CLINICAL STUDY PROTOCOL
AMENDMENT 1

A Prospective, Single Arm Study to Evaluate the PK, PD and Usability of Abaloparatide-sMTS in Postmenopausal Women with Low Bone Mineral Density

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

Protocol Number: Protocol BA058-05-022

Protocol Date: 18 March 2019

IND Number: 73,176

Study Sponsor: Radius Health, Inc. (Radius)
[redacted]
Tel: (617) 551-4700; Fax: [redacted]

Contract Research Organization (CRO) Pharmaceutical Research Associates, Inc
9755 Ridge Drive
Lenexa, Kansas 66219

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LIST OF ABBREVIATIONS

Abbreviation	Term
°C	Degree Celsius
°F	Degree Fahrenheit
µg	Microgram
µL	Microliter
µmol	Micromole
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the concentration-time curve
BMD	Bone mineral density
bpm	Beats per minute
BSAP	Bone-specific alkaline phosphatase
cAMP	Cyclic adenosine monophosphate
cm	Centimeter
C_{max}	Maximum plasma concentration
CRF	Case report form
CSR	Clinical study report
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of Treatment
g	Gram
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
Geo	Geometric
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed consent form
IRB	Institutional review board
IU	International unit
IV	Intravenous
kg	Kilogram
L	Liter
MedDRA	Medical dictionary for regulatory activities
mg	Milligram

Abbreviation	Term
mL	Milliliter
mmHg	Millimeter of mercury
ng	Nanogram
PA	Posterior-anterior
PD	Pharmacodynamic
pg	Picogram
PK	Pharmacokinetic
PMO	Post-menopausal Osteoporosis
PT	Prothrombin time
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone related peptide
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
sMTS	Solid microstructured transdermal system
SOA	Schedule of Assessments
SOC	System organ class
s-PINP	Serum procollagen type 1 N propeptide
TEAEs	Treatment emergent adverse events
TSH	Thyroid stimulating hormone
TSQM-9	Treatment satisfaction questionnaire for medication short form
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
WHO	World Health Organization

SYNOPSIS

Name of Sponsor/Company:
Radius Health, Inc. (RADIUS)

Name of Investigational Product:
Abaloparatide-solid microstructured transdermal system (sMTS) (formerly called BA058)

Name of Active Ingredient:
Abaloparatide

Protocol Number: BA058-05-022	**Phase:** 1b	**Country:** United States

Title of Study:
A Prospective, Single Arm Study to Evaluate the PK, PD and the Usability of Abaloparatide-sMTS in Postmenopausal Women with Low Bone Density

Study center(s): Pharmaceutical Research Associates, Inc, Lenexa, Kansas

Objectives:

Primary:

- The primary objective of this study is to evaluate the ability of subjects to self-administer abaloparatide-sMTS (300 µg) over a period of 29 days based on pharmacokinetics (PK) and pharmacodynamic (PD) markers.

Secondary:

- The secondary objective is to evaluate the usability of abaloparatide-sMTS as measured by incidence of user errors, overall subject acceptability, preference, satisfaction and adherence to study therapy.
- Other secondary objectives include an evaluation of overall safety and tolerability of abaloparatide-sMTS as assessed by treatment emergent adverse events (TEAEs), vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), ECGs, laboratory tests (chemistry, hematology, urinalyses) and local tolerance.

Study Design and Methodology:

In this study, the effectiveness of subjects to self-administer 300 µg abaloparatide-sMTS once-daily on the thigh for 5 minutes for a period of 29 days will be assessed through PK and PD (bone biomarker) analyses. Before the start of treatment, subjects will receive training on abaloparatide-sMTS application. During the study, the subjects will record their user experience, incidence of user errors; the subject and investigator will both assess local tolerance (symptoms [subject] and signs [investigator] of local skin reactions). On study visit days, subjects will self-administer abaloparatide-sMTS and will have blood samples drawn for PK and PD measurements, including an evaluation of subject preference parameters. The detailed study design will be as follows:

Screening Period (Days -67 to -8):

The initial period will be the Screening Period where clinical evaluations will be done from Days -67 to -8 which includes signing of the informed consent, medical history, comprehensive physical

examination, measurement of vital signs, ECG, hematology, serum chemistry (including calcium, albumin, and phosphorus), coagulation tests, urinalysis, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and serum pregnancy testing if needed. Urine will be collected for urinalysis and urine drug and alcohol screen. In addition, a 24 hour urine collection will begin on Day -8 and patients will bring in their sample on Day -7.

If a subject does not have a recent (within 12 months) bone mineral density (BMD) scan, a scan will be performed to ensure the subject meets the BMD requirement. Note: Every effort will be made to enroll subjects with a T-score of -2.0 or lower but > -5.0; for those with scores higher than -2.0, preference should be given to subjects with lower BMD scores.

Pre-Treatment Period (Days -7 to -1):

Based on screening evaluations, eligible subjects will enter a 1-week pre-treatment period where vitamin D and calcium supplementation will be initiated.

Treatment Period, Day 1:

Subjects will be admitted to the clinical research facility on Day 1 of the treatment period. Subjects who continue to meet the study criteria will undergo a symptom-directed physical exam and assessments of vital signs, ECG, updated medical history including concomitant medications, and review of any adverse events (AEs). Other predose assessments include: blood collections for PK, hematology, serum chemistry (including calcium, albumin, and phosphorus), coagulation tests, urinalysis, cyclic adenosine monophosphate (cAMP), and baseline measurements of s-PINP. Urine will be collected for urinalysis and for drug and alcohol testing. The application site will be prepared and cleaned, and predose assessment of the application site will be done by the investigator and the subject.

Immediately before initial dosing (Day 1), the subject will be trained in abaloparatide-sMTS application and instructed how to perform a self-assessment of symptoms of local skin reaction of the application site. After the training, the subject will assess the application site for symptoms of local skin reactions prior to application of abaloparatide-sMTS and will then self-administer the study drug. A subject diary will be provided for recording of user errors in abaloparatide-sMTS application, patch adhesion, and assessment of local tolerance (symptoms of local skin reactions).

Self-assessments of symptoms of local skin reaction will be performed by the subject 5 minutes after application of abaloparatide-sMTS and 1 hour after application of abaloparatide-sMTS on the day of clinic visits. Subject will also be instructed to conduct this assessment of symptoms of local skin reactions, user errors, and an assessment of patch adhesion, beginning Day 1 until Day 29 or end of treatment (EOT) visit.

Investigators will perform an assessment of signs of local skin reaction on the application site prior to abaloparatide-sMTS application, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour after abaloparatide-sMTS application.

Subject preference for treatment attributes, and acceptability will also be assessed by the subjects. Pharmacokinetic measurements will be assessed at 10 minutes, 20 minutes, 30 minutes, 1, 1.5, 2, 3 and 4 hours after application of abaloparatide-sMTS. Pulse rate will be recorded 15 minutes after abaloparatide-sMTS application with a repeat ECG taken 1 hour after abaloparatide-sMTS application. Blood will be drawn for assessment of cAMP at 30 minutes after abaloparatide-sMTS application and for assessment of serum calcium, albumin, and phosphorus at 4 hours after abaloparatide-sMTS application.

