-**	**-**	**-**
Days	**-21 to -1**	**1**	**14**	**31**	**61**	**91**	**121**	**151**	**181**	**211**	**241**	**271**	**301**	**331**	**361**	Any day within 21 days after EOS visit	Day 31 after last visit	Day 61 after last visit	Day 91 after last visit	Day 181 after last visit
Window period for visit (± days)	**0**	**0**	**0**	**1**	**3**	**3**	**3**	**3**	**14**	**3**	**3**	**3**	**3**	**3**	**3**	**5**	**5**	**5**	**5**	**5**
Periodontal examination[f]	X	←========== At (a) EOS visit and (b) when clinically required ==========→																		
Height (At V1) and Weight	X			X					X							X				X
12-lead ECG	X	←========== when clinically required ==========→																		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Lifestyle restrictions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray[h]	X																			
Study specific assessments for efficacy																				
DXA for BMD (Lumbar spine, total hip, femoral neck)[i]	X								X						X					X
Thoracic and Lumbar Spine X-ray[j]	X	←==========At (a) EOS visit (B) ET visit and (c) when clinically required ==========→																		
Immunogenicity[k]		X	X	X	X	X			X	X	X	X			X	X	X	X	X	X
Clinical Pharmacology Assessments (PK & PD sampling)																				
Blood sample collection for PK & PD assessment[l]		←==========→																		
Study IMP Administration																				
Randomization		X														X[e]				
IMP Administration		X							X							X*				
Injection site assessment[m]		X							X							X*				
Ongoing Participant Review																				
AE		X	←==========→																	
SAE		X	←==========→																	
Concomitant medication		X	←==========→																	

Phase	Screening	Treatment Period														Transition-extension period*				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOS)**	**16**	**17**	**18**	**19**	**20 (ET)**
End of Month	**-**	**-**	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**-**	**-**	**-**	**-**	**-**
Days	**-21 to -1**	**1**	**14**	**31**	**61**	**91**	**121**	**151**	**181**	**211**	**241**	**271**	**301**	**331**	**361**	Any day within 21 days after EOS visit	Day 31 after last visit	Day 61 after last visit	Day 91 after last visit	Day 181 after last visit
Window period for visit (± days)	**0**	**0**	**0**	**1**	**3**	**3**	**3**	**3**	**14**	**3**	**3**	**3**	**3**	**3**	**3**	**5**	**5**	**5**	**5**	**5**

Footnotes:
EOS: End-of-Study Visit; ET: End of transition extension period visit. 1 month is 30 days.
*****Only applicable for the study participants who (a) will be randomized in reference arm ***AND*** (b) have completed PK assessments during 12-month treatment period. Separate consent will not be taken for entering in to transition extension period, consent for the transition extension period will be taken at screening visit only.

a. Must be signed before first study-related activity.
b. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 10.1.8, Regulatory, Ethical, and Study Oversight Considerations.
c. Recheck eligibility criteria as applicable at baseline.
d. Medical history includes substance usage, smoking status, alcohol consumption, past history of fracture, history of hip fracture in parents.
e. Data for patients must be frozen before initiating the transition-extension period randomization so to ensure blinding for initial 12-month study is not affected. Considering that all data entry needs to be completed before randomization for transition-extension period, patient can be randomized in the transition-extension period for up to 21 days after completion of EOS visit of double-blind period of the initial 12 months study.
f. Periodontal examination to rule out risk factors for ONJ at screening and as clinically required during study including switching period as applicable.
g. Pre-dose vitals: Within 1 hour prior to each dosing in clinical facility
h. Chest X-ray (PA view), if not done in last 3 months.
i. DXA scan performed in the past will not be considered during screening for eligibility assessment. Bone mineral density will be measured using DXA scan will be performed exclusively for screening and eligibility criteria assessment at the lumbar spine, total hip during screening period. Screening DXA will be used as baseline DXA.
j. Additional lateral spine X-rays may be taken in cases of a suspected clinical vertebral fracture.
k. Immunogenicity sampling at Pre-dose (baseline), at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361. For switching period, additional samples will be collected at Pre-third dose (baseline), at day 2, 31, 61, 91 and 181 with respect to third dosing.
Note: Blood sample for immunogenicity on day 181 and 361 will be collected prior to 2nd & 3rd dose administration.
l. Serum C-terminal telopeptide for type I collagen [CTX] and Serum N-terminal propeptide of type 1 collagen [P1NP] for bone resorption and serum denosumab for PK in hours at pre-dose (0.000 hour) and at 4.000, 12.000 (Day 1), 24.000 (Day 2), 48.000 (Day 3), 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 168.000 (Day 8),

Phase	Screening	Treatment Period														Transition-extension period*				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (EOS)**	**16**	**17**	**18**	**19**	**20 (ET)**
End of Month	**-**	**-**	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**-**	**-**	**-**	**-**	**-**
Days	**-21 to -1**	**1**	**14**	**31**	**61**	**91**	**121**	**151**	**181**	**211**	**241**	**271**	**301**	**331**	**361**	Any day within 21 days after EOS visit	Day 31 after last visit	Day 61 after last visit	Day 91 after last visit	Day 181 after last visit
Window period for visit (± days)	**0**	**0**	**0**	**1**	**3**	**3**	**3**	**3**	**14**	**3**	**3**	**3**	**3**	**3**	**3**	**5**	**5**	**5**	**5**	**5**

216.000 (Day 10), 240.0000 (Day 11), 264.000 (Day 12), 312.000 (Day 14), 360.000 (Day 16), 408.000 (Day 18), 504.000 (Day 22), 624.000 (Day 27), 792.000 (Day 34), 1008.000 (Day 43), 1344.000 (Day 57), 1680.000 (Day 71), 2016.000 (Day 85), 2352.000 (Day 99), 2688.000 (Day 113), 3024.000 (Day 127), 3360.000 (Day 141), 3840.000 (Day 161), 4320.000 (Day 181) (before the second dose), and at 5040.000 (Day 211; Month 7), 5760.000 (Day 241; Month 8), 6480.000 (Day 271; Month 9), 7200.000 (Day 301; Month 10), 7920.000 (Day 331; Month 11), and 8640.000 (Day 361; Month 12) hours after the first dose. The venous blood samples will be withdrawn at pre third dose, 24.000 (Day 2), 720.000 (Day 31), 1440.000 (Day 61), 2160.000 (Day 91), 2880.000 (Day 121), 3600.000 (Day 151) and 4320.000 (Day 181) hours post dose following third dose administration. Post dose samples during the whole study will be collected on ambulatory basis. Only through PK sample will be collected along with immunogenicity sample.

Note: Samples for PD evaluation [CTX and P1NP] should be collected in morning under fasting condition.

m. Injection site assessment will be performed after every injection at 30 minutes (± 5 min) post dose.

2. Introduction

Denosumab of Intas is biosimilar denosumab candidate under development by Intas Pharmaceutical Limited (Biopharma Division). Denosumab of Intas is already approved by Indian drug licensing authority- Drug Controller General (India) for marketing in Indian population since 2018.

2.1. Background

Osteoporosis is characterized by low bone mass, microarchitectural disruption, and skeletal fragility, resulting in decreased bone strength and an increased risk of fracture. Decreased bone strength is related to many factors other than bone mineral density (BMD), including rates of bone formation and resorption (turnover), bone geometry (size and shape of bone), and microarchitecture. The World Health Organization (WHO) has defined diagnostic thresholds for low bone mass and osteoporosis based upon BMD measurements compared with a young adult reference population (T-score).

The common therapeutic approach is to decrease bone loss with the use of antiresorptive agents such as estrogens, selective estrogen receptor modulators (SERMs) and bisphosphonates, anabolic agents like PTH (analogues)- teriparatide, abaloparatide; sclerostin inhibitor- romosozumab; RANKL inhibitor- denosumab.

Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

For detailed information regarding denosumab of Intas, refer to the Investigator's Brochure (IB) of denosumab of Intas. For detailed information regarding Prolia®, refer to the latest prescribing information / summary of product characteristics of Prolia.

2.2. Study Rationale

As per regulatory requirement, a comparative clinical study to establish Pharmacokinetic, Pharmacodynamic and Immunogenicity equivalence is required to conclude therapeutic equivalence to obtain marketing authorization of a biosimilar investigational product. This is a multicenter, randomized, double-blind, active-controlled study in approximately 552 postmenopausal women with osteoporosis. FDA specifically requested for assessment of immunogenicity after switching from denosumab-ref. Hence the subset of patients who were included for PK, on denosumab-ref, will be shifted to denosumab-ref or denosumab, and then assessed for immunogenicity.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of denosumab [denosumab and denosumab-ref] may be found in the Investigator's Brochure for denosumab and Summary of Product Characteristics for denosumab-ref. Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with denosumab and denosumab-ref are justified by the anticipated benefits that may be afforded to participants with postmenopausal osteoporosis.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the pharmacokinetic parameters of denosumab and denosumab-ref in postmenopausal women with osteoporosis.	• Pharmacokinetics: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ after first dose of denosumab and denosumab-ref
To compare the pharmacodynamic effect of treatment with denosumab and denosumab-ref on bone mineral density (BMD) and bone resorption marker in postmenopausal women with osteoporosis*	• Mean percentage change in BMD at lumbar spine from baseline to 12 months between denosumab and denosumab-ref • Pharmacodynamics: E_{max} and $AUEC_{0-t}$ of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab-ref***** *****To be considered as secondary endpoint for USFDA submission.
Secondary	
To compare the efficacy of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Incidence of clinical fracture between denosumab and denosumab-ref over 12 months.
To compare the pharmacodynamic effects of the treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 06 months between denosumab-test and denosumab-ref • Mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months between denosumab and denosumab-ref • Pharmacodynamics: T_{max} of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab-ref • Pharmacodynamics: E_{max}, $AUEC_{0-t}$,T_{max} of % reduction from baseline serum N-terminal propeptide of type 1 collagen (P1NP) after first dose of denosumab and denosumab-ref • Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref • Mean percentage reduction in CTX serum concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref

To compare the immunogenicity of denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Incidence of anti-denosumab antibody in denosumab and denosumab-ref arm over 12 months.
To compare the safety of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis	• Monitoring of adverse events and lab parameters in denosumab and denosumab-ref arm
To evaluate the safety and immunogenicity of denosumab and denosumab-ref after single transition from denosumab-ref to denosumab and denosumab-ref in postmenopausal women with osteoporosis* *To be considered as secondary endpoint for USFDA submission.	• Incidence of anti-denosumab antibody in denosumab and denosumab-ref arms after single transition from denosumab-ref • Assesment for difference in PK or PD in patients who are found to be immunogenic • Monitoring of adverse events and lab parameters in denosumab and denosumab-ref arm arms after single transition from denosumab-ref

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

3.1. Hypothesis

The primary clinical hypothesis is that in postmenopausal women with osteoporosis, the primary pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ after first dose of denosumab will be equivalent to denosumab-ref. Likewise, the primary pharmacodynamics parameter (Only for EMA) E_{max} and $AUEC_{0-t}$ of % reduction from baseline serum CTX after first dose of denosumab will be equivalent to that of those receiving denosumab-ref. It is further hypothesized that mean percentage change in BMD of lumbar spine from baseline to 12 months in participants receiving denosumab will be equivalent to that of those receiving denosumab-ref. The safety hypothesis is that the safety profile of denosumab will be similar to denosumab-ref in women with osteoporosis.

4. Study Design

4.1. Overall Design

This is a randomized, double-blind, active-controlled, parallel-arm, multicenter study comparing the pharmacokinetics, pharmacodynamics, safety, immunogenicity, and clinical efficacy of denosumab of Intas (60 mg/ml) with Prolia in postmenopausal women with osteoporosis between the ages of 55 to 90 years.

Approximately 552 participants will be randomized in a 1:1 ratio to receive denosumab or denosumab-ref, in a blinded fashion for the duration of the 12-month treatment period. All randomized patients will be undergoing efficacy (BMD and fracture incidence), safety and immunogenicity assessment at specified sampling schedule according to Section 8.

All 552 patients (276 patients per arm) will be evaluated for BMD and immunogenicity assessment for initial 1-year treatment.

Approximately 296 patients (148 patients per arm) per arm will be enrolled for the PK assessment and PD biomarker (CTX) assessment for initial 1-year treatment.

136 patients (68 patients per arm) will be included in the immunogenicity assessment for extension 6-month phase of the study.

For the transition-extension period (Single switch from denosumab-ref arm):
This randomized, double-blind, transition-extension period is to investigate the safety, tolerability, immunogenicity, and efficacy (BMD and fracture incidence) of denosumab in participants with postmenopausal osteoporosis who transitioned from the denosumab-ref arm, compared with subjects who continue with denosumab-ref treatment after completion of double-blind period of the initial 12 months study. After completion of 12 months of treatment period, only participants who are (a) randomized in reference arm ***AND*** (b) have undergone PK assessments during double-blind period of the initial 12 months study will be re-randomized for transition-extension period. Data for patients must be frozen before initiating the transition-extension period randomization so to ensure blinding for initial 12-month study is not affected. Considering that all data entry needs to be completed before randomization for transition-extension period, patient can be randomized in the transition-extension period for up to 21 days after completion of EOS visit of double-blind period of the initial 12 months study.

At Month 12, participant meeting criteria described above from the randomized, double-blind period of the initial 12 month study will be randomized again in a 1:1 ratio to either continue on denosumab-ref or be transitioned/switched to denosumab for additional 6 months (single dose of denosumab). Study participants will receive single-dose of denosumab 60 mg of either denosumab or denosumab-ref at Month-12. Subject safety and immunogenicity will be assessed in all subjects at Month 15 and 18; BMD will be assessed at Month 18. Assumption is approximately 120 patients in denosumab-ref arm who would have undergone PK assessments will be completing double-blind period of the initial 12 months study and will be randomized in the transition-extension period (~68 in denosumab-ref and ~68 in denosumab). The PK, PD samples collected in these patients will be assessed for impact of immunogenicity on PK and PD only if there is immunogenicity identified in a particular patient either clinically or by immunogenicity bioanalysis.

Study participants who withdraw from the transition-extension period will be asked to return to the site for the ET Visit procedures to be performed. At the ET visit, participants will undergo all procedures they would have undergone at Month 18.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

4.2.1. Trial Design

As per regulatory requirement, a comparative clinical study to establish Pharmacokinetic, Pharmacodynamic and Immunogenicity equivalence is required to conclude therapeutic equivalence to obtain marketing authorization of a biosimilar investigational product. This is a multicenter, randomized, double-blind, active-controlled study in approximately 552 postmenopausal women with osteoporosis. The primary objective of study designed to prove the pharmacokinetics and pharmacodynamics equivalence of denosumab with denosumab-ref after the first dose. In addition, the study will assess the effect of treatment with denosumab compared with denosumab-ref on BMD of lumbar spine from baseline to 06 and 12 months.

