Radius Health, Inc. (RADIUS)

22 Boston Wharf Road, 7th Floor
Boston, MA 02210 USA

(617) 551-4000

Abaloparatide-SC

CLINICAL STUDY PROTOCOL: BA058-05-019

A Randomized, Double-blind, Placebo-controlled, Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of Abaloparatide-SC for the Treatment of Men with Osteoporosis

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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Protocol Version History

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Original	12 October 2017
Amendment 1	09 January 2018
Amendment 2	30 October 2018
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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP), as required by the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) GCP E6 (R2) guidance.

In addition, I have read the clinical study protocol with the title of: *A Randomized, Double-blind, Placebo-controlled, Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of Abaloparatide-SC for the Treatment of Men with Osteoporosis*, Amendment 6 dated 30 March 2021, and agree to the following conditions:

- To conduct this study in accordance with the design and provisions of this clinical study protocol.
- To await Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval for the protocol and informed consent (IC) before initiating enrollment into the study. If approval is suspended or terminated by the IRB/IEC the principal investigator will notify the Sponsor immediately.
- To ensure that the requirements for obtaining IC are met and to obtain IC from subjects before their enrollment into the study.
- To provide sufficient and accurate financial disclosure and update information if any relevant changes occur during the investigation and for 1 year following the completion of the study.
- To collect and record data as required by this protocol into the case report form (CRF).
- To maintain the confidentiality of all information received or developed in connection with this protocol.
- To conduct this study in accordance with the ICH GCP guideline, the Declaration of Helsinki, and all applicable regulatory requirements.
- To permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.
- To maintain study documentation for the period of time required.
- To report all adverse events (AEs) within the specified timeframe to Radius Health, Inc. (RADIUS) or their designee.
- To report all serious AEs/incidents within 24 hours after becoming aware of the event to the Contract Research Organization and enter the data into the Electronic Data Capture system.
- To adhere to the publication policy of RADIUS Health, Inc. for data collected during this study.

Signature of Principal Investigator	Date
Print Name	Site Number

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LIST OF ABBREVIATIONS

Abbreviation	Term
aBMD	Areal bone mineral density
AE	Adverse event
AFF	Atypical femoral fracture
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BSAP	Bone-specific alkaline phosphatase
BUN	Blood urea nitrogen
BVF	Bone volume fraction
cAMP	Cyclic adenosine monophosphate
C_{max}	Maximum plasma concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
FDA	Food and Drug Administration
FRAX	Fracture Risk Assessment
GCP	Good clinical practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good laboratory practice
G_{mean}	Geometric mean
GMP	Good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Term
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of mercury
MMRM	Mixed Model for Repeated Measures
ONJ	Osteonecrosis of the jaw
ORX	Orchidectomized
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMM	Pattern-mixture model
PP	Per-Protocol
PT	Prothrombin time
PTH	Parathyroid hormone
$PTHR_1$	Parathyroid hormone related protein type 1 receptor
PTHrP	Parathyroid hormone related peptide
PTT	Partial thromboplastin time
Q1, Q3	Interquartile range
QA	Quality assurance
QCT	Quantitative computed tomography
QT	Total depolarization and repolarization time
QTc	Total depolarization and repolarization time corrected with heart rate
R^0	Non-G protein-coupled
RANK	Receptor activator of nuclear factor kappa-B
RBC	Red blood cell
RG	G protein-coupled
rhPTH	Recombinant human parathyroid hormone

Abbreviation	Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
s-CTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	Standard deviation
SHBG	Sex hormone binding globulin
sMTS	Solid microstructured transdermal system
SOC	System organ class
SOP	Standard operating procedure
s-PINP	Serum procollagen type I N-terminal propeptide
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal phase half-life
TEAEs	Treatment-emergent adverse events
t_{max}	Time to reach maximum plasma concentration following drug administration
TSH	Thyroid stimulating hormone
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
US	United States
vBMD	Volumetric bone mineral density
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title: A Randomized, Double-blind, Placebo-controlled, Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of Abaloparatide-SC for the Treatment of Men with Osteoporosis

Protocol Number: BA058-05-019

Test Drug: Abaloparatide 80 μg for subcutaneous injection

Study Objectives and Endpoints

Objective: The primary objective of this prospective controlled study is to evaluate the efficacy and the safety of abaloparatide-subcutaneous (SC) 80 μg per day compared to placebo in men with osteoporosis.

Endpoints

The primary efficacy endpoint is the percent change from baseline in lumbar spine bone mineral density (BMD) at 12 months.

The key secondary efficacy endpoints are:

- Percent change from baseline in total hip BMD at 12 months
- Percent change from baseline in femoral neck BMD at 12 months

Additional secondary efficacy endpoints are:

- Percent change from baseline in:
  - Lumbar spine BMD at 3 and 6 months
  - Total hip BMD at 3 and 6 months
  - Femoral neck BMD at 3 and 6 months
  - Ultra-distal radius BMD at 3, 6, and 12 months
  - Distal one-third radius BMD at 3, 6, and 12 months
- Log ratio of post-baseline over baseline in:
  - Serum procollagen type I N-terminal propeptide (s-PINP) at 1, 3, 6, and 12 months
  - Serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) at 1, 3, 6, and 12 months
- Proportion of subjects experiencing BMD gains from baseline of > 0%, > 3%, and > 6% at the lumbar spine, femoral neck, and total hip at 3, 6, and 12 months
- Incidence of new clinical fractures at 12 months
- Proportion of subjects converting from the categories of osteoporosis to osteopenia or to normal at 12 months, where:
  - Osteoporosis is defined as lumbar spine or total hip BMD T-score ≤ -2.5.

  - Osteopenia is defined as one of the following:
    - Lumbar spine > -2.5 and total hip BMD T-score > -2.5 and < -1.0
    - Lumbar spine > -2.5 and < -1.0 and total hip BMD T-score > -2.5
  - Normal is defined as lumbar spine and total hip BMD T-score ≥ -1.0.
- The percent change in total hip and femoral neck volumetric BMD (vBMD) as measured by quantitative CT (QCT) from baseline to 12 months. QCT will be performed in a subset of subjects at a selected number of study sites.

For those subjects who consent to pharmacokinetic (PK) sample collection, the PK endpoints are:

- The plasma concentration of abaloparatide based on sparse PK sampling at the following visits:
  - Month 6: postdose PK samples collected 45 minutes (±15 minutes) and 2.5 hours (±0.5 hour) after abaloparatide-SC injection
  - Month 9: postdose PK samples collected 20 minutes (±10 minutes) and 4 hours (±0.5 hour) after abaloparatide-SC injection
  - Month 12: a predose sample and a postdose sample collected 1.5 hours (±0.5 hour) after abaloparatide-SC injection

The safety endpoints are:

- Overall safety and tolerability of abaloparatide-SC in men with osteoporosis as assessed by adverse events (AE), vital signs, electrocardiograms (ECGs), laboratory tests of chemistry and hematology, urinalyses, local tolerance, and presence of antibodies

Subgroup analyses (e.g., age, geography, Fracture Risk Assessment, FRAX [if applicable], prior fracture, and baseline BMD, s-PINP, testosterone, and estradiol levels) may be performed and will be described in the Statistical Analysis Plan.

Study Population

Men aged 40 to 85 years with primary osteoporosis or osteoporosis associated with hypogonadism.

Inclusion Criteria

1. The subject is a healthy ambulatory male from 40 to 85 years of age (inclusive) with primary osteoporosis or osteoporosis associated with hypogonadism.
2. The subject has a BMD T-score (based on the male reference range as assessed by the central imaging vendor) of:
   a. ≤ -2.5 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by dual energy X-ray absorptiometry (DXA); or

b. ≤ -1.5 and with radiologic evidence of vertebral fracture or a documented (radiograph films or report) history of low-trauma nonvertebral fracture sustained in the past 5 years.
c. Men older than 65 years may be enrolled if they have a BMD T-score ≤ -2.0 even if they do not meet the fracture criteria.

3. The subject is in good general health as determined by medical history and physical examination (including vital signs) and is without evidence of a clinically significant abnormality in the opinion of the Investigator, or none for which there is a reasonable chance of interfering with the subject's health and/or medical treatment during the study. The subject has a body mass index (BMI) of 18.5 to 33, inclusive. The BMI is derived from the subject's height and weight. In the case where a subject's height cannot be adequately assessed (e.g., due to vertebral compression fractures or scoliosis), the subject's historical height (as documented in the subject's medical record) will be used to derive the BMI.
4. Hypogonadal subjects whose doses of androgens have been stable for at least 12 months before randomization are eligible and may continue therapy during the study.
5. The subject has serum calcium (albumin-corrected), parathyroid hormone (PTH), serum phosphorus and alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value and who meets all other entry criteria must have a normal bone-specific alkaline phosphatase to be enrolled. Any subject with a TSH value outside of the normal range must have central laboratory reported T3 and free T4 values within the normal ranges to be enrolled.
6. The subject has serum 25-hydroxyvitamin D values ≥ 20 ng/mL and within the normal range. Subjects with serum 25-hydroxyvitamin D levels < 20 ng/ml may be treated with vitamin D and retested once during the Screening Period.
7. The subject's systolic blood pressure is ≥ 100 and ≤ 155 mmHg, diastolic blood pressure is ≥ 40 and ≤ 95 mmHg, and heart rate is ≥ 45 and ≤ 100 bpm (taken sitting or supine). Any recorded values outside of these ranges and assessed by the Investigator to be not clinically significant must be reviewed with the Medical Monitor and Sponsor for approval prior to enrollment.
8. The subject has no clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells and platelets, or usual serum biochemistry: electrolytes, renal function, liver function and serum proteins that might be expected to interfere with the subject's health and/or medical treatment during the study.
9. In subjects who have partners of childbearing potential, the subject and his partner should abstain from sexual intercourse, or use highly effective contraceptive measures (e.g., oral contraceptive and condom, intrauterine device [IUD] and condom, or diaphragm with spermicide and condoms; other forms of contraception must be approved by the Medical Monitor) when engaging in sexual intercourse throughout the study, and for at least 90 days after the last dose of abaloparatide.
10. The subject has read, understood, and signed the written informed consent form.

Exclusion Criteria

General exclusion criteria:

1. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal BMD, defined as having at least 2 radiologically evaluable vertebrae within L1–L4 as assessed by the central imaging reader.

   Anatomically abnormal vertebrae are excluded if:

   - They are clearly abnormal and non-assessable within the resolution of the system; or
   - There is a more than 1.0 T-score difference between the vertebra in question and adjacent vertebrae.
2. A BMD T-score of ≤ -3.5 at the total hip, femoral neck or lumbar spine based upon the male reference range.
3. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
4. Fragility fracture within the past 12 months.
5. History of severe vertebral fracture or > 2 moderate vertebral fractures.
6. History of bone disorders (e.g., Paget's disease) other than osteoporosis.
7. Subjects with clinical signs of hypogonadism present at screening who plan to initiate testosterone replacement.
8. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine.
9. History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances to a degree that would interfere with the interpretation of study data or compromise the safety of the subject.
10. History of Cushing's disease, growth hormone deficiency or excess, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year.
11. History of significantly impaired renal function (serum creatinine > 177 μmol/L or > 2.0 mg/dL). If the serum creatinine is > 1.5 and ≤ 2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must be ≥ 37 mL/min.
12. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin).
13. History of osteosarcoma at any time.
14. Subjects with hereditary disorders predisposing to osteosarcoma.
15. History of nephrolithiasis or urolithiasis within the past 5 years.
16. Subjects known to be positive for Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV)-1 or HIV-2. Testing is not required in the absence of clinical signs and symptoms suggestive of HIV infection or acute or chronic hepatitis.

Medication-related exclusion criteria:

17. Known history of hypersensitivity to any of the test materials or related compounds.
18. Prior treatment with PTH- or parathyroid hormone related protein (PTHrP)-derived drugs, or bone anabolic drugs including abaloparatide, teriparatide, or PTH(1-84).
19. Prior treatment with intravenous (IV) bisphosphonates at any time or oral bisphosphonates within the past 3 years. Subjects who had received a short course of oral bisphosphonate therapy (3 months or less) may be enrolled as long as the treatment occurred 6 or more months prior to enrollment.
20. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or other bone-acting investigational agents at any time. Limited use of gallium citrate/nitrate for diagnostic purposes (i.e., a gallium scan) is not exclusionary.
21. Prior treatment with calcitonin or tibolone in the past 6 months.
22. Prior treatment with denosumab within the past 18 months.
23. Treatment with anticonvulsants that affect vitamin D metabolism (phenobarbital, phenytoin, carbamazepine, or primidone) or with chronic heparin within the 6 months prior to the Screening Period.
24. Treatment with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) within the past 90 days.
25. Daily treatment with oral, intranasal, or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of all corticosteroids (for seasonal allergies or asthma) is not exclusionary.
26. Exposure to an investigational drug within the 12 months prior to the Screening Period.

Lifestyle-related exclusion criteria:

27. Abnormal nutritional status (as assessed by the Investigator), vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day. Short term use of high doses of vitamin D to increase endogenous vitamin D levels for study entry is not exclusionary.
28. Subject is known to consume > 2 alcoholic drinks per day, to use illegal drugs, or to abuse tobacco or marijuana (medicinally or recreationally where legal) within 12 months of the Screening Period. The Investigator must determine and document use vs. abuse of tobacco or marijuana.

Design and Methodology

Number of Subjects

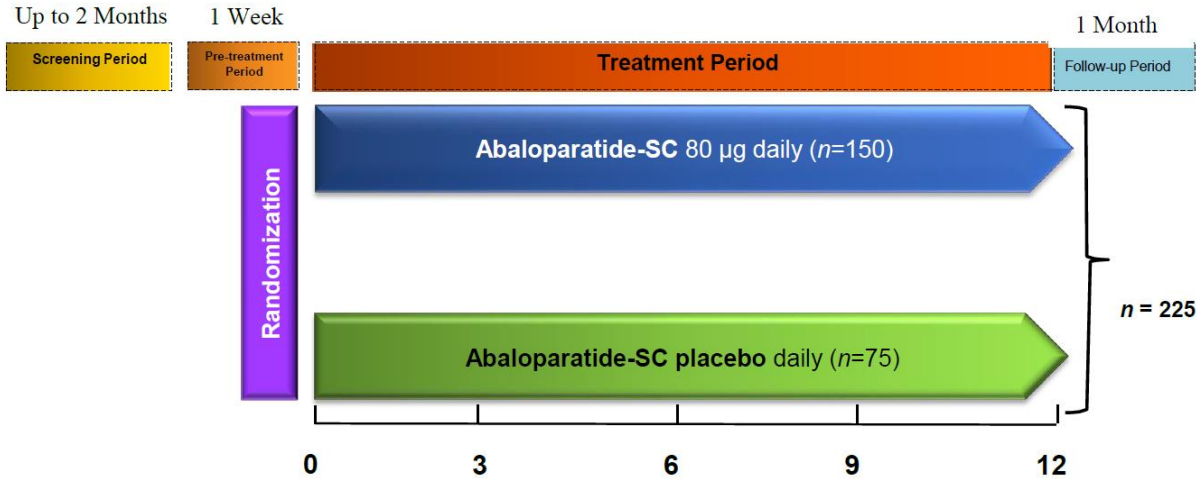
Approximately 225 men will be enrolled into the study.

Design

This is a randomized, double-blind, placebo-controlled, Phase 3, multicenter study enrolling approximately 225 subjects at approximately 40 study sites designed to evaluate the efficacy and safety of abaloparatide-SC 80 µg per day for the treatment of osteoporosis in men. The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), and a Treatment

Period (12 months) with a final visit 1 month after the last dose of study medication (Follow-up Visit). Eligible subjects will be randomized, on a 2:1 basis, to receive either abaloparatide-SC 80 µg per day or matched-SC placebo injections for 12 months to determine the effect of abaloparatide on lumbar spine BMD and other bone health-related endpoints. Both groups of subjects will undergo protocol-specified procedures (Schedule of Assessments and Procedures, Table 3) including BMD and fracture assessments. The study design is presented in the figure below.

Protocol BA058-05-019 Study Design



Study Visits

All subjects will have clinic visits for study-related procedures at Day 1, Month 1, Month 3, Month 6, Month 9, and Month 12, with a Follow-up Visit 1 month after the last dose of study medication. For the purposes of this study 1 month is equal to 30 days.

Treatments Administered

Eligible subjects will be randomly allocated, using a 2:1 randomization ratio using a permuted block randomization on Day 1 to receive treatment with either blinded abaloparatide-SC 80 µg per day or daily abaloparatide-SC placebo injections, respectively. Treatment will be blinded to subjects, Investigators, and the Sponsor throughout the study unless unblinding is necessary for subject treatment in the case of medical emergency, and with exception of Sponsor pharmacovigilance and/or regulatory personnel as needed for suspected unexpected serious adverse reaction (SUSAR) reporting purposes. All subjects will be provided calcium and vitamin D to ensure that their daily intake is in the range of calcium 500–1000 mg/day and vitamin D 400-800 IU/day, or a dose determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need.

Procedures and Assessments

Refer to the Schedule of Events for full details about the procedures and assessments required at each study visit.