Following completion of Day 1 study activities, the subject will be sent home with the diary and a 2-week supply of abaloparatide-sMTS for self-administration together with locally sourced vitamin D

and calcium supplements. The subject will be instructed to self-administer abaloparatide-sMTS every day, take the vitamin D and calcium supplements, and complete the subject diary entries as outlined above.

Treatment Period, Day 15 and Day 29/EOT:

On Days 15 and 29, the subject will be readmitted to the clinical research facility. A review of AEs and concomitant medications will be conducted and predose assessments will include: symptom-directed physical exam, vital sign measurements, ECG, blood collections for PK, hematology, serum chemistry (including calcium, albumin, and phosphorus), coagulation tests, urinalysis, cAMP, and s-PINP. Following completion of the predose assessments, the subject will self-administer the product. Used abaloparatide-sMTS and swab for residual drug and swab residuals will be collected.

Symptoms of local skin reaction will be assessed by the subject (prior to application of abaloparatide sMTS, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour after abaloparatide-sMTS application) and recorded in the subject diary. The subject will also assess patch adhesion and user errors. Subjects will also complete user experience assessments including: treatment satisfaction questionnaire for medication short form (TSQM9) Global Satisfaction and convenience domains; 5-point Likert-like scale of acceptability; and subject preference for treatment attributes.

The study staff will review the prior entries in the diary and provide additional training on how to complete the diary, as needed. In addition, the study staff will conduct an investigator assessment of signs of local skin reactions.

Post application assessments will include blood draws for cAMP, serum calcium, albumin, and phosphorus urinalysis. PK measurements will be assessed 10 minutes, 20 minutes, 30 minutes, 1, 1.5, 2, 3, and 4 hours after abaloparatide-sMTS application.

On Day 15, the subject will be resupplied with abaloparatide-sMTS, and vitamin D and calcium supplements. Subjects will be instructed to continue recording user experience, acceptability and preferences for treatment attributes, user errors, patch adhesion, symptoms of local skin reactions, and information on study drug accountability in the subject diary.

Follow-up Visit (Day 36)

A follow up visit 7-days following Visit 5/EOT can be done either in clinic or remotely via a phone follow up. Assessment of local tolerance will be conducted for subjects with ongoing signs or symptoms of local skin reactions and a review of AEs and concomitant medications will be done.

Number of subjects (planned):

Approximately 22 subjects will be enrolled and treated to ensure a minimum of 18 subjects complete the 29-day treatment and study procedures. Note: Every effort will be made to enroll subjects with a T-score of -2.0 or lower but > -5.0; for those with scores higher than -2.0, preference should be given to subjects with lower BMD scores.

Diagnosis and main criteria for inclusion and exclusion criteria:

Inclusion criteria:

Subjects will be included in the study if they meet all of the following inclusion criteria:

1. Healthy ambulatory female from 50 to 85 years of age (inclusive)

2. Postmenopausal for at least 2 years. Postmenopausal status will be established by a history of amenorrhea for at least 2 years, and negative serum pregnancy test or an elevated serum follicle-stimulating hormone (FSH) value of ≥ 30 IU/L.
3. BMD T-score based on the female reference range <-1.0 and >-5.0 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by dual energy X-ray absorptiometry (DXA). Note: Every effort will be made to enroll subjects with a T-score of -2.0 or lower but > -5.0; for those with scores higher than -2.0, preference should be given to subjects with lower BMD scores.
4. Good general health as determined by medical history and physical examination (including vital signs), has a body mass index of up to 33 kg/m^2, and is without evidence of clinically significant abnormality that may increase the risk associated with study participation or investigational product administration, or may interfere with compliance or the interpretation of study results, and would make the subject inappropriate for this study in the opinion of the Investigator
5. Serum calcium (albumin-corrected), intact parathyroid hormone (PTH), serum phosphorus, alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Subjects with minor elevations or reductions in serum calcium may be enrolled if serum ionized calcium is normal. Any subject with an elevated alkaline phosphatase value, and who meets all other entry criteria would be required to have a normal bone-specific alkaline phosphatase to be enrolled
6. Serum 25-hydroxyvitamin D values ≥ 20 ng/mL.
7. Resting 12-lead electrocardiogram at screening shows no clinically significant abnormality.
8. Systolic blood pressure is ≥ 100 and ≤ 155 mmHg, diastolic blood pressure is ≥ 40 and ≤ 95 mmHg, and heart rate is ≥ 45 and ≤ 100 bpm (taken sitting)
9. No clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells, and platelets, or usual serum chemistry, including electrolytes, renal function, liver function and serum proteins, that might be expected to interfere with the subject's health and/or medical treatment during the study
10. Read, understood, and signed the written informed consent form
11. Hemoglobin value ≥ 12.0 g/dL.

Exclusion criteria:

Subjects who meet any of the following exclusion criteria will be excluded from the study:

1. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis
2. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine
3. History of Cushing's disease, hypo- or hyper-parathyroidism or malabsorptive syndromes within the past year
4. History of significantly impaired renal function (serum creatinine > 177 μmol/L or > 2.0 mg/dL). If serum creatinine is > 1.5 and ≤ 2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must be ≥ 37 mL/min
5. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin)
6. History of osteosarcoma at any time
7. History of nephrolithiasis or urolithiasis within the past 5 years

8. Application site (thigh) compromised by scars, inflammation or skin conditions to an extent that may compromise uniformity of abaloparatide-sMTS application or drug delivery (nevi, plaques, tattoos, scars, piercing, etc.)

Medication-related exclusion criteria:

9. Known history of hypersensitivity to any of the test materials or related compounds
10. Prior therapeutic treatment with PTH- or PTH-related peptide (PTHrP)-derived drugs, or bone anabolic drugs including abaloparatide, teriparatide, or PTH(1-84). Subjects who received abaloparatide in prior Phase 1 studies are not excluded
11. Prior treatment with intravenous bisphosphonates at any time or oral bisphosphonates within the past year (12 months). Subjects who have 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
12. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or bone-acting investigational agents at any time
13. Prior treatment with calcitonin or tibolone in the past 6 months
14. Treatment with denosumab within the past 18 months
15. 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
16. Treated with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) within the past 90 days.
17. Prior treatment with selective estrogen receptor modulators (except hormone replacement therapy) within past 6 months or daily treatment with oral, intranasal, or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of all corticosteroids (for seasonal allergies or asthma) is not exclusionary. Use of low dose oral corticosteroids (eg, ≤ 5 mg/day of prednisone or the relative equivalent dose of another corticosteroid) is also not exclusionary.
18. Participation is another clinical trial with any investigational drug or device within 3 months or 5 half-lives of the investigational drug (if known), whichever is longer, of study drug administration.

