NCT # NCT03710889

Radius Health, Inc. (RADIUS)

950 Winter Street, Waltham, MA 02451 USA

[redacted]

Abaloparatide-SC

CLINICAL STUDY PROTOCOL: BA058-05-020

An Open-label, Single-arm, Multicenter Study to Evaluate the Early Effects of Abaloparatide on Tissue-based Indices of Bone Formation and Resorption

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.

Document type:	Clinical Study Protocol
IND number	73,176
Version number:	Amendment 2 - 05 November 2018
Development phase:	3
Study Site:	Multicenter

Protocol Version History

Version number	Version date
Original	14 December 2017
Amendment 1	9 February 2018

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (Title 21 CFR Part 11, 50, 54, 56, 312, and International Conference on Harmonization (ICH) GCP Guideline E6 (R2)):

In addition, I have read the study protocol titled "An Open-label, Single-arm, Multicenter Study to Evaluate the Early Effects of Abaloparatide on Tissue-based Indices of Bone Formation and Resorption, amendment 2 dated 05 November2018, and agree to the following:

- To conduct this study in accordance with the design and provisions of this protocol.
- To await institutional review board (IRB) approval for the protocol and informed consent (IC) before initiating enrollment into the study.
- 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 one 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 International Conference on Harmonisation (ICH), the Declaration of Helsinki, and applicable regulatory requirements.
- To permit study-related monitoring, audits, IRB 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 for data collected during this study.

Signature of Principal Investigator	Date
Print Name	Site Number

AMENDMENT 1 RATIONALE

This amendment updates and supersedes BA058-05-020 Clinical Study Protocol dated 14 December 2017 for all investigative sites. The key revisions are as follows:

- Revised inclusion criteria for acceptable serum 25-hydroxyvitamin D values
- Removed all references to the subject's assessment of local tolerance after injection
- Removed vitamin D and calcium dose requirement from Month 3 and Month 4 as shown in Table 1.
- Added BMD assessment to Section 7.2.10 and to Table 1.
- Removed references to and discussion of "incident" vertebral fractures in Section 7.7.2. This assessment tool will not be included in the protocol

The protocol was updated to reflect these changes and to correct administrative and consistency errors. Full details of changes are presented in the "Protocol Amendment 1 Summary of Changes".

AMENDMENT 2 RATIONALE

This amendment updates and supersedes BA058-05-020 Amendment 1 Clinical Study Protocol dated 9 Feb 2018 for all investigative sites. The key revisions are as follows:

- Calcium will be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld.
- 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 within 30 days of the original test date. If upon reanalysis, the values fall within the inclusion/exclusion criteria, the subject may enter the study.
- Added calcium withholding days to Figure 1.

The protocol was updated to reflect these changes and to correct administrative and consistency errors. Full details of changes are presented in the "Protocol Amendment 2 Summary of Changes".

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LIST OF ABBREVIATIONS

Abbreviation	Term
°C	Degree Celsius
°F	Degree Fahrenheit
µg	Microgram
µL	Microliter
µmol	Micromole
AE	Adverse event
ALT	Alanine aminotransferase
AP	Anterior posterior
AST	Aspartate aminotransferase
BFR/BS	Bone formation rate
BMD	Bone mineral density
BMI	Body mass index
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
Cm	Centimeter
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
Ct.Po/Ct.Ar	Cortical porosity
s-CTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ES/BS	Eroded surface
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus infection
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board

Abbreviation	Term
IU	International unit
IV	Intravenous
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
MAR	Mineral apposition rate
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MF/BS	Modeling-based formation
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MS/BS	Mineralizing surface
ng	Nanogram
oMF/BS	Overflow modeling-based formation
OS/BS	Osteoid surface
O.Th	Osteoid thickness
OV/BV	Osteoid volume
PA	Posterior-anterior
PI	Principal Investigator
s-PINP	Serum procollagen type I N propeptide
pQCT	Peripheral quantitative computed tomography
RANK	Receptor activator of nuclear factor kappa-B
RBC	Red blood cell
RmF/BS	Remodeling-based formation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SERMs	Selective estrogen receptor modulators
SOC	System organ class
SOP	Standard operating procedure
TEAEs	Treatment emergent adverse events
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

Abbreviation	Term
W.Th	Wall thickness

1. PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Radius Health, Inc. (RADIUS)</td></tr>
<tr><td colspan="2">Name of Investigational Product:
Abaloparatide-SC</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
abaloparatide</td></tr>
<tr><td colspan="2">Title of Study:
An Open-label, Single-arm, Multicenter Study to Evaluate the Early Effects of Abaloparatide on Tissue-based Indices of Bone Formation and Resorption</td></tr>
<tr><td colspan="2">Study center(s): Approximately 5 in the United States</td></tr>
<tr><td>Studied period (years):
Estimated date first subject enrolled: April 2018
Estimated date last subject completed: January 2019</td><td>Phase of development: 3</td></tr>
<tr><td colspan="2">Objectives:
The objectives of this study are to:
1. Demonstrate the early effects of abaloparatide on tissue-based bone formation and resorption indices
2. Assess the degree to which increased bone formation is achieved by modeling, remodeling, and overflow bone formation
3. Relate the early indices of tissue-based bone formation and bone resorption to those measured using biochemical markers of bone turnover.
Endpoints:
• Change from baseline to 3 months in dynamic indices of bone formation in the relevant bone envelopes (cancellous, endocortical, intracortical, and periosteal)
– Mineralizing surface (MS/BS)
– Mineral apposition rate (MAR)
– Bone formation rate (BFR/BS)
• Structural indices in the relevant bone envelopes at Month 3
– Cortical porosity (Ct.Po/Ct.Ar)
• Static indices in the relevant bone envelopes at Month 3
– Osteoid volume (OV/BV)
– Osteoid surface (OS/BS)</td></tr>
</table>

- Osteoid thickness (O.Th)
- Wall thickness (W.Th)
- Eroded surface (ES/BS)

- Change from baseline to 3 months in special histomorphometric variables in the relevant bone envelopes
  - Remodeling, modeling, and overflow modeling-based formation (RmF/BS, MF/BS, oMF/BS)
- Change in serum procollagen type I N-terminal propeptide (s-PINP) and carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) from baseline to 1 and 3 months
- Correlations of tissue-based indices of bone formation and bone resorption with s-PINP and s-CTX
- Overall safety and tolerability of abaloparatide in postmenopausal women with osteoporosis.

Methodology:

This is an open-label, single-arm, multicenter study of postmenopausal women with osteoporosis. The study is designed to measure the early effects of abaloparatide on tissue-based bone formation using samples obtained by iliac crest bone biopsy after quadruple fluorochrome labeling. The study will consist of a Screening Period (up to 1 month), a Pretreatment Period (approximately 1 month), a Treatment Period (3 months), and a Month 4 visit one month after the last dose of study medication. Biopsies are to be obtained at 3 months of treatment for the following reasons:

- This is the optimal time for changes in biochemical markers of bone turnover to predict changes in BMD after 18 months of treatment with abaloparatide (Radius, data on file).
- Longer periods of time increase the risk that the initial set of labels will be resorbed, which would seriously confound the results.
- Comparisons to the 3-month results for teriparatide from the AVA Osteoporosis Study will be possible.

There will be a sub-study at selected sites to collect pQCT data and extend an additional 3 months of study drug administration for a total of 6 months of treatment.

Details of the schedule of measurements, endpoints and statistical analysis methods will be described in a separate document for the sub-study.

Number of subjects (planned):
Approximately 25

Diagnosis and main criteria for inclusion:

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible to participate in this study:

1. The subject is a healthy ambulatory postmenopausal female from 50 to 85 years of age (inclusive) with osteoporosis.
2. The subject has been postmenopausal for at least 5 years. Postmenopausal status will be established by a history of amenorrhea for at least 5 years and by an elevated follicle-stimulating hormone (FSH) value of $\geq$ 30 IU/L.
3. The subject has a BMD T-score $\leq$ -2.5 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by Dual energy X-ray absorptiometry (DXA) *or* lumbar spine or hip BMD T-score $\leq$ -2.0 with a history of low trauma vertebral, forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture sustained within 5 years prior to enrollment. These fractures must be documented by radiograph or hospital report.
4. The subject is in good general health as determined by medical history and physical examination (including vital signs), has a body mass index (BMI) of 18.5 to 33, inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator.
5. The subject has serum calcium (albumin-corrected), PTH (1-84), phosphorus, and alkaline phosphatase levels all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value, and who meets all other entry criteria, is required to have a normal bone-specific alkaline phosphatase result to be enrolled.
6. The subject has serum 25-hydroxyvitamin D values $\geq$ 20 ng/mL and within the normal range. Subjects with serum 25-hydroxyvitamin D levels < 20 ng/ml may be treated with vitamin D3 and re-tested once.
7. The subject's resting 12-lead electrocardiogram (ECG) obtained during screening shows no clinically significant abnormality.
8. The subject has read, understood, and signed the written informed consent form.

Exclusion Criteria

Subjects with any of the following characteristics are not eligible to participate in the study:

General exclusion criteria.

1. Presence of abnormalities of the lumbar spine that would prohibit assessment of lumbar spine BMD, defined as having at least 2 radiologically evaluable vertebrae within L1-L4.
2. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
3. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis.

4. Clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells (WBC) and platelets, coagulation, or usual serum chemistry: electrolytes, renal function, liver function and serum proteins
5. Unexplained elevation of serum alkaline phosphatase.
6. History of radiotherapy (radiation therapy), other than radioiodine.
7. History of bleeding disorder that would preclude a bone biopsy, in the opinion of the Investigator.
8. 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.
9. History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism, or malabsorptive syndromes within the past year.
10. 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 ≥ 30 mL/min.
11. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin).
12. History of osteosarcoma at any time, or a history of hereditary disorders which would predispose the subject to osteosarcoma.
13. History of nephrolithiasis or urolithiasis within the past five years.
14. Subjects known to be positive for hepatitis B, hepatitis C, human immunodeficiency virus infection (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

15. Known history of hypersensitivity to any of the test materials, related compounds, or tetracyclines.
16. Prior treatment with PTH or PTHrP drugs, including abaloparatide.
17. Prior treatment with IV bisphosphonates at any time, or oral bisphosphonates within the past three 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.
18. Treatment with fluoride or strontium in the five years prior to the Screening Period or prior treatment with gallium nitrate, or with any unapproved bone-acting investigational agents at any time.
19. Treatment with calcitonin, SERMs (such as raloxifene or tamoxifen), or tibolone, in the past 6 months prior to the Screening Period. Estrogens administered as hormone

replacement therapy with or without progestins are not exclusionary.

20. 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.
21. Prior treatment with denosumab.
22. Daily treatment with oral, intranasal or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of corticosteroids (for seasonal allergies or asthma) is not exclusionary.
23. Prior treatment with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus).
24. Exposure to an investigational drug within the 12 months prior to the Screening Period.

Lifestyle-related exclusion criteria

25. Abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption, significant recent weight change), vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day.
26. Subject is known to abuse alcohol or use illegal drugs within 12 months of the Screening Period.

Investigational product, dosage and mode of administration:

Abaloparatide 80 µg for subcutaneous injection

Duration of treatment:

3 months; 6 months at selected sites in the sub-study

Reference therapy, dosage and mode of administration:

Not applicable

Duration of Subject Participation

Participation will be up to 6 months (3 months total treatment duration; 6 months total treatment for subjects at selected sites in the sub-study).

Statistical methods:

Subject demographics and baseline characteristics will be summarized using descriptive statistics.

Sample size

A sample size of 21 completers will provide at least 90% power to detect a statistically significant change from baseline in cancellous MS/BS (%) for abaloparatide at 3 months of 9.2%, assuming a standard deviation of 12.0%. The study is planned to enroll approximately 25 subjects to accommodate a drop-out rate of 15%, including those with non-evaluable bone biopsy. Additional subjects may be enrolled if the number of evaluable biopsies is insufficient to achieve this power.

Analysis population

The primary population for all efficacy analyses will be the Bone-Biopsy Population, which

is defined as all enrolled subjects who received a biopsy. The primary population for all safety analyses will be the Safety Population, which will be defined as all enrolled subjects who received at least one dose of abaloparatide.

Efficacy analysis

The primary endpoint of this study is the change from baseline to 3 months in mineralizing surface (MS/BS) in the cancellous bone envelope. Paired t-tests will be used to compare the differences in dynamic indices between the two time-points derived from the two sets of double labels using the Bone-Biopsy Population. If the normality assumption of efficacy variable is not satisfied at the 0.01 significance level and if visual inspection of the data deems it necessary, an appropriate nonparametric test, such as the Wilcoxon signed-rank test, will be used to evaluate the primary endpoint. No adjustments for multiplicity will be made. A p-value < 0.05 will be considered statistically significant.

The change and percent change in s-PINP and s-CTX from baseline will be summarized descriptively. The relationship between bone turnover markers and histomorphometric parameters will be explored using the linear regression method.

Safety

Safety analyses will be descriptive in nature and will include incidence and severity of adverse events and abnormalities in clinical laboratory tests, vital signs, ECGs, and Investigator assessment of local tolerance. All adverse events prior to the first dose of abaloparatide will be summarized separately.

2. INTRODUCTION

2.1. Background

Abaloparatide (marketed as TYMLOS™ in the United States) 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 > 1000-fold greater selectivity for the G protein-coupled (R^G) vs the non-G protein-coupled (R^0) conformation of $PTHR_1$ (Hattersley, 2016). Differential $PTHR_1$-R^G binding with abaloparatide results in potent and transient intracellular cyclic AMP (cAMP) signaling. In nonclinical studies, the transient $PTHR_1$ activation with abaloparatide strongly favors bone anabolism with a limited effect on bone resorption (Makino, 2015).

Abaloparatide is approved in the United States for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Abaloparatide was shown in Study BA058-05-003 (ACTIVE) to reduce the risk of vertebral and nonvertebral fractures compared to placebo, and to increase hip BMD more than teriparatide (Miller, 2016).

2.2. Disease and Study 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, 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 United States (US), there are an estimated 2 million osteoporotic fractures annually (Litwic, 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).

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, 2017), or the monoclonal antibody, denosumab, that inhibits the action of osteoclasts by binding to the 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. Teriparatide has delayed and modest effects on increasing BMD at the total hip and femoral neck, and on decreasing BMD at the distal 1/3 radius.

The increase in cortical porosity that can occur may result in maladaptive effects on cortical bone microarchitecture (Bilezikian, 2007).

The short-term anabolic effects of teriparatide have been demonstrated in histomorphometric analyses of a single transiliac crest bone biopsy after administration of two sets of tetracycline labels (quadruple labeling) (Lindsay, 2006). One month of treatment stimulated bone formation on cancellous and endocortical surfaces by both modeling-based and remodeling-based formation. Likewise, the same technique demonstrated stimulation of bone formation after 3 months of treatment with teriparatide, but inhibition of bone formation in subjects treated with the antiresorptive agent, denosumab (Dempster, 2016, AVA Osteoporosis Study). In this study, early stimulation of bone formation by teriparatide was observed in cancellous, endocortical, intracortical and periosteal envelopes. The stimulation of bone formation was due to an increase in remodeling-based formation (27%), overflow modeling-based formation (9%), and modeling-based formation (6%) (Dempster, 2017).

The effects of abaloparatide on bone histomorphometry were recently reported in a subset of subjects in the ACTIVE trial (Moreira, 2017). Biopsies were obtained at 12 to18 months (average 15.5 months) from subjects treated with either abaloparatide, teriparatide, or placebo. Few differences were detected among the three treatments, likely due to the fact that only cancellous bone was studied, as well as the late timing of the biopsies when the effects of the anabolic agents were declining.

2.3. Quadruple Label Technique

The purpose of this study is to assess the early effects of abaloparatide in postmenopausal women with osteoporosis using tissue-based indices of bone metabolism and to relate these indices to biochemical markers of bone turnover. All four bone envelopes (cancellous, endocortical, intracortical, and periosteal) will be examined in iliac crest biopsies after fluorochrome labeling. The quadruple labeling technique has previously been described by Lindsay (Lindsay, 2006).

As noted above, this novel labeling technique has been found to be highly effective in two studies demonstrating the early effects of anabolic therapy with PTH (1-34) on bone formation in subjects with osteoporosis. It has also been used successfully to investigate the early effects of PTH (1-84) replacement in subjects with hypoparathyroidism (Rubin, 2011). Recently, a quadruple label protocol proved to be particularly useful in elucidating the mechanism of action of the sclerostin antibody, romosozumab, in the treatment of osteoporosis (Chavassieux, 2017). In quadruple-labeled biopsies taken at two months, the bone formation rate was dramatically increased compared to pretreatment levels. However, in biopsies taken at 12 months with conventional double-labeling, bone formation rate was reduced compared to placebo treatment. If the quadruple-labeling protocol had not been employed, it would have been difficult to explain the large increments in bone mineral density, cancellous bone volume, trabecular connectivity, and cortical thickness achieved by romosozumab treatment. The principal advantage of the technique is that it allows measurement of dynamic bone formation variables before and after initiation of a drug treatment in a single biopsy. This eliminates the side-to-side variability in the traditional paired biopsy study design and, in any case,

such a design is not practical to study early effects (within 3 months) of drug administration. In the quadruple labeling technique, two different fluorochromes (demeclocycline HCl and tetracycline HCl) are used for the pre-treatment and on-treatment labels. The difference in color of each fluorochrome allows any label to be unambiguously identified as a pre-treatment or on-treatment label, even if only one set of labels is present in a particular forming osteon.

To prepare for biopsy, subjects will be given two sets of fluorochrome labels in the following way. The first set of labels will be given to all subjects in standard format: 3 days of demeclocycline HCl (150 mg, four times per day), a 12-day intermission, and 3 more days of demeclocycline (same dose). After the first set of labels has been administered, daily administration of 80 µg abaloparatide will commence. This treatment will be continued during administration of the second set of labels and until the day of biopsy. Approximately 23-26 days before the Month 3 visit, a second set of double labels will be administered following the same schedule, but this time using tetracycline HCl (250 mg, four times daily for 3 days on, 12 days off, 3 days on).

Standard transiliac crest bone biopsies will be performed 5 to 8 days after the last day of tetracycline administration following standard procedures (See Section 7.2.10). The biopsies will be embedded in methyl methacrylate and prepared in a standard fashion for histomorphometric analysis. Serial sections from each subject will be examined under UV light for evaluation of tetracycline labels and under polarized light after staining with toluidine blue for evaluation of reversal and cement lines.