During the Screening Period, informed consent will be obtained, eligibility for study entry assessed, and screening evaluations performed, including baseline lumbar and thoracic spine radiographs, BMD assessments by DXA, serum total testosterone, sex hormone binding globulin, and baseline laboratory tests.

- Subjects whose laboratory tests do not fall within the specified ranges as detailed in the inclusion/exclusion criteria may have the samples redrawn and the tests repeated once during the Screening Period. If upon retesting, the values fall within the inclusion/exclusion criteria, the subject may enter the study.
- Subjects who do not meet the vitamin D entry criterion (their 25-hydroxyvitamin D is less than 20 ng/ml) may receive vitamin D supplementation and be retested once during the Screening Period as may subjects with minor elevations of PTH. All subjects enrolled following retesting must have safety labs within 30 days of randomization (Day 1).

Following these evaluations, eligible subjects will enter the Pretreatment Period of the study and will be given daily calcium and vitamin D supplements, which will continue until the end of the Treatment Period. Subjects will also receive training in the use of the injector pen for self-administration.

At Day 1, the subject will have baseline assessments including bone turnover markers, immunogenicity testing, DXA of the wrist, and QCT measurement at the hip (at a subset of sites).

During the Treatment Period, subjects will self-administer a single subcutaneous dose of the randomly assigned study medication once a day. Subjects will have clinic visits for study-related protocol procedures at Day 1, Month 1, Month 3, Month 6, Month 9, and Month 12. Study procedures will include the measurement of BMD by DXA and collection of serum samples to assess markers of bone turnover. At each visit, clinical fractures will also be assessed. Serum samples for evaluation of calcium after study drug administration and immunogenicity testing will be drawn at specified visits during the Treatment Period.

Statistical Considerations

The primary population for efficacy analyses will be the Intention-to-Treat (ITT) Population, defined as all subjects randomized into this study. The primary population for safety analyses will be the Safety Population, defined as all subjects who received at least one dose of study medication. The Per-Protocol Population will include all ITT subjects who did not have any significant protocol deviations and will be used for supportive analyses.

Sample Size

A study sample size of 225 subjects (150 in the abaloparatide-SC group and 75 in the placebo group) will provide at least 99% power to detect a mean difference of 6.5% in the percentage change from baseline in lumbar spine BMD at 12 months between the abaloparatide-SC and the placebo groups at a 2-sided alpha of 0.01, assuming a standard deviation (SD) of 6.0% and a drop-out rate of 10%.

For the key secondary endpoints, this total sample size of 225 subjects will have 96% power to detect a 2.2% mean difference (SD = 3.5%) of percent change in total hip BMD at 12 months

and 80% power to detect a 2.0% mean difference (SD = 4.1%) of percent change in femoral neck BMD at 12 months.

Baseline Comparisons

Baseline characteristics, medical history, physical examination, vital signs, and ECGs will be summarized using standard descriptive statistics by treatment group.

Efficacy Analysis

The primary and key secondary efficacy endpoints will be analyzed using a fixed-sequence testing procedure to control the family-wise error rate for any joint distribution of hypothesis test statistics. To claim statistical significance at the 2-sided level of 1%, the following 3 fixed-sequence tests will be performed in sequential order. At any step of the sequential testing, if the treatment difference is not statistically significant at the 1% level then all the subsequent comparisons following the fixed sequence cannot be claimed statistically significant.

1. Percent change from baseline in BMD at the lumbar spine at 12 months
2. Percent change from baseline in BMD at the total hip at 12 months
3. Percent change from baseline in BMD at the femoral neck at 12 months

P-values for treatment comparisons of all other efficacy endpoints will be generated to support the study findings without any adjustments for multiplicity.

For the analysis of BMD data, the primary analysis will be based on a pattern-mixture model (PMM) analysis with multiple imputation using the wash-out imputation method. This method uses sequential regression and wash-out imputation methodology to impute missing values after a subject's discontinuation from the study. The missing primary endpoint values for subjects in the abaloparatide-SC group will be imputed with the observed baseline and data from the placebo group; no intermediate values from the abaloparatide-SC group will be used in the imputation for the abaloparatide-SC group. For subjects in the placebo group, intermediate observed values from the completers in the placebo group will be used while imputing missing values during the 12-month Treatment Period. The PROC MI methodology for imputation of monotone missing data patterns will be used to impute the outcome variables at consecutive visits in a sequential (chain) manner. Each of these imputed datasets will be analyzed using analysis of covariance (ANCOVA) with treatment and DXA instrument manufacturer as fixed effects and the baseline lumbar spine BMD as a covariate. Results from all imputed datasets will be combined using PROC MIANALYZE for overall statistical inference. The statistical tests will be 2-sided comparing abaloparatide-SC to placebo; 99% CIs will be presented together with the estimated p-values.

Analysis of bone turnover markers, s-PINP and s-CTX, will be based on the ratio of the post-baseline value relative to the baseline value at each visit. The transformation of the $\log_e$ ratio of post-baseline versus baseline value will be used to normalize the distributions of the s-PINP and s-CTX parameters. The analysis comparing abaloparatide-SC with placebo will use a PMM analysis with multiple imputation using the wash-out imputation method, as described for BMD.

Safety Analysis

Safety analysis will be analyzed descriptively and will include the following parameters:

- Treatment-emergent AEs (TEAEs)
- Changes in vital signs (including orthostatic blood pressure [BP]), ECGs, and laboratory (hematology, serum chemistry, and urinalysis) tests
- Investigator and subject assessment of local tolerance
- Presence of antibodies

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Safety

Recent health status will be obtained, the diary reviewed, and AEs collected at each visit and vital signs will be performed at each clinic visit. Laboratory assessments of chemistry and hematology, and urinalyses will be obtained at screening, and at Month 1, Month 6, and Month 12. A final visit will take place 1 month after the last dose of study medication.

Any subject who demonstrates decreases in BMD ≥ 7% from baseline of this study at the lumbar spine or total hip will have the assessment repeated and, if confirmed, will be notified by the Investigator, and be withdrawn from the study. Subjects sustaining a radiologically confirmed incident vertebral or nonvertebral fragility fracture will be informed of the finding and will be counseled as to treatment options and may discontinue or choose to remain on the study. Should a subject who experiences an incident clinical vertebral or nonvertebral fragility fracture choose to remain in the study, he will be asked to sign an additional informed consent form explaining the potential risks and benefits of remaining in the study.

Duration of Subject Participation:

Participation will be up to 16 months (12 months total treatment duration).

1. INTRODUCTION

1.1. Background

Human parathyroid hormone (PTH) is a naturally occurring 84 amino acid hormone and is primarily a regulator of calcium homeostasis (Mannstadt et al, 1999). PTH acts directly on bone to increase calcium resorption, on the gastrointestinal system to increase calcium absorption, and on the kidney to increase calcium reabsorption and 1,25-dihydroxyvitamin D production. In turn, PTH levels are tightly regulated by calcium and vitamin D levels. When given intermittently at low doses, PTH has a well-documented anabolic effect on bone, and can increase bone mineral density (BMD) in a number of intact animal models and in osteoporotic subjects (Dempster et al, 1993).

Abaloparatide (marketed as TYMLOS® in the United States [US]) is a novel, synthetic, 34 amino acid peptide designed to be a potent and selective activator of the PTH/PTH-related protein (PTHrP) type 1 receptor ($PTHR_1$) signaling pathway with 41% homology to PTH[1–34]) and 76% homology to human PTHrP[1–34]. Abaloparatide is differentiated from PTH and PTHrP ligands based on its high affinity and > 1,000-fold greater selectivity for the G protein-coupled (RG) vs the non-G protein-coupled (R^0) conformation of $PTHR_1$ (Hattersley et al, 2016). Differential $PTHR_1$-RG binding with abaloparatide results in potent and transient intracellular cyclic adenosine monophosphate (cAMP) signaling. In nonclinical studies, the transient $PTHR_1$ activation with abaloparatide strongly favors bone anabolism with a limited effect on bone resorption (Makino et al, 2015). Thus, abaloparatide was developed with the expectation that it would be effective at increasing BMD and reducing fracture in individuals with osteoporosis, but with a limited effect on bone resorption and a reduced risk of hypercalcemia.

1.1.1. Disease and Study Drug Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to enhanced fragility and increased risk of fractures (Rizzoli et al, 2001). This disease is characterized by low BMD and fractures. The fractures associated with the greatest morbidity and mortality, as well as economic burden to society, together make up the clinically significant and medically relevant group termed major osteoporotic fractures. In the US, there are an estimated 2 million osteoporotic fractures annually (Litwic et al, 2014). The number of osteoporotic fractures is projected to increase in both men and women by more than 3-fold over the next 50 years as a result of the aging population (WHO 2007).

Although osteoporosis predominantly affects postmenopausal women, approximately 20% of men over the age of 50 years will sustain an osteoporotic-related fracture in their lifetime. In 2005, the total cost of treatment and rehabilitation for fractures in men in the US was $4.1 billion and this is projected to rise to $6.8 billion in 2025 (IOF 2014). Most men experience bone loss with aging and low BMD is frequent in older men and a risk factor for fracture. Many different risk factors may contribute to bone loss and fracture risk in men, including most importantly hypogonadism, glucocorticoids, and excessive alcohol use (Ebeling 2008). Additionally, some men develop osteoporosis without apparent cause, so-called idiopathic osteoporosis (Khosla 2008).

Bone remodeling occurs through the action of osteoclasts, which are involved in the resorption of bone followed by the formation of new bone by osteoblasts. In addition to continued use of calcium and vitamin D, the current therapeutic approach to the treatment of osteoporosis through inhibition of bone resorption includes agents such as bisphosphonates (Rosen 2005) or monoclonal antibody denosumab, that inhibits the action of osteoclasts by binding to receptor activator of nuclear factor kappa-B (RANK) ligand. An alternative approach has been to tip the balance between osteoblastic bone formation and osteoclastic resorption through the use of parathyroid hormone receptor modulation using teriparatide (rhPTH[1–34]).

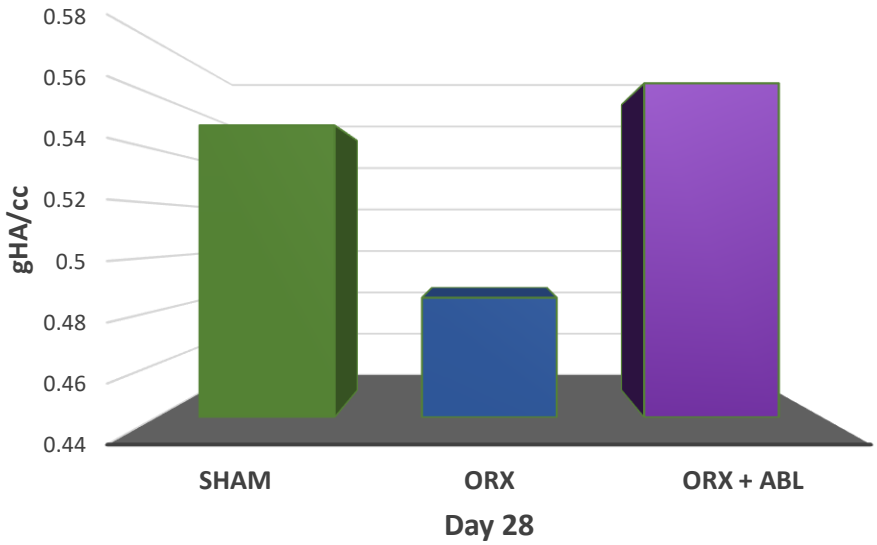
Until recently, teriparatide has been the only approved osteoporosis treatment in which the major mode of action is stimulation of bone formation (anabolic) rather than suppression of bone resorption. The efficacy of teriparatide has important limitations related to its delayed and modest effects on increasing BMD at the total hip and femoral neck, and on decreasing BMD at the distal one-third radius. The increase in cortical porosity that can occur may result in maladaptive effects on cortical bone microarchitecture (Bilezikian 2007). Abaloparatide has been evaluated in a number of nonclinical and clinical studies for its potential as a novel treatment for osteoporosis. Based on the biology of the PTH_1 receptor signaling pathway, abaloparatide is designed to have less resorptive and hypercalcemic effects than PTH, resulting in a greater net anabolic effect. Abaloparatide has recently been approved in the US for the treatment of women with postmenopausal osteoporosis at high fracture risk. In addition to their role in the management of postmenopausal osteoporosis, bisphosphonates, denosumab, and teriparatide have also been approved for the treatment of osteoporosis in men or to increase bone mass in men with osteoporosis.

1.1.2. Study Drug Development

1.1.2.1. Nonclinical Studies in Male Animals

Abaloparatide was tested in a non-Good Laboratory Practice (GLP) pharmacology study (16RADL120) using a male rat castration (orchidectomized [ORX]) model of osteoporosis. Male rats underwent ORX or sham surgery at approximately 3 months of age and following a 4-week bone depletion period. Treatment was then initiated with either abaloparatide (20 µg/kg/d, n = 8) or vehicle (n = 8) once daily for an additional 4-weeks. After 8 weeks of androgen deficiency, the ORX group had 13% lower L4 BMD and 17% lower trabecular bone volume fraction (BVF), compared with sham controls. After 4 weeks of treatment, the abaloparatide treated group had a 17% greater L4 BMD, 50% greater BVF, and 33% greater trabecular thickness compared with ORX controls (all $p < 0.0001$), Figure 1. Trabecular bone pattern factor was 39% lower compared with ORX controls ($p < 0.05$), suggesting a more organized and better-connected trabecular architecture. The abaloparatide group also had 24% greater BVF and 29% greater trabecular thickness, compared with sham controls (both $p < 0.01$). These data demonstrate that abaloparatide reversed vertebral BMD loss and restored trabecular microarchitectural deterioration in ORX rats by increasing trabecular bone volume and thickness.

Figure 1: L4 Vertebral Body BMD after 4 Weeks of Treatment in Male Rats



Two rodent GLP nonclinical studies were completed evaluating abaloparatide effects on male reproduction following repeated subcutaneous administration. A 4-week repeat-dose toxicology study with male fertility assessment (BA058-114) and a definitive male fertility study with an early embryonic development component (SBL062-288) were performed. In both studies, Abaloparatide failed to produce adverse effects in male fertility indices, fecundity, early embryonic development, and spermatogenesis at exposures up to 128-fold human exposure (animal: human exposure multiple) based on a human area under the concentration-time curve (AUC) of 1546 pg*hr/mL from Study BA058-05-001B and AUC from the rat 28-day repeat-dose toxicology Study BA058-114.

Abaloparatide was tested in repeat-dose toxicity studies in male rats up to 70 µg/kg for up to 26 weeks (BA058-114, BA058-115 and 7801-124), and in male monkeys at 10 µg/kg for up to 39 weeks (BA058-119 and 7801-125). The conclusions from the repeat-dose toxicity studies were consistent with a primary pharmacology of abaloparatide associated with a new bone formation in male animals. There were no significant differences in safety, tolerability or histopathological findings between male and female animals noted in these studies. These nonclinical results are consistent with abaloparatide having positive bone anabolic effect in male animals.

1.1.2.2. Clinical Studies

There are 19 completed and ongoing clinical studies which comprise the abaloparatide-subcutaneous (SC) and abaloparatide-solid microstructured transdermal system (sMTS) clinical development program. The abaloparatide-SC clinical trial program consists of 11 clinical trials, including a large pivotal Phase 3 study (BA058-05-003) followed by an open-label extension (Study BA058-05-005) and Phase 2 studies in postmenopausal women with osteoporosis (abaloparatide-SC Studies BA058-05-002 and BA058-05-002 extension as well as BA058-05-007, an abaloparatide-sMTS study in which abaloparatide-SC at a dose of 80 µg was

used as the active comparator) and Phase 1 studies in healthy postmenopausal women, healthy male and female subjects, and subjects with renal impairment.

In the pivotal Phase 3 study (BA058-05-003, the ACTIVE trial), 2,463 postmenopausal women were randomized to receive daily 80 µg abaloparatide-SC (n = 824), placebo (n = 821), or teriparatide 20 µg (n = 818) (rhPTH 1-34) for 18 months. In this trial, abaloparatide-SC and teriparatide significantly reduced the risk of new morphometric vertebral fractures, by 86% and 80%, respectively, compared to placebo. Abaloparatide-SC significantly reduced nonvertebral, major osteoporotic and clinical fractures compared to placebo. Compared to teriparatide, abaloparatide significantly reduced major osteoporotic fractures. The Kaplan-Meier plots indicate an early and sustained fracture risk reduction of nonvertebral, major osteoporotic and clinical fractures with abaloparatide-SC treatment. Abaloparatide-SC has an acceptable safety profile, and consistent with reduced abaloparatide-SC-mediated calcium mobilization, the rates of hypercalcemia were lower in the abaloparatide-SC group compared to the teriparatide group.

In the ACTIVExtend trial (BA058-05-005), subjects who were in the abaloparatide-SC or placebo arms were transitioned to oral alendronate 70 mg weekly. Subjects who received 18 months of abaloparatide-SC followed by 6 months of alendronate experienced no new morphometric vertebral fractures from Study 005 baseline and continued to have statistically significant reductions in nonvertebral, major osteoporotic, and clinical fractures when compared to subjects who previously received 18 months of placebo followed by 6 months of alendronate. These results validate the osteoporosis treatment paradigm of build (with an anabolic agent), and then maintain and consolidate gains (with an antiresorptive agent).