Lifestyle-related exclusion criteria:

19. Abnormal nutritional status as assessed by the investigator including abnormal diets and excessive or unusual vitamin or herbal intakes; vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day. Short term use of high doses of vitamin D to bolster endogenous vitamin D levels for study entry during the screening period is not exclusionary
20. Active drug or alcohol dependence or abuse (excluding tobacco or medicinal or recreational marijuana use where legal unless there is evidence of abuse) within 12 months of the screening period; or evidence of such abuse (in the opinion of the investigator).

Investigational product, dosage and mode of administration:

The 300 µg abaloparatide-sMTS will be applied to the thigh and worn for 5 minutes once a day, according to the Instructions for Use

Duration of treatment:

The study will consist of a Screening Period, a 1-week Pre-treatment period, a treatment period of 29 days and a 7-day follow-up period. Any subject that has a reported treatment-related AE during the study will be followed until complete resolution or stabilization, or until the subject is lost to follow-up.

Reference therapy, dosage and mode of administration:

N/A

Criteria for evaluation:

Pharmacokinetics/ Pharmacodynamics:

Pharmacokinetics Measurements:

Individual plasma concentrations of abaloparatide will be tabulated by visit and sampling time and summarized descriptively. Individual and summary profiles will also be plotted. The plasma concentration-time profiles of abaloparatide will be analyzed using non-compartmental methods, and calculations will be made using the actual time since dose. Data permitting, the PK parameters maximum plasma concentration (C_{max}), time of maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC0-t), area under the curve extrapolated to infinity (AUC0-inf), elimination rate constant (λz), and half-life (t1/2) will be derived. Derived PK parameters will be listed and summarized by visit. Descriptive statistics (mean, standard deviation [SD], coefficient of variation [CV%], minimum, median, maximum, geometric mean, and geometric CV%) will be provided by visit (Day 1, Day 15, and Day 29).

Pharmacodynamic Measurements:

Measurements of s-PINP will be summarized descriptively for each visit. Changes and percent changes from baseline, as well as ratio of post-baseline value over baseline value, will be summarized descriptively with 90% confidence interval by visit. Individual and summary profiles will also be plotted.

The actual values, change from baseline values, and the percentage change from baseline values for serum calcium (albumin-corrected), serum phosphorus, and cAMP will be summarized using descriptive statistics by visit and timepoint.

User experience measurements:

User errors and user preference data will be tabulated and summarized descriptively.

For the Treatment Satisfaction Questionnaire for Medication – Short Form (TSQM-9), only the global satisfaction and convenience domains will be assessed. The mean TSQM-9 score (±standard error [SE]) for each domain will be tabulated for Day 15 and Day 29 for the subjects who complete the study.

The mean (±SE) of the subject acceptability score will be tabulated for Days 1, 15, and 29.

Pending data availability, the association between subject preference for treatment attributes and subsequent acceptability and satisfaction will be evaluated separate for outcome (effectiveness/safety) and other attributes (duration, frequency of use, mode of intake).

Safety:

All 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.

Medical history, physical examination, demographics and baseline characteristics will be summarized and presented. Medical history will be presented by MedDRA system organ class and preferred term, 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.

Descriptive statistics for laboratory data (including serum calcium and albumin), vital signs (including orthostatic BP), and ECGs will be provided by visit and time point (when applicable). For laboratory data, vital signs and ECGs, absolute results and changes from baseline (and changes from predose for ECG heart rate) will be presented.

Sample Size and Power Calculation:

The study being performed is a hypothesis generating study and the sample size is based on previous trial experience without a formal power calculation.

Statistical methods:

The log transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} will be compared among the visits, using Day 1 as the reference in the comparison. Point estimates and 90% CIs for differences in PK parameter values between visits will be obtained.

Summary tabulations will display the number of observations, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

Demographics and baseline characteristics of the subject population will be summarized. Summary tables, including frequency counts or descriptive statistics, as appropriate, will be prepared for AEs, serious AEs (SAEs), AESIs, AEs resulting in discontinuation of treatment or withdrawal from the study, and changes in clinical laboratory tests. In addition, subject listings will be presented for AEs, vital signs, clinical laboratory tests, ECGs, local tolerance, and user experience assessments.

1. INTRODUCTION

1.1. Background

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

Abaloparatide (marketed as TYMLOS® in the United States [US]) was approved for use on 28 April 2017 in the US for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Abaloparatide is a novel, synthetic, 34 amino acid peptides designed to be a potent and selective activator of the PTH/PTH-related protein (PTHrP) type 1 receptor ($PTHR_1$) signaling pathway with 41% homology to PTH[1–34]) and 76% homology to human PTHrP[1–34]. Abaloparatide is differentiated from PTH and PTHrP ligands based on its high affinity and > 1,000-fold greater selectivity for the G protein-coupled (RG) vs the non-G protein-coupled (R^0) conformation of $PTHR_1$ (Hattersley 2016). Differential $PTHR_1$-RG 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). Thus, abaloparatide was developed with the expectation that it would be effective at increasing BMD and reducing fracture in individuals with osteoporosis, but with a limited effect on bone resorption and a reduced risk of hypercalcemia.

TYMLOS is supplied in a single-patient-use prefilled pen that delivers 80 µg of abaloparatide as a subcutaneous (SC) injection into the periumbilical region of the abdomen. Abaloparatide administered as a SC injection is referred to throughout this document as abaloparatide-SC. RADIUS, in collaboration with 3M, has developed a short wear time intradermal method of administration for abaloparatide to provide an alternative route of administration that may be preferred by some patients, thus, reducing a barrier for anabolic therapy. This is referred to as the abaloparatide-solid Microstructured Transdermal System (abaloparatide-sMTS).

Abaloparatide-sMTS is a drug device combination product consisting of Abaloparatide: $ZnCl_2$ [redacted], HCl [redacted], coated onto the sMTS array and contained within the following packaging system:

- The primary packaging components with a delivery function includes:
  - An array patch for adhering the drug formulation-coated sMTS array to the skin
  - An insert that holds and protects the coated array patch and inserts it into an applicator
- The primary packaging components with a protective function includes:

  - A pod that holds the insert
  - A lid heat sealed to the edges of the pod
- The secondary packaging includes:
  - A desiccant
  - A foil patch, heat sealed, that contains the sealed pod and desiccant.

The applicator is a spring powered device that, when pressed against the skin of the thigh, inserts the drug formulation-coated sMTS array tips into the dermis at a predetermined force. In contrast to traditional transdermal delivery systems, the sMTS array penetrates the stratum corneum to deliver the drug formulation following a short wear time (5 minutes).

1.1.1. Disease and Study Drug Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to enhanced fragility and increased risk of fractures (Rizzoli 2001). This disease is characterized by low BMD and fractures. The fractures associated with the greatest morbidity and mortality, as well as economic burden to society, together make up the clinically significant and medically relevant group termed major osteoporotic fractures. In the US, there are an estimated 2 million osteoporotic fractures annually (Litwic 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).