From screening to end of study (EOS visit) and during transition-extension period, study participants will be supplied with supplementary products containing at least 1000 mg calcium and at least 400 IU vitamin D (in containers with required number of tablets to suffice until next visit, including additional tablets for the window period) throughout the study at defined intervals.

4.2.2. Selection of Endpoints

Primary endpoints are Mean percentage change in bone mineral density (BMD) at lumbar spine from baseline to 12 months, pharmacokinetics (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of denosumab) and pharmacodynamics ($AUEC_{0-t}$ of % reduction from baseline serum CTX) after first dose of IMP.

According to USFDA[1] and EMA guidelines[2] for biosimilars these endpoints are justified to compare and assess efficacy, PK and PD profile of denosumab.

The co-primary endpoints mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months which is also in line with the guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis[3].

Incidence of anti-denosumab antibody in denosumab and denosumab-Ref arms at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361 in line with EMA guidelines and for switching period, additional samples will be collected at), at day 2, 31, 61, 91 and 181 after third dosing is also in line with USFDA guidelines for biosimilars to compare the immunogenicity.

4.2.3. Blinding, Control, Study Phase/Periods, IMP Groups

An active control is used to determine the sensitivity of the pharmacodynamic, pharmacokinetic and surrogate endpoints in this study. Randomization will be used to minimize bias in the assignment of participants to IMP groups, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across IMP groups, and to enhance the validity of statistical comparisons across IMP groups. Blinded IMP will be used to reduce potential bias during data collection and evaluation of pharmacodynamic, pharmacokinetic and surrogate endpoints.

Detailed information of blinded and unblinded study person have been mentioned in section 6.3.

4.2.4. Selection of the Trial Population

At menopause, estrogen deficiency impairs the normal cycle by increasing osteoclastic resorption activity without a corresponding increase in osteoblastic activity and the amount of bone resorbed therefore is greater than the amount deposited leading to a net loss of bone. Study population chosen to be included in the current study will be in line with previous studies and approved indication of Prolia[4,5] as well as in general representative of population in real-world use in whom denosumab is prescribed by physician. Prolia® is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy[5].

The guidelines for prevention and treatment of osteoporosis in general indicate age, sex, low body mass index, previous fragility fracture, low BMD, parental history of hip fracture, glucocorticoid treatment, current smoking, alcohol intake of 3 or more units daily, and causes of secondary osteoporosis as major risk factors for osteoporotic fracture.[6]

American Association of Clinical Endocrinologists/ American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update[7], defines patient with osteoporosis as *"T-score of −2.5 or lower in the lumbar spine (antero-posterior), femoral neck, total hip, or 1/3 radius (33% radius), even in the absence of a prevalent fracture*". It also further defines patients with osteoporosis at high risk of fracture as following: *"R23:Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than −3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk."* Regarding need of pharmacotherapy it further states "*Pharmacologic therapy is strongly recommended for patients with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius."*

In registration study of denosumab for treatment of osteoporosis- FREEDOM trial, postmenopausal female aged 60-90 years with BMD T Score of at least -2.5 but not lower than -4.0 were included. Radiologic evidence of baseline vertebral fracture was not required (CDTL review of BLA 125,320/125,331 denosumab page no.16).[8]

Considering above criteria, population planned for enrollment in our study represents high risk of osteoporosis (postmenopausal women, BMD T score of -2.5 to -4.0, aged 55-90 years with exclusion of patient with either 1 severe or 2 moderate vertebral fracture) and it is in line with innovator registration trial as well as current practice guidelines.

4.2.5. Choice of Control Group

Prolia is an approved biologic in the USA and EU for treatment of osteoporosis in postmenopausal women. denosumab is being developed as a biosimilar to Prolia.

4.2.6. Study-Specific Ethical Design Considerations

Thorough scientific evaluation of any promising IMP before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure.

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

As with all clinical and PK studies, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of intravenous indwelling catheters is permitted in this study. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the PK, PD and immunogenicity of the study IMP. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. This is an acceptable amount of blood within physiological limits and to be collected over this time period from the population in this study based upon the standard of the ICMR guidelines.[9]

4.2.7. Concomitant Medication

The doses and overall treatment regimens for two of the concomitant medications used as non-investigational medicinal products during this trial, i.e. calcium and vitamin D products, are according to the recommendations in the respective products' labelling for the indication of reference drug as well as in line with clinical practice guidelines.

4.3. Justification for Dose

Participants randomised in the study will be dosed according to the approved labelling of reference drug, Prolia. The recommended dose of Prolia is 60 mg administered as a subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. During this study, total 2 doses of 60 mg/mL subcutaneous injections of denosumab will be administered.

4.4. End of Study Definition

Study Completion Definition

A participant is considered to have completed the study if she has completed all assessment of the study at 12 months or 18 months as applicable.

End of Study Definition

The end of study is considered as the date of the last scheduled study assessment shown in the Schedule of Activities or for the last participant in the study globally. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

5. Study Population

Screening for eligible participants will be performed within 21 days before administration of the study IMP. Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. These documents can be made available for review in redacted electronic forms. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the medical monitor and resolve any issues before enrolling a participant in the study. Waivers are not allowed to be used. The Investigator will be authorized to randomize/enroll the participants upon review and approval of eligibility criteria by the study Medical Monitor.

For a discussion of the statistical considerations of participant selection, refer to Section 9.1.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria are met:

1. Participant must sign an ICF to participate in the study indicating that she understands the purpose of, and procedures required for the study as described in this protocol and is willing to and will be able to adhere to requirement of the protocol.
2. Participant must be 55 to 90 years of age (both inclusive), at the time of signing the informed consent.
3. Participants who are medically/clinically stable on the basis of physical examination, medical history, vital signs, chest x-ray PA view, 12-lead ECG and clinical laboratory parameters performed at screening. Any abnormalities or deviation from normal, must be consistent with the underlying illness in the study population and judged by investigator to be not clinically significant. This determination must be recorded in the participant's source documents and initialed by the investigator.
4. Participants whose absolute bone mineral density T-score is $\leq$ -2.5 and $\geq$ -4.0 at the lumbar spine as measured by DXA (dual-energy x-ray absorptiometry), confirmed by the independent central imaging team
5. At least two vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA, confirmed by the independent central imaging team
6. Body weight between 50 kg and 90 kg (both inclusive) at screening.
7. Postmenopausal ambulatory female and not considered to be of child-bearing potential if:
    a. Women are considered post-menopausal and not of child-bearing potential if,

i. They have had 12 months of natural (spontaneous) amenorrhea (no vaginal bleeding or spotting) with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) OR
ii. Six months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL; OR
iii. Have had surgical bilateral oophorectomy (with or without hysterectomy) at least six months ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment if she is considered not of child-bearing potential.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Documented medical history of clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances
2. Documented medical history of known allergies, hypersensitivity, or intolerance to denosumab or its excipients (refer to the IB)
3. History of any prior use of denosumab
4. Documented medical history of metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as Paget's disease, osteomalacia, osteogenesis imperfecta, osteopetrosis, rheumatoid arthritis, ankylosing spondylitis or any other joint disease limiting mobility, Cushing's disease, hyperprolactinemia, malabsorption syndrome
5. Documented medical history of latex or dry natural rubber allergy
6. Contraindications to the use of denosumab or Vitamin D and Calcium as per IB/local prescribing information at screening and/or baseline
7. Documented medical history and/or current evidence of any of the following oral/dental conditions
   a) Prior history or current evidence of osteomyelitis or osteonecrosis of the jaw.
   b) Active dental or jaw condition which requires oral surgery.
   c) Planned invasive dental procedure expected during study period.
   d) Current evidence non-healed dental or oral surgery.
   e) Current evidence of poor oral hygiene
   f) Ill-fitting denture
8. Current hyper- or hypocalcemia, defined as albumin-adjusted serum calcium outside the normal range at screening. Serum calcium levels may be retested once in case of an elevated/low serum calcium level as assessed by the clinical laboratory. Final decision to include the patient based on the risk of hypocalcemia to be taken by the Investigator.
9. History of frequent occurrence of hypocalcemia, history of severe hypocalcemia or presence of diseases that can precipitate hypocalcemia frequently (like malabsorption syndromes (for example celiac disease, history of excision of small intestine etc.) and severe renal impairment)
10. Current, uncontrolled hyper- or hypoparathyroidism and history of hypoparathyroidism, per participant report or chart review. PTH outside the normal range (15-65 pg/mL) as assessed by central laboratory
11. Current, uncontrolled hyper- or hypothyroidism, defined as thyroid stimulating hormone outside of the normal range (TSH-0.465 to 4.68 mIU/L) at screening.

12. 25 (OH) Vitamin D lower than 20 ng/mL as assessed by the central laboratory at Screening. Vitamin D repletion will be permitted, and participants may be rescreened once.
13. History of external beam or implant radiation therapy involving the skeleton.
14. History and /or presence of 1 severe fracture or 2 moderate vertebral fractures
15. Patients with bone metastases or a history of malignancies affecting bones.
16. Smokers or who have smoked within last 06 months prior to start of the study.
17. Documented medical history of major surgery, (e.g. requiring general anesthesia) within 12 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.
    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.
18. Documented medical history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.
19. Documented medical history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.
20. Documented medical history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 1 year before Screening
21. Lymphoma, leukemia, or any malignancy (current or suspected) within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years; carcinoma in situ of the cervix; or malignancy, which is considered cured with minimal risk of recurrence
22. QTc interval >470 msec or QT interval >480 msec in participants with bundle branch block.
    Note: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB). It is either machine-read or manually over-read.
23. Administration of bisphosphonate as follows: -
    c) IV Bisphosphonate in the past 3 years
    d) Oral bisphosphonates treatment for osteoporosis
        i. More than 3 years of cumulative use
        ii. Any dose received within 6 months prior to randomization
        iii. More than 1 month of cumulative use between 6 and 12 months prior to randomization
24. Teriparatide or any PTH analogs treatment received within 12 months prior to randomization.
25. Systemic oral or transdermal estrogen, SERMs, or calcitonin treatment of more than 1 month of cumulative use within 6 months prior to randomization.
26. Androgen deprivation or hormonal ablation therapy of more than 1 month of cumulative use within 6 months prior to randomization.
27. Tibolone or cinacalcet treatment received within 3 months prior to randomization
28. Systemic glucocorticoids: ≥ 5 mg prednisone equivalent per day for more than 10 days within 3 months prior to randomization.
29. Abnormal laboratory values
    a. General: Any laboratory abnormality which, in the opinion of the Investigator, will prevent the patient from completing the study or interfere with the interpretation of the study results.
    b. Liver transaminases:

i. Serum aspartate aminotransferase (AST) ≥3.0 × upper limit of normal (ULN)
ii. Serum alanine aminotransferase (ALT) ≥3.0 × ULN

c. Alkaline phosphatase and bilirubin ≥1.5 × ULN
d. Creatinine clearance estimated using Cockcroft Gault formula is <30 mL/min

30. Taken any prohibited therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study IMP
31. Received any investigational IMP 30 days or 5 half-lives (whichever is longer) before the signing the consent or is currently enrolled in an investigational study
32. Unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. This includes but is not limited to hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the investigator.

    Note: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones) is acceptable if the participant otherwise meets entry criteria.
33. Any other clinical/social/ psychiatric condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
34. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study IMP is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

- Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.

5.3.1. Alcohol and Tobacco

- Alcohol-containing products are not permitted throughout the study period.
- Use of tobacco products/smoking will not be allowed from 6 months before screening until after EOS. Participants will be instructed to abstain from the same.

These details will be captured based on patient history.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study IMP/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information

includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Retesting

At the Screening Visit, the results of the required laboratory tests must be within the limits specified in the inclusion criteria. Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility). The investigator may consider the participant eligible if the previously abnormal laboratory test result is within acceptable range as per inclusion/exclusion criteria, on a repeat testing. Informed consent obtained at the beginning of the screening period also covers the partial rescreening for allowed parameters; therefore, reconsenting is not required.

If the results of clinical laboratory tests are outside the normal reference ranges, the participant may be included only if the Investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the Investigator.

Rescreening

If a participant does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the participant eligibility criteria (in the opinion of the investigator the reason for the initial screen failure has been resolved or is not applicable anymore), the participant may be rescreened once only. Another 21-day rescreening period will start from date that new ICF is signed. Participants who are rescreened will be assigned a new participant number. During full rescreening, all screening procedures have to be performed as defined in SoA. Participants who fail to meet the serum 25 (OH) Vitamin D criterion during the full rescreening may still enter the retesting.

6. Study IMP and Concomitant Therapy

Study IMP is defined as any investigational IMP(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study IMP Administered

The study IMP denosumab, 60 mg, will be provided as pre-filled syringe for subcutaneous injection. Participants will be injected with study IMP at site as defined in SoA.

Table 2. IMP details

ARM Name	denosumab	denosumab-ref
Study IMP Name	Denosumab	Prolia®
Manufacturer	Intas Pharmaceuticals Ltd., India	Amgen Europe B.V. (EU-licensed product)
Dose Formulation	Solution for injection in single-use prefilled syringe	Solution for injection in single-use prefilled syringe
Unit Dose Strength(s)	60 mg/mL	60 mg/mL
Dosage Level(s)	60 mg once every 6 months	60 mg once every 6 months
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental drug	Active comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Study IMP administration must be captured in the source documents and the case report form (CRF).

denosumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Other Protocol-Required Therapies

All other protocol-required drugs (ie, vitamin D and calcium supplements) that are commercially available will be provided by the Sponsor. The investigator will be responsible for obtaining supplies of these drugs.

From screening to end of study, participants will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of at least 1000 mg calcium and at least 400 IU vitamin D. In addition, participants with a serum 25 (OH) Vitamin D level of < 20 ng/mL at screening will be repeated and retested during screening.

Where available, vitamin D3 preparations should be used; if vitamin D3 is not available, use of vitamin D2 preparations is acceptable.

If a participant develops hypercalcemia over the course of the study, the principal investigator may use his/her medical judgment and reduce the calcium and/or vitamin D supplementation to maintain serum calcium concentration within the normal range. If a participant develops hypocalcemia over the course of the study, appropriate additional supplementation should be instituted as deemed acceptable by local guidelines, to maintain serum calcium concentration within the normal range. If a participant is unable to tolerate the daily calcium or vitamin D supplementation, the formulation may be changed, or the dose lowered. The intolerance as well as the resolution (i.e., change in formulation or dosage) should be documented in the source documents.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Investigational Medicinal Product Receipt and Storage

The Sponsor shall supply adequate units of investigational products for dose administration purpose. The received investigational products at CRO pharmacy will be verified for the sealed condition of packs and adequacy of label as per applicable regulatory and other requirements.