Abaloparatide-SC demonstrated an increase in BMD at the lumbar spine, total hip, femoral neck, and ultra-distal radius in osteoporosis subjects, consistent with the fracture risk reduction. The results from the ACTIVE trial and the first 6 months of the ACTIVExtend trial, together with the entire data set from the abaloparatide-SC development program, support the safety and efficacy of abaloparatide-SC for the reduction of fractures in postmenopausal women with osteoporosis.

At the 43-month timepoint, the previous abaloparatide-SC treated subjects, who received up to 2 years of treatment with alendronate, had a significant 84% relative risk reduction ($p < 0.0001$) in the incidence of new vertebral fractures compared with women who received placebo followed by alendronate for up to 2 years. They also demonstrated a 39% risk reduction in nonvertebral fractures ($p = 0.038$), a 34% risk reduction in clinical fractures ($p = 0.045$) and a 50% risk reduction in major osteoporotic fractures ($p = 0.011$) compared with women who received placebo followed by alendronate.

The adverse events (AEs) were comparable between abaloparatide-SC treated subjects and the previous placebo group. The incidences of cardiovascular AEs including serious adverse events (SAEs) were similar between groups. There have been no cases of osteonecrosis of the jaw (ONJ) or atypical femoral fracture (AFF) in the entire abaloparatide-SC development program.

Overall, the clinical results of abaloparatide-SC-mediated early vertebral and nonvertebral fracture risk reduction and increases in BMD are consistent with the known anabolic mechanism of action, changes in bone turnover markers and nonclinical results.

For the most up-to-date information on clinical studies with abaloparatide, refer to the abaloparatide Investigator's Brochure (IB).

1.2. Study Rationale

As noted above, abaloparatide-SC recently became the second bone anabolic agent to be approved for the treatment of postmenopausal osteoporosis. While other agents from both anabolic and antiresorptive classes of anti-osteoporosis therapies have also been approved for the treatment of osteoporosis in men, the safety and efficacy of abaloparatide has yet to be demonstrated in osteoporotic men. However, given the existence of an enhanced therapeutic response to abaloparatide-SC in postmenopausal women at high risk of fracture, as well as the substantive morbidity and mortality burden associated with osteoporotic fractures, confirmation of a similarly robust effect of abaloparatide-SC in men is indeed a clinical priority. The present study seeks to provide that confirmation, in order for abaloparatide-SC to be made available to men with osteoporosis and whose clinical need remains unmet by currently available therapies.

1.3. Dose Rationale

The approved dose of abaloparatide-SC in the US for the treatment of postmenopausal women at a risk for fracture is 80 µg per day, this is also the proposed dose in the European Union (EU). While the long-term treatment of men with abaloparatide-SC has not been evaluated, Phase 1 studies have been conducted to evaluate pharmacokinetics following a single administration of abaloparatide-SC, at a dose of 80 µg in both male and female subjects, the proposed dose selected for the present study.

To provide a comparison of pharmacokinetics (PK) and safety for male and female subjects, the data from 3 recent Phase 1 clinical trials were pooled (BA058-05-010 was a bioavailability/maximum tolerated dose study, BA058-05-011 was a study in subjects with varying degrees of renal disease, BA058-05-012 was a study to determine the effects of abaloparatide-SC on total depolarization and repolarization time / total depolarization and repolarization time corrected with heart rate (QT/QTc) and BA058-05-014 was a study done to provide initial evaluation of the bioequivalence of abaloparatide administered subcutaneously from 2 similar pen injectors to healthy male and female subjects). Summary PK data are presented in Table 1. The 90% CIs for the ratio of AUC and for the ratio of maximum serum concentration (C_{max}) between males and females were generated based on an analysis of variance (ANOVA) model with sex as fixed effect. Maximal time (t_{max}) values were compared using a t-test. These results show that there were no differences in the systemic exposure of abaloparatide-SC between male and female subjects following a single administration of abaloparatide-SC at a dose of 80 µg.

Table 1: Summary of PK Data in Subjects Treated with Abaloparatide-SC 80 µg (Pooled Data[#])

Parameters (Unit)	Statistics	Female	Male
AUC_{last} (pg*h/mL)	n	64	92
	Mean (SD)	664.49 (349.232)	670.41 (345.728)
	Median	618.50	567.53
	Q1, Q3	469.68, 743.95	390.45, 926.21
	Min, Max	128.0, 2288.3	156.9, 1832.0
	MSE	43.654	36.045
	G_{mean}	591.28	588.07
	Ratio of Male/Female (90% CI) [1]		0.9946 (0.8664, 1.1417)
	Ratio of Male/Female (90% CI) [2]		1.0049 (0.8781, 1.1501)
$AUC_{0-\infty}$ (pg*h/mL)	n	61	88
	Mean (SD)	703.39 (359.555)	724.75 (363.382)
	Median	644.00	618.39
	Q1, Q3	505.33, 775.74	428.35, 980.34
	Min, Max	194.0, 2325.4	176.2, 1923.0
	MSE	46.036	38.737
	G_{mean}	632.53	641.28
	Ratio of Male/Female (90% CI) [1]		1.0138 (0.8861, 1.1600)
	Ratio of Male/Female (90% CI) [2]		1.0323 (0.9056, 1.1768)
C_{max} (pg/mL)	n	64	92
	Mean (SD)	524.69 (168.997)	467.17 (152.786)
	Median	507.00	455.00
	Q1, Q3	416.00, 618.00	366.00, 545.00
	Min, Max	198.0, 1140.0	214.0, 928.0
	MSE	21.125	15.929
	G_{mean}	498.86	443.77
	Ratio of Male/Female (90% CI) [1]		0.8896 (0.8153, 0.9706)
	Ratio of Male/Female (90% CI) [2]		0.8943 (0.8195, 0.9758)
t_{max} (h)	n	64	92
	Mean (SD)	0.40 (0.191)	0.42 (0.177)
	Median	0.33	0.33
	Q1, Q3	0.25, 0.50	0.25, 0.50
	Min, Max	0.3, 1.1	0.3, 1.1
	MSE	0.024	0.018
	G_{mean}	0.36	0.39
	P-value [3]		0.4177
$t_{½}$ (h)	n	62	89
	Mean (SD)	1.26 (2.270)	1.07 (0.565)
	Median	0.96	0.95
	Q1, Q3	0.77, 1.11	0.67, 1.30
	Min, Max	0.5, 18.7	0.4, 3.2
	MSE	0.288	0.060
	G_{mean}	0.97	0.96

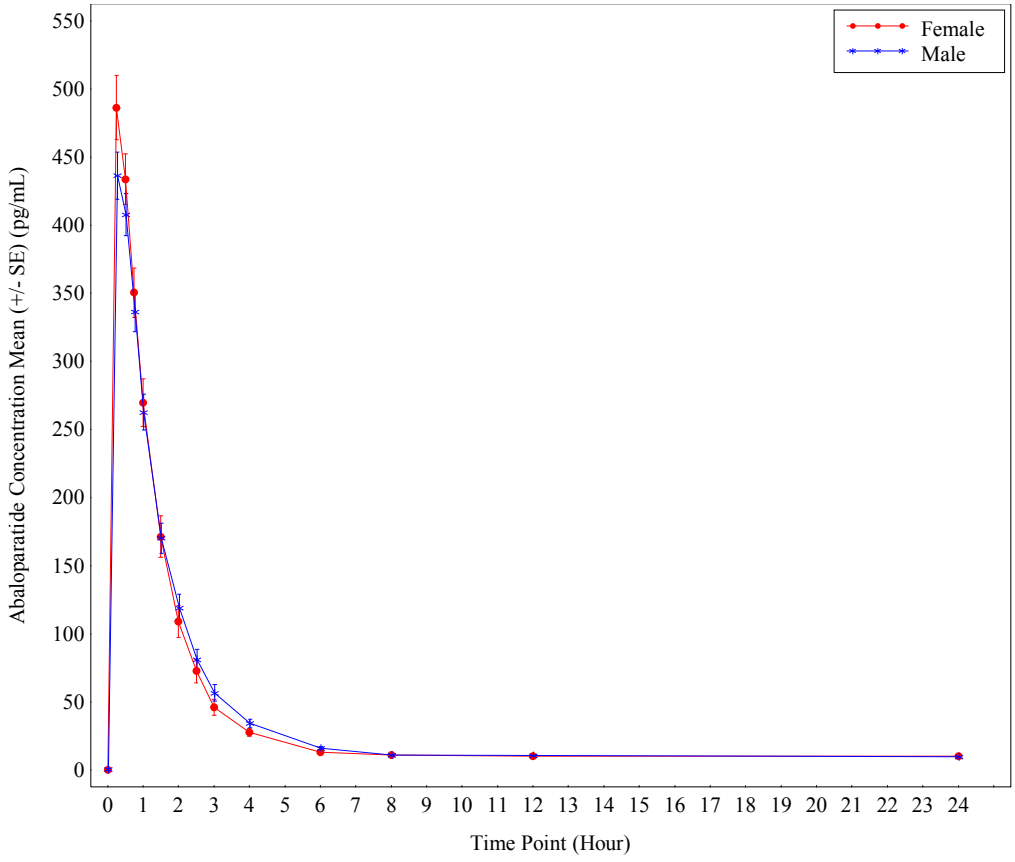
[#] The data include studies BA058-05-010, BA058-05-011, BA058-05-012, and BA058-05-014. Ten female subjects and 17 male subjects in Study BA058-05-014 received 2 doses of abaloparatide-SC; both PK profiles are included in the summary table.

[1] Ratio is based on ANOVA model with sex as fixed effect.

[2] Ratio is based on ANOVA model with sex and study as fixed effects.
[3] P-value is based on T-test
$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; C_{max} = maximum plasma concentration; G_{mean} = geometric mean; MSE = standard error of the mean;.Q1, Q3 = interquartile range; SD = standard deviation; $t_{1/2}$ = apparent terminal phase half-life; t_{max} = time to reach maximum plasma concentration following drug administration.
Postdose BQL values were set to half the LLOQ for computation of mean postdose concentration values.

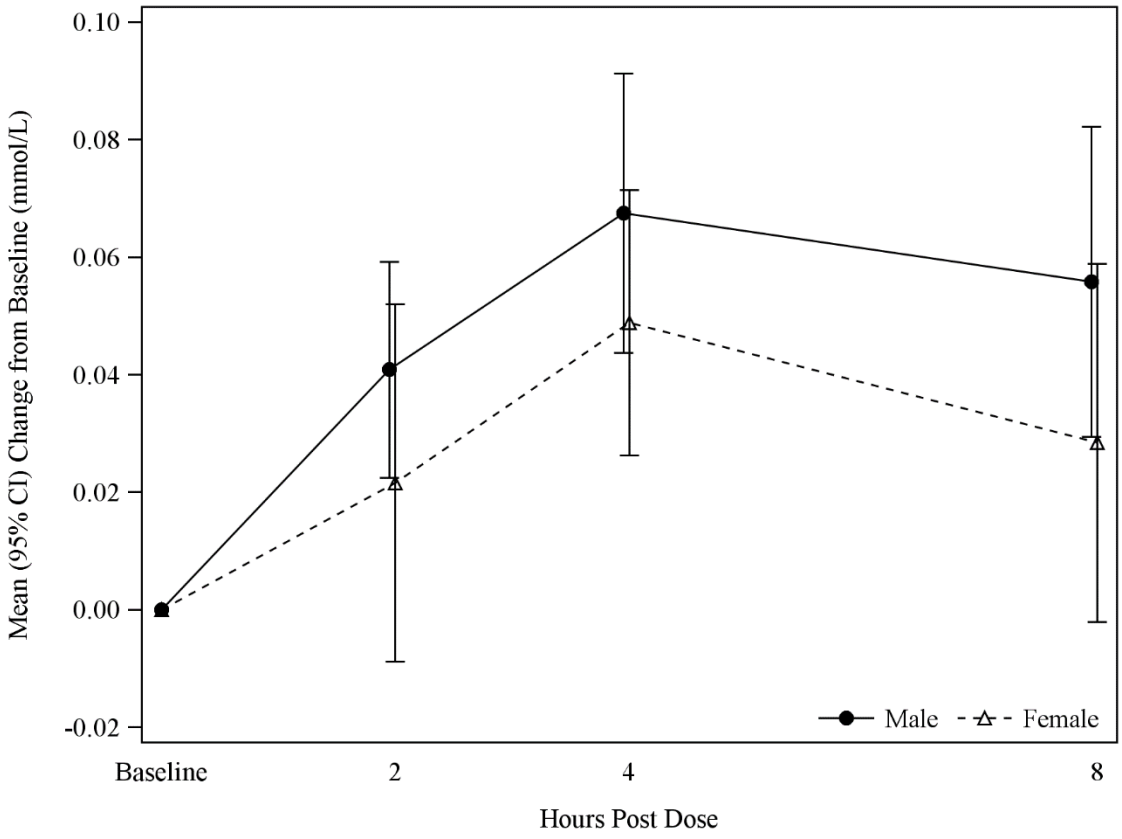
There were also no apparent differences in abaloparatide clearance (Figure 2).

Figure 2: PK Concentration over Time in Subjects Treated with Abaloparatide-SC 80 µg (Pooled Data[#])



[#] The data include studies BA058-05-010, BA058-05-011, BA058-05-012, and BA058-05-014.

Figure 3: Study BA058-05-012 – Mean (95% CI) Change from Baseline in Serum Calcium over Time by Gender for Abaloparatide 80 µg Treatment (Safety Population)



In the clinical trial of women with postmenopausal osteoporosis (BA058-05-003), abaloparatide-SC caused increases in serum calcium concentrations, evident at 4-hours post administration. Serum calcium concentrations were assessed in both male and female subjects in Study BA058-05-012. In this study, male and female subjects were dosed with a single injection of 80 µg of abaloparatide-SC. Serum calcium levels were measured at baseline, and at 2, 4, and 8 hours postdose. Although the levels across time were slightly higher in males than in females (Figure 3), the temporal pattern of change in serum calcium concentration was similar, with the maximal concentrations observed approximately 4 hours after dosing.

Table 2: Pooled Treatment-Emergent Adverse Events – Differences Between Male and Female Subjects in Phase 1 Studies (BA05805-010, BA05805-010, BA05805-011, BA05805-012, and BA05805-014) *

System Organ Class Preferred Term	Female (N = 54) n (%)	Male (N = 77) n (%)
At Least one TEAE	25 (46.3)	16 (20.8)
Cardiac disorders	2 (3.7)	1 (1.3)
Bundle branch block left	1 (1.9)	0
Palpitations	1 (1.9)	0
Postural orthostatic tachycardia syndrome	0	1 (1.3)
Gastrointestinal disorders	4 (7.4)	4 (5.2)
Nausea	3 (5.6)	4 (5.2)
Abdominal distension	1 (1.9)	0
Abdominal pain	1 (1.9)	0
Diarrhoea	1 (1.9)	0
Vomiting	0	1 (1.3)
General disorders and administration site conditions	9 (16.7)	4 (5.2)
Injection site erythema	8 (14.8)	3 (3.9)
Injection site pruritus	5 (9.3)	0
Application site erythema	1 (1.9)	0
Chills	0	1 (1.3)
Injection site haemorrhage	0	1 (1.3)
Infections and infestations	1 (1.9)	0
Viral upper respiratory tract infection	1 (1.9)	0
Investigations	1 (1.9)	0
Blood pressure increased	1 (1.9)	0
Metabolism and nutrition disorders	1 (1.9)	1 (1.3)
Decreased appetite	1 (1.9)	1 (1.3)
Musculoskeletal and connective tissue disorders	1 (1.9)	1 (1.3)
Musculoskeletal pain	1 (1.9)	0
Myalgia	0	1 (1.3)
Nervous system disorders	13 (24.1)	10 (13.0)
Headache	11 (20.4)	7 (9.1)
Dizziness postural	2 (3.7)	2 (2.6)
Dizziness	1 (1.9)	2 (2.6)
Paraesthesia	0	1 (1.3)
Somnolence	0	1 (1.3)

System Organ Class Preferred Term	Female (N = 54) n (%)	Male (N = 77) n (%)
Respiratory, thoracic and mediastinal disorders	2 (3.7)	1 (1.3)
Dyspnoea	1 (1.9)	0
Oropharyngeal pain	1 (1.9)	0
Nasal congestion	0	1 (1.3)
Productive cough	0	1 (1.3)
Skin and subcutaneous tissue disorders	1 (1.9)	0
Erythema	1 (1.9)	0
Vascular disorders	1 (1.9)	0
Orthostatic hypotension	1 (1.9)	0

Each subject was counted once for the same system organ class and the same preferred term.
Preferred terms were sorted by descending order of counts by female and male.
TEAE = treatment-emergent adverse event

Abaloparatide has been studied in the male population, and differences in treatment-emergent adverse events (TEAEs) were observed between males and females (Table 2). In pooled data across 4 Phase 1 studies (BA05805- 010, BA05805-011, BA05805-012, and BA05805-014), 25 of 54 females (46.3%) and 16 of 77 males (20.8%) experienced at least one TEAE.