Using two sets of fluorochrome labels, which differ in their color under fluorescent light enables one to distinguish the first and second sets of labels, even when only single labels are present. Using standard histomorphometry, mineral apposition rate and mineralizing surface can be measured for the two separate labeling periods, and bone formation rates can be calculated. The technique has two key advantages over paired biopsies. First, only one biopsy is required. Second, each subject serves as his or her own pretreatment control, eliminating problems caused by the large intersubject variability in histomorphometric variables.

2.4. Bone Histomorphometry Results from Study BA058-05-003

In Study BA058-05-003, a subset of subjects at selected centers was asked to undergo a bone biopsy (Moreira, 2017). Biopsies were obtained after the subjects had received between 12 and 18 months of treatment and were obtained primarily to assess safety. Qualitative histological analysis of biopsies from abaloparatide-treated subjects revealed normal bone microarchitecture without evidence of adverse effects on mineralization or on the formation of normal lamellar bone. There were no bone marrow abnormalities or marrow fibrosis, nor was there presence of excess osteoid or woven bone. There were few significant differences among the three treatment groups in a standard panel of static and dynamic histomorphometric indices. The mineral apposition rate was higher in the teriparatide-treated group than in the placebo-treated group. The eroded surface was lower in the abaloparatide-treated group than in the placebo-treated group. Cortical porosity was higher in both the abaloparatide- and the teriparatide-treated groups than in the placebo-treated group.

2.5. Study Rationale

The purpose of this study is to assess the early effects of abaloparatide in postmenopausal women with osteoporosis using tissue-based indices of bone metabolism obtained by iliac crest bone biopsy after quadruple tetracycline labeling and to relate these indices to biochemical markers of bone turnover. All four bone envelopes (cancellous, endocortical, intracortical, and periosteal) will be examined.

2.6. Dose Rationale

The approved dose of abaloparatide in the US for the treatment of postmenopausal women at a risk for fracture is 80 µg per day.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

1. Demonstrate the early effects of abaloparatide on tissue-based indices of bone formation and resorption
2. Assess the degree to which increased bone formation is achieved by modeling, remodeling, and overflow bone formation
3. Relate the early indices of tissue-based bone formation and bone resorption to those measured using biochemical markers of bone turnover

3.2. Endpoints

- Change from baseline to 3 months in dynamic indices of bone formation in the relevant bone envelopes (cancellous, endocortical, intracortical, and periosteal)
  - Mineralizing surface (MS/BS)
  - Mineral apposition rate (MAR)
  - Bone formation rate (BFR/BS)
- Structural indices in the relevant bone envelopes at Month 3
  - Cortical porosity (Ct.Po/Ct.Ar)
- Static indices in the relevant bone envelopes at Month 3
  - Osteoid volume (OV/BV)
  - Osteoid surface (OS/BS)
  - Osteoid thickness (O.Th)
  - Wall thickness (W.Th)
  - Eroded surface (ES/BS)
- Change from baseline to 3 months in special histomorphometric variables in the relevant bone envelopes
  - Remodeling, modeling, and overflow modeling-based formation (RmF/BS, MF/BS, oMF/BS)
- Change in serum procollagen type I N-terminal propeptide (s-PINP) and carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) from baseline to 1 and 3 months
- Correlations of tissue-based indices of bone formation and bone resorption with s-PINP and s-CTX
- Overall safety and tolerability of abaloparatide in postmenopausal women with osteoporosis.

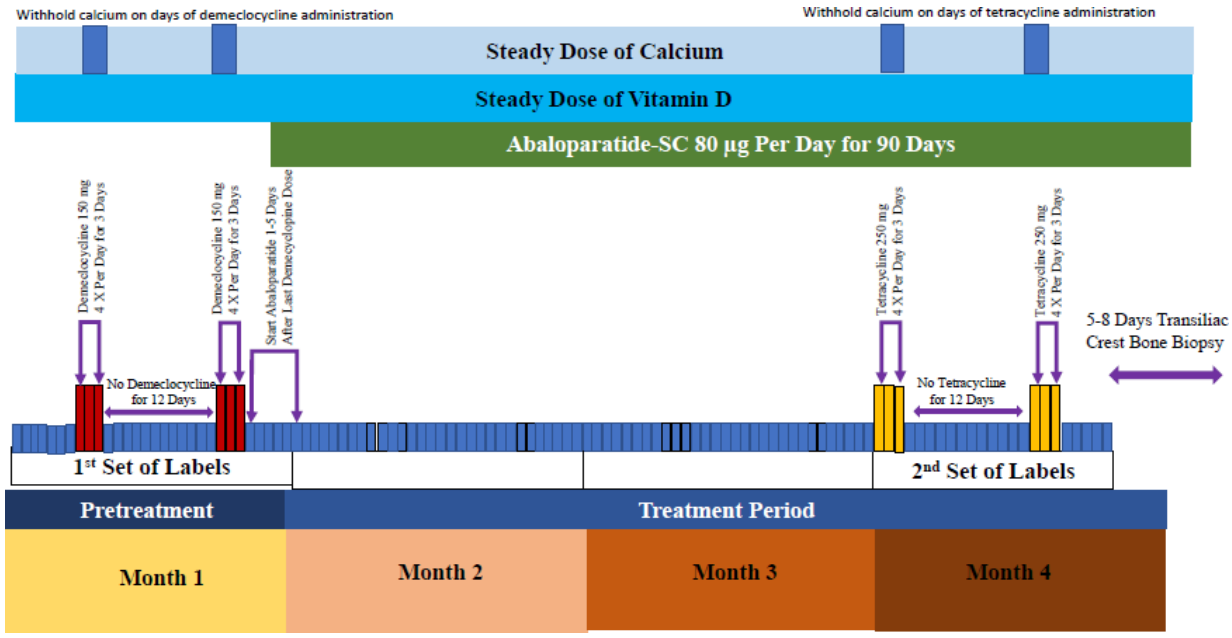
4. STUDY DESIGN

4.1. Description of the Study Design

This is an open-label, single-arm, multicenter study enrolling approximately 25 postmenopausal women with osteoporosis at approximately 5 study centers. The study is designed to measure the early effects of abaloparatide on tissue-based bone formation and resorption variables based on samples obtained by iliac crest bone biopsy after fluorochrome labeling. The study will consist of a Screening Period (up to 1 month), a Pretreatment Period (approximately 1 month), a Treatment Period (3 months), and a Month 4 visit one month after the last dose of study medication. Biopsies are to be obtained at 3 months of treatment for the following reasons:

- This is the optimal time for changes in biochemical markers of bone turnover to predict changes in BMD after 18 months of treatment with abaloparatide (Radius, Data on file)
- Longer periods of time increase the risk that the initial set of labels will be resorbed, which would seriously confound the results
- Comparisons to the 3-month results for teriparatide from the AVA Osteoporosis Study will be possible (Dempster, 2016)

Figure 1: **BA058-05-020 Study Design, Including Schematic of Bone Biopsy Labeling Procedure**



Full details of the protocol required assessments can be found in the Schedule of Assessments and Procedures (Section 7.2.1).

There will be a sub-study at selected sites to collect pQCT data and extend an additional 3 months of study drug administration for a total of 6 months of treatment.

Details of the schedule of measurements, endpoints and statistical analysis methods for the sub-study will be described in a separate document.

5. SELECTION OF STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible to participate in this study:

1. The subject is a healthy ambulatory postmenopausal female from 50 to 85 years of age (inclusive) with osteoporosis.
2. The subject has been postmenopausal for at least 5 years. Postmenopausal status will be established by a history of amenorrhea for at least 5 years and by an elevated follicle-stimulating hormone (FSH) value of ≥ 30 IU/L.
3. The subject has a BMD T-score ≤ -2.5 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by DXA *or* lumbar spine or hip BMD T-score ≤ -2.0 with a history of low trauma vertebral, forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture sustained within 5 years prior to enrollment. These fractures must be documented by radiograph or hospital report.
4. The subject is in good general health as determined by medical history and physical examination (including vital signs), has a body mass index (BMI) of 18.5 to 33, inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator.
5. The subject has serum calcium (albumin-corrected), PTH (1-84), phosphorus, and alkaline phosphatase levels all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value, and who meets all other entry criteria, is required to have a normal bone-specific alkaline phosphatase result 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 D3 and re-tested once.
7. The subject's resting 12-lead electrocardiogram (ECG) obtained during screening shows no clinically significant abnormality.
8. The subject has read, understood, and signed the written informed consent form.