Enough quantities of labels will be provided along with the IMP shipment for affixing on the IMP. The labels will be designed to capture all the relevant information as required by the regulatory agency/study.

CRO pharmacy custodian or designated study personnel will ship sufficient quantity of IMP for conduct of the study to respective sites. The shipment of inventory log will be maintained at CRO site.

Preparation/Handling/Storage

All study IMP must be stored at controlled temperatures ranging from 2°C to 8°C (36°F to 46°F). Prior to administration, study IMP may be allowed to reach room temperature (up to 25°C/77°F) in the original packaging. Once removed from the refrigerator, study IMP must not be exposed to temperatures above 25°C/77°F. It should not be frozen or exposed to direct light.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received and any discrepancies are reported and resolved before use of the study IMP.

Refer to the most recent version of IMP manual for additional guidance on study IMP preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study IMP received at the site is inventoried and accounted for throughout the study. The study IMP administered to the participant must be documented on the IMP accountability form. All study IMP will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the study IMP containers.

Only participants enrolled in the study may receive study IMP and only authorized site staff will administer study IMP. All study IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Potentially hazardous materials containing hazardous liquids such as used PFS should be disposed of immediately in a safe manner and therefore will not be retained for IMP accountability purposes.

Study IMP will not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study IMP from, nor store it at, any site other than the study sites agreed upon with the Sponsor. Further guidance and information for the final disposition of unused study IMPs are provided in the most recent version pharmacy manual/study site operational manual.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

6.2.2. Retention Samples

IMP samples will be retained in required amount and at required places as per applicable regulatory guidelines.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Procedures for Screening and Randomization

At the Screening visit, patients enrolling into the study will be assigned a unique screening number. This number will be serially allocated as per the chronological sequence of entering into the trial at each site and will also incorporate the site identity. The specimen of screening number will be combination of Site number like 101, 102, 103……., Project number: 0774-19 and followed by serial number like 01, 02, 03, etc. as per the chronological order of entering of patient at each site. Hence, specimen of screening number will be like 101-0774-19-01, 101-0774-19-02……and so on.

All patients enrolled must be identifiable throughout the study. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff.

Dynamic central randomization will be implemented in conducting this study. At the randomization visit after ensuring that a patient meets all eligibility criteria, participants will be assigned to 1 of 2 IMP groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of participants across IMP groups within the levels of each individual stratification factor: age (≥65, <65) and prior osteoporosis treatment status (present, absent). Based on the algorithm, the IWRS will assign a unique IMP code, which will dictate the IMP assignment and matching study IMP kit for the participant.

Before the study is initiated, the log in information & directions for the IWRS will be provided to each site.

These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list or equivalent mechanism will be produced by or under the responsibility of Lambda Clinical Trial Supply Management using a validated system. The assigned patient number will be recorded in the CRF of the patient. The identification of patient will be based on the kit number.

After completion of 1-year study participants (who are randomized for Reference arm and involved in PK analysis) will be re-randomized on either Test or Reference arm using IWRS for further six month immunogenicity and safety evaluation.

Central randomization schedule will be generated using SAS® Version 9.4 or higher (SAS Institute Inc., USA) or equivalent software before the commencement of the study by the biostatistician who is not involved in the conduct of the study. In case randomization schedule will be prepared by vendor or third party, then same will be generated as per their SOPs.

Unblinded study staff involved in dispensing of study drug and verification of dispensed study drugs will be accountable for ensuring compliance to randomization schedule.

Every attempt should be made for participants to receive their first injection of IP on the day of randomization. If this is not possible, participants must receive the first injection of IP within 72 hours of randomization. A participant will be considered enrolled once a randomization number is assigned. It is therefore very important randomization only after the participant's eligibility and willingness to participate has been confirmed, as the participant cannot be 'unenrolled'.

6.3.2. Procedures of blinding

Instructions provided in this section are overarching description of operational procedures. Investigators are instructed to always refer to latest version of respective study plans/manuals for detailed and latest information.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. The essential aim of masking, therefore, is to prevent identification of the treatments by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

Participant, investigator staff, persons performing the assessments and all other study personnel who could have an impact on the outcome of the study will be blinded to the identity of the treatment from the time of randomization until final database lock after efficacy assessment. All members (except dosing nurse and pharmacist at site) of the site team will be blinded to treatment assignments while the study is in progress. All roles for each study staff member should be clearly documented on the Site Delegation Log. The Delegation Log should be signed by the Principal Investigator. In case a site is experiencing unexpected extreme situations, the Medical Monitor's permission might be granted to switch the study staff member from the blinded to the unblinded.

Dosing nurse and pharmacist at site (unblinded to the treatment assignment): A qualified nurse and pharmacist at site who will be performing all the subcutaneous injections (denosumab) to study participants during the study duration; must not perform any study assessments; will not complete eCRFs and must not be involved in any other aspect of the study or communicate details of the treatment to anyone. The treating nurse should, however, assess subject safety immediately following injection (ie, they will perform the post-injection assessment; the blinded physician/site personnel should not perform this assessment) and record the findings in the source documents. There should not be mentioned of allocation. The treating nurse must be the same throughout the study.

At CRO, there will be separate group of blinded and unblinded study personnel will be created and their role will be clearly defined in project management plan. In brief, there will be clear

separation of roles and responsibilities for blinded and unblinded personnel throughout the study. Personnel who have access to treatment codes (eg, personnel directly involved with bioanalysis of serum samples, unblinded monitors performing IP accountability and logistics, and clinical supplies personnel, etc.) will not divulge the codes to subjects, Investigators, site staff, clinical trial management (CTM), medical monitor, central reading personnel. CRA, personal involved in PK analysis and biostatistician, project manager, CDM team who are directly involved in the conduct of the study will remain blinded to treatment assignments while the study is in progress. If necessary, the sponsor/CRO pharmacovigilance and/or Safety Review Team may be required to unblind a subject if an adverse event (AE) meets criteria of a suspected unexpected serious adverse reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements. In this event, the Sponsor/CRO PV and/or Safety Review Team will not divulge the treatment code to any other personnel involved in reporting, obtaining, and/or reviewing the clinical evaluations. Once the designated masked vs. unmasked roles are delineated and the site study staff have started to perform them, the roles cannot be switched or reversed at any time during the conduct of the study. Refer to project management plan for detailed and current blinding procedures.

Data that may potentially unmask the IMP assignment (i.e., study IMP preparation/accountability data, IMP allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the masking is maintained and the potential for bias is minimized. Unmasking will only occur in the case of participant emergencies (see section 6.3.2.1) and at the conclusion of the study.

Drug dispensing logs, drug accountability forms and other papers identifying treatment allocation are kept in a separate binder in a locked cupboard to which the investigator does not have access. The subject will during the informed consent process be informed, both verbally and in writing, to not disclose her treatment allocation to the investigator. Trial staff is provided training in the importance of maintaining masking, and trial medication delegates/trial coordinators are also helped to set up systems at the clinic.

The sponsor clinical trial team (i.e. data manager, statistician, trial manager, trial coordinator, medical writer, safety monitor and sponsor's responsible medical officer) will be blinded to treatment allocation until breaking of the blinding. The blinding will be broken when the trial database is declared clean and locked.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study IMP records at the site(s) to verify that randomization/dispensing has been done accurately.

There is a risk of unblinding for those patients who were part of PK assessment on denosumab-ref who will be subsequently stratified to either denosumab or denosumab-ref. Every effort will be made to ensure blinding. The key endpoints BMD, CTX, PK and PD are all objective assessments.

6.3.2.1. Emergency unblinding of treatment assignment

As both arms contain the same treatment (denosumab injection), there is very limited possibility of emergency unblinding of treatment assignment. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. The IWRS will be programmed with blinding-breaking instructions. While the responsibility to break the IMP code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its

designee/study medical monitor if possible to discuss the particular situation, before breaking the blinding unless this could delay emergency treatment of the participant. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. If a participant's IMP assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blinding.

The investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, participant number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the participant in case emergency unblinding is required at a time when the investigator and backup are unavailable.

The modalities for opening the blind of the treatment after the data transferred to biostatistics for statistical analysis will be described in statistical analysis plan (SAP). Individual sealed envelope containing participant treatment details will be provided to investigator to break the treatment information in case of emergency. Unblinding at the study site for any other reason will be considered a protocol deviation. Refer to the site operational manual for instructions on process of unblinding. The principal investigator is strongly encouraged to contact the medical monitor before unblinding any participant's treatment assignment but must do so within 1 working day after the event.

An assessment will be done by the appropriate site personnel and the Study Lead after an emergency unblinding to assess whether or not study drug should be discontinued for a given participant.

6.4. Study IMP Compliance

Study IMP will be administered as a subcutaneous injection by qualified study-site personnel. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study IMP and study participant identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study IMP.

Study-site personnel will maintain a log of all study IMP administered. Study IMP supplies for each participant will be inventoried and accounted for.

6.5. Dose Modification

Dose modification is not allowed during the participation of the study.

All efforts should be made to administer study IMP within the defined study visit windows (refer to SoA). If study IMP cannot be administered within the target visit date, the dose has to be considered missed.

If a dose of study IMP is missed, IMP administration will be done only after discussion with medical monitor/sponsor. However, no modification must be done for schedule of assessments and efficacy measurement should be done according to Day 1 of the study.

6.6. Continued Access to Study IMP after the End of the Study

The Sponsor will evaluate the appropriateness of continuing to provide denosumab to participants randomized to study IMP after evaluating the primary efficacy outcome measures and safety data gathered in the study. These analyses may be conducted prior to completion of

the study. Post-trial access will be provided in line with requirement of local regulations and guidelines.

6.7. Treatment of Overdose

For this study, any dose of denosumab greater than 60 mg per dose or dose more frequently than prescribed frequency (with consideration of allowed window period as per protocol) will be considered an overdose.

Overdose with denosumab has not been reported. Neither the effects of overdose of denosumab nor an antidote to overdose are known. Sponsor does not recommend specific treatment for an overdose.

As a general guidance in the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities based on pharmacodynamics of study IMP until 5 half-life of IMP.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding drug discontinuation or withdrawal of participant with overdose will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study IMP to last study visit. Concomitant therapies should also be recorded beyond last study visit only in conjunction with serious adverse events that meet the criteria outlined in Serious Adverse Events in Section 8.6.1.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study IMP must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use including start and stop dates, dosing regimen, route of administration, and indication/reason for use. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Table 3. Prohibited medication

Medications listed below will be prohibited during the study, including the use of other investigational products and medications known or suspected to affect bone metabolism (except calcium and vitamin D).	
Drugs affecting bone metabolism	• Strontium (including strontium ranelate and over-the-counter strontium preparations) • Fluoride (for treatment of osteoporosis)

	• Vitamin K and vitamin K analogues (for treatment of osteoporosis) • Activated vitamin D (1,25-dihydroxyvitamin D or 1-hydroxyvitamin D) • IV bisphosphonates • Oral bisphosphonates (cumulative dosing regimens of ≤ 1 month are acceptable) • Denosumab (other than study drugs) • Teriparatide or any PTH analogs • Systemic oral or transdermal estrogen (cumulative dosing regimens of ≤ 1 month are acceptable, vaginal preparations and estrogen creams will be allowed at any time) • SERMs (cumulative dosing regimens of ≤ 1 month are acceptable) • Calcitonin (cumulative dosing regimens of ≤ 1 month are acceptable) • Tibolone (cumulative dosing regimens of ≤ 1 month are acceptable) • Cinacalcet • Androgen deprivation/hormone ablation therapy or hormone replacement therapy • Prolonged (i.e., >1 months) oral glucocorticoid therapy at a prednisone equivalent dose of ≥5.0 mg/day (tapering glucocorticoid courses of < 1 month duration are permitted regardless of dose; inhaled or topical glucocorticoids are permitted) • Any cathepsin K inhibitor • Any other investigational treatment targeting bone turnover

If a participant receives any prohibited therapy(ies) while being on-study, further IMP administration must be discontinued. However, every effort should be made to have the participant continue participation in the study and complete all activities defined in SoA.

If a participant discontinues IP and begins an approved alternative osteoporosis therapy, every effort should be made to have the participant continue participation in the study and complete all activities defined in SoA.

7. Discontinuation of Study IMP and Participant Discontinuation/Withdrawal

Participant can discontinue study treatment and/or be withdrawn from the study because of the appearance of a new health condition suspected to require appropriate care, unacceptable AEs, refusal to continue treatment, or at the investigator's discretion based on his or her clinical judgment if he/she believes that continuation would be detrimental to the participant's well-being.

7.1. Discontinuation of Study IMP

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study IMP. If a participant discontinues study IMP for any reason before the end of the study, scheduled assessments off study IMP should be continued.

Subjects meeting the following criteria will be withdrawn from the study treatment. All withdrawn subjects from the study treatment will be followed up till the end of study as per schedule of activities.

- The participant withdraws consent to receive study IMP
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study IMP
- Concomitant medications: Consumption of co-medication / requirement to consume co-medication that can affect the safety of the participant continuing in the trial as per the investigator; Consumption of prohibited medication as mentioned in section 6.8

If a participant discontinues study IMP definitely for any reason before the end of the study visit but is still willing to collaborate in providing further data by continuing on study, the participant will remain in the study to be evaluated for further collection of information on primary endpoint as well as immunogenicity. These participants to be provided Standard of Care as per investigator and participant agreement.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Investigator must determine the primary reason for a participant's premature withdrawal from the study and record this information on the eCRF and in the source document. If premature withdrawal from the study occurs for any reason, if possible, End of Study visit as described in Section 1.3 (SoA) should be conducted. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

A participant will be withdrawn from the study for any of the following reasons:

- Consent is withdrawn: Subjects have the right to withdraw from the trial at any time for any reason. If withdrawal occurs, the subject will be requested to come for a complete follow-up examination.

- Non-compliance: The subject may be withdrawn from the trial at the discretion of the Investigator if it is judged that participant is non-compliant to study assessment and schedule and it can cause safety concerns.

- Protocol deviation:
  - Participant entered in the study in violation of the protocol and there is safety concern.
  - Any deviations from the protocol-prescribed dose regimen and/or dose delay for the study drug.
  - Participant can be withdrawn from trial after consultation with the sponsor, if participant's continued participation in trial affects his/her safety due to protocol deviation
- Pregnancy: A female participant with pregnancy will be withdrawn from the trial.
- Lost to follow-up
- Death

If the participant withdraws consent for disclosure of future information, the sponsor can retain and continue to use any data collected before such a withdrawal of consent.