Based on these results, which demonstrated no apparent difference in the systemic exposure of abaloparatide-SC between males and females across 4 different Phase 1 clinical trials, together with Phase 3 safety and efficacy data showing significant increases in BMD in osteoporotic women following 6, 12, and 18 months of treatment with abaloparatide-SC, the 80-µg dose is therefore an appropriate dose for the treatment of men with osteoporosis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Endpoint

The primary objective of this prospective controlled study is to evaluate the efficacy and the safety of abaloparatide-SC 80 µg per day compared to placebo in men with osteoporosis. The primary efficacy endpoint is the percent change from baseline in lumbar spine BMD at 12 months.

2.2. Secondary Endpoints

The key secondary efficacy endpoints are:

- Percent change from baseline in total hip BMD at 12 months
- Percent change from baseline in femoral neck BMD at 12 months

Additional secondary efficacy endpoints are:

- Percent change in baseline in:
  - Lumbar spine BMD at 3 and 6 months
  - Total hip BMD at 3 and 6 months
  - Femoral neck BMD at 3 and 6 months
  - Ultra-distal radius BMD at 3, 6, and 12 months
  - Distal one-third radius BMD at 3, 6, and 12 months
- Log ratio of post-baseline over baseline in:
  - Serum procollagen type I N-terminal propeptide (s-PINP) at 1, 3, 6, and 12 months
  - Serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) at 1, 3, 6, and 12 months
- Proportion of subjects experiencing BMD gains from baseline of > 0%, > 3%, and > 6% at the lumbar spine, femoral neck, and total hip at 3, 6, and 12 months
- Incidence of new clinical fractures at 12 months
- Proportion of subjects converting from the categories of osteoporosis to osteopenia or to normal at 12 months, where:
  - Osteoporosis is defined as lumbar spine or total hip BMD T-score ≤ -2.5.
  - Osteopenia is defined as as one of the following:
    - Lumbar spine > -2.5 and total hip BMD T-score > -2.5 and < -1.0
    - Lumbar spine > -2.5 and < -1.0 and total hip BMD T-score > -2.5
  - Normal is defined as lumbar spine and total hip BMD T-score ≥ -1.0.

- The percent change in total hip and femoral neck volumetric BMD as measured by quantitative CT (QCT) from baseline to 12 months QCT will be performed in a subset of subjects in a selected number of study sites.

For those subjects who consent to PK sample collection, the PK endpoints are:

- The plasma concentration of abaloparatide based on sparse PK sampling at the following visits:
  - Month 6: postdose PK samples collected 45 minutes (±15 minutes) and 2.5 hours (±0.5 hour) after abaloparatide-SC injection
  - Month 9: postdose PK samples collected 20 minutes (±10 minutes) and 4 hours (±0.5 hour) after abaloparatide-SC injection
  - Month 12: a predose sample and a postdose sample collected 1.5 hours (±0.5 hour) after abaloparatide-SC injection

The safety endpoints are:

- Overall safety and tolerability of abaloparatide-SC in men with osteoporosis as assessed by AEs, vital signs, electrocardiograms (ECGs), laboratory tests of chemistry and hematology, urinalysis, local tolerance, and presence of antibodies

Subgroup analysis (e.g., age, geography, FRAX (if applicable), prior fracture, and baseline BMD, s-PINP, testosterone and estradiol levels) may be performed and will be described in the Statistical Analysis Plan (SAP).

3. STUDY DESIGN

3.1. Description of the Study Design

This is a randomized, double-blind, placebo-controlled, Phase 3, multicenter study enrolling approximately 225 subjects at approximately 40 study sites designed to evaluate the efficacy and safety of abaloparatide-SC 80 µg per day for the treatment of osteoporosis in men. The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), and a Treatment Period (12 months) with a Follow-up Visit 1 month after the last dose of study medication.

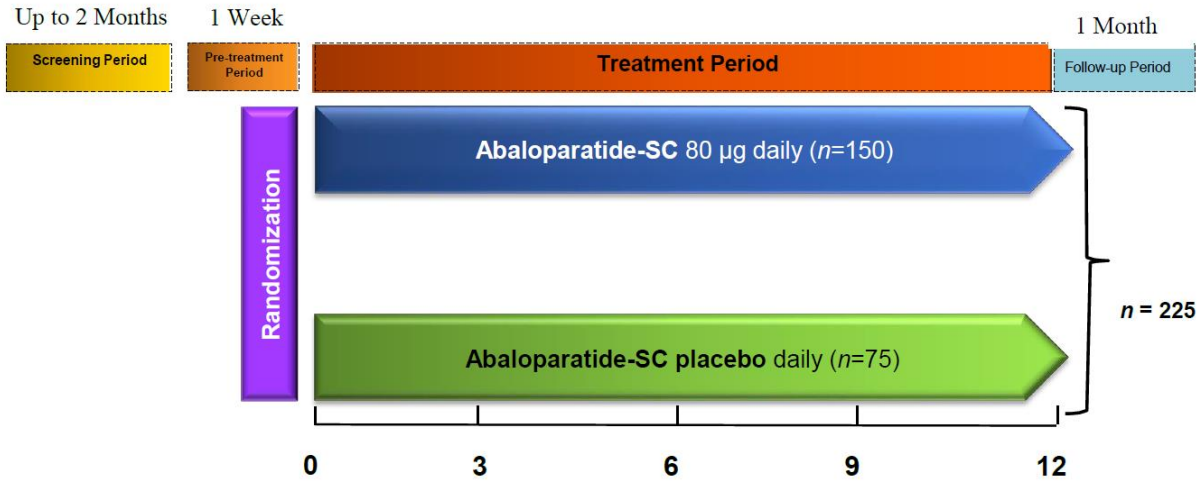
During the Screening Period, informed consent will be obtained, eligibility for study entry assessed, and screening evaluations performed. Subjects who are eligible for the study, on the basis of screening evaluations, will enter the Pretreatment Period of the study and will have additional baseline assessments.

Subjects who remain eligible for study participation will be randomly allocated, using a 2:1 randomization ratio on Day 1 to receive treatment with either blinded abaloparatide-SC 80 µg per day or daily placebo injections, respectively. Treatment will be blinded to subjects and Investigators throughout the study except in a medical emergency where the identity of study medication is necessary to appropriately treat the subject (Section 5.7). The Sponsor pharmacovigilance/regulatory personnel may also be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting purposes.

All subjects will receive calcium 500–1000 mg/day and vitamin D 400–800 IU/day, or a dose determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need.

The study design is presented in Figure 4, below. All subjects will undergo safety, BMD, bone marker, and fracture assessments at regular intervals, according to the Schedule of Assessments and Procedures (Table 3). Subjects will be asked if they are willing to provide PK samples to evaluate the amount of abaloparatide in the plasma at various timepoints. Those subjects who consent to this sparse PK sampling will have samples collected at Months 6, 9, and 12 as shown in Table 4.

Figure 4: Study BA058-05-019 Design



4. SELECTION OF STUDY POPULATION

To participate in this study, a subject must meet all of the inclusion criteria listed in Section 4.1 and none of the exclusion criteria listed in Section 4.2. Subjects who were screened and excluded from this study will be recorded in the electronic case report form (eCRF), as well as the reason why they were screen failures.

4.1. Inclusion Criteria

1. The subject is a healthy ambulatory male from 40 to 85 years of age (inclusive) with primary osteoporosis or osteoporosis associated with hypogonadism.
2. The subject has a BMD T-score (based on the male reference range as assessed by the central imaging vendor) of:
   a. ≤ -2.5 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by dual energy X-ray absorptiometry (DXA); or
   b. ≤ -1.5 and with radiologic evidence of vertebral fracture or a documented history of low-trauma nonvertebral fracture sustained in the past 5 years.
   c. Men older than 65 years may be enrolled if they have a BMD T-score ≤ -2.0 even if they do not meet the fracture criteria.
3. The subject is in good general health as determined by medical history and physical examination (including vital signs) and is without evidence of a clinically significant abnormality in the opinion of the Investigator, or none for which there is a reasonable chance of interfering with the subject's health and/or medical treatment during the study. The subject has a body mass index (BMI) of 18.5 to 33, inclusive. The BMI is derived from the subject's height and weight. In the case where a subject's height cannot be adequately assessed (e.g., due to vertebral compression fractures or scoliosis), the subject's historical height (as documented in the subject's medical record) will be used to derive the BMI.
4. Hypogonadal subjects whose doses of androgens have been stable for at least 12 months before randomization are eligible and may continue therapy during the study.
5. The subject has serum calcium (albumin-corrected), PTH, serum phosphorus and alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value and who meets all other entry criteria must have a normal bone-specific alkaline phosphatase to be enrolled. Any subject with a TSH value outside of the normal range must have central laboratory reported T3 and free T4 values within the normal ranges to be enrolled.
6. The subject has serum 25-hydroxyvitamin D values ≥ 20 ng/mL and within normal range. Subjects with serum 25-hydroxyvitamin D levels < 20 ng/ml may be treated with vitamin D and retested once during the Screening Period.
7. The subject's systolic blood pressure is ≥ 100 and ≤ 155 mmHg, diastolic blood pressure is ≥ 40 and ≤ 95 mmHg, and heart rate is ≥ 45 and ≤ 100 bpm (taken sitting or supine). Any recorded values outside of these ranges and assessed by the Investigator to be not

clinically significant must be reviewed with the Sponsor Medical Monitor for approval prior to enrollment.

8. The subject has no clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells, and platelets, or usual serum biochemistry: electrolytes, renal function, liver function and serum proteins that might be expected to interfere with the subject's health and/or medical treatment during the study.
9. In subjects who have partners of childbearing potential, the subject and his partner should abstain from sexual intercourse, or use highly effective contraceptive measures (e.g., oral contraceptive and condom, intrauterine device [IUD] and condom, or diaphragm with spermicide and condoms; other forms of contraception must be approved by the Medical Monitor) when engaging in sexual intercourse throughout the study, and for at least 90 days after the last dose of abaloparatide.
10. The subject has read, understood, and signed the written informed consent form (ICF).

4.2. Exclusion Criteria

General exclusion criteria:

1. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal BMD, defined as having at least 2 radiologically evaluable vertebrae within L1–L4 as assessed by the central imaging vendor.

   Anatomically abnormal vertebrae are excluded if:

   - They are clearly abnormal and non-assessable within the resolution of the system; or
   - There is a more than 1.0 T-score difference between the vertebra in question and adjacent vertebrae.
2. A BMD T-score of ≤ -3.5 at the total hip, femoral neck, or lumbar spine based upon the male reference range.
3. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
4. Fragility fracture within the prior 12 months.
5. History of severe vertebral fracture or > 2 moderate vertebral fractures.
6. History of bone disorders (e.g., Paget's disease) other than osteoporosis.
7. Subjects with clinical signs of hypogonadism present at screening who plan to initiate testosterone replacement.
8. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine.
9. History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances to a degree that would interfere with the interpretation of study data or compromise the safety of the subject.

10. History of Cushing's disease, growth hormone deficiency or excess, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year.
11. History of significantly impaired renal function (serum creatinine > 177 μmol/L or > 2.0 mg/dL). If the serum creatinine is > 1.5 and ≤ 2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must be ≥ 37 mL/min.
12. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin).
13. History of osteosarcoma at any time.
14. Subjects with hereditary disorders predisposing them to osteosarcoma.
15. History of nephrolithiasis or urolithiasis within the past 5 years.
16. Subjects known to be positive for Hepatitis B, Hepatitis C, human immunodeficiency virus (HIV)-1 or HIV-2. Testing is not required in the absence of clinical signs and symptoms suggestive of HIV infection or acute or chronic hepatitis.

Medication-related exclusion criteria:

17. Known history of hypersensitivity to any of the test materials or related compounds.
18. Prior treatment with PTH- or PTHrP-derived drugs, or bone anabolic drugs including abaloparatide or teriparatide, or PTH(1-84).
19. Prior treatment with intravenous (IV) bisphosphonates at any time or oral bisphosphonates within the past 3 years. Subjects who had received a short course of oral bisphosphonate therapy (3 months or less) may be enrolled as long as the treatment occurred 6 or more months prior to enrollment.
20. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or other bone-acting investigational agents at any time. Limited use of gallium citrate/nitrate for diagnostic purposes (i.e., a gallium scan) is not exclusionary.
21. Prior treatment with calcitonin or tibolone in the past 6 months.
22. Prior treatment with denosumab in the past 18 months.
23. Treatment with anticonvulsants that affect vitamin D metabolism (phenobarbital, phenytoin, carbamazepine, or primidone) or with chronic heparin within the 6 months prior to the Screening Period.
24. Treatment with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) within the past 90 days
25. Daily treatment with oral, intranasal, or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of all corticosteroids (for seasonal allergies or asthma) is not exclusionary.
26. Exposure to an investigational drug within the 12 months prior to the Screening Period.

Lifestyle-related exclusion criteria:

27. Abnormal nutritional status (as assessed by the Investigator), vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day. Short term use of high doses of vitamin D to increase endogenous vitamin D levels for study entry is not exclusionary.
28. Subject is known to consume > 2 alcoholic drinks per day, to use illegal drugs, or to abuse tobacco or marijuana (medicinally or recreationally where legal) within 12 months of the Screening Period. The Investigator must determine and document use vs. abuse of tobacco or marijuana.

4.3. Participant Withdrawal or Termination

4.3.1. Reasons for Withdrawal or Termination

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care.

The Investigator must withdraw subjects from the study for the following reasons:

- Continuing significant deterioration from baseline (≥ 7%) of BMD at spine or hip (after confirmation of the finding)
- Hypercalcemia as described in Section 4.7.1
- Severe hypersensitivity to abaloparatide
- Refusal of treatment
- Inability to complete study procedures
- Lost to follow-up

The Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Serious AEs (as described in Section 7.1.3)
- A complex of AEs which, in the judgment of the Investigator justifies treatment cessation
- Serious intercurrent illness
- Noncompliance
- Protocol deviations
- Administrative reasons

Subjects will be offered the opportunity to discontinue from the study for the following reasons after site consultation with the Study Medical Monitor:

- Incident vertebral or nonvertebral fragility fracture

Should a subject who experiences a clinical vertebral or nonvertebral fragility fracture choose to remain in the study, they will be asked to sign an additional ICF further explaining the potential risks and benefits of remaining in the study.

If a subject withdraws from the study due to the ongoing coronavirus disease 2019 (COVID-19) global pandemic, this information will be captured in the eCRF so that it can be described in the clinical study report at the end of the study, in line with the Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (FDA 2021).

The reason for the withdrawal should be recorded in the eCRF as COVID-19, if applicable, and include as many details as possible (e.g., the subject had a positive test result or decided to withdraw from the study due to personal choice related to COVID-19 concerns).

4.3.2. Handling of Participant Withdrawals or Terminations

If a subject is withdrawn or discontinued from the study, the reason for withdrawal from the study is to be recorded in the source documents and on the CRF. All subjects withdrawn prior to completing the study should be encouraged to complete study procedures scheduled for the Month 12/Early Termination visit as soon as possible, and to return in 1 month for a Follow-up Visit. All AEs should be followed as described in Section 7. Subjects who discontinue or are withdrawn from the study will not be replaced.

4.4. Concomitant Medications

Calcium (500–1000 mg/day) and vitamin D (400–800 IU/day) supplements, or a dose determined by the Investigator and approved by the Sponsor Medical Monitor, according to the subject's need, are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. The doses and schedule of calcium and vitamin D supplements, which are part of the study medication protocol, should be adhered to and not be changed other than for medical necessity. The supplements should be taken in the evening with or without food or as otherwise instructed by the Investigator.

For any required concomitant chronic medication, such as statins or antihypertensives, the subject must be on a stable dose for 90 days prior to study entry and every effort should be made to maintain a stable dose during study participation. If a medication or dose has not been consistent for 90 days prior to study entry, recent changes must have been due to reasons other than lack of control of the underlying medical condition, i.e., the underlying medical condition for which chronic medication is required must be well-controlled.

The occasional use of over-the-counter medications at labeled doses (e.g., ibuprofen or acetaminophen) for headache or minor discomfort is allowed. These are to be recorded in the source records and entered in the appropriate CRF. Subjects should not take any other medications, including over-the-counter medications, herbal medications, or mega-doses of vitamins during the study without prior approval of the Investigator.

If it becomes necessary for a subject to take any other medication during the study, the specific medication(s) and indication(s) must be discussed with the Investigator. All concomitant

medications taken during the course of the study must be recorded in the subject's medical record or source document and transcribed into the eCRF.

4.5. Prohibited Medications

Please refer to Section 4.2 for medication-related exclusion criteria.

Subjects cannot take any medications, including over-the-counter, non-prescription medication, with the exception of those noted in Section 4.4, within 72 hours prior to dosing on Day 1.

In addition, subjects are ineligible for the study if they have an abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption).

Occasional short term (≤ 3 months) use of corticosteroids for seasonal allergies or asthma is not prohibited. Subjects who require chronic treatment with either an anticonvulsant (phenobarbital, phenytoin, carbamazepine, or primidone), or with heparin will be discontinued.