5.2. Exclusion Criteria

Subjects with any of the following characteristics are not eligible to participate in the study:

General exclusion criteria

1. Presence of abnormalities of the lumbar spine that would prohibit assessment of lumbar spine BMD, defined as having at least 2 radiologically evaluable vertebrae within L1-L4.
2. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
3. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis.
4. Clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells (WBC) and platelets, coagulation, or usual serum chemistry: electrolytes, renal function, liver function and serum proteins.
5. Unexplained elevation of serum alkaline phosphatase.
6. History of radiotherapy (radiation therapy), other than radioiodine.
7. History of bleeding disorder that would preclude a bone biopsy, in the opinion of the Investigator.
8. 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.
9. History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism, or malabsorptive syndromes within the past year.
10. 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 ≥ 30 mL/min.
11. History of any cancer within the past 5 years (other than basal cell or squamous cell cancer of the skin).
12. History of osteosarcoma at any time or a history of hereditary disorders which could predispose the subject to osteosarcoma.
13. History of nephrolithiasis or urolithiasis within the past five years.
14. Subjects known to be positive for hepatitis B, hepatitis C, human immunodeficiency virus infection (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

15. Known history of hypersensitivity to any of the test materials, related compounds, or tetracyclines.
16. Prior treatment with PTH or PTHrP drugs, including abaloparatide.
17. Prior treatment with IV bisphosphonates at any time or oral bisphosphonates within the past three 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.
18. Treatment with fluoride or strontium in the five years prior to the Screening Period, or prior treatment with gallium nitrate, or with any unapproved bone-acting investigational agents at any time.
19. Treatment with calcitonin, SERMs (such as raloxifene or tamoxifen), or tibolone, within the 6 months prior to the Screening Period. Estrogens administered as hormone replacement therapy with or without progestins are not exclusionary.
20. 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.
21. Prior treatment with denosumab.
22. Daily treatment with oral, intranasal or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of corticosteroids (for seasonal allergies or asthma) is not exclusionary.
23. Prior treatment with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus).
24. Exposure to an investigational drug within the 12 months prior to the Screening Period.

Lifestyle-related exclusion criteria

25. Abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption, significant recent weight change), vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day.
26. Subject is known to abuse alcohol or use illegal drugs within 12 months of the Screening Period.

5.3. Participant Withdrawal or Termination

5.3.1. 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:

- Hypercalcemia as described in Section 5.7.1;
- 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 adverse events (as described in Section 8.1.2);
- A complex of adverse events which, in the judgment of the Investigator, justifies treatment cessation;
- Serious intercurrent illness;
- Non-compliance;
- Protocol violations;
- 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, she will be asked to sign an additional Informed Consent Form further explaining the potential risks and benefits of remaining in the study.

5.3.2. 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 case report form. All subjects withdrawn prior to completing the study should be encouraged to complete study procedures scheduled for the Month 3/Early Termination visit and to return in one month for a follow-up visit. The Sponsor Medical Monitor will decide if the tetracycline labeling procedure and bone biopsy will be performed as part of the Early Termination visit. All adverse events should be followed as described in Section 8. Subjects who discontinue or are withdrawn from the study may be replaced.

5.4. Concomitant Medications

Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld. The doses and schedule of calcium and vitamin D supplements (Section 7.2.5) 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. Calcium (500–1000 mg) and vitamin D (400–800 IU) supplements will be sourced locally by the site and provided to the subjects at the expense of the Sponsor.

Two different fluorochromes (demeclocycline HCl and tetracycline HCl) are used for the pre-treatment and on-treatment labels. Instructions for administration of fluorochromes is detailed in Section 7.2.6 and Section 7.2.9.

For any required concomitant medication, such as statins or antihypertensives, the subject must be on a stable dose at study entry and every effort should be made to maintain a stable dose during study participation.

The occasional use of over-the-counter medications at approved doses (eg, ibuprofen or acetaminophen) for headache or minor discomfort is allowed. These are to be recorded on the appropriate eCRF. 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.

5.5. Prohibited Medications

Please refer to Section 5.2 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 5.4, 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 (≤ 1 week) use of inhaled 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.

5.6. 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) 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

The study may resume once concerns about safety, protocol compliance, or data quality are addressed and satisfy the Sponsor, IRB, and/or Regulatory Agencies, if applicable.

5.7. Temporary Suspension of Treatment

The Investigator has the right to suspend treatment with study medication for up to 7 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 (eg, a planned procedure), or important social or administrative events. The reason for the suspension of treatment is to be documented in the eCRF and in source documents.

When treatment is restarted, the subject should resume treatment with the next scheduled dose and continue until the scheduled End-of-Treatment.

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

5.7.1. Treatment Algorithm in Subjects Who Develop Hypercalcemia

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 upper limit of normal (ULN) (inclusive), the Investigator will confirm hypercalcemia by drawing a new serum sample as soon as possible after the result is received.

If a subject's predose serum calcium is elevated on repeated testing, calcium and vitamin D supplementation should be withheld. If the subject's serum calcium remains elevated 1 to 2 weeks after calcium and vitamin D supplementation is withheld, dosing of study medication should be stopped. Treatment can be restarted if other causes of hypercalcemia are excluded after consultation with the Sponsor. Treatment with study medication should not be suspended for greater than 7 days.

6. STUDY DRUG ADMINISTRATION AND MANAGEMENT

6.1. Study Medication

6.1.1. Abaloparatide

Abaloparatide 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 mcg/1.56 mL.

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

6.2. Packaging, Labeling and Storage

6.2.1. Packaging and Labeling

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

All Investigational Product (IP) will be supplied to study sites packaged and labeled according to local regulations with a statement that all IP is limited to investigational use only. A detailed study drug dispensation plan will be provided in the Pharmacy Manual.

6.2.2. Storage

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

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

6.3. 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 on the eCRFs. Subject numbers will be assigned as follows:

XXX YYY, where:

- XXX represents the study site number;
- YYY represents the subject ID number

6.4. Dosing and Administration

Subjects will self-administer a single daily dose of 80 µg of study medication (abaloparatide) 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 procedures. Study personnel may administer the study medication during clinic visits.

Subjects will be trained by study personnel during the Pretreatment Period how to self-inject study medication with the abaloparatide injection pen. If a subject requires assistance with study medication administration, an individual (eg, 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 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 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 of the abdomen, rotating the site of injection each day, and administered at approximately the same time every 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. The subject is to remain under observation for a minimum of 60 minutes after the initial injection. A blood pressure measurement will be taken 60 minutes after the injection. Subjects are to be instructed to self-inject at home in a location where they have the ability to sit or lie down.

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

6.5. 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 two methods: subject diaries and measuring residual drug in the cartridge.

Discrepancies between expected and actual dosing will be assessed and discussed with the subject. All discrepancies, causes and subject retraining will be documented in the medical charts, and recorded in the eCRF as appropriate. If a subject does not take all study medication (abaloparatide) as required, the reason for the missed dose is to be discussed with the subject during the visit.

Although calcium and vitamin D are considered concomitant medications for this study, missed doses of calcium and vitamin D will be determined by performing a pill count. If a subject demonstrates continued noncompliance with required abaloparatide dosing despite educational efforts, the Investigator should contact the Sponsor Medical Monitor to discuss discontinuation of the subject from the Study.

6.6. Study 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.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Procedures

The study-specific assessments are detailed in this section and outlined in Table 1. Any results falling outside of the reference ranges may be repeated one time at the discretion of the Investigator.

7.2. Study Schedule

This study is comprised of six clinic visits. Study assessments are to be performed according to the Schedule of Events (Table 1). There is a ± 4-day window for each clinic visit, other than the Day 1 for which there is a +4-day window and Month 4 visit for which there is a ± 7-day window.

The study will consist of a Screening Period (up to 1 month), a Pretreatment Period (approximately 1 month), a Treatment Period (3 months), and a Month 4 Visit (one month). During the Treatment Period, subjects will have clinic visits for study-related protocol procedures at Day 1, Month 1, and Month 3. For the purpose of this study, one month is equal to 30 days.

7.2.1. Schedule of Assessments and Procedures

A comprehensive Schedule of Assessments and Procedures is presented in Table 1.

Table 1: Schedule of Assessments and Procedures

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pre-treatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±7 days) Month 4
Informed consent	X					
Verification of entry criteria	X	X				
Review of medical history[a]	X	X	X	X	X	X
Physical examination[b]	X					
Symptom directed physical examination		X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X
Weight and height measurements[d]	X		X	X	X	X
12-lead Electrocardiogram[e]	X		X		X	X
Urinalysis (dipstick)[f]	X		X	X	X	
Chemistry blood collection[g]	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					
1,25-dihydroxy vitamin D level	X					
FSH	X					
Thyroid stimulating hormone	X					
Injection training for subjects		X				
Dispense calcium and vitamin D supplements[n]	X	X	X	X		

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pre-treatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±7 days) Month 4
Study medication (abaloparatide) administration			Daily abaloparatide administration until and including the day of bone biopsy			
Demeclocycline (dispense and administration)		X[h]				
Tetracycline (dispense and administration)				X[i]		
Transiliac crest bone biopsy[j]					X	
Serum markers of bone metabolism (PINP and CTX)			X	X	X	
AP and lateral lumbar and thoracic spine radiographs	X					
Clinical assessment of new fractures[k]		X	X	X	X	X
Collect blood for immunogenicity testing			X		X	
BMD of lumbar spine, total hip, and femoral neck	X				X	
Investigator assessment of local tolerance (dermal reactions assessment)			X	X	X	
Subject diary review[l]			X	X	X	
Document AEs and concomitant medications[m]	At any time, question subject at each visit					
Drug supply/resupply/accountability		X	X	X	X	

[a] Including alcohol and tobacco use assessment.

[b] 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 not present at screening should be reported as AEs.

[c] Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse 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. Only blood pressure, pulse rate, and respiration rate are to be recorded one hour post-dose. Supine and standing blood pressure measurements will be performed at each visit during the Treatment Period.

[d] Height is to be measured in the standing position with shoes off using a medical stadiometer.

[e] An ECG will be recorded immediately prior to dosing and one hour post-dose during the Treatment Period.

[f] 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.

[g] Serum chemistry will be measured predose at Visits 3, 4, and 5.