The Investigator will discuss the appropriate therapy with each participant who withdraws early from this study. Determination of the appropriate follow-up therapy will be left to the discretion of the Investigator.

Sponsor or CRO will train the investigators to ensure that there will be no or minimal drop-out of subjects in the trial with in the 12 months of treatment period. Importance of extension of study for the participants who are only randomized in reference arm during 12 months study and involved in PK along with PD assessment, will be communicated and explained to the investigator. The relevance of the generated scientific data will be explained.

7.3. Lost to Follow up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, at least 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). There should be time interval of at least 4 weeks (or justified) between each contact attempt. These contact attempts should be documented in the participant's medical records.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site. Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

Investigator should follow-up with all procedures as per GCP to ensure that there is minimal subject drop-out with in the initial 12 months of treatment. If there is drop-out, every effort should be made to get the patient back in the trial. The effort made by the investigator should be discussed with sponsor and documented. Investigator is expected to ensure 100% follow-up of patients who are re randomized further for 6-month study period. Reasons for missing data, if any, will have to be documented. While consenting, the importance of compliance with the study procedure should be explained to the patients.

8. Study Assessments and Procedures

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, and safety measurements applicable to this study.

- Study assessments and procedures will be performed only after written informed consent is obtained.
- Study assessments and procedures will be captured in detail in study site operation manual.
- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study IMP. (Note: Investigator should assess and intervene immediately for any safety related issues without prior discussion with the medical monitor, however the medical monitor should be updated as soon as possible.)
- 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 participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- IP administration must be the last procedure after all other study visit procedures have been completed.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Schedule of Activities for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

The total blood volume for the study is approximately 407 + 10 mL or 544 + 10 mL as applicable.

Table 4. Volume of blood to be collected from each participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	No. of Samples per following up Participant (entered in Transition-extension period)	Approximate Total Volume of Blood (mL)[a]	Approximate Total Volume of Blood for following up Participant (mL)[a] (entered in Transition-extension period)
Safety (including screening and post-IMP assessments)					
Hematology	2	5	7	10	14
Serum chemistry	6	5	7	30	42

Serology	2	1	1	2	2
Serum β-hCG pregnancy tests	2	1	1	2	2
Albumin-adjusted calcium	2	14	19	28	38
25 (OH) Vitamin D	2	5	7	10	14
Efficacy					
Pharmacokinetic samples	3.5	34	42	119[c]	147[c]
Pharmacodynamic samples	3.5	34	42	119[d]	147[d]
Immunogenicity	8.5	10	16	85	136
Loss by use of indwelling intravenous cannula	0.5	4	4	2	2
Approximate Total[b]				407[e]	544 [e]

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Repeat or additional unscheduled samples may be taken for additional analysis for safety reasons or technical issues with the samples.
c. Only applicable to those participants who are going for assessment of PK.
d. Only applicable to those participants who are going for assessment of PD.
e. Total blood loss will be applicable according to participation of patient in PK and PD assessment (Transition-extension period).
Note: An indwelling intravenous cannula may be used for blood sample collection.

8.1. Study Procedure

All study procedures and the timing when they must be performed are detailed in the Section 1.3 (SoA). All data obtained for these assessments must be supported in the participants' source documentation. Investigators are instructed to always follow latest version of study plans/ manual for detailed information.

Prior to undergoing any study specific procedures participants must read and sign the consent form. All study procedures and the timing when they must be performed are detailed in the Section 1.3. All data obtained for these assessments must be supported in the participants' source documentation.

This study will be initiated only after getting required permission from regulatory authority and Institutional/Independent Ethics Committees and after registration with the Clinical Trial Registry, India. Prior to study initiation, all the investigators will be made familiar with the requirements and obligations of Good Clinical Practices (GCP). Investigators and other site personnels will undergo study-specific training before the initiation of trial. The study will be carried out according to the protocol in accordance with declaration of Helsinki and CDSCO "Good Clinical Practice" guidelines after approval from IEC/IRB.

Written informed consent will be obtained from each participant prior to screening for the study. If the participant is unable to read/write, an impartial witness should be present during the entire informed consent process, which must provide his/her signature in consent form.

The screening date is defined as the date the ICF is signed. The enrollment date is defined as the date of randomization. Day 1 is defined as the day the first dose of study IMP is administered. All on-study (post Day 1) visits are to be calculated from the Day 1 visit. If a participant's visit is delayed, their subsequent visit date is not to be shifted, and is always to be calculated from the Day 1 visit. Study procedures for a specific visit may be completed on multiple days as long as all the procedures are completed within the visit window.

8.2. Hospitalization

Hospitalization is a not a requirement of protocol. Considering that PK and PD are co-primary endpoints, it is important that investigators adhere to the timepoint described for PK and PD

samples. If investigator consider 24-48 hours housing to ensure the adherence to the PK and PD sampling schedule due to logistic or administrative issues, this hospitalization will not be considered an SAE.

8.3. Unscheduled Visits

During the trial, in case of need, the participant can visit the study center and/or contact the investigator on any day apart from the scheduled day of visit. If required, the participant will be investigated and treated as per the Investigator's discretion. All relevant details of such unscheduled visits/contacts will be documented in the eCRF.

8.4. Efficacy Assessments

8.4.1. Evaluations

8.4.1.1. Dual-energy X-ray Absorptiometry

Bone density measurements will be performed by DXA. The same DXA machine must be used for all study procedures for a particular participant for the duration of the study. Eligibility will be determined by a central DXA reading. All on-study DXA scans will be submitted to and analyzed by the central imaging vendor. A separate procedure manual provided by the central imaging vendor will give specific instructions for acquisition of scans as well as performance of Instrument Quality Control.

DXA scan performed in the past will not be considered during screening. Bone mineral density will be measured using DXA scan will be performed exclusively for screening and eligibility criteria assessment at the lumbar spine, total hip during screening period. Lumbar spine scans must include L1 through L4. Detailed instructions for scan acquisition can be found in the separate manual provided by the central imaging vendor.

For total hip, femoral neck DXA scans, the left side should be used for all scans at all study visits. If the right side must be used (eg, due to implants) or is inadvertently used at baseline, then it must be used consistently throughout the study. If a subject fracture the hip that has been scanned during the study up to the time of fracture, no further scans will be obtained.

All DXA scan data will be submitted electronically to the central imaging vendor for analysis.

Sites unable to submit data electronically can submit on compact disc or other media as specified in the DXA Procedural Manual, but electronic submission is preferred.

After analysis by the central imaging vendor, the study site may be asked to re-acquire a scan due to mispositioning or other technical reasons. The study site must comply with the requests from the central imaging vendor. Repeat scans must be performed as soon as possible after the request is received.

The results from the central imaging vendor will be used as the final data for statistical analysis.

8.4.1.1.1. Screening BMD Assessment

To determine eligibility based on BMD T-score, lumbar spine DXA scans will be analyzed by the central imaging vendor. To facilitate subject scheduling, the Day 1/baseline lumbar spine DXA scan may be taken with the lumbar spine DXA scan performed during screening. Lumbar spine vertebrae with artifacts or conditions (visible on the DXA scan) affecting the accuracy of the analysis may be excluded from the DXA analysis in order to determine eligibility. To be

eligible for the study, subjects must have at least two evaluable lumbar vertebrae on the DXA scan and the BMD must meet the criteria outlined in Section 5.1.

8.4.1.2. Lateral Spine X-ray Assessments

For assessment of prevalent vertebral fractures at screening/baseline, which will be performed by a radiologist at the central imaging center, a visual semiquantitative grading scale will be used[10]:

- SQ grade 0 (SQ0) = no fracture
- SQ grade 1 (SQ1) = mild fracture, 20% to 25% reduction in vertebral height (anterior, middle, or posterior)
- SQ grade 2 (SQ2) = moderate fracture, 25% to 40% reduction in height
- SQ grade 3 (SQ3) = severe fracture, greater than 40% reduction in height

Details and specific requirement of X-ray will be mentioned in imaging manual.

For assessment of incident vertebral fracture, x-rays will be scored blinded to treatment but not to sequence. The semiquantitative grading scale will be used. New vertebral fractures are defined as fractures in previously undeformed vertebrae. Worsening of pre-existing vertebral fractures will also be assessed. Worsening is defined as an increase of at least 1 grade on the semiquantitative scale. Investigators will be alerted by the central imaging vendor when a new or worsening vertebral fracture is identified.

If a subject presents with acute back pain likely related to a new vertebral fracture at a time point other than when a scheduled lateral spine x-ray is obtained during the primary analysis period, and occurrence of a vertebral fracture is suspected, unscheduled lateral spinal x-rays will be obtained for submission to the central imaging facility for evaluation. The central imaging vendor will inform the sites if a new or worsening vertebral fracture is identified; however, these x-rays may also be read locally if necessary, to support the subject's medical care. Only fractures confirmed by the central imaging vendor will be included for the analyses.

8.4.1.3. Clinical Fracture Recording

Information on suspected clinical vertebral fractures will be recorded and will include date of fracture, anatomical site(s) of fracture(s), degree of trauma involved and treatment.

8.4.1.3.1. Suspected Clinical Vertebral Fractures

If a participant reports back pain that is considered by the investigator to be possibly due to a new or worsening vertebral fracture, a confirmatory lateral spine x-ray will be taken and the back pain (but not a vertebral fracture) will be recorded as an adverse event. The lateral spine x-rays as well as copies of other diagnostic images (computerized tomography or magnetic resonance imaging) and/or radiology report, surgical report, or discharge summary will be submitted to the central imaging vendor for confirmation of fracture. To confirm a clinical vertebral fracture, at least one new or one worsening (ie, change by at least 1 SQ grade) vertebral fracture have to be identified by the central imaging vendor on lateral spine x-rays. The central imaging vendor will inform the sites of any new or worsening vertebral fractures; however, x-rays taken upon reporting of back pain may also be read locally if necessary, to support subject medical care. Only clinical vertebral fractures confirmed by the central imaging vendor will be included for the statistical analysis.

8.4.1.3.2. Nonvertebral Fractures

Information about any nonvertebral fractures and level of trauma causing the fracture while on study will be recorded. A copy of radiographs or other diagnostic images such as computerized tomography or magnetic resonance imaging confirming the fracture, and/or a copy of the

radiology report, surgical report, or discharge summary should be obtained and included in the subject's study records. Copies of the radiographs, diagnostic images and/or radiology report, surgical report, clinical notes, or discharge summary will be submitted to the central imaging vendor for confirmation of fracture. If the radiograph or diagnostic image is not available, then, at minimum, a copy of the radiology report, surgical report, clinical notes, or discharge summary should be submitted to the central imaging vendor. Additional information about nonvertebral fractures will be entered into the eCRF, eg, details regarding the type of fracture and other pertinent data.

8.4.1.4. Pharmacodynamics

Venous blood samples of approximately 3.5 mL will be collected for measurement of serum CTX and PINP at time points specified. Please refer to section 1.3 for further information.

8.5. Safety Assessments

- Adverse events will be reported and followed by the investigator as specified in Section 8.6 and Appendix 10.3.
- Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.
- Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.
- The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.5.1. Demographic Characteristics

Demographic data will include age, sex, and self-reported race/ethnicity.

8.5.2. Medical History

The Principal Investigator, or a licensed physician who has been delegated by the Principal Investigator, will obtain a detailed medical history and complete a physical examination at predefined time points.

Medical history includes clinically significant diseases, including chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, and ophthalmic history); surgeries; cancer history; reproductive status including years since menopause; previous ECGs. History of fractures will also be obtained, and will include date of fracture, anatomical site(s) of fracture(s), and degree of trauma involved. The investigator or designee will collect information about the prior and/or current use of tobacco and alcohol and substance use. All findings are to be recorded on the CRF.

8.5.3. Medication History

Pre-study therapies for treatment of osteoporosis and other therapies affecting bone metabolism administered up to 3 years before first dose of study IMP must be recorded at screening as defined in eligibility criteria. The therapy name, indication, dose, unit, frequency, start date and stop date will be recorded.

Information on other prior medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to Day 1 will be recorded on the eCRF. The therapy name, indication, start date and stop date will be recorded.

Concomitant medications administered from screening to randomization will be recorded as a medication history on the eCRF.

8.5.4. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the general examination and cardiovascular, respiratory, gastrointestinal, neurological systems. A pelvic, breast, or rectal examination will not be required for the screening or on-study physical examinations unless specific evaluation is deemed necessary by the principal investigator. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height (using a stadiometer, to be measured without shoes) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes or jacket) will also be measured and recorded at SoA defined timepoints.

Throughout the study, targeted physical examination will be conducted at each visit as per signs and symptoms of participant as per standard care.

8.5.5. Vital Signs

Vital signs will include temperature, blood pressure and pulse obtained in the sitting position after the subject has sat quietly for at least 5 minutes.

8.5.6. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting. Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling (for safety measures) or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw (for safety measures). 12-lead ECG will be obtained at timepoints outlined in the SoA using an ECG machine and heart rate and various intervals such as PR, QRS, QT, and corrected QT (QTc) by Bazett's formula will be calculated. Investigator must document his/her review of the ECG in source documents.

8.5.7. Clinical Safety Laboratory Assessments

All protocol-required laboratory tests, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor be notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.5.8. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing entry criteria.

- Pregnancy testing (serum) should be conducted at screening visit. Additional pregnancy tests can be performed at any visit during the study period as per investigator's discretion.

8.5.9. Periodontal Examination

- Periodontal examination will be done to rule out risk factors for ONJ at screening and at EOS. Periodontal examination will be done at any visit during study as per investigator's discretion.

8.5.10. Injection site assessment

- Injection site assessment will be performed after every injection at 30 minutes (± 5 min) post dose. If any abnormalities observed than it will be documented.

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

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) for the duration of the study.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study IMP or study procedures, or that caused the participant to discontinue the study IMP (see Section 7).

8.6.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and special reporting situations, whether serious or non-serious, will be collected from the start of IMP until end-of-study visit or at end-of-switching period as applicable at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study IMP but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) and not in the AE section.

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately after their knowledge of the event, and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP or study participation, the investigator must promptly notify the sponsor.

8.6.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. A consistent methodology of open-ended, non-directive/non-leading verbal questioning should be adopted for eliciting adverse event information at all participant evaluation timepoints. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.6.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.6.9), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3. All the ongoing adverse events at EOS visit will be followed up till resolution/ stabilization/ 30 days (whichever is earlier). Adverse/ medical events occurring before starting study treatment but after signing the informed consent form will be recorded on the medical history/ current medical conditions of case report form.