4.6. Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the principal investigator (PI), and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient compliance with protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Decision of Sponsor.

Study may resume once concerns about safety, protocol compliance, or data quality are addressed and satisfy the Sponsor, IRB/IEC, and/or regulatory agencies, if applicable.

4.7. Temporary Suspension of Treatment

The Investigator has the right to suspend treatment with study medication for up to 14 continuous days or 28 cumulative days, without withdrawal of the subject from the study. Reasons for temporary suspension of treatment may include a medical reason unrelated to an adverse event (e.g., a planned procedure), or important social or administrative events. The reason for the suspension of treatment is to be documented in the CRF and in source documents. Such subjects should not be unblinded as to study medication.

When treatment is restarted, the subject should resume treatment with the next scheduled dose and continue until the scheduled End-of-Treatment. If the treatment suspension is due to a medical emergency and study medication needs to be unblinded, please refer to Section 5.7 for the procedures to be followed.

Subjects who develop hypercalcemia or hypercalciuria during the study are to have treatment with calcium and vitamin D temporarily suspended as described below.

4.7.1. Treatment Algorithm in Subjects Who Develop Hypercalcemia

Hypercalcemia is defined as any serum calcium (albumin-corrected) that is ≥ 0.3 mg/dL (equivalent to > 0.08 mmol/L) above the upper limit of normal (ULN). For this study, the normal range, ULN and lower limit of normal (LLN) for serum calcium (albumin-corrected) are determined by the central laboratory.

For any predose serum calcium (albumin-corrected) value which is ≥ 0.3 to 1.0 mg/dL, corresponding to ≥ 0.08 to 0.25 mmol/L, above the ULN (inclusive), confirm hypercalcemia by drawing a new serum sample as soon as possible after the result is received (Figure 5).

- If the repeat serum calcium (albumin-corrected) is above the LLN up to < 0.3 mg/dL (equivalent to < 0.08 mmol/L) above the ULN, the subject should continue study drug administration together with Calcium and vitamin D supplementation.
- If a subject's predose serum calcium is elevated on repeat testing, calcium and vitamin D supplementation should be withheld. The subject is to continue study drug administration during this interval.
- If the subject's predose serum calcium remains elevated 1-2 weeks after calcium and vitamin D supplementation is withheld, dosing of study drug should be stopped.

Treatment can be restarted if other causes of hypercalcemia are excluded after consultation with the Sponsor. Treatment with study drug should not be suspended for greater than 14 days.

If the subject continues in the study (with calcium and vitamin D supplements) and had an episode of a predose serum calcium (albumin-corrected) value of ≥ 0.3 to 1.0 mg/dL (corresponding to ≥ 0.08 to 0.25 mmol/L) above the ULN, repeat testing of the predose serum calcium (albumin-corrected).

- If the subject's serum calcium (albumin-corrected) value again returns to normal when not taking calcium and vitamin D supplements, the subject may continue in the study without calcium and vitamin D supplements.
- If the retest is still elevated, contact the Sponsor Medical Monitor to assess whether the subject is to be discontinued from the study.

For any serum calcium (albumin-corrected) value > 1.0 mg/dL above the ULN:

- Discontinue calcium and vitamin D supplements and discontinue the study drug as soon as the result is received. Confirm hypercalcemia by drawing a new serum sample as soon as possible.
- If the result of the retest remains > 1.0 mg/dL above the ULN, perform a second retest after 3 days without calcium and vitamin D supplements and study drug.
  - If the second retest is normal, the subject may continue in the study and resume study drug including the calcium and vitamin D supplements.

  - If the second retest is still elevated, contact the Sponsor Medical Monitor to assess whether the subject is to be discontinued from the study.

- If the subject continues in the study and has a repeat episode of serum calcium > 1.0 mg/dL above the ULN, contact the Sponsor Medical Monitor to assess whether the subject is to be discontinued from the study.

4.7.2. Treatment Algorithm in Subjects Who Develop Hypercalciuria

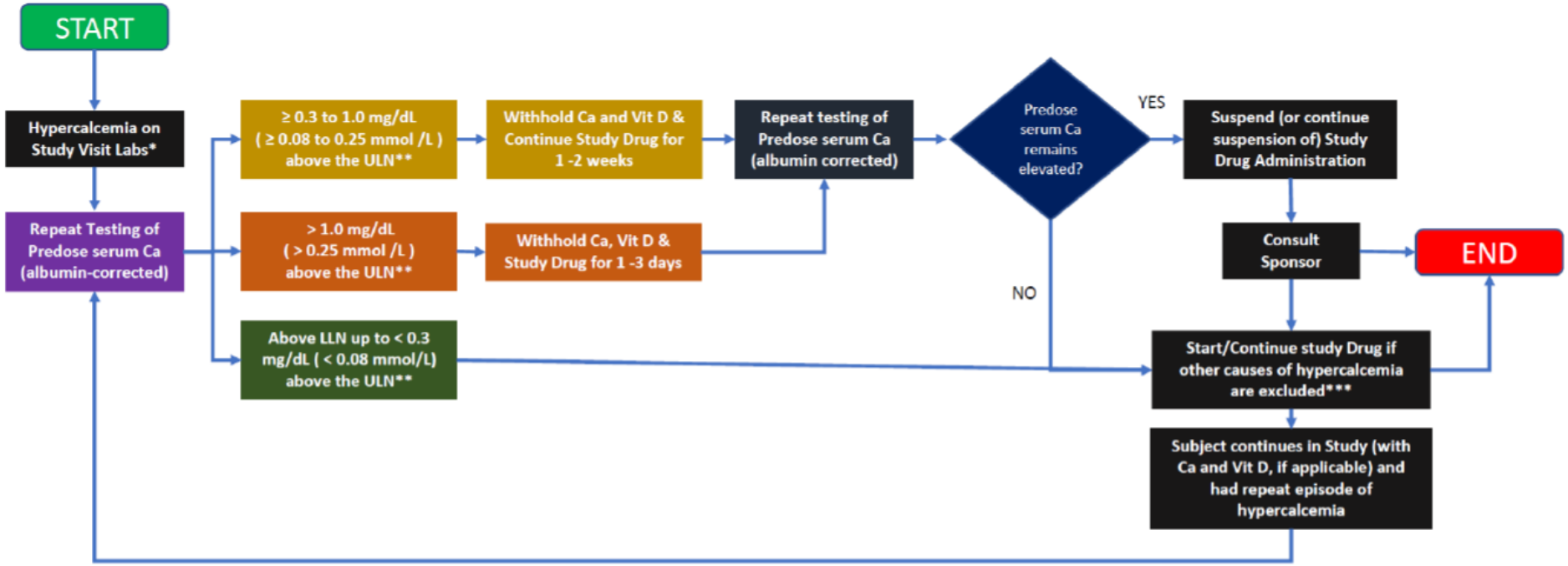
For a urine calcium:creatinine ratio > 0.4 mg/mg, corresponding to > 1.131 mmol/mmol, check the subject's predose serum calcium and apply the algorithm outlined in Section 4.7.1 if calcium is elevated.

If the calcium:creatinine ratio is > 0.4 mg/mg and the serum calcium is normal:

- Discontinue calcium and vitamin D supplements and recheck urine calcium:creatinine values after 7 days.
  - If the urine calcium:creatinine ratio continues to be > 0.4 mg/mg in the presence of normal serum calcium, the subject may continue in the study under medical supervision (and without receiving additional calcium and vitamin D supplements).
  - If the urine calcium:creatinine ratio returns to normal, the subject may restart calcium and vitamin D supplements and continue in the study.
- If the subject restarts the serum calcium and vitamin D supplements and hypercalciuria returns, calcium and vitamin D supplementation should be terminated. The subject may continue in the study under medical supervision.

Therefore, subjects with hypercalciuria will not be discontinued from the study in the absence of hypercalcemia except at the discretion of the Investigator.

Figure 5: Treatment Algorithm in Subjects Who Develop Hypercalcemia



*For any predose serum calcium (albumin-corrected) > 1.0 mg/dL (> 0.25 mmol/L) above the upper limit of normal (ULN), immediately discontinue calcium, vitamin D, and study drug
**ULN, lower limit of normal, and normal ranges are determined per the central laboratory
*** If applicable, also consider restarting/continuing vitamin D and calcium supplementation after consultation with the Sponsor

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

5.1. Study Medication

5.1.1. Abaloparatide-SC and Placebo

Abaloparatide-SC injection is supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-subject-use pen. The pen is intended to deliver 30 once daily abaloparatide doses of 80 µg in 40 µL of solution. Each pen contains 3120 µg/1.56 mL.

Placebo is formulated similarly but without active abaloparatide and will be similarly supplied as a sterile, colorless, clear solution in a glass cartridge which is pre-assembled into a disposable single-subject-use pen. The pen is intended to deliver 30 once daily placebo doses of 80 µg in 40 µL of fluid when inserted into the Pen Injector device.

Additional information will be provided to clinical sites in a separate Pharmacy Manual including instructions on how to use the injection pen.

5.1.2. Calcium and Vitamin D Supplements

Calcium (500–1000 mg) and vitamin D (400–800 IU) supplements will be sourced locally by the site and provided to subjects at the expense of the Sponsor.

5.2. Packaging, Labeling and Storage

5.2.1. Packaging and Labeling

Abaloparatide-SC and placebo will be supplied and packaged as identical injection pens. All packaging operations will be performed in accordance with Good Manufacturing Practices (GMP).

Study medication will be provided and replaced via the interactive response technology (IRT) on clinic visit days. If clinic visits are not possible, study medication may also be delivered to the subject's home. Labeling will include a caution statement and other information required by local regulatory authorities. A detailed study drug dispensation plan will be provided in the Pharmacy Manual.

Calcium and vitamin D supplements will be provided as packaged by the manufacturer and will not be relabeled for the study.

5.2.2. Storage

While at the clinical site, abaloparatide and placebo injection pens must be stored in a secure, limited access, temperature monitored refrigerator at 2° to 8°C (36° to 46°F) until dispensed for use to a study subject or until returned to the Sponsor.

After the abaloparatide-SC or placebo injection pen is used for the first time, the pen may be stored for 30 days at room temperature, 68°F to 77°F (20°C to 25°C). Unused pens should be refrigerated until initial use. Instructions regarding the storage and handling of the study drug after dispensation to subjects will be provided to sites in the Pharmacy Manual.

Calcium and vitamin D supplements should be stored according to the manufacturer recommendations on the bottle.

5.3. Treatment Assignment

All subjects who sign informed consent for the study will be assigned a unique 6-digit subject number which will be used to identify subjects throughout the study and in the eCRFs.

[redacted]

Subjects who meet all inclusion criteria and none of the exclusion criteria and successfully complete the Screening and Pretreatment Periods of the study will be assigned sequentially to a randomized treatment group on Day 1 of the Treatment Period. Subjects will only receive one study ID at the time of screening and therefore will not receive a new identifier at randomization. During the randomization transaction, the IRT will randomly allocate a treatment assignment and dispense the appropriate kit number for the subject's treatment. Information regarding treatment assignment will reside solely within the IRT, as part of the study blinding. Once a kit number has been assigned, it may not be reused. Refer to the IRT manual for additional details on IRT instructions.

Prior to study start, the Sponsor statistician will be responsible for overseeing the preparation of the master randomization scheme that will be used to package study medication into kits and for the IRT.

5.4. Dosing and Administration

Subjects will self-administer a single daily dose of 80 µg of study medication during the Treatment Period.

The first self-administration is to occur at the study site under observation. On the days of clinic visits, study medication **must be administered in the clinic** to accommodate pre-injection and post-injection procedures; study personnel may administer the study medication. For the Month 12 visit, subjects should be instructed to bring the study drug dispensed at the last study visit and to administer the study drug onsite.

Subjects will be trained by study personnel during the Pretreatment Period how to self-inject study medication with the abaloparatide-SC/Placebo injection pen. If a subject requires assistance with study medication administration, an individual (e.g., a family member) who has been trained by study personnel may provide assistance.

Subjects will also be provided written instructions on how to use the abaloparatide-SC/Placebo injection pen. Subjects will be instructed by the study site to inspect the contents of their injection pen before each injection. If the cartridge contents are not clear and colorless, or if the contents contain particles, the subjects will be instructed not to use the pen and to contact the study site for further guidance. Injections should be administered in the morning and preferably at the same time each day. If a dose is missed, the dose should be administered as soon as possible up to 12 hours after the missed injection. Any time thereafter, the dose should be skipped and the drug should be administered at the next scheduled time the following day. All injections are to be given in the periumbilical region, rotating the site of injection each day. If it is deemed medically necessary by the Investigator for an injection to be administered at a site other than the abdomen, the alternate site of injection is to be recorded and the reason for the change documented in the medical chart and eCRF as a protocol deviation. On the first day of study medication administration, the subject should self-inject while in a sitting or lying position at the study site and remain in that

position for approximately 5 minutes. Within 5 minutes, and 1 hour post-injection, the injection site will be evaluated by the Investigator using the scale provided by RADIUS. The subject is to remain under observation for a minimum of 60 minutes after the initial injection. An orthostatic blood pressure measurement will be taken 60 minutes after the injection. On the days when blood sampling is required after study medication injection, the subject is to remain in the vicinity of the clinic for the blood collections scheduled up to 4 hours post-injection. Subjects are to be instructed to self-inject at home in a location where they have the ability to sit or lie down.

To assess injection site reactions, the location, date, and time that each dose of study medication was administered must be recorded by the subject in the diary beginning on Day 2 and continuing through Day 7 in Month 1 (Visit 4) and beginning on Day 2 and continuing through Day 7 in Month 9 and entered in the diary.

Subjects will be instructed to use a new pen after each 30-day period. At each clinic visit during the Treatment Period, the used and unused abaloparatide-SC or placebo injection pens must be returned. Compliance, AEs, and use of concomitant medications should be reviewed upon drug re-supply and documented accordingly in the drug accountability log and eCRF.

5.5. Treatment Compliance

To ensure treatment compliance, the Investigator or designee will supervise all study drug administration that occurs at the site. At each study visit, the Investigator or designee will review subject compliance with study drug administration and remind the subject of study drug dosing requirements. Subject compliance will be ascertained by 2 methods: subject diaries and measuring the residual drug in the cartridge.

Discrepancies will be discussed with the subjects, documented in the medical charts, and recorded in the eCRF as appropriate. If a subject does not take all study medication (abaloparatide-SC, placebo, calcium, and vitamin D supplements), the reason for the missed dosing is to be recorded by the subject in their diary.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the Investigator should contact the Medical Monitor to discuss discontinuation of the subject from the study.

5.6. Drug Accountability

The Investigator or designated site staff will maintain records documenting the dates and amounts of the following:

- Study drug received
- Study drug dispensed to the subjects
- Study drug returned by the subjects
- Study drug returned to RADIUS/designee or destruction of study drug on site

Subjects will be instructed to return all used and unused study drug to the site. The study drug will be retained at the site until inventoried by the study monitor and approved for destruction or return. The study monitor will verify study drug records and inventory throughout the study.

5.7. Unblinding of Study Medication

5.7.1. Medical Emergency

Breaking the treatment blind for a subject should be done only in the event of a medical emergency where the identity of study medication is necessary to appropriately treat the subject. The Investigator may unblind the treatment received by the subject through the IRT. The IRT will automatically document and record any such unblinding and notify the Sponsor Medical Monitor of the unblinding event. The study monitor will not be apprised of the actual treatment assignment. In addition, the Sponsor Medical Monitor has the ability to unblind the study medication in a medical emergency.

If the Investigator determines that the medical event that resulted in unblinding of the study medication is not treatment related (relationship is documented as "none"; see Section 7.1.1 for definitions of relationship), the subject may continue treatment and participation in the study, providing no more than 14 days has elapsed since the last dose of study medication (refer to Section 4.7 for details regarding temporary suspension of treatment). If the subject discontinues from further treatment with study medication, they should undergo the Month 12/Early Termination and the Month 13 Follow-up Visit as outlined in Section 6.2.7, and the Schedule of Assessments and Procedures (Table 3).

6. STUDY PROCEDURES AND SCHEDULE

6.1. Study Procedures

6.1.1. Study-Specific Procedures

The study-specific assessments are detailed in this section and outlined in Table 3. Any results falling outside of the reference ranges may be repeated once time during the Screening Period at the discretion of the Investigator.

6.2. Study Schedule

This study is comprised of 9 clinic visits. Study assessments are to be performed according to the Schedule of Assessments and Procedures (Table 3). There is a ± 4-day window for each clinic visit.

The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), a Treatment Period (12 months), and a Follow-up Visit (1 month). During the Treatment Period, subjects will have clinic visits for study-related protocol procedures at Day 1, Month 1, Month 3, Month 6, Month 9, and Month 12. The active phase of the study will be considered complete when the last subject undergoes the last visit. For the purpose of this study, 1 month is equal to 30 days.

6.2.1. Schedule of Assessments and Procedures

A comprehensive Schedule of Assessments and Procedures is presented in Table 3.

Due to the ongoing COVID-19 pandemic, arrangements may also be made, contingent on the subject's consent and in compliance with country, state, and local requirements, to have a study visit conducted at the subject's home by site staff. If this occurs, blood and/or urine samples may be collected at the subject's home and then sent to the central laboratory for processing and analysis. Study drug may also be delivered to the subject's home, if needed, to enable the subject to continue administering their study drug daily.