[h] Eighteen days before Day 1 of the Treatment Period (Visit 3), subjects who remain eligible for study participation will begin the first bone biopsy labeling procedure with administration of 150 mg demeclocycline 4 times daily for 3 days followed by a 12-day intermission, and then demeclocycline for 3 additional days at the same dose.

[i] Approximately 23 to 26 days before Month 3 (Visit 5), subjects will begin the second bone biopsy labeling procedure with administration of 250 mg tetracycline 4 times daily for 3 days followed by a 12-day intermission, and then tetracycline for 3 additional days at the same dose.

[j] Transiliac crest bone biopsy 5-8 days after last tetracycline dose. Sponsor Medical Monitor will decide if included in Early Termination Visit.

[k] 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.

[l.] Subject will be instructed on completion of diary in the Pretreatment Period to include administration of medications for bone biopsy labeling procedure. The subject medication diary will be reviewed by study personnel at each study visit during the Treatment Period to ensure subject compliance.

[m] 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.

[n] Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld.

7.2.2. 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 institutional review board (IRB) must be used. The Investigator or designee must record the date when the ICF was signed in the subject's source document.

7.2.3. 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.

7.2.4. 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.

7.2.5. Screening (Visit 1)

Signed informed consent will be obtained and eligibility for study entry assessed. 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 calcium and vitamin D supplements. This should be continued through the Treatment Period according to the subject's need, so that they have an intake of at least 1200 mg/day of calcium and 800-1000 IU/day of vitamin D. Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline, where calcium administration will be withheld. The following baseline screening evaluations will be performed:

- Obtain Informed Consent
- Verification of study entry criteria
- Review of medical history
- Physical examination
- Blood pressure and vital signs (see Section 7.3)
- Weight and height (see Section 7.3)

- 12-lead ECG
- Laboratory testing of serum chemistry, hematology, urine dipstick, and coagulation
- PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels
- FSH and TSH levels
- Lumbar and thoracic spine radiographs (anteroposterior and lateral)
- BMD assessments of lumbar spine, total hip and femoral neck by dual X-ray absorptiometry (DXA)
- AE and concomitant medication review from signing of the informed consent

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 within 30 days of the original test date. If upon reanalysis, the values fall within the inclusion/exclusion criteria, the subject may enter the study. Subjects who do not meet the 25-hydroxyvitamin D entry criterion may receive vitamin D supplementation and be retested one time. Similarly, subjects with minor elevations of PTH may be retested one time after vitamin D supplementation. All subjects enrolled following retesting must have safety laboratory results reported within 30 days prior to enrollment.

All AEs, including serious adverse events (SAEs), will be recorded from the time of signing of the informed consent and through the 30 days after the last dose of study medication.

7.2.6. Pretreatment (Visit 2)

All subjects will receive calcium and vitamin D until the end of the Treatment Period, according to the subject's need so that they have an intake of at least 1200 mg/day of calcium and 800-1000 IU/day of vitamin D. Subjects should be on a stable dose of calcium and vitamin D for 30 days prior to initiating the double labeling procedure. Subjects will undergo training for medication self-administration and for completion of diary, to include administration of medications for bone biopsy labeling procedure. Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld. The following procedures will be performed:

- Verification of study entry criteria
- Review of medical history
- Symptom directed physical exam (see Section 7.3)
- Blood pressure and vital signs (see Section 7.3)
- Clinical assessment of new fractures

- AE and concomitant medication review
- Dispense demeclocycline, vitamin D and calcium
- Drug accountability
- Subject injection training

Eighteen (18) days before Day 1 of the Treatment Period (Visit 3), subjects who remain eligible for study participation will begin the first bone biopsy labeling procedure with administration of 150 mg demeclocycline 4 times daily for 3 days followed by a 12-day intermission, and then demeclocycline for 3 additional days at the same dose. Demeclocycline should be taken on an empty stomach, at least 1 hour before meals and 2 hours after a meal with a full glass of water.

7.2.7. Treatment Period

At each clinic visit during the Treatment Period, recent health status will be obtained, the diary reviewed, adverse events and concomitant medications collected, drug supply / resupply and accountability, and blood pressure and vital signs performed. Laboratory assessments of serum chemistry, hematology and urinalyses will be obtained at Day 1, Month 1, and 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. 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.

Bone turnover marker assessments (s-PINP and s-CTX) will be performed on the Day 1, Month 1 and Month 3 visits (Visits 3, 4, and 5, respectively).

7.2.8. Day 1 (Visit 3)

- Review of medical history
- Symptom directed physical exam (see Section 7.3)
- Blood pressure and vital signs (see Section 7.3)
- Weight and height measurement (see Section 7.3)
- 12-lead ECG
- Laboratory testing of serum chemistry (predose), hematology, and urine dipstick
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessments of new fractures
- Collect blood for immunogenicity testing
- Subject diary review

- AE and concomitant medication review
- Dispense abaloparatide, vitamin D and calcium
- First dose of abaloparatide will be administered by the subject in clinic
- Investigator assessment of local tolerance after injection
- Drug accountability

7.2.9. Month 1 (Visit 4)

- Review of medical history
- Symptom directed physical exam (see Section 7.3)
- Blood pressure and vital signs (see Section 7.3)
- Weight and height measurements (see Section 7.3)
- Laboratory testing of serum chemistry (predose), hematology, and urine dipstick
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessment of new fractures
- Review subject diary
- AE and concomitant medication review
- Dispense abaloparatide, vitamin D and calcium
- Self-administration of study medication when directed by site staff after completion of predose activities
- Investigator assessment of local tolerance after injection
- Drug accountability

Approximately twenty-three (23) to twenty-six (26) days prior to Visit 5, subjects will begin the second bone biopsy labeling procedure with administration of 250 mg tetracycline 4 times daily for 3 days followed by a 12-day intermission, and then tetracycline for 3 additional days at the same dose. Tetracycline should be taken on an empty stomach, at least 1 hour before meals and 2 hours after a meal with a full glass of water.

7.2.10. Month 3/Early Termination (Visit 5)

- Review of medical history
- Symptom directed physical exam (see Section 7.3)
- Blood pressure and vital signs (see Section 7.3)
- Weight and height measurements (see Section 7.3)
- 12-lead ECG

- Laboratory testing of serum chemistry (predose), hematology, and urine dipstick
- Coagulation blood testing
- PTH level
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessment of new fractures
- Collect blood for immunogenicity testing
- Review subject diary
- AE and concomitant medication review
- Self-administration of last dose of study medication when directed by site staff after completion of predose activities
- Investigator assessment of local tolerance after injection
- BMD assessments of lumbar spine, total hip and femoral neck by dual X-ray absorptiometry (DXA)
- Transiliac crest bone biopsy 5-8 days after last tetracycline dose (Sponsor together with the Medical Monitor should determine if included in Early Termination Visit)
- Drug accountability

7.2.11. Month 4 (Visit 6)

- Review of medical history
- Symptom directed physical examination (see Section 7.3)
- Blood pressure and vital signs (see Section 7.3)
- Weight and height measurements (see Section 7.3)
- 12-lead ECG
- Clinical assessment of new fractures
- All AEs and concomitant medications review

7.2.12. Unscheduled Visit

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

7.3. 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.

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse 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. Only blood pressure, pulse rate, and respiration rate are to be recorded one hour post-dose. Supine and standing blood pressure measurements will be performed at each visit during the Treatment Period. After screening, any clinically significant abnormal findings in vital signs should be reported as AEs.

7.4. 12-Lead Electrocardiogram

A standard, 12-lead ECG 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 one hour post-dose during the Treatment Period. After screening, any clinically significant abnormal findings in ECGs should be reported as AEs.

7.5. Laboratory Evaluations

7.5.1. Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be collected at time points indicated in the Schedule of Assessments and Procedures in Table 1. All clinical laboratory blood samples will be sent to a central laboratory for analysis and testing. A list of study clinical laboratory tests is in Table 2.

- 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 within 30 days of the original test date. If upon reanalysis, 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 as may subjects with minor elevations of PTH. All subjects enrolled following retesting must have safety labs within 30 days of randomization (Day 1).

Table 2: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (dipstick) [a]	Additional Tests
Hemoglobin	Sodium	pH	PTH (1–84)[b]
Hematocrit	Potassium	Glucose	25-hydroxyvitamin D[c]
			1,25-dihydroxy vitamin D[c]
WBC count with differential in absolute counts	Chloride	Protein	Coagulation[b]
RBC count	Inorganic phosphorus	Ketones	FSH[c]
Mean corpuscular volume (MCV)	Albumin	Bilirubin	TSH[c]
Mean corpuscular hemoglobin concentration (MCHC)	Total protein	Blood	
Mean corpuscular hemoglobin (MCH)	Glucose	Urobilinogen	
Platelet count	Blood urea nitrogen (BUN)	Specific gravity	
	Creatinine	Nitrite	
	Uric acid	Leukocytes	
	Aspartate aminotransferase (AST)		
	Alanine aminotransferase (ALT)		
	Gamma-glutamyltranspeptidase (GGT)		
	Creatine phosphokinase (CPK)		
	Alkaline phosphatase		
	Total bilirubin		
	Lactate dehydrogenase (LDH)		
	Total Cholesterol		
	Triglycerides		
	Total calcium		

[a] Local laboratory, send to a central lab for microscopy if test is positive for micro-organisms
[b] Only required at Screening and Visit 5 (Month 3/Early Termination)
[c] Only required at Screening

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. After screening, clinically significant changes in laboratory tests that occur during the course of the study are to be reported as adverse events.