8.6.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor, local regulatory authority and Ethics committee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority, other regulatory agencies and any other authority as per the local regulations about the safety of a study IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

The sponsor or its designee will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.6.5. Pregnancy

Current protocol is planning to enroll post-menopausal women without any child-bearing potential as defined in eligibility criteria. Following is a general guideline for pregnancy reporting if required:

- Details of all pregnancies in female participants if any, will be collected after the start of study IMP and until end-of-study visit.
- If a pregnancy is reported, the investigator should inform the sponsor immediately of learning of the pregnancy using the appropriate pregnancy notification form(s) and should follow the procedures outlined in Appendix 10.3.
- Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study IMP.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or abnormal outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy for medical reasons will be reported as a SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study IMP by the investigator will be reported to the sponsor as described in Section 8.6.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.6.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

For the purposes of this study, the fractures (serious or non-serious) will be considered anticipated disease-related event due to underlying disease. Because these events are typically associated with the disease under study or disease progression, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the disease-related event page in the participant's CRF.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE or a SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.*

  AND/OR
- *The investigator considers that the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression*

  AND/OR
- *The investigator considers that there is a reasonable possibility that the event was more likely related to study IMP than underlying disease.*

8.6.7. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical IMP (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requiring a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the adverse event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the adverse event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium").

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the adverse event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values.

8.6.8. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical IMP (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requiring a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.6.9. Adverse Events of Special Interest

In order to fully evaluate certain events of interest during the study, following adverse events of clinical interest, based on nonclinical studies conducted with denosumab, will be collected:

- Potential osteonecrosis of the jaw events
- Hypocalcemia (defined as per below table)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Corrected serum calcium of <LLN - 8.0 mg/dL: <LLN - 2.0mmol/L; Ionized calcium <LLN -1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL: <2.0 - 1.75 mmol/L; Ionized calcium <1.0 -0.9 mmol/L; Symptomatic	Corrected serum calcium of <7- 6.0 mg/dL: <1.75 – 1.5mmol/L; Ionized calcium <0.9 -0.9 mmol/L; Hospitalization indicated	Corrected serum calcium of < 6.0 mg/dL: <1.5 mmol/L; Ionized calcium <0.8 mmol/L; Life-threatening consequences	Death

- Potential atypical femoral fracture events
- Injection site reaction
- Serious infection leading to hospitalization
- Hypersensitivity reaction including dermatologic reactions

All AESI should be notified to sponsor or its designee as early as possible and preferably within 24 hours of occurrence. If any AESI meets criteria for seriousness, then it will be notified to EC and regulatory agencies as per SAE reporting timelines captures in section 8.6.1.

8.7. Pharmacokinetics

Blood samples will be collected only in prespecified number of patients as defined in section 9.1 for pharmacokinetics assessment of denosumab and denosumab-ref.

8.7.1. Evaluations

Venous blood samples of approximately 3.5 mL will be collected for measurement of concentrations of denosumab and denosumab-ref as specified in the SoA.

Samples collected for analyses of denosumab and denosumab-ref concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers.

Sample collection after first dose and prior to second dose:

The venous blood samples will be withdrawn at pre-dose (0.00 hour) and at 4.000, 12.000 (Day 1), 24.000 (Day 2), 48.000 (Day 3), 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 168.000 (Day 8), 216.000 (Day 10), 240.000(Day 11), 264.000 (Day 12), 312.000 (Day 14), 360.000(Day 16), 408.000 (Day 18), 504.000 (Day 22), 624.000 (Day 27), 792.000 (Day 34), 1008.000 (Day 43), 1344.000 (Day 57), 1680.000 (Day 71), 2016.000 (Day 85), 2352.000 (Day 99), 2688.000 (Day 113), 3024.000 (Day 127), 3360.000 (Day 141), 3840.000 (Day 161), 4320.000 (Day 181) hours post dose following first dose administration.

The venous blood samples will be withdrawn at 5040.000 (Day 211; Month 7), 5760.000 (Day 241; Month 8), 6480.000 (Day 271; Month 9), 7200.000 (Day 301; Month 10), 7920.000 (Day 331; Month 11), and 8640.000 (Day 361; Month 12) hours post dose following first dose administration. The venous blood samples will be withdrawn at Pre third dose, 24.000 (Day 2), 720.000 (Day 31), 1440.000 (Day 61), 2160.000 (Day 91), 2880.000 (Day 121), 3600.000 (Day 151) and 4320.000 (Day 181) hours post dose following third dose administration.

*Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration and day 361 before 3rd dose administration respectively.

Window period for Sampling of PK and PD analysis

The pre-dose blood samples for first dose will be collected within a period of 60 minutes before dosing. Post-dose sample at 4.000 hours will be collected within ± 30 minutes from schedule time. Post-dose samples at 12.000 (Day 1) and 24.000 (Day 2), will be collected within ± 1 hours from schedule time. Post-dose samples from 48.000 hours (Day 3) to 408.000 (Day 18) hours will be collected within ± 4 hours from schedule time. Sample from 504.000 (Day 22) to 792.000 (Day 34) will be collected within ± 1 day from schedule time. Samples from 1008.000 (Day 43) to 3840.000 (Day 161) will be collected within ± 3 day from schedule time. However, 4320.000 (Day 181) hours post-dose sample will be collected prior to second-dose administration.

Sample from 5040.000 (Day 211) to 8640.000 (Day 361) through Day 541 will be collected within ± 3 day from schedule time. However, the pre-dose blood samples for third dose will be collected within a period of 60 minutes before dosing. Post dose samples not collected within this time frame from scheduled time will be documented as sampling deviations.

All, post dose samples during the whole study will be collected on ambulatory basis.

Note: Blood sample collection (PK assessment) will be collected first if other activities are coinciding. At visits during which serum samples for the determination of multiple aspects of denosumab and denosumab-ref will be taken, one sample of sufficient volume can be used.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The actual date and time (24-hour clock time) of each sample will be recorded. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.7.2. Blood Sample Handling for PK, PD and Immunogenicity Analysis

An instruction manual will be prepared with detailed information on blood sample collection, separation, storage and shipment of bioanalytical samples for PK, PD and Immunogenicity estimation.

8.7.3. Analytical Procedures

8.7.3.1. Bioanalytical Plan

Bioanalytical study plan for Pharmacokinetic measurement will be prepared before study sample analysis. The analysts concerned will not have access to the randomization schedule till the completion of bioanalytical phase. All collected samples will be analyzed. If any participant is dropped out after dosing and no post dose samples are collected, then pre-dose sample of such participant will not be analyzed. In the extension phase of study, PK blood collection will be done for all ongoing trial patients but, PK measurement will be done for only anti-drug antibody positive patients.

8.7.3.2. Pharmacokinetics measurements

Serum samples of participants will be assayed for denosumab using ELISA based method at Lambda Therapeutic Research, Limited, Ahmedabad which is validated according to the international guidelines. The analysis of participant samples will be done using a calibration curve with quality control samples. The details for the preparation of the calibration curve and quality control samples, analytical run organization and the analytical run acceptance criteria as discussed in the respective in-house procedure or bioanalytical study plan will be followed during analysis. The criteria for repeat analysis, as defined in the respective in-house procedure, will be followed. Incurred sample reproducibility will be performed to confirm the reliability of the study data. Sample selection will be based on the procedure and acceptance of the results will be as per the in-house SOP. The results will be presented in the bioanalytical report.

Primary aliquot used for study sample analysis will be discarded after completion of analysis. Any missing samples will be reported as `M' and non-reportable concentration values due to insufficient volume or any other reason as per in-house procedure will be reported as 'NR'.

8.7.4. Pharmacokinetic Parameters and Evaluations

8.7.4.1. Parameters

The following pharmacokinetic parameters will be computed for denosumab, using non-compartmental model of Phoenix® WinNonlin® Version 8.1 or higher (Certara L.P.)

- Primary PK Parameters: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of denosumab after first-dose
- Secondary PK Parameters: T_{max}, AUC_%Extrap_obs, λ_z, V_d/F, Cl/F, and $t_{1/2}$ of denosumab after first dose; T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_z, and $t_{1/2}$ of denosumab after second and individual patient's PK parameters after third dose

Pharmacokinetic Parameters:		
C_{max}	:	Maximum measured concentration.

Pharmacokinetic Parameters:		
AUC_{0-t}	:	Area under the concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
$AUC_{0-\infty}$	:	Area under the concentration versus time curve from time zero to infinity. Where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable concentration and λ_z is the terminal rate constant.
T_{max}	:	Time of the maximum measured concentration.
λz	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last three or more non-zero concentration values.
$t_{1/2}$	:	The terminal half-life will be calculated as $\ln(2)/\lambda_z$.
AUC_%Extrap_obs	:	The residual area in percentage will be determined by the formula, $[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100$
Cl/F	:	Total body clearance will be calculated using the formula, $[Dose/AUC_{0-\infty}]$.
V_d/F	:	Volume of distribution based on terminal phase will be calculated using the formula, $[Dose/(\lambda_z \times AUC_{0-\infty})]$.

For all the above computations, actual time points of the sample collection will be used. All concentration values below the lower limit of quantification will be set to zero for the pharmacokinetic and statistical calculations. No value of λ_z, $AUC_{0-\infty}$, AUC_%Extrap_obs, Cl/F, V_d/F or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

8.7.4.2. Pharmacokinetic analysis

Pharmacokinetic analysis will be performed on the available concentration data of all the eligible patients. Criteria for exclusion of pharmacokinetic parameters (for first dose only) will be as follows:

- Three consecutive missing or non-reportable samples in before actual T_{max} may significantly influence all pharmacokinetic parameter estimations. Inclusion of parameters in the statistical analysis may mislead the final outcome. Hence, all pharmacokinetic parameters will be excluded.
- Three consecutive missing or non-reportable samples in elimination phase (i.e. after T_{max}) may significantly influence the AUC_{0-t} and elimination phase dependent parameters ($AUC_{0-\infty}$, $t_{1/2}$, λ_z, AUC_%Extrap_obs, V_d, Cl). Inclusion of such parameters in the statistical analysis may mislead the final outcome. Hence, AUC_{0-t} and elimination phase dependent parameters ($AUC_{0-\infty}$, $t_{1/2}$, λ_z, AUC_%Extrap_obs, V_d, Cl) will be excluded.
- Patient having pre-dose value >5% of C_{max}. [Note: statistical analysis with including the same will be provided for additional information].
- Patients without measurable concentrations or who have only very low concentrations from the reference medicinal product will be excluded from the pharmacokinetic and statistical analyses for the PK comparison of test product with reference product. According to EMA

Guidance (Doc. Ref. CPMP/QWP/EWP/1401/98 Rev.1/Corr**), a patient is considered to have very low concentrations if his/her AUC_{0-t} is less than 5% of reference medicinal product geometric mean AUC_{0-t}, calculated without inclusion of data from the outlying patient. [Note: statistical analysis with including the same will be provided for additional information, this criterion will be applicable for analysis of EMA only.]

8.8. Genetics and/or Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

8.9. Pharmacodynamics

Serum CTX and serum P1NP as biomarkers for bone resorption are being evaluated in this study. Other samples may be used for research to develop methods, assays related to this study.

8.9.1. Evaluation

Venous blood samples of approximately 3.5 mL will be collected for measurement Serum CTX and serum P1NP as biomarkers for bone resorption of denosumab and denosumab-ref from all participant prespecified for PK assessment in each arm as specified in the Schedule of Activities (SoA) .

Blood samples for PD analysis will be collected in all participants who will be undergoing PK assessment.

, same window period will be applicable as described in PK section.

Note: Samples for PD evaluation [CTX and P1NP] should be collected in morning under fasting condition.

Sample collection after first dose and prior to second dose:

The venous blood samples will be withdrawn at pre-dose (0.000 hour) and at 4.000, 12.000 (Day 1), 24.000 (Day 2), 48.000 (Day 3), 72.000 (Day 4), 96.000 (Day 5), 120.000 (Day 6), 168.000 (Day 8), 216.000 (Day 10), 240.000 (Day 11), 264.000 (Day 12), 312.000 (Day 14), 360.000 (Day 16), 408.000 (Day 18), 504.000 (Day 22), 624.000 (Day 27), 792.000 (Day 34), 1008.000 (Day 43), 1344.000 (Day 57), 1680.000 (Day 71), 2016.000 (Day 85), 2352.000 (Day 99), 2688.000 (Day 113), 3024.000 (Day 127), 3360.000 (Day 141), 3840.000 (Day 161), 4320.000 (Day 181) hours post dose following first dose administration.

The venous blood samples will be withdrawn at 5040.000 (Day 211; Month 7), 5760.000 (Day 241; Month 8), 6480.000 (Day 271; Month 9), 7200.000 (Day 301; Month 10), 7920.000 (Day 331; Month 11), and 8640.000 (Day 361; Month 12) hours post dose following first dose administration.

The venous blood samples will be withdrawn at pre third dose, 24.000 (Day 2), 720.000 (Day 31), 1440.000 (Day 61), 2160.000 (Day 91), 2880.000 (Day 121), 3600.000 (Day 151) and 4320.000 (Day 181) hours post dose following third dose administration.

*Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration and day 361 before 3rd dose administration respectively.

Window period will be applicable as mentioned in section 8.8.1.

8.9.2. Analytical procedure

8.9.2.1. Pharmacodynamic measurement

Bioanalytical study plan for Pharmacodynamic analysis will be prepared before study sample analysis. The analysts concerned will not have access to the randomization schedule till the completion of bioanalytical phase. All collected samples will be analyzed. If any participant is dropped out after dosing and no post dose samples are collected, then pre-dose sample of such participant will not be analyzed. In the extension phase of study, PD blood collection will be done for all ongoing trial patients but, PD analysis will be done for only anti-drug antibody positive patients.

Serum samples will be analyzed for CTX and P1NP by using validated methods at Lambda Therapeutic Research Ltd., Ahmedabad. The details for the analytical run organization, analytical run acceptance criteria and criteria for repeat analysis as mentioned in the respective in-house procedure or respective bioanalytical study plan will be followed during analysis. Incurred sample reproducibility will be performed to confirm the reliability of the study data. Sample selection will be based on the procedure and acceptance of the results will be as per the in-house SOP. The results will be presented in the bioanalytical report.

Primary aliquot used for study sample analysis will be discarded after completion of analysis. Any missing samples will be reported as `M' and non-reportable concentration values due to insufficient volume or any other reason as per in-house procedure will be reported as 'NR'.