Table 3: Schedule of Assessments and Procedures

	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Procedure	***Study Day/Month:***	**Screening**	**Pretreatment**	**Day 1**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Early Termination**	**Month 13 Follow-up**
Visit Window (Days)		**N/A[1]**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 7**
Informed consent		X								
Verification of entry criteria		X	X							
Physical examination [2]		X								
Review of medical history [3]		X								
Symptom-directed physical examination			X	X	X	X	X	X	X	X
Vital signs[4]		X	X	X	X	X	X	X	X	X
Weight measurement		X		X	X		X		X	
Height measurement[5]		X	X	X	X	X	X	X	X	X
Electrocardiogram[6]		X		X					X	X
Urinalysis (dipstick)[7]		X			X		X		X	
Chemistry blood collection		X			X		X		X	
Hematology blood collection		X			X		X		X	
Coagulation (PT and PTT) blood collection		X							X	
PTH (1–84)		X							X	
25-hydroxyvitamin D level		X							X	
1,25-dihydroxy vitamin D level		X							X	
Total testosterone and SHBG		X							X	
Estradiol		X								
Thyroid stimulating hormone[8]		X								
PK samples (see Table 4)							X	X	X	
Study medication assignment via IRT				X						
Injection training for subjects			X							

Table 3: Schedule of Assessments and Procedures (Continued)

	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Procedure	***Study Day/Month:***	**Screening**	**Pretreatment**	**Day 1**	**Month 1**	**Month 3**	**Month 6**	**Month 9**	**Month 12/ Early Termination**	**Month 13 Follow-up**
Visit Window (Days)		**N/A[1]**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 4**	**± 7**
Calcium and vitamin D supplements			Daily administration							
Study medication administration				Daily administration						
Serum markers of bone metabolism (s-PINP and s-CTX)				X	X	X	X		X	
Serum calcium and albumin[9]				X	X	X	X	X		
24-hour urine collection (for calcium:creatinine and creatinine clearance)[10]				X		X				
Radiologic (lumbar and thoracic vertebrae) assessments		X								
Symptom driven spinal radiologic assessment			At any time							
Clinical assessment of new fractures[11]			X	X	X	X	X	X	X	
BMD of lumbar spine, total hip, and femoral neck by DXA[12]		X				X	X		X	
BMD of wrist by DXA[13]				X		X	X		X	
vBMD of hip by QCT[14]				X					X	
Sample for immunogenicity testing[15]				X	X	X	X	X	X	X
Investigator assessment of local tolerance (dermal reactions assessment)				X	X	X	X	X		
Subject assessment of local tolerance[16]				X				X		
Subject diary review[17]				X	X	X	X	X	X	
Document AEs and concomitant[18] medications		At any time, question subjects at every visit								
Drug supply/resupply/accountability				X	X	X	X	X	X	

1. The window for screening activities is 60 days. Due to the ongoing COVID-19 pandemic or other local/widespread emergencies, if there is a delay in the screening process that would result in a subject remaining in screening for greater than 60 days, the Medical Monitor should be contacted. All safety laboratory results must be reported within 30 days prior to randomization.
2. A complete physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in physical examinations should be reported as AEs.
3. Including alcohol and tobacco use assessment.
4. Blood pressure, heart rate, body temperature, and respiration rate are to be recorded predose at each study visit. Only blood pressure, heart rate and respiration rate are to be recorded one-hour post dose at each study visit during the Treatment Period. All blood pressure assessments need to be orthostatic.
5. Height is to be measured at each visit in the standing position using a medical stadiometer.
6. ECGs are to be performed predose and one-hour postdose during the Treatment Period.
7. All routine urinalysis will be performed on a sample freshly voided during the visit and sent to a central lab for microscopy if test is positive for micro-organisms via dipstick.
8. Reflex testing of T3 and free T4 will be performed by the central laboratory for any out-of-range TSH result.
9. Serum calcium and albumin will be measured predose from the standard chemistry panel on Month 1 and Month 6, and from a separate blood draw at Day 1, Month 3 and Month 9 and 4 hours post dose at Day 1, Month 1, Month 3, Month 6, and Month 9.
10. A 24-hour urine collection will be collected at Day 1 and Month 3 and will be used for urinary calcium and urinary creatinine measurements. Subjects will discard the first void and begin a 24-hour urine collection on the day prior to the clinic visit.
11. If the subject reports that a fracture has occurred, remind the subject to bring X-rays and any medical reports of the fracture to the next clinic visit. Documentation must be obtained on all new fractures that occur during the study. This documentation should be maintained in the source documents.
12. Each DXA for a given subject should be performed on the same machine, and if available, preferably by the same technician. For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken up to 35 days prior to the beginning of the Screening Period, with a study-approved scanner, may be used to determine study eligibility.
13. The first wrist DXA will be performed prior to study drug administration on Day 1 and should be performed on the same machine, and if available, preferably by the same technician.
14. QCT performed in a subset of subjects at selected study sites.
15. Samples will be drawn prior to treatment on Day 1, Months 1, 3, 6, 9, and 12, and the Follow-up Visit scheduled at 1 month after the last dose of study medication.
16. The subject will maintain a diary of their assessment of local tolerance beginning on Day 2 and continuing through Day 7 in Month 1, and beginning on Day 2 and continuing through Day 7 in Month 9.
17. The subject medication diary will be reviewed by study personnel at each study visit to ensure subject compliance.
18. AEs and SAEs will be recorded on the case report forms starting from the time of subject entry into the Screening Period (Visit 1) of the study (signed informed consent) until 30 days after the last dose of study medication. All AEs will be followed until resolution or stabilization. Any SAEs that occur at any time after completion of the study, which are considered by the Investigator to be related to study treatment, must be reported to the Sponsor or its designee.

AE = adverse event; BMD = bone mineral density; DXA = dual energy X-ray absorptiometry; IRT = Interactive response technology; PT = Prothrombin time; PTH = Parathyroid hormone; PTT = Partial thromboplastin time; QCT = quantitative CT; s-CTX = serum carboxyl-terminal cross-linking telopeptide of type I collagen; s-PINP = serum procollagen type I N-terminal propeptide; SAE = serious adverse event; SHBG = Sex hormone binding globulin; vBMD = volumetric bone mineral density

Table 4: Schedule for Pharmacokinetic Sample Collections

Study Visit	Predose	Postdose				
	Within 10 min before injection	20 min ± 10 min	45 min ± 15 min	1.5 hours ± 0.5 hours	2.5 hours ± 0.5 hours	4 hours ± 0.5 hours
Month 6			X		X	
Month 9		X				X
Month 12	X			X		

Note: This schedule only applies to those subjects who consent to have PK samples collected during the study.
min = minute; PK = pharmacokinetics

6.2.2. Informed Consent Process

Each subject must sign and date a study-specific informed consent form (ICF) before any study-specific procedures can be performed. The consent forms will comply with all applicable regulations governing the protection of human subjects. An ICF, approved by RADIUS and the site's IRB/IEC must be used. The Investigator or designee must record the date when the ICF was signed in the subject's source document.

6.2.3. Assigning Subject Numbers

Once a subject has signed an ICF, a subject number will be assigned. The subject will retain this number for the entire study.

6.2.4. Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight.

Medical history will be elicited from each subject during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

Subjects included into the study based on a history of low-trauma nonvertebral fractures must have sufficient source documentation in the form of a medical report or radiographic films as evidence of such history.

6.2.5. Screening Period (Visit 1)

Signed informed consent will be obtained and eligibility for study entry assessed. The following baseline screening evaluations will be performed:

- Physical examination
- Review of medical history, including alcohol, tobacco, and drug use
- Review of concomitant medications
- Height
- Weight
- ECG
- Orthostatic blood pressure and vital signs
- Lumbar and thoracic spine radiographs (anteroposterior and lateral)
- BMD assessments of lumbar spine, total hip, and femoral neck by DXA
  - BMD T scores may be rounded off to the nearest tenth (i.e., rounded off to one decimal point) for the purpose of assessing study eligibility per protocol.

  - For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken with a study-approved scanner up to 35 days prior to the beginning of the Screening Period may be used to determine subject eligibility.

- Laboratory testing of serum chemistry, hematology, coagulation, and urine dipstick
- PTH, 25-hydroxyvitamin D, and 1,25-dihydroxy vitamin D level
- Serum total testosterone and sex hormone binding globulin (SHBG)
- Estradiol and TSH level

Subjects who do not meet the 25-hydroxyvitamin D entry criterion may receive vitamin D supplementation and be retested once during the Screening Period. Similarly, subjects with minor elevations of PTH may be retested one time after vitamin D supplementation. Subjects whose laboratory tests do not fall within the specified ranges as detailed in the inclusion/exclusion criteria may have the samples redrawn and the tests repeated once during the Screening Period. If upon retesting, the values fall within the inclusion/exclusion criteria, the subject may enter the study. All subjects enrolled following retesting must have safety laboratory results reported within 30 days prior to randomization.

The window for screening activities is 60 days. Due to the ongoing COVID-19 pandemic or other local/widespread emergencies, there may be screening process delays. In the case of screening process delays that result in a subject remaining in the Screening Period for greater than 60 days, the Medical Monitor should be contacted. All safety laboratory results must be reported within 30 days prior to randomization.

Any AEs will be recorded beginning on the day that the subject signs the informed consent.

6.2.6. Pretreatment Period (Visit 2)

Subjects who are eligible for the study on the basis of screening evaluations will enter the Pretreatment Period of the study and will be provided the calcium and vitamin D supplements required until the next study visit. All subjects will be required to commence calcium 500–1000 mg/day and vitamin D supplements 400–800 IU/day (or doses determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need). Subjects will also undergo training for medication self-administration during this period; AEs will be recorded, and the following procedures will be performed:

- Symptom-directed physical exam, including assessment for potential vertebral fracture
- Verification of study entry criteria
- Height
- Orthostatic blood pressure and vital signs
- Clinical assessment of new fractures
- Instruct subject on procedures and provide with supplies for collecting a 24-hour urine sample (the sample is to be collected on the day prior to Day 1)
- Injection training for subjects

6.2.7. Treatment Period

Subjects who remain eligible for study participation will be randomly allocated through the IRT, using a 2:1 randomization ratio on Day 1 to receive treatment with either blinded abaloparatide-SC 80 µg per day or daily 80-µg placebo injections, respectively. Treatment will be blinded to the Sponsor, subjects, and Investigators throughout the study except in a medical emergency where the identity of study medication is necessary to appropriately treat the subject (Section 5.7). The Sponsor pharmacovigilance/regulatory personnel may also be unblinded for SUSAR reporting purposes. During the Treatment Period, subjects will self-administer a single subcutaneous dose of study medication once a day.

At each clinic visit during this period, recent health status will be obtained, the diary reviewed, AEs collected, and orthostatic blood pressure and vital signs performed. Laboratory assessments of chemistry and hematology and urinalyses will be obtained at Month 1, Month 6, and Month 12, and a 24-hour urine will be collected on the day prior to Visit 1 and on the day prior to Visit 5 (Month 3). Clinical assessments for fracture will be performed at each visit. Source documentation (imaging report and/or film along with other supporting documentation as appropriate) will be collected from each site to confirm fracture.

Subjects will have BMD assessed by DXA at the lumbar spine, total hip, and femoral neck at screening and Months 3, 6 and 12, and at the wrist on Day 1 and Months 3, 6 and 12. Volumetric BMD at the hip will be assessed by QCT on Day 1 and at Month 12. QCT will be performed in a subset of subjects at a selected number of study sites based upon availability. Bone turnover marker assessments (s-PINP and s-CTX) will be performed on Day 1, and Months 1, 3, 6, and 12.

6.2.8. Visit 3 (Day 1)

- A 24-hour urine collection will be collected. Subjects will discard the first void and begin a 24-hour urine collection on the day prior to the clinic visit
- Symptom driven physical exam, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- ECGs (predose and one-hour postdose)
- Orthostatic blood pressure and vital signs
- Height
- Weight
- Serum calcium and albumin (predose and 4 hours post dose)
- Measurement of volumetric bone density at the hip by QCT
- Clinical assessment of new fractures
- AE and concomitant medication review
- Wrist DXA
- Bone turnover markers (s-PINP and s-CTX)

- Randomization and study medication (abaloparatide-SC or placebo) will be assigned through the IRT
- Dispense study medication
- First dose of study medication will be administered by the subject in clinic
- Investigator assessment of local tolerance, within 5 minutes and at 1 hour following administration
- Instruct subject on completion of diary, including subject assessment of local tolerance, within 5 minutes and at 1 hour following administration, will need to be done beginning on Day 2 and continuing through Day 7 of Month 1.

6.2.9. Visit 4 (Month 1)

- Symptom driven physical exam, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- Orthostatic blood pressure and vital signs
- Height
- Weight
- Laboratory testing of serum chemistry, hematology, and urine dipstick
- Serum calcium and albumin (predose and 4 hours post dose)
- Dispense study medication
- Self-administration of study medication when directed by site staff after completion of predose activities
- Clinical assessment of new fractures
- AE and concomitant medication review
- Bone turnover markers (s-PINP and s-CTX)
- Investigator assessment of local tolerance, within 5 minutes and at 1 hour following administration
- Review subject diary
- Provide subject with supplies for collecting a 24-hour urine sample (the sample is to be collected on the day prior to the Month 3 visit).

6.2.10. Visit 5 (Month 3)

- A 24-hour urine collection will be collected. Subjects will discard the first void and begin a 24-hour urine collection on the day prior to the clinic visit
- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing

- Orthostatic blood pressure and vital signs
- Height
- BMD assessments of lumbar spine, total hip, femoral neck, and wrist by DXA
- Bone turnover markers (s-PINP and s-CTX)
- Dispense study medication
- Self-administration of study medication when directed by site staff after completion of predose activities
- Serum calcium and albumin (predose and 4 hours post dose)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Investigator assessment of local tolerance, within 5 minutes and at 1 hour following administration
- Review subject diary

6.2.11. Visit 6 (Month 6)

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- Height
- Weight
- Orthostatic blood pressure and vital signs
- Dispense study medication
- Self-administration of study medication when directed by site staff after completion of predose activities
- Only for subjects who consent to provide PK samples: Collect PK samples at 45 minutes (±15 minutes) and 2.5 hours (±0.5 hour) after injection
- Laboratory testing of serum chemistry, hematology, and urine dipstick
- Serum calcium and albumin (predose [from chemistry panel] and 4 hours post dose)
- BMD assessments of lumbar spine, total hip, femoral neck, and wrist by DXA
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Investigator assessment of local tolerance, within 5 minutes and at 1 hour following administration

- Review subject diary

6.2.12. Visit 7 (Month 9)

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- Orthostatic blood pressure and vital signs
- Height
- Dispense study medication
- Self-administration of study medication when directed by site staff after completion of predose activities
- Only for subjects who consent to provide PK samples: Collect PK samples at 20 minutes (±10 minutes) and 4 hours (±0.5 hour) after injection
- Serum calcium and albumin (predose and 4 hours postdose)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Investigator assessment of local tolerance, within 5 minutes and at 1 hour following administration Instruct subject on completion of diary, including subject assessment of local tolerance, within 5 minutes and at 1 hour following administration, beginning on Day 2, and continuing through Day 7 in Month 9
- Review subject diary

6.2.13. Visit 8 (Month 12)/Early Termination Visit

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- ECG
- Weight
- Height
- Orthostatic blood pressure and vital signs
- Only for subjects who consent to provide PK samples and attend the Month 12 visit: Collect a predose sample within 10 minutes before injection
- Self-administration of study medication when directed by site staff after completion of predose activities using medication dispensed at Visit 7 (Note: Applicable only to subjects completing a Month 12 visit)

- Only for subjects who consent to provide PK samples and attend the Month 12 visit: Collect a postdose sample at 1.5 hours (±0.5 hour) after injection
- PTH, 25-hydroxyvitamin D, and 1,25-dihydroxy vitamin D level
- Laboratory testing of serum biochemistry, hematology, coagulation and urine dipstick
- BMD assessments of lumbar spine, total hip, femoral neck, and wrist by DXA
- Measurement of volumetric bone density at the hip by QCT
- Bone turnover markers (s-PINP and s-CTX)
- Serum total testosterone and SHBG
- Clinical assessment of new fractures
- AE and concomitant medication review
- Review subject diary

6.2.14. Visit 9/Safety Follow-up

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect blood for immunogenicity testing
- Record vital signs
- Height
- ECG
- All AEs, including SAEs, will be recorded from the time of signing of the informed consent and up to the 30 days after the last dose of study medication
- All subjects who remain antibody positive will continue to be followed for immunogenicity testing every 6 months until their result is antibody negative

6.2.15. Unscheduled Visit

If the subject returns to the clinic for an unscheduled visit (e.g., to follow-up on an abnormal laboratory test), the procedures performed at this visit will be recorded in the eCRF and source documentation.

6.3. Vital Signs and Physical Examinations

A complete physical examination (review of all body systems), height, weight, and vital signs assessment will be performed at screening.

A complete physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in physical examinations should be reported as AEs.