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.

7.5.2. Serum Markers of Bone Metabolism

Blood samples will be taken to measure efficacy related markers of bone metabolism at Day 1, Month 1, and Month 3 or early termination. Serum procollagen type I N-terminal propeptide (s-PINP) and serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) will be measured in all subjects.

7.5.3. 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.

7.6. Bone Biopsy Processing Procedure

The bone cores will be processed without decalcification and embedded in methyl methacrylate. Three levels of transverse sections from each biopsy block will be cut 100 micron apart using a Leica SM 2500E Polycut microtome. In each level, two adjacent sections at 7-microns and one adjacent 20-micron thick sections will be collected. The two 7-micron adjacent sections will be stained with toluidine-blue (ethanol base) and Goldner's trichrome, respectively. The toluidine-blue stained section will be used to demonstrate bone cells, osteons, and cement lines. The trichrome stained section will be used to demonstrate osteoid. The 20-micron section will be left unstained for visualization of tetracycline labels. Each section will be subjected to histomorphometric analysis using computerized image analysis as previously described (Dempster, 2001; Dempster 2017). All variables will be calculated and expressed according to the guidelines of the ASBMR's Bone Histomorphometry Committee (Dempster, 2013).

7.7. Imaging Procedures

All imaging measurements (spine radiographs and BMD by DXA) will be performed according to the procedures outlined in the Imaging Charter and Imaging Manuals which will be provided as a separate document.

7.7.1. Dual Energy X-ray Absorptiometry (DXA)

All subjects will have areal bone density (aBMD) measurements taken via DXA of the lumbar spine, total hip, femoral neck, at Screening (Visit 1). Lumbar spine scans must include L1 through L4. Hip scans will include the entire proximal femur to about 2 cm below the lesser trochanter.

7.7.2. 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 vertebral fractures using the Genant Semi-quantitative (SQ) Scoring method (Genant, 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).

Subjects will 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 eCRFs and source documents.

7.7.3. Treatment and Imaging at Selected Sites

Selected sites will follow expanded treatment and imaging procedures. Sites following expanded procedures will be provided instructions and details in a separate document for the sub-study.

Additional treatment and imaging procedures at selected sites includes:

- Abaloparatide treatment for total of 6 months
- pQCT of the forearm and tibiae performed at the pretreatment visit (Visit 2), at Month 3 (Visit 5), and at Month 6 (Visit 7).

7.8. Discontinuation from the Study

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

Subjects sustaining a radiologically confirmed incident vertebral 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.

Subjects who decide they do not wish to participate in the study further should return for the assessments indicated for the Month 3/Early Termination and 30 days later for the Month 4 Visit in the Schedule of Assessments and Procedures (Table 1). If they fail to return for these assessments for unknown reasons, every effort (eg, by telephone, email, and letter for a minimum of three attempts) should be made and documented in the subject's study file.

7.8.1. 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.

7.8.2. 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 of the early termination of the study.

8. ADVERSE EVENT AND SERIOUS ADVERSE EVENT DOCUMENTATION

8.1. 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 and determine reporting requirements to the Sponsor as well as the IRB.

8.1.1. Adverse Events

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.

8.1.2. Serious Adverse Events

A serious adverse event (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 inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (ie, 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events 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 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).

8.1.3. Recording Adverse Events

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 case report form and by collection of source documents.

For both serious and non-serious adverse events, the Investigator must determine the intensity of the event and the relationship of the event to study drug administration. 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.

Relationship	Definition
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.

8.1.4. Serious Adverse Event (SAE) 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 to RADIUS Pharmacovigilance. These events will be followed until resolution or stabilization. The reference safety information for this study is included in the Investigator Brochure, 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 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.

8.1.5. Follow-up of Adverse Events

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

8.1.6. 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 (eg, 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.

8.1.7. 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 Institutional Review Boards (IRBs)/EU central ethics committees (ECs) of related, unexpected SAEs.

The Investigator is responsible for notifying the Sponsor, CRO, and local IRB, local EC, 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 3/Early Termination visit (Visit 5), and it is determined to be related either to a study procedure or study drug, the Investigator or his/her designee must notify the Sponsor and will communicate that information to the IRB within one business day of knowledge of the event. The contact may be by phone or e-mail.

8.2. 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.

8.3. 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, eg, dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis Plan

A comprehensive Statistical Analysis Plan (SAP) will be completed and approved prior to database lock. All statistical tests will be two-sided with a significance level of 5%, unless otherwise specified.

9.2. Statistical Hypothesis

9.3. Analysis Datasets

9.3.1. Population for Analysis

The primary population for all efficacy analyses will be the Bone-Biopsy Population, which is defined as all enrolled subjects who received a biopsy. The primary population for all safety analyses will be the Safety Population, which will be defined as all enrolled subjects who received at least one dose of abaloparatide.

9.4. Description of Statistical Methods

9.4.1. General Approach

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.

9.4.2. Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint of this study is the change from baseline to 3 months in mineralizing surface (MS/BS) in the cancellous bone envelope. Paired t-tests will be used to compare the differences in dynamic indices between the two time-points derived from the two sets of double labels using the Bone-Biopsy Population. If the normality assumption of the efficacy data is not satisfied at the 0.01 significance level and if visual inspection of the data deems it necessary, an appropriate nonparametric test, such as the Wilcoxon signed-rank test, will be used to assess changes from baseline. No adjustments for multiplicity will be made. A p-value < 0.05 will be considered statistically significant.

9.4.3. Analysis of Secondary Endpoint(s)

Secondary efficacy endpoints of tissue-based indices of bone formation and bone resorption will be analyzed in the same manner as the analysis of the primary efficacy endpoint using the Bone Biopsy Population.

The change and percent change from baseline in bone turnover makers (s-PINP and s-CTX) will be summarized descriptively at each visit (1 and 3 months) using the Bone-Biopsy and the Safety Populations.

Linear regression analyses will be used to assess the relationships between efficacy endpoints of tissue-based indices of bone formation and bone resorption and changes in bone turnover markers at each visit, including changes in MS/BS and BFR/BS in each envelope to changes in s-PINP, changes in intracortical MS/BS and BFR/BS to changes in s-CTX, MS/BS and BFR/BS in each envelope at Month 3 to s-PINP at Months 1 and 3, intracortical MS and BFR/BS at Month 3 to s-CTX at Month 3, and ES/BS in each envelope and cortical porosity at Month 3 to s-CTX at Month 3. The analyses include scatter plots, Pearson's correlation coefficient, and slopes of simple regression models using the Bone-Biopsy Population.

9.4.4. 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.

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

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

Descriptive statistics for clinical laboratory data (including serum calcium and albumin), vital signs (including blood pressure), ECGs, and Investigator assessment of local tolerance will be provided by 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).

Concomitant medications will be coded using the WHO Drug Dictionary and summarized by number and percentage of subjects using each class and preferred drug term.

9.4.5. Adherence and Retention Analyses

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

9.4.6. Baseline Descriptive Statistics

Medical history, physical examination, demographics and baseline characteristics will be summarized and presented. 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.

9.4.7. Interim Analyses

There are no interim analyses planned for this study.

9.4.8. Tabulation of Individual Response Data

Individual efficacy and safety data will be tabulated as appropriate.

9.5. Sample Size Calculation

In the AVA study of teriparatide and denosumab (Dempster, 2016), the mean (± SD) change from baseline in cancellous MS/BS (%) for teriparatide was 13.90 (± 9.38) at 3 months. In the ACTIVE study, the median % change from baseline in s-PINP at 3 months was 60% for abaloparatide and 94% for teriparatide. The ratio between the 2 groups is approximately 2/3 (= 60%/94%).

Using the same ratio and the results for teriparatide obtained from the AVA study, we can assume that the mean change from baseline in cancellous MS/BS (%) for abaloparatide at 3 months will be 9.2% (= 13.90*2/3). Assuming a standard deviation (SD) of 12.0%, a sample size of 21 completers will provide at least 90% power to detect a statistically significant change from baseline in cancellous MS/BS (%) for abaloparatide at 3 months of 9.2%. The study is planned to enroll approximately 25 subjects to accommodate a drop-out rate of 15%, including those with non-evaluable bone biopsy. Additional subjects may be enrolled if the number of evaluable biopsies is insufficient to achieve this power.

9.6. Measures to Minimize Bias

Not applicable.

9.7. Enrollment/Randomization/Masking Procedures

Not applicable.

10. ADMINISTRATIVE REQUIREMENTS

10.1. Ethical Considerations

This clinical study will be conducted in accordance with the current version of ICH Harmonized Tripartite Guidelines 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 Regulations for the Protection of Human Subjects of Research codified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312, 21 CFR Part 314, and ICH GCP E6.

The IRB 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 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 by the Investigator or RADIUS or designee, as allowable by local applicable laws and regulations.

10.2. 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.

10.3. 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 (ie, efficacy assessments) will require IRB 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.

10.4. 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 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.

10.5. Subject 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.

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

With the subject's approval, and as approved by the site's IRB, 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. The storage facility will be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each subject, maintaining 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.

10.7. 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.

10.8. 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.

10.9. 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.

10.10. 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.

10.11. 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 centers.

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

REFERENCES

Bilezikian JP. Anabolic therapy for osteoporosis. Women's Health (Lond). 2007;3:243-253.