Spinal fractures have also been associated with poor outcomes and high mortality rates (Suzuki 2008). It has been reported that once a patient had sustained a vertebral fracture, the risk of a subsequent vertebral fracture increases by >300% and the risk of a subsequent hip fracture increased by 200% (Black 1999). Additional studies have shown that almost half of the patients with a prior vertebral fracture will experience additional vertebral fractures within 3 years, many within the first year (Robinson 2002; Lindsay 2001). Those patients who sustained a vertebral body fragility fracture showed a prolonged course that can lead to significant disability even one year later (Suzuki 2008). Patients with a diagnosis of osteoporosis who have had any fracture have an 86% increase in their risk for another fracture (Kanis 2004). With the severity of these implications, prevention of a secondary fracture has become a primary focus from a patient care and societal standpoint.

Major osteoporotic fractures (those of the wrist, shoulder, hip and clinical spine) account for 94% of the fracture risk for women with low or minimal trauma (Ensrud 2016). Major osteoporotic fractures contribute to accumulated frailty such that the Frailty Index is significantly larger in those elderly women who have experienced a major osteoporotic fracture. As a result, these women have worsening frailty and greater morbidity after a major osteoporotic fracture (Li 2015). The Frailty Index was associated with a predicted increase in the risk of falls, fractures, death and overnight hospitalizations (Li 2014). Consequently, prevention of clinically significant and medically relevant major osteoporotic fractures will reduce health care costs and benefit

postmenopausal women due to reduced frailty, reduced risk of falls, fractures, hospitalizations and death.

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

Until recently, teriparatide has been the only approved osteoporosis treatment in which the major mode of action is stimulation of bone formation (anabolic) rather than suppression of bone resorption. The efficacy of teriparatide has important limitations related to its delayed and modest effects on increasing BMD at the total hip and femoral neck; and 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). Abaloparatide has been evaluated in a number of nonclinical and clinical studies for its potential as a novel treatment for osteoporosis. Based on the biology of the PTH_1 receptor signaling pathway, abaloparatide was designed to have less resorptive and hypercalcemic effects than PTH, resulting in a greater net anabolic effect.

1.1.2. Study Drug Development

1.1.2.1. Nonclinical Studies

A comprehensive nonclinical program including dermal tolerance, dermal sensitization, and general toxicology studies have been conducted in multiple species (rat, guinea pig, rabbit, minipig and monkey) for abaloparatide-SC and is considered supportive for abaloparatide-sMTS. Additionally, dermal tolerance, dermal sensitization, and general toxicology studies with abaloparatide-sMTS are ongoing or planned. The findings from the completed studies support the conclusion that abaloparatide-sMTS is well tolerated, with no new significant safety risks identified as compared to abaloparatide-SC. Full details of the nonclinical development program for abaloparatide are provided in the Investigator's Brochure (IB).

1.1.2.2. Clinical Studies

There are 19 completed or ongoing clinical studies which comprise the abaloparatide-SC (subcutaneous) and the abaloparatide-sMTS (transdermal) clinical development programs. The abaloparatide-SC clinical trial program consists of 11 completed clinical trials, including a large pivotal Phase 3 study (BA058-05-003) followed by an open-label extension (BA058-05-005).

The abaloparatide-sMTS clinical trial program consists of 4 completed Phase 1 and Phase 2 studies, and an ongoing Phase 1 study (BA058-05-015) to select an optimized formulation and dose for abaloparatide-sMTS to be used in the Phase 3 study.

Additional details for the completed clinical studies and the ongoing study BA058-05-015 can be found in the most recent IB.

1.1.2.2.1. Abaloparatide-SC

In the pivotal Phase 3 study (BA058-05-003, the ACTIVE trial), 2,463 postmenopausal osteoporotic women were randomized to receive daily 80 µg abaloparatide-SC (n=824), placebo (n=821), or teriparatide 20 µg (n=818) (rhPTH 1-34) for 18 months. In this trial, abaloparatide-SC and teriparatide significantly reduced the risk of new morphometric vertebral fractures, by 86% and 80%, respectively, compared to placebo. Abaloparatide-SC significantly reduced nonvertebral, major osteoporotic and clinical fractures compared to placebo. Compared to teriparatide, abaloparatide significantly reduced major osteoporotic fractures. The Kaplan-Meier plots indicate an early and sustained fracture risk reduction of nonvertebral, major osteoporotic and clinical fractures with abaloparatide-SC treatment. Abaloparatide-SC was generally safe with acceptable tolerability in postmenopausal women with osteoporosis; the most common adverse reactions (incidence ≥ 5%) were hypercalciuria, dizziness, nausea, headache and palpitations. Consistent with reduced abaloparatide-SC-mediated calcium mobilization, the rates of hypercalcemia were lower in the abaloparatide-SC group compared to the teriparatide group.

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

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

In Study BA058-05-005, after 25 and 43 months of treatment (18 months abaloparatide, 1-month transition, followed by 6 or 24 months of alendronate, respectively), the reductions in new vertebral fracture for abaloparatide/alendronate vs placebo/alendronate-treated subjects show long-term vertebral fracture reduction of 90% after 25 months and 84% after 43 months. In the ACTIVExtend trial the AEs were comparable between subjects previously treated with abaloparatide-SC and the previous placebo group.

There have been no cases of osteosarcoma, osteonecrosis of the jaw or atypical femoral fracture in the entire abaloparatide-SC clinical development program. In non-clinical studies, a dose dependent incidence of osteosarcomas was seen in both male and female rats treated with abaloparatide- and in a positive control group treated with hPTH (1-34).

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

1.1.2.2.2. Abaloparatide-sMTS

To date, several different abaloparatide-sMTS formulations have been evaluated in a total of 4 Phase 1 studies and 1 Phase 2 study, including an abaloparatide-sMTS PBS formulation (abaloparatide phosphate buffered saline [PBS]) and an optimized formulation (abaloparatide $ZnCl_2$·HCl).

The abaloparatide-sMTS PBS formulation had similar abaloparatide C_{max} but lower abaloparatide AUC than the abaloparatide-SC 80 µg reference treatment. This abaloparatide-sMTS formulation was evaluated in 3 completed Phase 1 studies in healthy postmenopausal women (BA058-05-004, BA058-05-006 and BA058-05-008). An overview of the design of these studies is provided in Figure 1. These studies were conducted to evaluate the PK, safety, and local tolerability of different doses of abaloparatide-sMTS and to evaluate the impact of the application site and the duration of application (wear time) on PK, safety, and local tolerability.