Height and weight will be measured with shoes off. Height is to be measured using a wall mounted stadiometer. When height cannot be accurately measured such as in cases of severe kyphosis or loss of height from vertebral compression fractures, a documented historical height (i.e., from government IDs, medical records, etc.) may be used.

Vital signs include orthostatic blood pressure (systolic and diastolic), temperature (oral), heart rate, and respiratory rate. These will be assessed following a 5-minute rest (seated or supine) and before blood sample collection. At visits when study drug is administered at the site, vital sign assessments will be collected before the dose of study drug. Supine and standing blood pressure measurements will be performed at each visit during the Treatment Period.

6.4. 12-Lead Electrocardiogram

Standard, 12-lead ECGs will be performed. A hard copy of the ECG should be printed and signed by the Investigator at the site. Any abnormalities should be noted and clinical relevance should be documented. An ECG will be recorded immediately prior to dosing and 1 hour postdose during the Treatment Period.

6.5. Laboratory Evaluations

6.5.1. Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be collected at time points indicated in the Schedule of Assessments and Procedures in Table 3. All clinical laboratory blood and 24-hour urine samples will be sent to a central laboratory for analysis and testing. A list of study clinical laboratory tests is in Table 5.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (Dipstick)[a]	Additional Tests
Hemoglobin	Sodium	pH	PTH (1–84)[b]
Hematocrit	Potassium	Glucose	25-hydroxyvitamin D[b]
			1,25-dihydroxy vitamin D[b]
WBC count with differential in absolute counts	Chloride	Protein	BSAP
RBC count	Inorganic phosphorus	Ketones	Estradiol[c]
MCV	Albumin	Bilirubin	Testosterone[b]
MCHC	Total protein	Blood	SHBG [b]
MCH	Glucose	Urobilinogen	TSH (T3 and Free T4)[c]
Platelet count	BUN	Specific gravity	
	Creatinine	Nitrite	
	Uric acid	Leukocytes	
	AST		
	ALT		
	GGT		
	CPK		
	Alkaline phosphatase		
	Total bilirubin		
	LDH		
	Total Cholesterol		
	Triglycerides		
	Total calcium		

a. Clinic only, if required by PI send to central lab for microscopy
b. Only required at Screening and Visit 8 or early termination (Month 12 visit)
c. Only required at Screening. Reflex testing for T3 and Free T4 will be performed by the central laboratory if TSH is outside the normal limits. Reflex testing for bone-specific alkaline phosphatase will be performed by the central laboratory if serum alkaline phosphatase is outside the normal limits.

ALT = alanine aminotransferase; AST = Aspartate aminotransferase; BSAP = bone-specific alkaline phosphatase; BUN = blood urea nitrogen; CPK = Creatine phosphokinase; GGT = gamma-glutamyl transpeptidase; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; PTH = parathyroid hormone; RBC = red blood cell; SHBG = sex hormone binding globulin; TSH = thyroid stimulating hormone; WBC = white blood cell

In the event of medically significant, unexplained, or abnormal clinical laboratory test values, the test(s) should be repeated and followed up until the results have returned to within the normal range or an adequate explanation for the abnormality is found. Clinically significant changes in laboratory tests that occur during the course of the study are to be reported as AEs.

The clinical laboratory will clearly mark all laboratory test values that are outside the normal range and the Investigator will indicate the clinical relevance of these out-of-range values.

6.5.2. Serum Markers of Bone Metabolism

Blood samples will be taken to measure efficacy related markers of bone metabolism at Day 1, Month 1, Month 3, Month 6, and Month 12 or early termination. S-PINP and s-CTX will be measured in all subjects.

6.5.3. Immunogenicity Testing

Serum samples for immunogenicity testing will be collected at Day 1 (Visit 3), Month 1 (Visit 4), Month 3 (Visit 5), Month 6 (Visit 6), Month 9 (Visit 7), Month 12 (Visit 8), and the Follow-up Visit scheduled at 1 month after the last dose of study medication (Visit 9). Samples will be tested for the presence of binding anti-abaloparatide antibodies, including determination of antibody titer. Any positive samples will be tested for the potential to neutralize abaloparatide in a cell-based assay. Additionally, positive samples will be tested for cross-reactivity to endogenous PTH and PTHrP. Any subjects who show presence of antibodies at the Follow-up Visit scheduled at 1 month following the last dose of study medication (Visit 9) will be retested at 6-month intervals post-study until antibody status return to negative.

The serum samples for immunogenicity testing will be analyzed and reported separately. All the planned analyses related to the immunogenicity results and antibody status will also be reported separately.

6.5.4. Pharmacokinetic Testing

A blood sample for PK analysis of abaloparatide will be collected using a 5 mL K3 EDTA tube with 0.1 mg/mL aprotinin at each time point indicated in the PK sample collection schedule (Table 4).

6.5.5. Specimen Preparation, Handling and Storage

The procedures for the collection, handling, and shipping of clinical laboratory samples are specified in a separate Laboratory Manual provided to each clinical site.

6.6. Imaging Procedures

All imaging measurements (BMD according to DXA and QCT) will be performed according to the procedures outlined in the Imaging Charter and Imaging Manuals which will be provided as a separate document. A central imaging laboratory will be utilized for all DXA and QCT readings. QCT will be performed in a subset of subjects at a selected number of study sites.

6.6.1. Dual Energy X-ray Absorptiometry

All subjects will have areal bone density (aBMD) measurements taken via DXA of the lumbar spine, total hip, femoral neck, at Screening (Visit 1), wrist at Day 1 (Visit 3); spine, total hip, femoral neck, and wrist at Month 3 (Visit 5), Month 6 (Visit 7), and Month 12 (Visit 8). Lumbar spine scans must include L1 through L4. Hip scans will include the entire proximal femur to about 2 cm below the lesser trochanter. DXA bone density assessments will be performed at the forearm to measure BMD of the distal one-third radius and ultra-distal radius. For hip and wrist scans, the same side should be used for all scans at all visits. If a subject fractures a hip or forearm being examined during the study, no further scans of either hip or forearm will be acquired.

For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken up to 35 days prior to the beginning of the Screening Period may be used to determine study eligibility. DXA scans should be performed using a study-approved scanner (and read by the study central DXA reader) up to 35 days prior to the subject's Screening Visit.

6.6.2. Quantitative Computed Tomography

A subset of subjects at a selected number of study sites will have volumetric BMD (vBMD) measurements taken via QCT of the hip on Day 1 (Visit 3) and Month 12 (Visit 8).

6.6.3. Clinical and Radiologic Evaluation of Fractures

All spine radiographs will be performed according to the procedures outlined in the Imaging Charter and Imaging Manual which will be provided as separate documents. All subjects will have X-rays taken to document fractures of the lumbar and thoracic vertebrae at Screening to confirm entry criteria. Radiographs of the lateral thoracic and lumbar spine will include coverage of T3 to S1. The lateral spine radiographs will be assessed for prevalent and incident vertebral fractures using the Genant Semiquantitative Scoring method (Genant et al, 1993).

- Grade 0: Normal (approximately < 20% reduction in anterior, middle, or posterior height)
- Grade 1: Mild fracture (approximately 20%–25% reduction in anterior, middle, or posterior height)
- Grade 2: Moderate fracture (approximately 25%–40% reduction in anterior, middle, or posterior height)
- Grade 3: Severe fracture (> 40% reduction in anterior, middle, or posterior height)

Incident radiological vertebral fractures occur in vertebrae with an increase in SQ score ≥ 1 at a Follow-up Visit. New incident radiological vertebral fractures occur in vertebrae that are not fractured (i.e., SQ score of 0) at Screening. Worsening incident radiological vertebral fractures occur in vertebrae with prevalent (i.e., pre-existing) fractures at baseline. Subjects will also be clinically evaluated for vertebral and nonvertebral fractures (wrist, hip, rib, etc.) which occur during the study. Should a clinical fracture occur, X-ray images and reports associated with the fracture must be obtained and maintained in the subject's medical record.

All fractures will be identified and evaluated as part of the disease assessment and will be documented in the case report forms and source documents.

6.7. Discontinuation from the Study

Subjects may voluntarily discontinue from the study for any reason at any time.

Any subject who demonstrates decreases in BMD ≥ 7% from baseline of this study at the lumbar spine or total hip will have the assessment repeated and, if confirmed, will be notified by the Investigator, and be withdrawn from the study. Subjects sustaining a radiologically confirmed incident vertebral or nonvertebral fragility fracture will be informed of the finding and will be counseled as to treatment options and may discontinue or choose to remain on the study. Those subjects who sustain an incident fracture during the study and elect to remain in the study will be asked to sign an additional informed consent document advising them of an increased risk for subsequent fracture.

Subjects who decide they do not wish to participate in the study further should return for the assessments indicated for the Month 12/Early Termination and 30 days later for the Month 13/Follow-up Visit in the Schedule of Assessments and Procedures (Table 3). If they fail

to return for these assessments for unknown reasons, every effort (e.g., telephone, email, and letter) should be made to contact them.

6.7.1. Withdrawal of Consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study-related contact.

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

6.7.2. Early Study Termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests.

The Investigator will be responsible for informing IRBs/IECs of the early termination of the study.

7. ADVERSE EVENT AND SERIOUS ADVERSE EVENT DOCUMENTATION

7.1. Evaluation of Safety

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and is mandated by regulatory agencies worldwide. All clinical studies sponsored by RADIUS will be conducted in accordance with Standard Operating Procedures (SOPs) that have been established to conform to regulatory requirements worldwide to ensure appropriate reporting of safety information.

All AEs are collected from the time of the informed consent until 30 days after last dose of investigational product. Where possible, a diagnosis rather than a list of symptoms should be recorded. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. The Investigator will assess all AEs for relationship to study drug. For information on the safety profile obtained to date for abaloparatide, please refer to the IB.

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH, 1995).

AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from Baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

An abnormal laboratory value will not be assessed as an AE unless it requires a therapeutic intervention or is considered by the Investigator to be clinically significant.

7.1.2. Serious Adverse Event

A SAE is any AE that results in any of the following:

- Death
- Life-threatening: The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the subject was at risk of death at the time of the

event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

- Required in-subject hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., substantial disruption of the ability to conduct normal life function)
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-subject hospitalization, or the development of drug dependency or drug abuse.

All AEs of osteosarcoma will be reported as SAEs. All reports of osteosarcoma, regardless of causality or expectedness, will be expedited to the FDA within 15 days of receipt. MedDRA preferred terms include osteosarcoma, osteosarcoma metastatic, osteosarcoma recurrent, extraskeletal osteosarcoma, extraskeletal osteosarcoma metastatic, extraskeletal osteosarcoma recurrent.

All treatment-related SAEs must be followed until resolution (subject has returned to baseline status of health) or until stabilization (the Investigator does not expect any further improvement or worsening of the reported event).

7.1.3. Recording an Adverse Event

All AEs/SAEs will be entered into the electronic database.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless they occur at a time other than the planned date or the pre-existing illness or disease worsens after enrollment into the study.

Fractures identified during the study are not to be recorded as AEs unless the subject is hospitalized, the fracture is complicated, or the Investigator considers the fracture to be unrelated to the subject's underlying osteoporosis. All fractures will be identified and evaluated as part of the disease assessment and will be documented in the CRF and by collection of source documents.

For both serious and non-serious AEs, the Investigator must determine the intensity of the event and the relationship of the event to study drug administration (abaloparatide and placebo). Intensity for each AE will be defined according to the following criteria:

Intensity	Definition
Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with normal daily activities.
Severe	Inability to perform normal daily activities.

If the intensity of an adverse event changes within a day, the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each intensity).

Relationship to blinded study drug administration will be determined by the Investigator according to the following criteria:

Relationship	Definition
None	No relationship between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or subject's clinical state.
Unlikely	The current state of knowledge indicates that a relationship to study drug is unlikely or the temporal relationship is such that study drug would not have had any reasonable association with the observed event.
Possible	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Probable	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

For the purpose of safety analyses, all AEs that are classified with a relationship to study medication administration of possible or probable will be considered treatment-related events.

7.1.3.1. Serious and Unanticipated Adverse Device Effects for Abaloparatide-SC

An adverse device effect (ADE) is defined as any adverse event related to the use of an investigational medical device (IMD). For the purposes of this protocol, abaloparatide-SC is the IMD. All ADEs should be reported as an AE per Section 7.1, which includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, any malfunction of the IMD, use error, or intentional misuse of the IMD (ISO/DIS 14155).

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the abaloparatide-SC device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application/IB, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Any UADE that occurs during the study from the time the subject signs the ICF until 30 days after the last dose of study medication must be reported within 24 hours of first awareness of the event using the SAE and the UADE report forms and emailing to PV@radiuspharm.com.

The Investigator and the Sponsor will immediately conduct an evaluation of any UADE occurring with abaloparatide-SC. The results of the evaluation will be reported to the IRB within 10 days of the Sponsor becoming aware of the event.

If it is determined by the Investigator and the Sponsor to present an unreasonable risk to study subjects, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. Termination will occur not later than 5 working days after the Investigator and the Sponsor makes this determination and not later than 15 working days after the Sponsor first receiving notice of the event. The Investigator and the Sponsor will not resume an investigation terminated under these conditions without an additional IRB approval.

7.1.4. Serious Adverse Event Reporting

Any SAEs that occur during the study from the time the subject signs the ICF until 30 days after the last dose of study medication must be reported within 24 hours of first awareness of the event using the SAE report form and emailing to PV@radiuspharm.com. Data should also be entered in the clinical trial eCRF.

Treatment-related SAEs will be followed until resolution or stabilization. The reference safety information for this study is the IB, which will be provided under separate cover to all Investigators.

Any SAEs that occur at any time after completion of the study, which the Investigator considers to be related to study drug, must be reported to the Sponsor or its designee.

The Investigator must submit the SAE to the IRB/ IEC in accordance with 21 CFR parts 56 and 312 as well as with applicable local regulations. Documentation of these submissions must be retained in the site study file.

7.1.5. Device Reporting

Abaloparatide-SC is a drug-device combination product. In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definition of a UADE that occurs with abaloparatide-SC (Section 7.1.3.1).

Any UADEs that occur during the study with abaloparatide-SC, from the time the subject signs the ICF until 30 days after the last dose of study drug, must be reported within 24 hours of first awareness that the event meets the definition of a reportable incident by entering data in the clinical trial eCRF. Treatment-related UADEs will be followed until resolution or stabilization, the condition is otherwise explained, or until the subject is lost to follow-up.

SAEs (initial reports and follow-up information) must be reported by the Investigator using the SAE report form; the form must be completed and emailed to PV@radiuspharm.com.

The Investigator will comply with the applicable local regulatory requirements relating to reporting to the IRB/IEC.

7.1.6. Follow-up of Adverse Events

All treatment-related AEs will be followed with appropriate medical management until resolved or stabilized.

UADEs will be followed until their medical outcome is determined, with periodic written reports about the status provided to the Sponsor.

7.1.7. Abuse, Misuse, Overdose, or Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor whether or not they result in an AE/SAE.

- Abuse – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (e.g., altering one's state of consciousness).
- Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose Note: this includes a situation where the test article is not used as directed at the dose prescribed by the protocol.
- Overdose – Intentional or unintentional injection of a dose of abaloparatide at least 2 times higher than the protocol-specified dose and is associated with clinical symptoms.
- Medication Error – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.1.8. Pregnancy

Any pregnancy for the partner of a study participant must be reported on the Partner's Pregnancy Report Form within 24 hours and emailed to the RADIUS Pharmacovigilance Department at PV@radiuspharm.com. Every effort should be made to gather information regarding the

pregnancy outcome. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

In subjects who have partners of childbearing potential, the subject and his partner should abstain from sexual intercourse, or use highly effective contraceptive measures (e.g., oral contraceptive and condom, IUD and condom, or diaphragm with spermicide and condoms; other forms of contraception must be approved by a Medical Monitor) when engaging in sexual intercourse throughout the study, and for at least 90 days after the last dose of abaloparatide.

7.1.9. Regulatory Agency, Institutional Review Board, Ethics Committee and Site Reporting

The Sponsor and/or the clinical contract research organization (CRO) are responsible for notifying the relevant regulatory authorities/US central IRBs/EU central IEC committees of related, unexpected SAEs.

The Investigator is responsible for notifying the Sponsor, CRO, and local IRB/IEC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

If a death occurs during the study or within 30 days after Month 12/Early Termination visit (Visit 8), and it is determined to be related either to a study procedure or a study drug, the Investigator or his/her designee must notify the Sponsor and will communicate that information to the IRB/IEC within one business day of knowledge of the event. The contact may be by phone or email.

7.2. Study Completion and Post-Study Treatment

The Investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study due to an adverse event or must refer them for appropriate ongoing care.

7.3. Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters. A subject should not be formally considered lost to follow-up until multiple attempts to contact the subject have been made, including at least 2 attempts to reach the subject by phone followed by a certified letter sent to the subject’s last known mailing address.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and Analytical Plans

A comprehensive SAP will be completed and approved prior to database lock. All statistical tests will be 2-sided with a significance level of 1%, unless otherwise specified.