Bone HG, Cosman F. Miller PD, Williams GC, Hattersley G, Hu M-y, Fitzpatrick LA. Papapoulos S. Sustained fracture risk reduction with sequential abaloparatide/alendronate: results of ACTIVExtend. ASBMR 2017 Annual Meeting. 1074. Abstract.

Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, Valter I, Fitzpatrick LA, Riis BJ, Christiansen C, Bilezikian JP, Black D. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend Trial. Mayo Clin Proc. 2017;92:200-210.

Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetic K, Muller R, Bilezikian J, Lindsay R. Effects of daily treatment with parathyroid hormone on bone architecture and turnover in subjects with osteoporosis: a paired biopsy study. J Bone Miner Res. 2001;16:1846-1853.

Dempster DW, Compston JE, Drezner MK, Glorieux FH, Kanis JA, Malluche H, Meunier PJ, Ott SM, Recker RR, Parfitt AM. Standardized nomenclature, symbols, and units for bone histomorphometry: a 2012 update of the report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res. 2013;28:2-17.

Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, Miller PD, Rao SD, Kendler DL, Lindsay R, Krege JH, Alam J, Taylor KA, Janos B, Ruff VA. Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: the AVA osteoporosis study. J Bone Miner Res. 2016;101:1353-1363.

Dempster D, Zhou H, Recker R, Brown J, Recknor C, Lewiecki EM, Miller P, Rao S, Kendler D, Lindsay R, Krege J, Alam J, Taylor K, Ruff V. Longitudinal changes in modeling- and remodeling-based bone formation with an anabolic vs. antiresorptive agent in the AVA Osteoporosis Study. ASBMR 2016 Annual Meeting. S51. Abstract.

Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, Miller PD, Rao SD, Kendler DL, Lindsay R, Krege JH, Alam J, Taylor KA, Melby TE, Ruff VA. Remodeling- and Modeling-Based Bone Formation With Teriparatide Versus Denosumab: A Longitudinal Analysis From Baseline to 3 Months in the AVA Study. J Bone Miner Res. 2017 Oct 12. doi: 10.1002/jbmr.3309.

Genant HK, Wu CY, van Kuijk KC, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8:1137-1148.

Hattersley G, Dean T, Corbin BA., Bahar H, Gardella TJ. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157:141-149.

Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, Nieves JW, Dempster DW. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. J Bone Miner Res. 2006;21:366-373.

Litwic A, Lekarz, Warwick D, Denniston E. Distal radius fracture: Cinderella of the osteoporotic fractures. Orthop Muscul Syst. 2014; 3:162-168.

Makino, A., Takagi, H., Sugiyama, H. Effects of Abaloparatide on the Expression of Bone Resorption-and Formation-related Factors in Osteoblastic Cells; a Comparison with Teriparatide. J Bone Miner Res, 30 (Suppl 1).

Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu M, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316:722-733.

Moreira CA, Fitzpatrick LA, Wang Y, Recker RR. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: the ACTIVE phase 3 trial. Bone. 2017;97:314-319.

Rizzoli R. Osteoporosis, genetics and hormones. J Mol Endocrinol. 2001;26:79-94.

Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med. 2005;353:59

Rubin MR, Dempster DW, Sliney J Jr, Zhou H, Nickolas TL, Stein EM, Dworakowski E, Dellabadia M, Ives R, McMahon DJ, Zhang C, Silverberg SJ, Shane E, Cremers S, Bilezikian JP. PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. J Bone Miner Res. 2011 Nov;26(11):2727-36.

World Health Organization (2007)

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Radius Health, Inc. (RADIUS)
950 Winter Street, Waltham, MA 02451
USA [redacted]

Abaloparatide-SC

Addendum to CLINICAL STUDY PROTOCOL: BA058-05-020

An Open-label, Single-arm, Multicenter Study to Evaluate the Early Effects of Abaloparatide on Tissue-based Indices of Bone Formation and Resorption

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.

Document type:	Clinical Study Protocol Addendum
IND number	73,176
Version number:	Version 3.0 (14 November 2018)
Development phase:	3
Study Site:	[redacted]

Confidentiality Statement

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1. PURPOSE OF THIS ADDENDUM

This is a single-site Addendum that applies to [redacted], based on Clinical Study Protocol BA058-05-020 Version 3.0, dated 14 November 2018.

Study assessments and procedures have been modified as follows and are presented in the Schedule of Assessments and Procedures (Table 1).

The treatment period is extended to six (6) months

1. Additional visits at Month 6 (Visit 7) and Month 7 (Visit 8) are added
2. Peripheral quantitative computed tomography (pQCT) of the forearm and tibiae is added at Pretreatment (Visit 2), Month 3 (Visit 5), and Month 6 (Visit 7)
3. "Discontinuation from the Study" has been updated to reflect the modified visit schedule
4. Early termination procedures have been updated to reflect the extended treatment period.

2. STUDY SCHEDULE

This study addendum is comprised of seven clinic visits. Study assessments are to be performed according to the Schedule of Events (Table 1). There is a ± 4-day window for each clinic visit, other than Day 1 for which there is a +4-day window and Month 7 (Visit 8) for which there is a ± 7-day window.

The study will consist of a Screening Period (up to 1 month), a Pretreatment Period (approximately 1 month), a Treatment Period (6 months), and a Month 7 Visit (one month). During the Treatment Period, subjects will have clinic visits for study-related protocol procedures at Day 1, Month 1, Month 3, Month 4, and Month 6. For the purpose of this study, one month is equal to 30 days.

Subjects consenting under the addendum will have data collected according to the length of their participation. An addendum subject who terminates at or before the Month 3 Visit will return for assessments as indicated in the Addendum Schedule of Assessments and Procedures for the Month 3 Visit and complete the study 30 days later at the Month 4 Visit (See Section 2.6 of the main protocol). Subjects who decide they do not wish to participate in the study following the Month 3 Visit should return for assessments as indicated in the Addendum, Schedule of Assessments and Procedures for Month 6/Early Termination Visit and 30 days later for the Month 7 Visit (see Section 2.9 of the main protocol).

2.1. Screening (Visit 1)

Signed informed consent will be obtained and eligibility for study entry assessed. 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 calcium and vitamin D supplements. This should be continued through the Treatment Period according to the subject's need, so that they have an intake of at least 1200 mg/day of calcium and 800-1000 IU/day of vitamin D. Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline, where calcium administration will be withheld. The following baseline screening evaluations will be performed:

- Obtain Informed Consent
- Verification of study entry criteria
- Review of medical history
- Physical examination
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height (see Section 7.3 of main protocol)
- 12-lead ECG
- Laboratory testing of serum chemistry, hematology, urine dipstick, and coagulation

- PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels
- FSH and TSH levels
- Lumbar and thoracic spine radiographs (anteroposterior and lateral)
- BMD assessments of lumbar spine, total hip and femoral neck by dual X-ray absorptiometry (DXA)
- AE and concomitant medication review from signing of the informed consent
- Dispense vitamin D and calcium

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 within 30 days of the original test date. If upon reanalysis, the values fall within the inclusion/exclusion criteria, the subject may enter the study. Subjects who do not meet the 25-hydroxyvitamin D entry criterion may receive vitamin D supplementation and be retested one time. Similarly, subjects with minor elevations of PTH may be retested one time after vitamin D supplementation. All subjects enrolled following retesting must have safety laboratory results reported within 30 days prior to enrollment.

All AEs, including serious adverse events (SAEs), will be recorded from the time of signing of the informed consent and through the 30 days after the last dose of study medication.

2.2. Pretreatment (Visit 2)

All subjects will receive calcium and vitamin D until the end of the Treatment Period, according to the subject's need so that they have an intake of at least 1200 mg/day of calcium and 800-1000 IU/day of vitamin D. Subjects should be on a stable dose of calcium and vitamin D for 30 days prior to initiating the double labeling procedure. Subjects will undergo training for medication self-administration and for completion of diary, to include administration of medications for bone biopsy labeling procedure. Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld. The following procedures will be performed:

- Verification of study entry criteria
- Review of medical history
- Symptom directed physical exam (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Peripheral quantitative computed tomography (pQCT) of the forearm and tibiae
- Clinical assessment of new fractures
- AE and concomitant medication review
- Dispense demeclocycline, vitamin D and calcium
- Drug accountability

- Subject injection training

Eighteen (18) days before Day 1 of the Treatment Period (Visit 3), subjects who remain eligible for study participation will begin the first bone biopsy labeling procedure with administration of 150 mg demeclocycline 4 times daily for 3 days followed by a 12-day intermission, and then demeclocycline for 3 additional days at the same dose.

Demeclocycline should be taken on an empty stomach, at least 1 hour before meals and 2 hours after a meal with a full glass of water.

2.3. Treatment Period

At each clinic visit during the Treatment Period, recent health status will be obtained, the diary reviewed, adverse events and concomitant medications collected, drug supply / resupply and accountability, and blood pressure and vital signs performed. Laboratory assessments of serum chemistry, hematology and urinalyses will be obtained at Day 1, Month 1, Month 3, and Month 6. 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. 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.

Bone turnover marker assessments (s-PINP and s-CTX) will be performed on the Day 1, Month 1 and Month 3 visits (Visits 3, 4, and 5, respectively).