A Phase 2, dose-range-finding study, Study BA058-05-007, was also conducted with the abaloparatide-sMTS PBS formulation to evaluate the PK, efficacy, and safety of 3 doses of abaloparatide-sMTS (50, 100, and 150 µg) compared to 80 µg abaloparatide-SC and placebo-sMTS in postmenopausal women with osteoporosis. An overview of the study design is provided in Figure 1. The results from this study did not support the selection of this abaloparatide-sMTS PBS formulation for further clinical development, although it did provide important insights into the exposure-response relationship between abaloparatide-sMTS and increases in BMD.

BA058-05-015 was a Phase 1 study initiated to select an optimized formulation and dose for abaloparatide-sMTS to be used in the Phase 3 study. From the pharmacokinetic data in this clinical study, it was determined that abaloparatide-sMTS Formulation W-1 (Abaloparatide: ZnCl2 [redacted], HCl [redacted]) 300 µg applied to the thigh for 5 minutes provides a single patch administration option with a similar PK profile (slow absorption with a similar time of maximum observed plasma concentration [t_{max}] and AUC) to abaloparatide-SC 80 µg and is expected to produce similar pharmacodynamic effects on BMD as the marketed abaloparatide-SC 80 µg treatment in the clinical setting. Additionally, abaloparatide-sMTS Formulation W-1 300 µg applied to the thigh for 5 minutes had an acceptable safety profile in the BA058-05-015 study.

Full details of the results of clinical trials conducted with abaloparatide-SC and abaloparatide-sMTS are provided in the IB.

1.2. Study Rationale

The purpose of this study is to evaluate the ability of subjects to self-administer 300 µg abaloparatide-sMTS over a period of 29 days based on analyses of pharmacokinetic (PK) and pharmacodynamic (PD) markers. The systemic exposure will be compared to historical exposure after treatment with abaloparatide SC as well as results from BA058-05-015,

Cohort 7, where subjects were treated with the same product as a single dose by a trained healthcare professional.

1.3. Dose Rationale

The dose of 300 µg of abaloparatide-sMTS, applied to the thigh for 5 minutes, was chosen based primarily on the comparability of its pharmacokinetic profile to that of the approved drug abaloparatide SC at 80 µg per day as was demonstrated in study BA058-05-015.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objective

The primary objective of this study is to evaluate the ability of subjects to self-administer 300 µg abaloparatide-sMTS over a period of 29 days based on pharmacokinetic (PK) and pharmacodynamic (PD) markers.

2.2. Primary Endpoint

The primary endpoint is the systemic exposure of the drug at Day 1, Day 15 and Day 29.

2.3. Secondary Endpoints

2.3.1. Pharmacodynamic (PD) Endpoints

- Percent change of s-PINP from baseline to Day 15 and Day 29.
- Change and percent change in serum calcium (albumin-corrected) from baseline to each post-dose timepoint.
- Change and percent change in serum phosphorus from baseline to each post-dose timepoint.
- Change and percent change in cAMP from baseline to each post-dose timepoint.

2.3.2. Other Endpoints

- Subject satisfaction and convenience of treatment as measured by Treatment Satisfaction Questionnaire for Medication (TSQM9) at Day 15 and Day 29
- Subject acceptability measurement (5-point Likert Scale) at Day 1, Day 15 and Day 29
- Subject preference for treatment attributes at Day 1, Day 15 and Day 29
- Investigator assessment of signs of local skin reaction using a 4-point scale at Day 1, Day 15 and Day 29
- Subject assessment of symptoms of local skin reaction using a 4-point scale from Day 1 through Day 29 as recorded in the subject diary
- Daily measurement of user errors as recorded in the subject diary
- Daily measurement of patch adhesion as recorded in the subject diary.

2.3.3. Safety and Tolerability Endpoints

AEs, vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), ECG, and laboratory tests (serum chemistry, hematology, coagulation, and urinalysis) will be assessed as per the schedule of assessment (SOA) (Table 1).

3. STUDY DESIGN

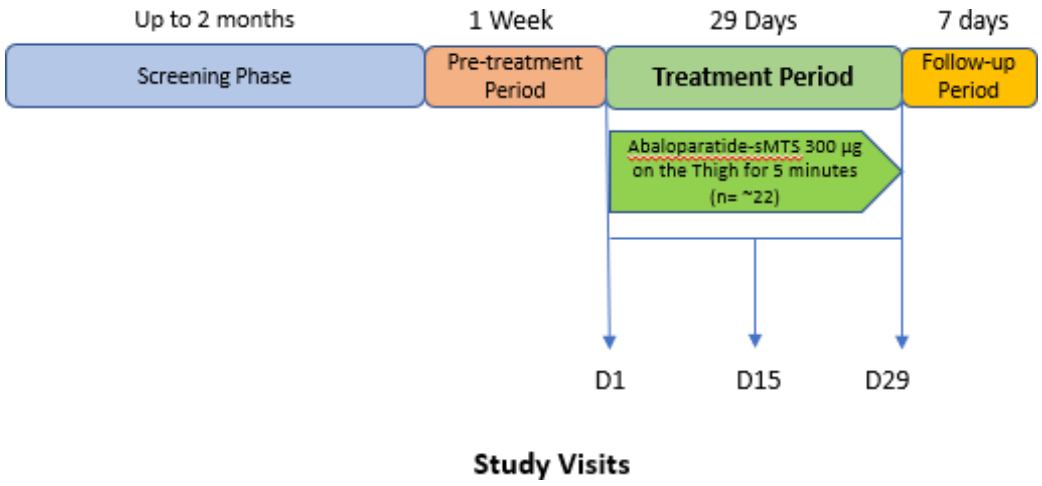
3.1. Description of the Study Design

This is an open-label study to evaluate the usability of the abaloparatide-sMTS by subjects with low BMD. The study will consist of a Screening Period (up to 2 months), a Pre-Treatment Period (1 week), a Treatment Period (1 month), and a 1 week Follow-Up after the last dose of study medication. Thus, subjects will be in the study for up to 4 months. Eligible subjects will undergo protocol specified procedures, including BMD (if dual energy x-ray absorptiometry [DXA] was done over 12 months prior to Screening) and bone turnover marker assessment. For the purpose of this study, 1 month is equivalent to 30 days.

All eligible subjects will be provided calcium and vitamin D to ensure that their daily intake is 1,200 mg/day and 800 IU/day, respectively, or a dose determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need.

All subjects will undergo safety, pharmacokinetic, bone turnover marker (s-PINP), and assessments of User Errors and Subject Preference Outputs according to the SOA (Table 1). The study design is presented in Figure 1, below.