8.2. Statistical Hypotheses

The primary objective of this study is to evaluate the efficacy and safety of abaloparatide-SC 80 µg per day compared to placebo in men with osteoporosis. The hypotheses to be tested are that abaloparatide is superior to placebo, and that the safety profile of abaloparatide-SC in osteoporotic men is similar to that of abaloparatide-SC in postmenopausal women with osteoporosis.

8.3. Analysis Datasets

8.3.1. Populations for Analysis

The primary population for all efficacy analyses will be the Intention-to-Treat (ITT) Population, which is defined as all subjects randomized into this study. The primary population for safety analyses will be the Safety Population, defined as all subjects who received at least one dose of study medication. The Per-Protocol (PP) Population will include all ITT subjects who did not have any significant protocol deviations and will be used for supportive analyses. The criteria for the exclusion from the PP Population will be appropriately documented prior to database lock and treatment unblinding.

8.4. Description of Statistical Methods

8.4.1. General Approach

Analyses will be presented by treatment group (abaloparatide-SC and placebo) and overall, when appropriate. Baseline is defined as the last value obtained prior to the first dose of study medication.

For categorical data, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. For continuous data, the number of subjects, mean, median, standard deviation (SD), minimum, interquartile range (Q1 and Q3), and maximum will be presented.

8.4.2. Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be the percent change in lumbar spine BMD from baseline to 12 months. The analyses will be based on the ITT Population.

The missing data from this study will be reviewed carefully to evaluate any missing data patterns. As this study was not designed to systematically collect data from subjects who discontinue treatment early, the “retrieved dropouts” approach for handling missing data is not applicable for this study. To appropriately address the possibility of data missing not at random, the primary analysis will be based on a pattern-mixture model (PMM) analysis with multiple

imputation using the wash-out imputation method. This method uses sequential regression and wash-out imputation methodology to impute missing values after a subject's discontinuation from the study. The missing primary endpoint values for subjects in the abaloparatide-SC group will be imputed with the observed baseline and data from the placebo group; no intermediate values from the abaloparatide-SC group will be used in the imputation for the abaloparatide-SC group. For subjects in the placebo group, intermediate observed values from the completers in the placebo group will be used while imputing missing values during the 12-month Treatment Period. The PROC MI methodology for imputation of monotone missing data patterns will be used to impute the outcome variables at consecutive visits in a sequential (chain) manner. Each of these imputed datasets will be analyzed using analysis of covariance (ANCOVA) with treatment and DXA instrument manufacturer as fixed effects and the baseline lumbar spine BMD as a covariate. Results from all imputed datasets will be combined using PROC MIANALYZE for overall statistical inference. The statistical tests will be 2-sided comparing abaloparatide-SC to placebo; 99% CIs will be presented together with the estimated p-values.

As a sensitivity analysis, the primary efficacy endpoint will also be analyzed using a Mixed Model for Repeated Measures (MMRM) analysis. The MMRM model will include the fixed effects of treatment, DXA instrument manufacturer, visit, and treatment-by-visit interaction, with the baseline lumbar spine BMD as a covariate. For the MMRM model, an unstructured variance-covariance matrix shared between the 2 treatment groups will be used to model the within-subject errors over the visits. The treatment comparison will be obtained by testing the contrast (difference in least squares mean) between the 2 treatment groups at Month 12 (Visit 8). The statistical tests will be 2-sided comparing abaloparatide-SC to placebo; 99% CIs will be presented together with the estimated p-values.

Sensitivity analyses for addressing the effect of the COVID-19 pandemic and supportive analyses using the last observation carried forward (LOCF) method to impute missing data will also be conducted.

8.4.3. Analysis of Secondary Endpoint(s)

The key secondary efficacy endpoints are:

- Percent change from baseline in total hip BMD at 12 months
- Percent change from baseline in femoral neck BMD at 12 months

Additional secondary efficacy endpoints are:

- Percent change from baseline in:
  - Lumbar spine BMD at 3 and 6 months
  - Total hip BMD at 3 and 6 months
  - Femoral neck BMD at 3 and 6 months
  - Ultra-distal radius BMD at 3, 6, and 12 months
  - Distal one-third radius BMD at 3, 6, and 12 months

- Log ratio of post-baseline over baseline in:
  - s-PINP at 1, 3, 6, and 12 months
  - s-CTX at 1, 3, 6, and 12 months
- Proportion of subjects experiencing BMD gains from baseline of > 0%, > 3%, and > 6% at the lumbar spine, femoral neck, and total hip at 3, 6, and 12 months
- Incidence of new clinical fractures at 12 months
- Proportion of subjects converting from the categories of osteoporosis to osteopenia or to normal at 12 months, where:
  - Osteoporosis is defined as lumbar spine or total hip BMD T-score ≤ -2.5.
  - Osteopenia is defined as one of the following:
    - Lumbar spine > -2.5 and total hip BMD T-score > -2.5 and < -1.0
    - Lumbar spine > -2.5 and < -1.0 and total hip BMD T-score > -2.5
  - Normal is defined as lumbar spine and total hip BMD T-score ≥ -1.0.
- The percent change in total hip and femoral neck volumetric BMD as measured by QCT from baseline to 12 months. QCT will be performed in a subset of subjects at a selected number of study sites.

Analyses of the primary and key secondary endpoints will follow a fixed-sequence testing approach to control the overall Type 1 error rate at the 2-sided significance level of 1%. To claim statistical significance at the 2-sided level of 1%, the following 3 fixed-sequence tests will be performed in sequential order. At any step of the sequential testing, if the treatment difference is not statistically significant at the 1% level then all the subsequent comparisons following the fixed sequence cannot be claimed statistically significant.

1. Percent change from baseline in BMD at the lumbar spine at 12 months
2. Percent change from baseline in BMD at the total hip at 12 months
3. Percent change from baseline in BMD at the femoral neck at 12 months

P-values for treatment comparisons of all other efficacy endpoints will be generated to support the study findings without any adjustments for multiplicity.

The analyses of the key secondary BMD endpoints will be performed using a PMM analysis with multiple imputation using the wash-out imputation method similar to the analysis for the primary efficacy endpoint, as stated in Section 8.4.2, with the appropriate baseline covariate. Sensitivity analyses using MMRM models, sensitivity analyses for addressing the effect of the COVID-19 pandemic, and supportive analyses using the LOCF method, as with the primary efficacy endpoint, will also be conducted.

The bone formation marker, s-PINP, and the bone resorption marker, s-CTX, will be analyzed based on the ratio of the post-baseline value relative to the baseline using a natural log transformation at each visit. The analysis will use a PMM analysis with multiple imputation using the wash-out imputation method similar to that described in Section 8.4.2.

Percent changes from baseline in BMD over time will be summarized using descriptive statistics by visit for each treatment group.

The bone formation marker, s-PINP, and the bone resorption marker, s-CTX, will be summarized descriptively by treatment group, with values, changes and percent changes from baseline, geometric mean values, and geometric mean values relative to baseline at each visit.

A BMD responder analysis by visit will be performed for those subjects who have both baseline and the relevant post-baseline BMD values. Three categories of BMD response will be evaluated: %BMD increase > 0%, > 3%, and > 6%. The response will be assessed at the lumbar spine, total hip, and femoral neck. Subjects who have BMD increase at all 3 skeletal sites at the same visit will be considered responders, with the primary time point at 12 months. No imputation of missing data will be implemented. The number and percentage of responders in each treatment group will be compared using either the Chi-square test or Fisher's exact test.

Kaplan-Meier estimates for the time to new clinical fracture at 12 months and the hazard ratio (99% CI) will be presented, with treatment comparisons based on the log-rank test.

The number and percentage of subjects for whom disease status (categories as defined in the secondary endpoints listed earlier in this section) has changed from osteoporosis at baseline to osteopenia, normal, or no change at 12 months will be analyzed using the Chi-square test.

The percent change from baseline in total hip and femoral neck volumetric BMD (vBMD) at 12 months, as measured by quantitative CT will be analyzed using a similar ANCOVA model as stated in Section 8.4.2.

The primary analyses of the secondary efficacy variables will be based on the ITT Population and will be repeated using the PP Population.

Subgroup analysis (e.g., age, geography, FRAX, prior fracture, and baseline BMD, s-PINP, testosterone, and estradiol levels) may be performed. Details of the subgroup analyses will be described in the SAP.

8.4.4. Pharmacokinetic Analyses

A population PK analysis will be performed on the sparse plasma concentration data of abaloparatide as described in the Pharmacometric Analysis Plan. This analysis may be expanded to include a population PK/exposure-response analysis of the percent change in BMD from baseline over time.

8.4.5. Safety Analyses

Unless otherwise specified, safety analyses will be conducted using the Safety Population and will be descriptive in nature.

Study drug exposure and study drug compliance will be calculated. The duration of study drug exposure, total dose received, and percent compliance will be summarized by treatment group.

All AEs will be coded using MedDRA. The number and percent of subjects who experienced TEAEs will be summarized by MedDRA system organ class (SOC), preferred term, and treatment group. Summaries will also be provided for severe TEAEs, SAEs, TEAEs leading to

study drug withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and TEAEs by maximum severity (mild, moderate, severe).

The number and percent of subjects who report TEAEs associated with hypercalcemia and hypercalciuria will be summarized by treatment group.

All AEs collected prior to the first dose of study drug will be summarized separately.

A listing of subjects who experience an UADE will be provided.

Descriptive statistics for laboratory data (including serum calcium and albumin), vital signs (including orthostatic blood pressure [BP]), ECGs, Investigator assessment of local tolerance, and subject assessment of local tolerance will be provided by treatment group and visit. For laboratory data, vital signs, and ECGs, absolute results and changes from baseline will be presented. In addition, laboratory test results will be classified as above normal limit, within normal limit, or below normal limit. Laboratory shift frequencies will be tabulated between the Screening Visit and relevant post-baseline visit(s).

For subjects in the abaloparatide-SC group, the anti-abaloparatide antibody assessment in the serum samples for immunogenicity testing will be categorized by 2 outcomes:

- Negative for anti-abaloparatide antibodies
- Positive for anti-abaloparatide antibodies

The number (%) of subjects in the above categories of abaloparatide antibodies will be summarized on Day 1 (Visit 3) and at Month 1 (Visit 4), Month 3 (Visit 5), Month 6 (Visit 6), Month 9 (Visit 7), Month 12 (Visit 8), and the Follow-up Visit scheduled approximately 1 month after the last dose of study medication (Visit 9) using the Antibody Population.

For those subjects with a positive anti-abaloparatide antibody present, the titer level, presence of neutralizing anti-abaloparatide antibodies (negative or positive), and assessment outcomes for cross-reactivity to PTH (negative or positive) and PTHrP antibodies (negative or positive), together with the neutralizing antibody status in subjects that are positive for PTH (negative or positive for the presence of PTH-neutralizing antibodies) or PTHrP (negative or positive for the presence of PTHrP-neutralizing antibodies), will be summarized by study visit.

The results of antibody analyses will be included in a separate report.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by number and percentage of subjects using each class and preferred drug term by treatment group.

8.4.6. Adherence and Retention Analyses

The number and percentage of subjects who withdraw from the study, with primary reason, will be summarized by treatment group.

8.4.7. Baseline Descriptive Statistics

Medical history, physical examination, demographics, and baseline characteristics will be summarized and presented by treatment group and overall. Medical history will be presented by MedDRA SOC and PT, summarizing the proportion of subjects who have a condition noted.

Results from the baseline physical examination will be summarized by body system as recorded in the eCRF.

8.4.8. Interim Analyses

There are no interim analyses planned for this study.

8.4.9. Additional Subgroup Analyses

Subgroup analysis (e.g., age, geography, FRAX (if applicable), prior fracture, and baseline BMD, s-PINP, testosterone, and estradiol levels) may be performed and will be described in the SAP.

8.4.10. Multiple Comparison/Multiplicity

As stated in Section 8.4.3, a fixed-sequence testing approach will be employed to control the Type 1 error rate at the 2-sided significance level of 1% for testing the primary and secondary efficacy endpoints. No other adjustments for multiple comparisons will be made.

8.4.11. Tabulation of Individual Response Data

Individual efficacy, PK, and safety data will be tabulated as appropriate.

8.4.12. Exploratory Analyses

Prespecified exploratory variables and analyses are described in Section 8.4.3.

8.5. Sample Size Calculation

A study sample size of 225 subjects (150 in the abaloparatide-SC group and 75 in the placebo group) will provide at least 99% power to detect a mean difference of 6.5% in the percentage change from baseline in lumbar spine BMD at 12 months between the abaloparatide-SC and the placebo groups at a 2-sided alpha level of 0.01, assuming a SD of 6.0% and a drop-out rate of 10%. For the key secondary endpoints, this total sample size of 225 subjects will have 96% power to detect a 2.2% mean difference (SD = 3.5%) of percent change in total hip BMD at 12 months, and 80% power to detect a 2.0% mean difference (SD = 4.1%) of percent change in femoral neck BMD at 12 months.

8.6. Measures to Minimize Bias

Not applicable.

8.7. Enrollment/Randomization/Masking Procedures

Abaloparatide-SC and placebo study medications will be prepared in a blinded fashion. Data will be reviewed in a blinded fashion and the analysis populations defined prior to database lock and unblinding.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Ethical Considerations

This clinical study will be conducted in accordance with the current version of the ICH Harmonized Guideline for Good Clinical Practice (GCP), with applicable local laws and regulations, and with the ethical principles laid down in the Declaration of Helsinki.

The Investigator will ensure that this study is conducted in full conformity with ICH GCP E6(R2).

The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or RADIUS or designee, as allowable by local applicable laws and regulations.

9.2. Subject Information and Informed Consent

The Investigator is responsible for obtaining written, informed consent from each subject interested in participating in this study before conducting any study-related procedures.

Written informed consent should be obtained after adequate, thorough, and clear explanation of the study objectives, procedures, as well as the potential hazards of the study. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by RADIUS or its designee.

9.3. Investigator Compliance

No modifications to the protocol should be made without the approval of both the Investigator and RADIUS. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. RADIUS will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the Investigator will contact RADIUS to discuss the planned course of action. If possible, contact should be made before the implementation of any changes. Any departures from protocol must be fully documented in the source documentation.

9.4. Access to Records

The Investigator must make the office and/or hospital records of subjects enrolled in this study available for review by site monitors at the time of each monitoring visit, audit by RADIUS Quality Assurance (QA) and inspection by the regulatory agencies. The records must also be available for inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The Investigator

must comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

9.5. Subject and Data Confidentiality

To maintain subject confidentiality, all eCRFs, study reports and communications relating to the study will identify subjects by assigned subject numbers. As required by federal regulations, the Investigator will allow RADIUS and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the eCRFs/SAE Forms and the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation, for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject before research activities begin.

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, and RADIUS and their representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of RADIUS.

9.6. Research Use of Stored Human Samples, Specimens, or Data

With the subject's approval, and as approved by the site's IRB/IEC, biological samples may be stored at a centralized facility determined by RADIUS. These samples could be used for retrospective biomarker research or analysis of clinical response to therapy and to improve current and future treatment outcomes. The storage facility will maintain the masking of the identity of the subject.

During the conduct of the study, any individual subject can choose to withdraw consent to have biological specimens stored for future research. When the study is completed, access to study data and/or samples will be provided through RADIUS.

9.7. Data Quality Assurance

RADIUS or its designated representative will conduct a study site visit to verify the qualifications of each Investigator, inspect clinical study site facilities as needed, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study subject. Study data for each enrolled subject will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. RADIUS will have read-only access to all data upon entry in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study data will be made to the eCRF and documented in an audit trail, which will be maintained within the clinical database.

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be conducted. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. In the case of an audit or inspection, the Investigator or a delegate will alert RADIUS, as soon as he/she becomes aware of the audit or inspection.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by RADIUS, its designees, and/or regulatory agencies. In signing this protocol, the Investigator understands and agrees to give access to the necessary documentation and files.

9.8. Monitoring

RADIUS is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the clinical database. The study will be monitored by RADIUS or its designee. Monitoring will be done by personal visits from a representative of RADIUS, or designee (site monitor), who will review the eCRFs, SAE Forms and source documents. The site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

9.9. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

RADIUS will provide the study sites with secure access to and training on the EDC application sufficient to permit site personnel to enter and correct information in the eCRFs on the subjects for which they are responsible for.

An eCRF will be completed for each subject who receives at least one dose of study drug. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject’s eCRF. Source documentation supporting the eCRF data should indicate the subject’s participation in the study and should document the dates and details of study procedures, AEs, other observations, and subject status.

The Investigator, or designated representative, should complete the eCRF in a timely manner after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The Investigator must provide formal approval of all the information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the Investigator is responsible.

RADIUS will retain the eCRF data, queries, and corresponding audit trail. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be provided to the site for placement in the Investigator's study file.

9.10. Study Records Retention

The Investigator will maintain study documents for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and RADIUS must be notified. No records will be destroyed without the written consent of RADIUS.

9.11. Publication and Data Sharing Policy

Publication of complete data from the study is planned. It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee composed of Investigators participating in the study and representatives from RADIUS as appropriate will be formed to oversee the publication of the study results, which will reflect the experience of all participating study sites.

Subsequently, individual Investigators may publish results from the study in compliance with their agreement with RADIUS.

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