2.4. Day 1 (Visit 3)

- Review of medical history
- Symptom directed physical exam (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height measurement (see Section 7.3 of main protocol)
- 12-lead ECG
- Laboratory testing of serum chemistry (pre-dose), hematology, and urine dipstick
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessments of new fractures
- Collect blood for immunogenicity testing
- Subject diary review
- AE and concomitant medication review
- Dispense abaloparatide, vitamin D and calcium
- First dose of abaloparatide will be administered by the subject in clinic
- Investigator assessment of local tolerance after injection
- Drug accountability

2.5. Month 1 (Visit 4)

- Review of medical history
- Symptom directed physical exam (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height measurements (see Section 7.3 of main protocol)
- Laboratory testing of serum chemistry (predose), hematology, and urine dipstick
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessment of new fractures
- Review subject diary
- AE and concomitant medication review
- Dispense abaloparatide, vitamin D, calcium and tetracycline
- Self-administration of study medication when directed by site staff after completion of predose activities
- Investigator assessment of local tolerance after injection
- Drug accountability

Approximately twenty-three (23) to twenty-six (26) days prior to Visit 5, subjects will begin the second bone biopsy labeling procedure with administration of 250 mg tetracycline 4 times daily for 3 days followed by a 12-day intermission, and then tetracycline for 3 additional days at the same dose. Tetracycline should be taken on an empty stomach, at least 1 hour before meals and 2 hours after a meal with a full glass of water.

Note: Subjects consenting under the addendum will have data collected according to the length of their participation. An addendum subject who terminates at or before the Month 3 Visit will return for assessments as indicated in the Addendum Schedule of Assessments and Procedures for the Month 3 Visit and complete the study 30 days later at the Month 4 Visit (Table 1).

2.6. Month 3 (Visit 5)

- Review of medical history
- Symptom directed physical exam (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height measurements (see Section 7.3 of main protocol)
- 12-lead ECG
- Laboratory testing of serum chemistry (pre-dose), hematology, and urine dipstick
- Coagulation blood testing
- PTH level
- Bone turnover markers (s-PINP and s-CTX)
- Peripheral quantitative computed tomography (pQCT) of the forearm and tibiae

- Clinical assessment of new fractures
- Collect blood for immunogenicity testing
- Review subject diary
- AE and concomitant medication review
- Self-administration of study medication when directed by site staff after completion of predose activities
- Investigator assessment of local tolerance after injection
- BMD assessments of lumbar spine, total hip and femoral neck by dual X-ray absorptiometry (DXA)
- Transiliac crest bone biopsy 5-8 days after last tetracycline dose (Sponsor together with Medical Monitor should determine if included should an addendum subject terminate study participation after initiating tetracycline labeling)
- Dispense abaloparatide, vitamin D and calcium
- Drug accountability

Note: Subjects who decide they do not wish to participate in the study following the Month 3 Visit should return for assessments as indicated in the Addendum, Schedule of Assessments and Procedures for Month 6/Early Termination Visit and 30 days later for the Month 7 Visit (Table 1).

2.7. Month 4 (Visit 6)

- Review of medical history
- Symptom directed physical examination (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height measurements (see Section 7.3 of main protocol)
- 12-lead ECG
- Clinical assessment of new fractures
- Review subject diary
- AE and concomitant medication review
- Dispense abaloparatide, vitamin D and calcium
- Self-administration of study medication when directed by site staff after completion of pre-dose activities
- Drug accountability
- Investigator assessment of local tolerance after injection

2.8. Month 6/Early Termination (Visit 7)

- Review of medical history
- Symptom directed physical exam (see Section 7.3 of main protocol)

- Blood pressure and vital signs (see Section 7.3 of main protocol)
- 12-lead electrocardiogram (ECG)
- Laboratory testing of serum chemistry (pre-dose), hematology, and urine dipstick
- PTH level
- Peripheral quantitative computed tomography (pQCT) of the forearm and tibiae
- Clinical assessment of new fractures
- BMD assessments of lumbar spine, total hip and femoral neck by dual X-ray absorptiometry (DXA)
- Review subject diary
- AE and concomitant medication review
- Self-administration of last dose of study medication when directed by site staff after completion of pre-dose activities
- Drug accountability
- Investigator assessment of local tolerance after injection

2.9. Month 7 (Visit 8)

- Review of medical history
- Symptom directed physical examination (see Section 7.3 of main protocol)
- Blood pressure and vital signs (see Section 7.3 of main protocol)
- Weight and height measurements (see Section 7.3 of main protocol)
    - 12-lead electrocardiogram (ECG)
    - Clinical assessment of new fractures
- AE and concomitant medications review

2.10. Unscheduled Visit

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

3. DISCONTINUATION FROM THE STUDY

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

Subjects sustaining a radiologically confirmed incident vertebral 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. Refer to Section 5.3.1 of the main protocol for details.

Subjects who decide they do not wish to participate in the study at or before the Month 3 Visit will return for assessments as indicated in the Addendum Schedule of Assessments and Procedures for Month 3 Visit and complete the study 30 days later at the Month 4 Visit.

Subjects who decide they do not wish to participate in the study following the Month 3 Visit should return for assessments as indicated in the Addendum, Schedule of Assessments and Procedures for Month 6/Early Termination and 30 days later for the Month 7 Visit (Table 1).

If they fail to return for these assessments for unknown reasons, every effort to contact them (eg, by telephone, email, and letter for a minimum of three attempts) should be made and documented in the subject's study file.

Table 1: Schedule of Assessments and Procedures

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pretreatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±4 days) Month 4	Visit 7 (±4 days) Month 6	Visit 8 (±7 days) Month 7
Informed consent	X							
Verification of entry criteria	X	X						
Review of medical history[a]	X	X	X	X	X	X	X	X
Physical examination[b]	X							
Symptom directed physical examination		X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X
Weight and height measurements[d]	X		X	X	X	X		X
12-lead Electrocardiogram[e]	X		X		X	X	X	X
Urinalysis (dipstick)[f]	X		X	X	X		X	
Chemistry blood collection[g]	X		X	X	X		X	
Hematology blood collection	X		X	X	X		X	
Coagulation (PT and PTT) blood collection	X				X			
PTH (1-84)	X				X		X	
25-hydroxyvitamin D level	X							
1,25-dihydroxy vitamin D level	X							
FSH	X							
Thyroid stimulating hormone	X							
Injection training for subjects		X						
Dispense calcium and vitamin D supplements[n]	X	X	X	X	X	X		
Study medication (abaloparatide) administration			Daily abaloparatide administration					

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pretreatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±4 days) Month 4	Visit 7 (±4 days) Month 6	Visit 8 (±7 days) Month 7
Demeclocycline (dispense and administration)		X_h						
Tetracycline (dispense and administration)				X_i				
Transiliac crest bone biopsy[j]					X			
Serum markers of bone metabolism (PINP and CTX)			X	X	X			
AP and lateral lumbar and thoracic spine radiographs	X							
Peripheral quantitative computed tomography (pQCT) of the forearm and tibiae		X			X		X	
Clinical assessment of new fractures[k]		X	X	X	X	X	X	X
Collect blood for immunogenicity testing			X		X			
BMD of lumbar spine, total hip, and femoral neck	X				X		X	
Investigator assessment of local tolerance (dermal reactions assessment)			X	X	X	X	X	
Subject diary review[l]			X	X	X	X	X	
Document AEs and concomitant medications[m]	At any time, question subject at each visit							
Drug supply/resupply/accountability		X	X	X	X	X	X	

[a] Including alcohol and tobacco use assessment.

[b] 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 not present at screening should be reported as AEs.

[c] Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse 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. Only blood pressure, pulse rate, and respiration rate are to be recorded one hour post-dose. Supine and standing blood pressure measurements will be performed at each visit during the Treatment Period.

[d] Height is to be measured in the standing position with shoes off using a medical stadiometer.

[e] An ECG will be recorded immediately prior to dosing and one hour post-dose during the Treatment Period.

[f] 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 microorganisms via dipstick.

[g] Serum chemistry will be measured pre-dose at Visits 3, 4, 5 and 7.

[h] Eighteen days before Day 1 of the Treatment Period (Visit 3), subjects who remain eligible for study participation will begin the first bone biopsy labeling procedure with administration of 150 mg demeclocycline 4 times daily for 3 days followed by a 12-day intermission, and then demeclocycline for 3 additional days at the same dose.

[i] Approximately 23 to 26 days before Month 3 (Visit 5), subjects will begin the second bone biopsy labeling procedure with administration of 250 mg tetracycline 4 times daily for 3 days followed by a 12-day intermission, and then tetracycline for 3 additional days at the same dose.

[j] Transiliac crest bone biopsy 5-8 days after last tetracycline dose. If an addendum subject terminates at or before Month 3, data will be collected according to the Addendum schedule for Month 3 (Visit 5) and study completion will occur at Month 4 (Visit 6). The Sponsor Medical Monitor will decide if the bone biopsy will be included at Month 3 (Visit 5).

[k] 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.

[l] The subject will maintain a diary of her assessment of local tolerance after each injection for one week beginning on Day1, Month 1 and Month 3. Subject will be instructed on completion of diary in the Pretreatment Period to include administration of medications for bone biopsy labeling procedure. The subject medication diary will be reviewed by study personnel at each study visit during the Treatment Period to ensure subject compliance.

m 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.

[n] Vitamin D supplements are required to be administered daily from the Pretreatment Period until the end of the Treatment Period. Calcium will also be administered daily, with the exception of the days of administration of demeclocycline and tetracycline where calcium administration will be withheld.

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