Figure 1: Study Design



4. SELECTION OF STUDY POPULATION

In order to participate in this study, a subject must meet all of the following inclusion criteria and none of the exclusion criteria. Subjects who were screened and excluded from this study will be recorded in the eCRF with the reason for the screen failures.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Healthy ambulatory female from 50 to 85 years of age (inclusive).
2. Postmenopausal for at least 2 years. Postmenopausal status will be established by a history of amenorrhea for at least 2 years, negative serum pregnancy test or an elevated serum follicle-stimulating hormone (FSH) value of ≥ 30 IU/L.
3. BMD T-score based on the female reference range of <-1.0 and >-5.0 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by DXA. Note: Every effort will be made to enroll subjects with a T-score of -2.0 or lower but > -5.0; for those with scores higher than -2.0, preference should be given to subjects with lower BMD scores.
4. Good general health as determined by medical history and physical examination (including vital signs), has a body mass index of up to 33 kg/m2, and is without evidence of clinically significant abnormality that may increase the risk associated with study participation or investigational product administration, or may interfere with compliance or the interpretation of study results, and would make the subject inappropriate for this study in the opinion of the Investigator
5. Serum calcium (albumin-corrected), intact PTH, serum phosphorus, alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Subjects with minor elevations or reductions in serum calcium may be enrolled if serum ionized calcium is normal. Any subject with an elevated alkaline phosphatase value, and who meets all other entry criteria would be required to have a normal bone-specific alkaline phosphatase to be enrolled
6. Serum 25-hydroxyvitamin D values ≥ 20 ng/mL.
7. Resting 12-lead electrocardiogram at screening shows no clinically significant abnormality.
8. Systolic blood pressure is ≥ 100 and ≤ 155 mmHg, diastolic blood pressure is ≥ 40 and ≤ 95 mmHg, and heart rate is ≥ 45 and ≤ 100 bpm (taken sitting)
9. No clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells, and platelets, or usual serum chemistry, including electrolytes, renal function, liver function and serum proteins, that might be expected to interfere with the subject's health and/or medical treatment during the study
10. Read, understood, and signed the written informed consent form
11. Hemoglobin value ≥ 12.0 g/dL

4.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from the study:

1. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis
2. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine
3. History of Cushing's disease, hypo- or hyper-parathyroidism or malabsorptive syndromes within the past year
4. History of significantly impaired renal function (serum creatinine > 177 μmol/L or > 2.0 mg/dL). If serum creatinine is > 1.5 and ≤ 2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must be ≥ 37 mL/min
5. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin)
6. History of osteosarcoma at any time
7. History of nephrolithiasis or urolithiasis within the past 5 years
8. Application site (thigh) compromised by scars, inflammation or skin conditions to an extent that may compromise uniformity of abaloparatide-sMTS application or drug delivery (nevi, plaques, tattoos, scars, piercing, etc.)

Medication-related exclusion criteria:

9. Known history of hypersensitivity to any of the test materials or related compounds
10. Prior therapeutic treatment with PTH- or PTHrP-derived drugs, or bone anabolic drugs including abaloparatide, teriparatide, or PTH(1-84). Subjects who received abaloparatide in prior Phase 1 studies are not excluded
11. Prior treatment with intravenous bisphosphonates at any time or oral bisphosphonates within the past year (12 months). Subjects who have 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
12. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or bone-acting investigational agents at any time
13. Prior treatment with calcitonin or tibolone in the past 6 months
14. Treatment with denosumab within the past 18 months
15. 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
16. Treated with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) within the past 90 days.

17. Prior treatment with selective estrogen receptor modulators (except hormone replacement therapy) or daily treatment with oral, intranasal, or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of all corticosteroids (for seasonal allergies or asthma) is not exclusionary. Use of low dose oral corticosteroids (eg, ≤ 5 mg/day of prednisone or the relative equivalent dose of another corticosteroid) is also not exclusionary.
18. Participation in another clinical trial with any investigational drug or device within 3 months or 5 half-lives of the investigational drug (if known), whichever is longer, of study drug administration.

Lifestyle-related exclusion criteria:

19. Abnormal nutritional status as assessed by the investigator including abnormal diets and excessive or unusual vitamin or herbal intakes; vitamin D intake of ≥ 4,000 IU/day or vitamin A intake of ≥ 10,000 IU/day. Short term use of high doses of vitamin D to bolster endogenous vitamin D levels for study entry during the screening period is not exclusionary
20. Active drug or alcohol dependence or abuse (excluding tobacco or medicinal or recreational marijuana use where legal unless there is evidence of abuse) within 12 months of the screening period; or evidence of such abuse (in the opinion of the investigator).

4.3. Subject Withdrawal or Termination

4.3.1. Reasons for Withdrawal or Termination

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

The Investigator may consider discontinuing subjects from the study for the following reasons:

- Severe hypersensitivity to abaloparatide or test materials
- Refusal of treatment
- Inability to complete study procedures
- Lost to follow-up
- Adverse events or laboratory abnormalities which, in the judgment of the Investigator, justifies treatment cessation
- Serious intercurrent illness
- Protocol violations
- Administrative reasons
- Incident vertebral or non-vertebral fragility fracture

4.3.2. Handling of Subject Withdrawals or Terminations

If a subject is withdrawn or discontinued from the study, the reason for withdrawal from the study must 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 Visit 5 / end of treatment (EOT) (Day 29) visit as soon as possible. All AEs should be followed as described in Section 7. Subjects who discontinue or are withdrawn from the study will not be replaced. Whenever a subject is discontinued prematurely, the Sponsor and the Medical Monitor must be notified.

4.4. Concomitant Medications

Subjects will be provided with calcium and vitamin D supplements to be administered daily from the Pretreatment Period until the end of the Treatment Period. The supplement dose will be determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the subject's need to ensure that their daily intake of calcium and vitamin D is 1,200 mg/day and 800 IU/day, respectively. The doses and schedule of calcium and vitamin D supplements should be adhered to and not be changed other than for medical necessity. The supplements should be taken as instructed by the Investigator.

For any required concomitant medication, such as statins or antihypertensives, the subject must be on a stable dose for 90 days prior to the first treatment visit (Day 1) 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 case report form. Subjects should not take any other medications, including over-the-counter medications, herbal medications, or mega-doses of vitamins during the study without the prior approval of the Investigator.

If it becomes necessary for a subject to take any other medication during the study, the specific medication(s) and indication(s) must be discussed with the Investigator. All concomitant medications taken during the course of the study must be recorded in the subject's medical record or source document and transcribed into the eCRF.

4.5. Prohibited Medications

Please refer to Section 4.2 for medication related exclusion criteria.

Subjects 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. The occasional use of over-the-counter medications (eg, ibuprofen or acetaminophen) for headache or minor discomfort will be allowed if discussed with the Investigator, recorded in the source documents, and in the subject's eCRF.

Use of corticosteroids for seasonal allergies or asthma is not prohibited. Use of low dose oral corticosteroids (eg, ≤ 5mg/day of prednisone or the relative equivalent dose of another corticosteroid) is also not exclusionary. Subjects who require chronic treatment with either an anticonvulsant (phenobarbital, phenytoin, carbamazepine or primidone), or with heparin will be discontinued.

4.6. Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the principal investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator 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 subjects.
- Insufficient compliance with protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Decision of Sponsor.

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

4.7. Temporary Suspension of Treatment

Due to the short nature of the study, temporary suspension of treatment is not an option for the Investigator. Any subject that is deemed inappropriate for continuing treatment will be withdrawn from the study and the reason will be noted in the CRF.