8.9.3. Pharmacodynamic parameters & analysis

8.9.3.1. Parameters

Pharmacodynamic effect for Serum C-terminal telopeptide (CTX) and Serum N-terminal propeptide of type 1 collagen (P1NP) will be assessed as % reduction from baseline. The following pharmacodynamic parameter will be computed for denosumab Serum C-terminal telopeptide (CTX) and Serum N-terminal propeptide of type 1 collagen (P1NP) using non-compartmental model of Phoenix® WinNonlin® Version 8.1 or higher (Certara L.P.)

For Serum C-terminal telopeptide (CTX):

- Primary PD Parameters: E_{max} and $AUEC_{0-t}$ after first dose (These will be primary parameters for EMA Submission only)
    - Secondary PD Parameters: T_{max} after first dose; T_{max}, E_{max} and $AUEC_{0-t}$ after second and individual patient's PD parameters after third-dose.

For Serum N-terminal propeptide of type 1 collagen (P1NP):

- Secondary PD Parameters: T_{max}, E_{max} and $AUEC_{0-t}$ after first, second and individual patient's PD parameters after third-dose.

Note: Pharmacodynamic effect for Serum C-terminal telopeptide (CTX) and Serum N-terminal propeptide of type 1 collagen (P1NP) will be assessed as decrease from the baseline.

Pharmacodynamic Parameters:		
E_{max}	:	Maximum % reduction from baseline.
$AUEC_{0-t}$	:	Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
T_{max}	:	Time of the maximum % reduction from baseline.

8.9.3.2. Pharmacodynamic analysis

Pharmacodynamic analysis will be performed on the available concentration data of all the eligible patients of the study. Criteria for exclusion of Pharmacodynamic parameters (for first dose only) will be as follows:

- Three consecutive missing or non-reportable samples before actual T_{max} may significantly influence all Pharmacodynamic parameter estimations. Hence, all Pharmacodynamic parameters will be excluded.
- Three consecutive missing or non-reportable samples in terminal phase (i.e. after T_{max}) may significantly influence the $AUEC_{0-t}$. Hence, $AUEC_{0-t}$ will be excluded.

8.10. Immunogenicity Assessments

8.10.1. Sampling Schedule for Immunogenicity evaluation

8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre-dose (baseline), at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361 with respect to first dosing. 8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre- third dose (baseline), at day 2*, 31, 61, 91 and 181 with respect to third dosing.

*Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration.

Blood sample for immunogenicity on day 361 will be collected prior to 3rd dose administration

Additionally, serum samples should also be collected at the final visit from participants who discontinued study IMP or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Window period for immunogenicity samples collection will be according to window period for visit as mentioned in SoA.

Serum 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 further characterize the immunogenicity of denosumab.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Predose sample may be used for establishing in study cut point or for method validation purposes.

8.10.2. Analytical Procedures

The detection and characterization of antibodies to denosumab will be performed using validated assay methods. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study IMP(s).

Bioanalytical study plan for Immunogenicity assessment will be prepared before study sample analysis. The analysts concerned will not have access to the randomization schedule till the completion of bioanalytical phase. All collected samples will be analyzed. If any participant is dropped out after dosing and no post dose samples are collected, then pre-dose sample of such

participant will not be analyzed. All samples collected in the extension phase of the study will be analyzed.

The serum samples for assessment of Immunogenicity will be analyzed by three-tiered approach at Lambda Therapeutic Research Limited, Ahmedabad. The anti-denosumab antibodies will be detected using a validated ELISA based screening assay. All samples deemed positive by the screening assay shall be re-assessed using ELISA based validated confirmatory assay and confirmed positive samples will be submitted for validated ELISA based titer assay and validated ligand binding based neutralizing antibody (NAb) assay. Respective positive and negative controls will be included in each assay. The details for the preparation of positive controls, negative controls, analytical run organization, analytical run acceptance criteria, determination of run specific cut points and criteria for repeat analysis as mentioned in the respective in-house procedure or respective bioanalytical study plan will be followed during analysis.

Primary aliquot used for study sample analysis will be discarded after completion of analysis. Any missing samples will be reported as `M' and non-reportable concentration values due to insufficient volume or any other reason as per in-house procedure will be reported as 'NR'.

Bioanalytical data including PK, PD and Immunogenicity will be transferred to Pharmacokinetics and Statistics team for further analysis.

8.11. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

Pharmacokinetic endpoint

Based on in-house data, total CV was found to be ~47% for AUC_{0-t} of denosumab. Hence, the sample size has been calculated considering the same using SAS with following estimates.

- T/R ratio = 95.0-105.0%
- CV% = 47% (AUC_{0-t})
- alpha = 5%
- Power = 90%
- 90% CI = 80.00-125.00%

Based on above estimates, 117 completers per arm will be required. Considering~20% dropouts/withdrawals and 1:1 treatment allocation ratio, 296 patients (148 patients per arm) will be required.

Pharmacodynamic endpoint

Based on the literature[11], back calculated inter subject CV was found to be ~13% for $AUEC_{0-t}$ in healthy volunteers for reduction from baseline for serum CTX. Hence, the sample size has been calculated considering the same using SAS with following estimates.

- T/R ratio = 95.0-105.0%
- CV% = 13% ($AUEC_{0-t}$)
- alpha = 2.5%
- Power = 90%
- 95% CI = 80.00-125.00%

Based on above estimates, 26 completers (13 completers per arm) will be required.
Considering ~20% dropouts/withdrawals and 1:1 treatment allocation ratio, 34 patients (17 patients per arm) will be required.

Immunogenicity assessment

A sample size of 54 completers per group would ensure that the upper bound of the 95% CI of ADA incidence will not be larger than 10% assuming no more than one patient per group is observed to be positive for ADA at the end of treatment duration and using a Clopper-Pearson exact method to calculate the 95% CI for a sample proportion. Considering ~20% dropouts/ withdrawals, 136 patients (68 patients per arm) will be required for immunogenicity assessment.

BMD assessments

An equivalence test of means using two one-sided equal-variance t-tests with sample sizes of 220 completers in each treatment group achieves 90% power at a 2.5% significance level when the equivalence limits are -1.45 and 1.45, the actual difference between the means is 0.0, and

the standard deviation is assumed as 4.20 in each group. Total 440 completers (220 in each treatment group) will be required to prove therapeutic equivalence between test and reference.

Considering above all approaches, ~20% dropouts/withdrawals and 1:1 treatment allocation ratio, **552 patients (276 patients per arm)** will be enrolled for BMD assessment.

9.2. Populations for Analyses

Analysis populations are defined as below.

- Safety set: The safety set is defined as all randomized patients who will receive at least one dose of study medication.

- Pharmacokinetic (PK) set: The PK set is defined as all patients who will complete the study and has no major protocol deviation which can significantly influence the pharmacokinetic parameter estimation.

- Pharmacodynamic (PD) set: The PD set is defined as all patients who will complete the study and has no major protocol deviation which can significantly influence the pharmacodynamic parameter estimation.

- Intent-To-Treat (ITT) set: The ITT set is defined as all randomized patients who will receive at least one dose of study medication.

  Sensitivity analysis will be performed on patients in ITT set for primary endpoint mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months. For this analysis, missing values of individual BMD of lumbar spine at 12 months will be imputed with value as baseline value ± 0.73 (i.e. half of equivalence limit 1.45 considered in the study). Imputation will be done with value as (baseline value - 0.73) for test and (baseline value + 0.73) for reference product.[12]Additionally, imputation will be done with value as (baseline value + 0.73) for test and (baseline value - 0.73) for reference product.

- Modified Intent-To-Treat (mITT) set: The mITT set is defined as all randomized patients who will receive at least one dose of study medication and will undergo at least one post-dose efficacy evaluation. Missing data will be imputed using last observation carried forward (LOCF) technique.

- Per-protocol (PP) set: The PP set is defined as all randomized patients who will complete the study with no major protocol deviations.

Safety set will be used for the safety and immunogenicity analysis, PK set will be used for pharmacokinetic analysis and PD set will be used for pharmacodynamic analysis. Patients included in ITT, mITT and PP set will be used for the evaluation of the efficacy end points.

9.3. Statistical Analyses

The statistical analysis plan will be finalized prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

All the statistical analysis will be performed using SAS® Version 9.4 or higher (SAS Institute Inc., USA).

9.3.1. PK and PD data

Descriptive statistics and statistical analysis will be performed on patients in PK set and PD set.

Analysis of Variance (ANOVA)

- **For USFDA:**

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose, ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose will be subjected to Analysis of Variance (ANOVA).

ANOVA model will include the term Centre, Centre*Formulation and Formulation as fixed effect.

If the Centre*Formulation interaction term is not statistically significant at a 5% level of significance, then the interaction term will be dropped from the model and the statistical analysis will be re-performed excluding the interaction term.

Each ANOVA will include calculation of LSMs, the difference between adjusted formulation means and the standard error associated with this difference. This statistical analysis will be performed using PROC MIXED of SAS procedure.

An F-test will be performed to determine the statistical significance of the effects involved in the model at a significance level of 5 % (alpha = 0.05).

Note: In case there is a centre with less than five patients, then that data will be pooled with the subsequent centre.

- **For EMA:**

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose, ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose will be subjected to Analysis of Variance (ANOVA).

ANOVA model will include the term Centre and Formulation as fixed effect.

Each ANOVA will include calculation of LSMs, the difference between adjusted formulation means and the standard error associated with this difference. This statistical analysis will be performed using PROC GLM of SAS procedure.

An F-test will be performed to determine the statistical significance of the effects involved in the model at a significance level of 5 % (alpha = 0.05).

Note: In case there is a centre with less than five patients, then that data will be pooled with the subsequent centre.

90%/95% confidence intervals

90% confidence intervals for the ratio of geometric least squares means of test and reference formulations will be calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose.

90% and 95% confidence intervals will be calculated and reported for ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Power

The power of the study will be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose and ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Ratio Analysis

Ratio of geometric least square means of test and reference formulations will be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose and ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Inter-Patient Variability

Inter-patient variability will be computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose and ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Missing and Non-Reportable Values
Any missing samples (M) or not reportable concentration values (NR) will not be included in the pharmacokinetic, pharmacodynamic and statistical analysis.

Bioequivalence criteria
For USFDA:

Based on the statistical results of 90% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for denosumab after first dose, conclusion will be drawn for Test Product-T vs. Reference Product-R.

Bioequivalence of the test product with that of the reference product will be concluded, if 90% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose.

For EMA:

Based on the statistical results of 90% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for denosumab after first dose and 95% confidence interval for the ratio of the geometric least square means for ln-transformed pharmacodynamic parameters E_{max} and $AUEC_{0-t}$ for % reduction from baseline Serum C-terminal telopeptide (Serum CTX) after first dose, conclusion will be drawn for Test Product-T vs. Reference Product-R.

Bioequivalence of the test product with that of the reference product will be concluded, if 90% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of denosumab after first dose and 95% confidence interval falls within the acceptance range of 80.00-125.00% for ln-transformed pharmacodynamic parameter E_{max} and $AUEC_{0-t}$ of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) after first dose.

9.3.2. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized using descriptive statistics by treatment.

9.3.3. Efficacy / Pharmacodynamic Data

Categorical variable will be summarized with frequency distribution. Continuous variables will be summarized with mean, standard deviation, median, minimum and maximum.

The primary endpoint is mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months.

A point estimate and a two-sided 95% confidence interval will be computed for the treatment groups and their differences. 95% CI will be calculated using ANCOVA considering baseline as a covariate.

Descriptive statistics for mean percentage change in BMD at lumber spine from baseline to 12 months will be calculated. Independent t-test will be used to evaluate the between treatment comparison.

The study conclusion will be based on the primary endpoint (PK & BMD/PD), which are independent from each other. Hence, multiplicity adjustment to control the study-wise overall Type I error rate would not be applicable.

Acceptance criteria: Therapeutic equivalence of the test with the reference treatment will be concluded if the 95% CI of the difference between test and reference for mean percentage change in BMD at lumber spine from baseline to 12 months is within the range of ± 1.45.

Note: Therapeutic equivalence of the test with the reference treatment will be claimed on ITT set for USFDA and on PP set for EMA.

Secondary endpoints of the study will be as below:

- Mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 06 months between denosumab and denosumab-ref

- Mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months between denosumab and denosumab-ref
- Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref
- Mean percentage reduction in CTX serum concentrations from baseline to 06 and 12 months between denosumab and denosumab-ref

Descriptive statistics for mean percentage change in BMD of lumber spine from baseline to 06 months and mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months will be calculated presented. Independent t-test will be used to evaluate the between treatment comparison.

Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) and in serum CTX concentrations from baseline to 06 and 12 months will be calculated and reported.

Fracture incidence rate will be provided and compared.

9.3.4. Immunogenicity Data

Incidence of anti-denosumab antibody at respective visits will be presented. The data post-switching will be presented separately as an amendment to the main report. In those patients who show clinical concerns or analytical concerns of immunogenicity, specific patients PK and PD will be assessed for interpreting the impact of immunogenicity on PK and PD.

9.3.5. Safety Data

All patients who have received at least one dose of the study medicine will be included in the safety evaluation. Result obtained when evaluating safety and tolerability (adverse events, vital signs, clinical laboratory tests that are out of the range) will be listed and evaluated by descriptive statistics.

Safety data collected after 12 months will be presented in separate tables and listings.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Current ICH Good Clinical Practice (GCP) Guidelines
- Good Clinical Practices Guidelines for conduct of clinical studies in India, formulated by the Central Drugs Standard Control Organisation and adopted by the Drugs Technical Advisory Board
- New Drugs & Clinical Trial Rules, 2019 of Central Drugs Standard Control Organization (CDSCO)
- Applicable local country-specific laws, guidelines and regulations

10.1.1.1. Investigator Responsibilities

The investigator is responsible for ensuring that: (a) the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements; (b) providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR; ICH guidelines; the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable); New Drugs and Clinical Trial Rules, 2019; and all other applicable local regulations; (c) 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/IEC and regulatory authority; (d) Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

10.1.1.2. Protocol Amendments

Neither the investigator nor the sponsor or its designee will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor or its designee and signed and dated by the investigator. Protocol amendments, if become necessary before initiation or during the course of a clinical trial, all such amendments should be submitted to the appropriate regulatory authority in writing along with the approval by the ethics committee, if available, which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and appropriate regulatory authority except when it is necessary to eliminate immediate hazards to the trial subject or when change involves only logistic or administrative or minor aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the appropriate regulatory authority. Administrative or logistic changes or minor amendments in the protocol should be notified to the appropriate regulatory authority

within thirty days. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor or its designee must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

10.1.1.3. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. The protocol, protocol amendments, ICF, Investigator 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.