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

5.1. Study Medication

All study medications are for investigational use only and are to be used only within the context of this study, and administration of treatment is to be carried out as described in Section 5.5. Abaloparatide-sMTS will be supplied to the study site by RADIUS.

5.1.1. Abaloparatide-sMTS

The abaloparatide-sMTS is enclosed in a collar assembly for loading onto a spring-loaded applicator. The abaloparatide-sMTS dose will be 300 µg.

Abaloparatide-sMTS is stored refrigerated at 2º to 8ºC (36º to 46ºF). The abaloparatide-sMTS will be removed from refrigeration approximately 1 hour prior to application. Please refer to the pharmacy manual for further details.

5.2. Packaging, Labeling and Storage

5.2.1. Packaging and Labeling

Abaloparatide-sMTS and applicators will be supplied to the study site by RADIUS. All packaging operations will be performed in accordance with Good Manufacturing Practices.

All study drugs will be labeled with a caution statement and other information required by local Regulatory Authorities.

5.2.2. Storage

All study medications (abaloparatide-sMTS) must be kept in a secure, limited-access storage area at 2° to 8°C (36° to 46°F) until dispensed for dosing or until returned to the Sponsor.

For Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT), when the product is applied during a clinic visit, the used arrays will be carefully placed in a supplied container using minimal manipulation and frozen for returning to the manufacturer for further inspection and analysis according to a supplied handling procedure manual. Refer to the pharmacy manual for additional details.

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

5.3. Study Medication Administration

Subjects will be encouraged to drink 8 ounces of water 1 to 2 hours prior to dosing.

Prior to the administration of study drug, the application site will be prepped and cleaned with an alcohol wipe, allowed to air dry, and then examined in order to assure that the area is not compromised. Each application site will be graded according to a 4-point scale by the investigator to assess signs of local skin reactions (at clinic visits; Section 6.6.2.1) and by the subject to assess symptoms of local skin reactions (each day during the treatment period; Section 6.6.2.2), prior to abaloparatide-sMTS application, immediately after removal of abaloparatide-sMTS, and at 1 hour after abaloparatide-sMTS application. For any severe local skin reactions, evaluations by the

subject will continue at 24 hour intervals until the reaction has stabilized or resolved (see Section 6.6.2.2).

Before initial use of abaloparatide-sMTS, the subject will be trained on the Instructions for Use and will demonstrate their ability to self-administer the abaloparatide-sMTS with the Investigator present. During subsequent applications, the subject will follow the Instructions for Use. It is important to note that if any component is damaged, the subject is to be instructed to replace the abaloparatide-sMTS patch with a new one and place the damaged patch in a container that was provided and to bring this together with the other used and unused abaloparatide-sMTS at the next clinic visit. Please refer to the pharmacy manual for additional details.

5.4. Treatment Assignment

All subjects who sign informed consent and continue to meet eligibility criteria for the study will be treated with abaloparatide-sMTS.

5.5. Dosing and Administration

The first self-administration of abaloparatide-sMTS will occur at the study site on Day 1, under observation.

Subjects will be trained by study personnel to self-administer study medication with the abaloparatide-sMTS patch and applicator; a single daily dose of 300 µg of abaloparatide-sMTS will be applied to the thigh for 5 minutes during the treatment period following the Instructions for Use. Please refer to the pharmacy manual for additional details on study drug administration.

The subject is to remain under observation for a minimum of 60 minutes after abaloparatide-sMTS. On the days when blood sampling is required after study medication administration, the subject is to remain at the vicinity of the clinic for the blood collections scheduled up to 4 hours after abaloparatide-sMTS application. Subjects are to be instructed to self-administer abaloparatide-sMTS application at a location where they have the ability to sit or lie down.

At each clinic visit during the Treatment Period, any used and unused abaloparatide-sMTS should be returned.

5.6. 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 will remind the subject of study drug dosing requirements.

Subject compliance will be ascertained by using the data entered on the subject diaries as well as the total used and unused abaloparatide-sMTS returned at each study visit.

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

5.7. Drug Accountability

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

- Study drug received at the study site
- Study drug dispensed to the subject
- Study drug returned by the subject
- Study drug returned to sponsor/designee or destruction of study drug on site

Subjects will be provided with a container and instructed to return all used and unused study drug to the site for destruction. 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.

6. STUDY PROCEDURES AND SCHEDULE

6.1. Study Procedures

6.1.1. Study Specific Procedures

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

6.2. Study Schedule

This study is comprised of 5 clinic visits with either a sixth visit or telephone call for Follow-up. Study assessments are to be performed according to the SOA (Table 1). There is a ± 2-day window for each clinic visit.

The study will consist of a Screening (up to 2 months), a Pre-treatment Period (1 week), a Treatment Period (29 days) and a Follow-up Period (7 days). During the Treatment Period, subjects will have clinic visits for study-related protocol procedures at Day 1, Day 15 and Day 29. The Treatment Period of the study will be considered complete when the last subject completes the last clinic visit.

6.2.1. Schedule of Assessments and Procedures

A comprehensive schedule for assessments and procedures is presented in the SOA (Table 1).

Table 1: Schedule of Assessments

Procedure	*Study Visit*	1	2	Treatment Period 3	4	5	6
	Visit Day	Screening (-67 to -8)	Pre-Treatment (-7 to -1)	Day 1	Day 15	Day 29 / End of Treatment (EOT)	Day 36 (Follow-up)
	Visit Window (Days)	N/A	± 2	± 2	± 2	± 2	± 2
Informed consent		X					
Verification of entry criteria		X					
Physical examination[1]		X					
Review of medical history[2]		X					
Symptom directed physical examination[1]			X	X	X	X	
Vital signs[3]		X		X	X	X	
Weight measurement		X	X	X	X	X	
Height measurement[4]		X					
ECG[5]		X		X	X	X	
Urinalysis (dipstick)[6]		X		X	X	X	
Chemistry blood collection[7]		X		X	X	X	
Serum calcium, albumin, phosphorus[8]				X	X	X	
Cyclic AMP[9]				X	X	X	
24 hour urine collection (for calcium:creatinine and creatinine clearance)[10]			X				
Hematology[7]		X		X	X	X	
Coagulation (PT and PTT) blood collection		X					
PTH (intact)		X					
25-hydroxyvitamin D level		X					
1,25-dihydroxyvitamin D level		X					
Estradiol, FSH		X					
Serum pregnancy		X					
Thyroid stimulating hormone		X					
Urine Drug and Alcohol Test[11]		X		X			
Subject training on study drug administration, completion of subject diary and assessment of symptoms of local skin reactions[12]				X			
Dispensing of calcium and vitamin D supplements			X	X	X		
Study drug administration[13]				Every day between Visit 3 and Visit 5, inclusive			
Collect used abaloparatide-sMTS and swab for residual drug and swab residuals				X	X	X	
BMD of lumbar spine, total hip and femoral neck by DXA[14]		X					
Investigator assessment of signs of local skin reaction[15]				X	X	X	