Status of enrolment of the trial subjects shall be submitted to the appropriate regulatory authority on quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier. Further, status report of each clinical trial, as to whether it is ongoing, completed or terminated, will be submitted to appropriate regulatory authority and ethic committee as per local regulations. In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, the detailed reasons for such termination shall be communicated to the appropriate regulatory authority within thirty working days of such termination and a summary report should be submitted within 3 months to IRB/IEC and appropriate regulatory authority.

10.1.1.4. Required Prestudy Documentation

The following documents must be provided to the sponsor or its designee before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572) or letter of undertaking by investigator, as applicable

- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor or its designee before enrollment of the first participant:

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

10.1.1.5. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor or its designee where required) will provide the IRB/IEC with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor or its designee approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor or its designee approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IRB/IEC)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IRB/IEC requests to fulfill its obligation

This study will be undertaken only after the IRB/IEC has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor or its designee has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor or its designee where required) will send the following documents and updates to the IRB/IEC for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)

- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor or its designee
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines (quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier)
- Reports of SAE, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IRB/IEC

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IRB/IEC for review and approval before implementation of the change(s).

At least once a year, the IRB/IEC will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor or its designee, where required) will notify the IEC/IRB about the study completion.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested 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.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

10.1.3. Informed Consent Process

Each participant must freely give informed, written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and patient information sheet that is/are used must be approved by the sponsor or its designee; by the reviewing IEC/IRB and appropriate regulatory authority and be in a language that the participant can read and understand. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the appropriate regulatory authority before such changes are implemented. The informed consent should be in accordance with principles that originated in

the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail in language potential participant may understand and comfortable with. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about her survival status. It also denotes that the participant agrees to allow her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, participants will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements where applicable, and the IRB/IEC or study center.

After having obtained the consent, a copy of the ICF must be given to the participant. The medical record must include a statement that written informed consent was obtained before the participant 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. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

Participants who are rescreened are required to sign a new ICF.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

The consent will mention that if participant discontinue before 12 months, follow-up for safety will be needed for up to 12 months, for scientific value. The consent will clearly mention that the subject is expected to follow-up for an additional period of 6 months after the initial 12 months treatment for assessment of safety and immunogenicity, if the investigators requests. It will be mentioned clearly the scientific importance of the follow-up information.

10.1.4. Data Protection

10.1.4.1. Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Participants will be assigned a unique identifier by the sponsor or its designee. Any participant records or datasets

that are transferred to the sponsor or its designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable local and global data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, independent auditor appointed by sponsor under confidentiality agreements, appropriate IRB/IEC members, and inspectors from regulatory authorities. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

PK, PD and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor or its designee cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.1.5. Publication Policy / Dissemination of Clinical Study Data

All information, including but not limited to information regarding denosumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

For all the publications related to this study, the Sponsor Publication Policy will be followed.

10.1.6. Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory, imaging data to central imaging vendor into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

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

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be provided in the monitoring plans and/or contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as per CTA after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct. A CRF must be completed for each participant enrolled in the study. Completed CRFs are the sole property of Intas Pharmaceutical Limited (Biopharma Division) and may not be made available in any form to third parties without written permission, except for authorized representatives of Intas Pharmaceutical Limited (Biopharma Division) and appropriate regulatory authorities.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).

Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

Data management
CDM will set up the study as specified in Data Management Plan. Data Validation including DCF (Data clarification Form, if applicable) / Query generation and resolution, medical coding, reconciliation of external data etc. will be done as per Data Management Plan (DMP). Detailed scope of Clinical Data Management will be described in the DMP. Medical coding will be done by using standard medical dictionaries such as MedDRA and/or WHODD.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data entered 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.

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; IMP receipt/dispensing/return records; study IMP administration information; and date of study completion and reason for early discontinuation of study IMP or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site

- Discharge summaries
- Diagnostic reports and summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

10.1.9.2. Study/site Termination

The sponsor or its 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 IMP 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 participants by the investigator
- Total number of participants 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 may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant’s interests. The Investigator shall promptly inform the participant and the participant should be seen as soon as possible for the assessments described in Section 8 for a discontinued or withdrawn participant. The investigator will be responsible to assure appropriate participant therapy and/or follow-up.

10.1.10. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

The monitor will review and verify: the diagnosis, medical history, inclusion/exclusion criteria, physical exams and vital signs, efficacy evaluations; safety and laboratory evaluations/tests, AEs and SAEs, concomitant medications and procedures, and the use of study IMP. Specific items required as source documents will be reviewed with the Investigator prior to the study.

In addition, the monitor will verify that standards of GCP were followed. This includes, but is not limited to: completion of regulatory documents (e.g., FDA Form 1572, financial disclosure, Institutional Review Board [IRB]/Independent Ethics Committee [IEC] approvals, submitting safety/progress reports, etc.) ensuring Informed Consent was adequately performed and documented, that study IMP dispensation and accountability was handled properly, SAEs were reported to the Sponsor and IRB/IEC in a timely manner, that the protocol was followed and that the rights and welfare of participants were protected.

Findings from the review of CRFs/eCRFs, source documents, and study conduct will be discussed with the Investigator. The dates of the monitoring visits will be recorded by the monitor in a sign-in log to be kept at the site.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Medical monitoring plan will be prepared according to standard procedure and followed during the study.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.1.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department or independent auditors appointed by sponsor may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.1.12. Record Retention

In compliance with the ICH/GCP guidelines and/or clinical trial agreements/contracts as applicable, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for period defined in clinical trial agreements/contract based on regulatory submission and requirement. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor or its designee. It is the responsibility of the sponsor or its designee to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor or its designee must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor or its designee.

If it becomes necessary for the sponsor or its designee or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.1.13. Insurance

Intas Pharmaceutical Limited (Biopharma Division) is the sponsor of this study and will finance this study.

Lambda Therapeutic Research Limited, Ahmedabad on behalf of the sponsor/designee will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him/her and the hospital, practice or institute in which they are employed and the liability of the Sponsor in respect of financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the applicable local law. As a precautionary measure, the investigator, the persons instructed by him/her and the hospital, practice or institute may be included in such cover in respect of work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance.

Lambda Therapeutic Research Limited, Ahmedabad on behalf of the Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the clinical laboratory. Further details can be found in laboratory manual.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (Local lab)	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	Total WBC count with differential in %: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.			
Clinical Chemistry (Central lab)	Blood urea nitrogen (BUN), Uric acid, Lactate dehydrogenase	Sodium, Potassium, Chloride Phosphate	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Serum PTH 1-84 Serum TSH 25 (OH) Vitamin D Albumin-adjusted Calcium[$],	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein, Albumin, Globulin, A/G ratio, Gamma-glutamyl transferase (GGT)
	Non-fasting random Glucose		Alkaline phosphatase	
Routine Urinalysis (Central lab)	• Specific gravity, • pH, glucose, protein, blood, ketones, urobilinogen, nitrite		• Microscopic examination • Red blood cells, White blood cells, epithelial cells, crystals, casts	
	Note: In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.			

Virology (Central lab)	• Human Immunodeficiency Virus (HIV-1 and HIV-2 Antibody and Antigen (p24) Evaluation) • Hepatitis B surface antigen (HBsAg) • Hepatitis C virus (HCV RNA or Hepatitis C Antibody Test)
Other Screening Tests (Central lab)	• Follicle-stimulating hormone (as needed) • Highly sensitive Serum human chorionic gonadotropin (hCG) pregnancy test
$ Albumin adjusted calcium will be performed at local lab.	

Investigators must document their review of each laboratory safety report in source documents and record in CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH] E2A).
Events <u>Meeting</u> the AE Definition
• 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 (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study IMP administration even though it may have been present before the start of the study. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period • Complications that occur as a result of protocol-mandated IMPs (e.g., invasive procedures such as vitreous hemorrhage). AEs that occur prior to assignment of study treatment that are related to a protocol-mandated IMP (e.g., invasive procedures). • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study IMP 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. All adverse events associated with an overdose or incorrect administration of study IMP should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.
- 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.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

a. Results in death

- Only the AE leading to death should be documented as SAE with an outcome of death. Stop date should be the date of death. Other events ongoing at the time of death should be recorded as outcome unknown.

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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 does not include the following:
  - rehabilitation facilities;
  - hospice facilities;
  - respite care (e.g, caregiver relief);
  - skilled nursing facilities;
  - same-day surgeries (as outpatient/same-day/ambulatory procedures),
  - planned hospitalization required by the protocol (e.g., for study treatment administration and intensive PK sampling),

- Hospitalization for a preexisting condition, provided that all of the following criteria are met: The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease. The participant has not suffered an AE.

- An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:
  - Hospitalization for an AE that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.
- Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Hospital admissions for transfusion sessions, anti-cancer therapy, social admission (e.g, subject has no place to sleep), administrative admission (e.g, for yearly physical examination), protocol-specified admission during a study (e.g, for a procedure required by the study protocol), hospitalization for observation without a medical AE, and/or surgeries planned before or during a study are not considered SAEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

d. Results in persistent 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- An anomaly detected at or after birth, or any anomaly that results in fetal loss

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical IMP to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, 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. Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on participant or event outcome or action criteria usually associated with events that pose a threat to a participant's life or vital functions. Seriousness (not severity) serves as the guide for

defining regulatory reporting obligations. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

10.3.3. Recording and Follow-Up of AE and/or 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 reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study intervention dosage adjusted/temporarily interrupted; study intervention permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; participant hospitalized/participant's hospitalization prolonged. The action taken to treat the AE should be recorded on the appropriate form of the CRF.
- The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study intervention or trial-related procedures until a final outcome can be reported.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor or its designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- During the study period, resolution of AEs to baseline grade or better (with dates) should be documented on the appropriate form of CRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the AE section of eCRF.
- A diagnosis (if known) should be recorded on the rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.
- In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the AE section of CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF.
- If vomiting results in severe dehydration, both events should be reported separately on the CRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the CRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF.

All AEs should be recorded separately on the AE section of CRF if it is unclear as to whether the events are associated.

- A persistent AE is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the AE section of CRF. The initial severity of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded. Details regarding any increases in severity will be captured on the source note. If the event becomes serious, it should be reported to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning that the event became serious; see Section for reporting instructions). The CRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.
- A recurrent AE is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on CRF.
- Please refer to section 8.6.7 for abnormal laboratory values and 8.6.8 for abnormal vital sign values.
- If the SAE was due to a hospitalization of the participant, a copy of the discharge summary should be made available to the Sponsor or its designee, upon request. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests may also be requested. Further, depending upon the nature of the SAE, Sponsor or its designee may request copies of applicable portions of the participant's medical records. In either case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or its designee.
- All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study intervention, must be recorded on the appropriate form of CRF and immediately reported to the Sponsor or its designee. Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the appropriate form of the CRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a participant with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the participant was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should

be recorded on the appropriate form of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

- A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History/Current Medical Conditions of CRF.
- A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE section of CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that subject is aware of but is easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that is incapacitating and results in the subject's inability to work or engage in their usual activities.

An event is defined as ‘serious’ when it meets at least 1 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 causality assessment is one of the criteria used when determining regulatory reporting requirements.

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. The investigator must use clinical judgment to determine the relationship. The investigator must also consult the Investigator’s Brochure (IB) and/or Product Information and /or reference safety information material provided by sponsor, as applicable, in his/her assessment.

The following components are to be used to assess the relationship between the test drug and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE). The investigator will use clinical judgment to determine the relationship.

- **Exposure:** Is there evidence that the participant was actually exposed to the test drug such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Temporal relationship of event onset to the initiation of study intervention:** Did the AE follow in a reasonable temporal sequence from administration of the test drug? Is the time of onset of the AE compatible with a drug-induced effect?

- **Likely cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
- **Dechallenge:** Was the dose of test drug discontinued or reduced?
    - If yes, did the AE resolve or improve partially or completely, within a reasonable time from medication discontinuation? If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.
      (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the test drug; or (3) the study is a single-dose drug study.)
- **Rechallenge:** Was the participant re-exposed to the test drug in this study?
    - If yes, did the AE recur or worsen? If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.
      (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study.)
      NOTE: If a rechallenge is planned for an adverse event which was serious and which may have been caused by the test drug, or if re-exposure to the test drug poses additional potential significant risk to the participant, then the rechallenge must be approved in advance by the medical monitor as per dose modification guidelines in the protocol.
- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology? The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

Causal Attribution Guidance for relationship with drug

- **Yes, there is a reasonable possibility of drug relationship:** There is a plausible temporal relationship between the onset of the adverse event and administration of the study intervention, the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention and, if applicable, reappears upon re-challenge.
  Depending on data collection method employed, drug relationship may be further graded as follows:
    - **CERTAIN:**
        - Event or laboratory test abnormality, with plausible time relationship to drug intake
        - Cannot be explained by disease or other drugs
        - Response to withdrawal plausible (pharmacologically, pathologically)

        - Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)
        - Rechallenge satisfactory, if necessary
        - **Key Features**: Temporal relationship, no other cause, withdrawal response plausible (dechallenge), rechallenge "definitive"
    - **PROBABLE/LIKELY:**
        - Event or laboratory test abnormality, with reasonable time relationship to drug intake
        - Unlikely to be attributed to disease or other drugs
        - Response to withdrawal (if performed) clinically reasonable
        - Rechallenge not required
        - **Key Features:** Temporal relationship, other cause unlikely, positive dechallenge
    - **POSSIBLE**:
        - Event or laboratory test abnormality, with reasonable time relationship to drug intake
        - Could also be explained by another equally likely cause e.g. disease or other drugs
        - Information on drug withdrawal may be lacking or unclear
        - **Key features:** Temporal relationship, other causes possible
- **No, there is not a reasonable possibility of drug relationship:** Study participant did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication).
  Depending on data collection method employed, drug relationship may be further graded as follows:
    - **UNLIKELY:**
        - Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
        - Disease or other drugs provide more plausible explanations
        - **Key Features:** Poor timing, other causes more likely
    - **CONDITIONAL/UNCLASSIFIED**
        - Additional data under examination
        - A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data is under examination.
        - **Key features:** Can't assess with the information available
    - **UNASSESSABLE/UNCLASSIFIABLE:**
        - A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.
        - **Key features:** Data elements concerning the event are inadequate and will not be available.

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 along with medical justification.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor or its designee. 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 sponsor or its designee.

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

Assessment of Expectedness

An "unexpected" AE is an AE that is not listed in the reference safety information or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the reference safety information referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the reference safety information listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the reference safety information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

Sponsor or its designee will be responsible for determining whether an AE is expected or unexpected.

For denosumab, the Investigator's Brochure will be considered reference safety information.

For Prolia®, the Summary of Product Characteristics (EMA) or Prescribing Information (US-FDA) as applicable will be considered reference safety information.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or its designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF
- The investigator will submit any updated SAE data to sponsor receipt of the information.
- The report of the SAE, after due analysis, shall be forwarded by the investigator to the appropriate regulatory authority, the chairperson of the ethics committee and the head of the institution where the trial has been conducted within fourteen days of the occurrence of the SAE.

- The sponsor or its representative and the investigator shall forward their reports on SAE of death after due analysis to the appropriate regulatory authority and the head of the institution where the clinical trial or bioavailability or bioequivalence study has been conducted within fourteen days of the knowledge of occurrence of SAE of death.

10.3.4. Reporting of SAEs

SAE Reporting to sponsor or its designee

- Electronic mail or facsimile transmission from investigator containing appropriately filled SAE form along with required deidentified details of participant is the preferred method of SAE reporting to sponsor or its designee.
- In rare circumstances and in the absence of computer or facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

10.4. Appendix 4: CENTRAL LABORATORY REFERENCE INTERVALS

BIOCHEMISTRY		
Parameter	Reference Interval	Units
A/G Ratio	1.2 – 2.2	-
Albumin	3.9 – 5.2	g/dL
Alkaline Phosphatase	55.0 – 137.0	U/L
ALT [SGPT]	10.0 – 56.0@	U/L
AST [SGOT]	15.0 – 46.0@	U/L
Bilirubin Total	0.2 – 1.5@	mg/dL
BUN [Blood Urea Nitrogen]	7.0 – 17.0#	mg/dL
Calcium	8.7 - 10.2	mg/dL
Chloride	97.3-107.0@	mmol/L
Creatinine,Serum	0.5 – 0.9@	mg/dL
GGT [gamma glutamyl transferase]	12.0 – 43.0#	U/L
Globulin	2.5 – 3.8#	g/dL
Plasma Random(casual) Glucose	AMERICAN DIABETES ASSOCIATION € DIABETES*: ≥200	mg/dL
Potassium, Serum	3.8-5.4@	mmol/L
Sodium	135.6-145.9@	mmol/L
Total Protein	6.9 – 8.6	g/dL
Urea	15.0 – 36.0#	mg/dL
Uric Acid	2.4-6.7#	mg/dL
HEMATOLOGY #		
Parameter	Reference Interval	Units
WBC (total)	4.2-11.5	X 103/µL
Neutrophils %	40 – 80	%
Lymphocytes %	20 – 40	%
Eosinophils %	1 – 6	%
Monocytes %	2 – 10	%
Basophils %	0 – 2	%
Neutrophils (abs)	2 – 7	X 103/ µL
Lymphocytes (abs)	1– 3	X 103/ µL
Eosinophils (abs)	0.02 – 0.5	X 103/ µL
Monocytes (abs)	0.2 – 1	X 103/ µL
Basophils (abs)	0.02 – 0.1	X 103/ µL
RBC count	3.8 – 4.8	X 10^6/ µL
Haemoglobin[Hb]	10.0 – 14.4@	g/dL
HCT	36.0 – 46.0	%
MCV	83.0 – 101.0	fL
MCH	27.0 – 32.0	pg
MCHC	31.5 – 34.5	g/dL
RDW SD	39.0 – 46.0	fl
RDW CV	11.6 – 14.0	%
Reticulocyte %	0.5-2.5	%
Reticulocyte (abs)	0.05-0.1	X 10^6/ µL

Platelet count	150 – 410	X 10^3/µL

URINANALYSIS #	
Parameter	Reference Interval
Chemical Analysis	
Specific Gravity	1.005 - 1.020
pH	5.0 – 8.0
Glucose	Negative
Protein	Negative
Bilirubin	Negative
Ketone	Negative
Urobilinogen	Negative
Erythrocytes	Negative
Leucocytes	Negative
Nitrite	Negative
Microscopic Examination	
Epithelial cell	0-10 / hpf (Females) & 0-2 / hpf (male)
Pus cells	<5 hpf ¥
RBCs	<5 hpf ¥
Casts	Absent [1¥]
Crystal	Absent[2¥]
Trichomonas	Absent
Yeast cells	Absent
Bacteria	Absent
Amorphous	Absent[3¥]
Urine Pregnancy Test (For Female)	Negative
Urine Microalbumin	Absent(< 20 mg/L)

MICROBIOLOGY AND SEROLOGY	
Parameter	**Reference Interval**
Anti HIV AB (I & II)	Non-Reactive
Western Blot for HIV-I	Negative
HbsAg	Non-Reactive
Anti HAV IgM	Non-Reactive
Anti HCV	Non-Reactive
Anti HbcIgM	Non-Reactive

IMMUNOLOGY #		
Parameter	Reference Interval	Units
TSH	Vitros EciQ Cobase411 0.465 to 4.68 0.270-4.2	mIU/L

IMMUNOLOGY #		
Parameter	Reference Interval	Units
iPTH	15-65	pg/mL

*ND = Not detectable

Source of reference interval is available from respective parameter SOP/procedure manual as applicable.

Textbook reference interval except β-hCG test for postmenopausal female on Vitros EciQ.

@ Establish range established by LTR Facility

€ In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing.

Reference: Standards of Medical Care In Diabetes-2018 in Diabetes Care (The Journal of Clinical & Applied Research & Education,Vol 41,suppl 1,Jan 2018) American Diabetes Association

¥ Colour Atlas of the Urinary Sediment, CAP, 2010, ISBN: 978-0-930304-87-4.

1¥ Hyaline and Granular cast may be found in urine of normal individuals.

2¥ Calcium oxalate and triple phosphate can be seen in healthy individuals.

3¥ Amorphous phosphate can be seen in healthy individuals.

10.5. Appendix 5: Protocol Amendment History

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

Summary of major changes in Amendment number 2.0 dated 14 Sep 2020

Sr. No.	Location in protocol	Description Protocol (Version 1.0; Dated 26 Mar 2020)	Change in the Text (List of Changes in version 2.0; Dated 14 Sep 2020)	Reason for the Change
1	List of Facilities	Bioanalytical services: • For Pharmacodynamic Services: Lambda Therapeutic Research Limited, Ahmedabad. • For Pharmacokinetic and Immunogenicity Services: Address : **Lambda Therapeutic Research Inc. 460 Comstock Road, Toronto, Ontario, M1L 4S4, Canada** Tel. No. : +1-416-752-3636 Fax. : +1-416-752-7610	Bioanalytical services (Pharmacodynamic, Pharmacokinetic and Immunogenicity assessments). Address : **Lambda Therapeutic Research Limited, Ahmedabad Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad – 382481. Gujarat, India** Tel. No. : +91-79-4020 2020 Fax No. : +91-79-4020 2021/22	All bio analytical services kept at Ahmedabad facility
2	Sponsor's Medical Monitor	Name : **Dr Inderjeet Singh** Tel. No. : 02717-660948 Fax No : 02717-660105 E-Mail: : inderjeet_singh@intaspharma.com	Name : **Dr. Dharma Rao Uppada** Tel. No. : 02717-660948 Fax No : 02717-660105 E-Mail: : Dharma_Uppada@intaspharma.com	Administrative change
3	Synopsis: and section 3.0 Objectives and Endpoints:	(….)	(…) Below secondary endpoint has been added • **Assessment for difference in PK or PD in patients who are found to be immunogenic**	Regulatory advice related strategy change
4	Synopsis and section 4.1: Overall Design	(….)	(….) **The PK, PD samples collected in these patients will be assessed for impact of immunogenicity on PK and PD only**	Regulatory advice related strategy change

Sr. No.	Location in protocol	Description Protocol (Version 1.0; Dated 26 Mar 2020)	Change in the Text (List of Changes in version 2.0; Dated 14 Sep 2020)	Reason for the Change
			if there is immunogenicity identified in a particular patient either clinically or by immunogenicity analysis.	
5	Other Protocol-Required Therapies	(…) From screening to end of study, participants will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of at least **600** mg calcium and at least 400 IU vitamin D. (…)	(…) From screening to end of study, participants will receive daily calcium and vitamin D supplementation that at a minimum should be in the range of at least **1000** mg calcium and at least 400 IU vitamin D. (…)	Update
6	Synopsis and Section 5.1	(…) 1. Participant must be 55 to **75** years of age (both inclusive), at the time of signing the informed consent. (…)	(…) 1. Participant must be 55 to **90** years of age (both inclusive), at the time of signing the informed consent. (…)	Regulatory advice related strategy change
7	Synopsis and Section 5.2	(…) 11. Current, uncontrolled hyper- or hypothyroidism, defined as thyroid stimulating hormone outside of the normal range (Total T3-1.49 to 2.60 nmol/L, Total T4-5.53-11.0 µg/dL, TSH-0.465 to 4.68 mIU/L) at screening (…)	(…) 11. Current, uncontrolled hyper- or hypothyroidism, defined as thyroid stimulating hormone outside of the normal range (TSH-0.465 to 4.68 mIU/L) at screening. (…)	Update

Sr. No.	Location in protocol	Description Protocol (Version 1.0; Dated 26 Mar 2020)	Change in the Text (List of Changes in version 2.0; Dated 14 Sep 2020)	Reason for the Change
8	Synopsis: Section 8.7, 8.9: Sampling Schedule for PK and PD evaluation	(…) **Sample collection after second dose:** The venous blood samples will be withdrawn at 4704.00 (Day 211; Month 7), 5376.00 (Day 241; Month 8), 6048.00 (Day 271; Month 9), 6720.00 (Day 301; Month 10), 7392.00 (Day 331; Month 11), and 8064.00 (Day 361; Month 12) hours post dose following first dose administration.	(…) **Sample collection after second dose:** The venous blood samples will be withdrawn at 5040.000 (Day 211; Month 7), 5760.000 (Day 241; Month 8), 6480.000 (Day 271; Month 9), 7200.000 (Day 301; Month 10), 7920.000 (Day 331; Month 11), and 8640.000 (Day 361; Month 12) hours post dose following first dose administration. **Sample collection after third dose: The venous blood samples will be withdrawn at pre third dose, 24.000 (Day 2), 720.000 (Day 31), 1440.000 (Day 61), 2160.000 (Day 91), 2880.000 (Day 121), 3600.000 (Day 151) and 4320.000 (Day 181) hours post dose following third dose administration.**	Regulatory advice related strategy change
9	Synopsis: Section 8.10: Sampling Schedule for Immunogenicity evaluation	8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre-dose (baseline), at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361 with respect to dosing. *Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration.	8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre-dose (baseline), at day 14, 31, 61, 91, 181*, 211, 241, 271 and 361 with respect to first dosing. **8.5 ml of blood will be withdrawn for estimation of Immunogenicity parameters at Pre- third dose (baseline), at day 2, 31, 61, 91 and 181 with respect to third dosing.***Note: Blood sample for immunogenicity on day 181 will be collected prior to 2nd dose administration and day 361 before 3rd dose administration respectively.	Regulatory advice related strategy change

Sr. No.	Location in protocol	Description Protocol (Version 1.0; Dated 26 Mar 2020)	Change in the Text (List of Changes in version 2.0; Dated 14 Sep 2020)	Reason for the Change
10	4.1. Overall Design	(…) Assumption is approximately 120 patients in denosumab-ref arm who would have undergone PK assessments will be completing double-blind period of the initial 12 months study and will be randomized in the transition-extension period **(~60 in denosumab-ref and ~60 in denosumab)**.	(…) Assumption is approximately 120 patients in denosumab-ref arm who would have undergone PK assessments will be completing double-blind period of the initial 12 months study and will be randomized in the transition-extension period **(~68 in denosumab-ref and ~68 in denosumab).** The PK, PD samples collected in these patients will be assessed for impact of immunogenicity on PK and PD only if there is immunogenicity identified in a particular patient either clinically or by immunogenicity bioanalysis.	Regulatory advice related strategy change
11	8. Study Assessments and Procedures	The total blood volume for the study is approximately 407 + 10 mL or **456 + 10** mL as applicable.	The total blood volume for the study is approximately 407 + 10 mL or **544 + 10** mL as applicable.	Update according to changes in sampling schedules
12	9.1. Sample Size Determination	(…)	(…) **Immunogenicity assessment** **A sample size of 54 completers per group would ensure that the upper bound of the 95% CI of ADA incidence will not be larger than 10% assuming no more than one patient per group is observed to be positive for ADA at the end of treatment duration and using a Clopper-Pearson exact method to calculate the 95% CI for a sample proportion. Considering ~20% dropouts/ withdrawals, 136 patients (68**	Regulatory advice related strategy change

Sr. No.	Location in protocol	Description Protocol (Version 1.0; Dated 26 Mar 2020)	Change in the Text (List of Changes in version 2.0; Dated 14 Sep 2020)	Reason for the Change
			patients per arm) will be required for immunogenicity assessment.	
13	Section 9.2: Populations for Analyses	(….) Modified Intent-To-Treat (mITT) set: The mITT set is defined as all randomized patients who will receive at least one dose of study medication and will undergo at least one post-dose efficacy evaluation. (…)	(…) • Intent-To-Treat (ITT) set: The ITT set is defined as all randomized patients who will receive at least one dose of study medication. Sensitivity analysis will be performed on patients in ITT set for primary endpoint mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 12 months. For this analysis, missing values of individual BMD of lumbar spine at 12 months will be imputed with value as baseline value ± 0.73 (i.e. half of equivalence limit 1.45 considered in the study). Imputation will be done with value as (baseline value - 0.73) for test and (baseline value + 0.73) for reference product. • Modified Intent-To-Treat (mITT) set: The mITT set is defined as all randomized patients who will receive at least one dose of study medication and will undergo at least one post-dose efficacy evaluation. Missing data will be imputed using last observation carried forward (LOCF) technique.	Regulatory advice related strategy change

Note: The above-mentioned changes are universal changes applicable to all respective sections of protocol.

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Investigator Agreement

Protocol Title: A Randomized, Double-Blind, Active-Controlled, Parallel Arm, Multicenter Study Comparing Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in Postmenopausal Women with Osteoporosis.

Protocol Number: 0774-19

I, the undersigned, have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. I agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of investigators and all other pertinent requirements of ICH E6 (R2) Guideline on Good Clinical Practice; New Drugs & Clinical Trial Rules, 2019 of CDSCO; Declaration of Helsinki (Fortaleza, 2013); as per any other applicable regulatory requirements.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study IMP, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(DD-MMM-YYYY)

Notes:

- If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.
- Please retain original page of the Investigator's declaration at the site and send a copy of this page to Lambda Therapeutic Research Limited, Ahmedabad.