Procedure	*Study Visit*	1	2	Treatment Period			6
	Visit Day	Screening (-67 to -8)	Pre-Treatment (-7 to -1)	3 Day 1	4 Day 15	5 Day 29 / End of Treatment (EOT)	Day 36 (Follow-up)
	Visit Window (Days)	N/A	± 2	± 2	± 2	± 2	± 2
Subject assessment of symptoms of local skin reaction[16]				Every day between Visit 3 and Visit 5, inclusive			X[23]
Subject assessment of patch adhesion[17]				Every day between Visit 3 and Visit 5, inclusive			
Subject assessment of pain[18]				Every day between Visit 3 and Visit 5, inclusive			
Subject assessment of user errors				Every day between Visit 3 and Visit 5, inclusive			
Assessment of subject preferences for treatment attributes				X	X	X	
Assessment of subject convenience and satisfaction (TSQM9)					X	X	
Assessment of subject acceptability (5-point Likert scale)				X	X	X	
Subject diary review[19]				X	X	X[24]	
Document AEs and concomitant medication[20]		After signing informed consent until follow up visit					
PK draw[21]				X	X	X	
Serum marker of bone metabolism (s-PINP) [22]				X	X	X	
Drug supply / Drug re-supply				X	X		
Drug Accountability					X	X	

1. 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 from the symptom-directed physical examinations should be reported as AEs.
2. Including alcohol and tobacco use assessment.
3. Blood pressure, pulse rate, body temperature, and respiration rate are to be recorded predose at each study visit. Only blood pressure, pulse rate and respiration rate are to be recorded 1 hour after abaloparatide-sMTS application at each study visit during the treatment period. All blood pressure assessments will be orthostatic. Pulse rate will also be obtained at 15 minutes after abaloparatide-sMTS application at Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
4. Height is to be measured at the screening visit/ Visit 1 in the standing position using a medical stadiometer.
5. During the Treatment Period, ECGs are to be performed predose after 5 minutes of rest and prior to any blood draw, and 1 hour after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
6. All routine urinalysis will be performed on a sample freshly voided during the visit and sent to a local laboratory for microscopy if test is positive for micro-organisms via dipstick.
7. Blood draw for serum chemistry and hematology will be done during the Screening (Visit 1) and at predose on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
8. Blood draw for serum calcium, albumin and phosphorus will be done at predose and at 4 hours after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
9. Blood draw for cAMP taken predose and at 30 minutes after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
10. A 24 hour urine collection will start on Day -8 and complete on the day of the pre-treatment visit (Day -7).
11. All subjects will have a urine drug screen for drugs of abuse and alcohol performed on the Screening Period (Visit 1), and on Day 1 (Visit 3).
12. When necessary, re-training may be done post Day 1 / Visit 3.
13. Study drug is self-administered daily beginning Day 1 (Visit 3) through Day 29 (Visit 5/EOT), inclusive. On Days 1, 15, and 29, subject will self-administer abaloparatide-sMTS at the study site.

14. BMD measured by DXA at Screening visit if most recent DXA was done over 12 months prior to screening.
15. Investigators will perform an assessment of the application site at each clinic visit prior to application of abaloparatide-sMTS, 5 minutes after application (ie, immediately upon removal of the patch), and 1- hour following abaloparatide-sMTS application. Signs of local skin reactions will be assessed using a 4-point scale, as described in Section 6.6.2.1.
16. The subject will maintain a diary to record their assessment of symptoms of local skin reactions for 29 days beginning on Day 1 (Visit 3). The subject will evaluate the application site prior to study drug administration, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour after abaloparatide-sMTS application. Symptoms of local skin reactions will be assessed using a 4-point scale as described in Section 6.6.2.2.
17. Subject assessment of patch adhesion immediately prior to abaloparatide-sMTS removal on each day of the treatment period from Day 1 (Visit 3) to Day 29 (Visit 5/EOT).
18. An assessment of pain (separate from the pain question on the 4-point scale for local tolerance) will be done after sMTS application.
19. The Subject Diary will be reviewed by study personnel at each study visit to ensure subject compliance.
20. AEs and SAEs will be recorded on the case report forms starting from the signing of the informed consent until 7 days after the last dose of study medication. All treatment-related 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.
21. Blood samples for measurement of plasma concentrations of abaloparatide will be taken at Day 1 (Visit 3), Day 15 (Visit 4) and on Day 29 (Visit 5/EOT). The pharmacokinetic measurements will be assessed predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours and 4 hours after abaloparatide-sMTS application.
22. Blood samples for s-PINP taken within 1-hour prior to dosing on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).
23. Assessed only for subjects with signs or symptoms of local skin reactions ongoing as of Day 29.
24. Subject will return diary to study site.

6.2.2. Informed Consent Process

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

6.2.3. Assigning Subject Numbers

A unique subject number will be assigned to each subject on Day 1. The subject number will be used as the primary subject identifier for the remainder of the study.

6.2.4. Subject and Disease Characteristics

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

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

6.2.5. Screening Period (Visit 1; Days -67 to -8)

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

- Obtain informed consent
- Verify subject eligibility
- Comprehensive physical examination
- Review of medical history, including alcohol, tobacco, and drug use
- Review of concomitant medications
- Orthostatic blood pressure and vital signs
- Height
- Weight
- 12 Lead ECG; subjects should be allowed to rest for 5 minutes preceding each ECG
- Urine dipstick
- Urine drug and alcohol test. The urine will be tested for the following drugs: amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, propoxyphene, and a marijuana screening test.
- Blood draw for serum chemistry, hematology
- Blood draw for coagulation testing: PT and PTT
- Blood draw for serum pregnancy (if needed)
- Blood draw for intact PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D level
- Blood draw for estradiol, FSH and TSH level
- BMD assessments of lumbar spine, total hip and femoral neck by DXA (if not available from the previous 12 months)
- Provide subject instructions for the 24 hour urine collection to be collected beginning Day -8 during the pre-treatment period

Subjects who do not meet the 25-hydroxyvitamin D entry criterion may receive vitamin D supplementation and be retested. Similarly, subjects with minor elevations of PTH may be retested 1 time after vitamin D supplementation. Subjects whose laboratory tests do not fall within the specified ranges as detailed in the inclusion/exclusion criteria may have the samples redrawn and the tests repeated once during the screening period.

Although the Screening Period is 60 days, all enrolled subjects must have the following safety laboratory results reported within 30 days prior to Day 1 (Visit 3): hematology, serum chemistry (including calcium and phosphorus), urinalysis, PTH (intact), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and serum pregnancy. These laboratory tests must be repeated for subjects who were screened more than 30 days prior to Day 1 (first day of treatment). A list of the laboratory tests can be seen in Table 2

Adverse events will be recorded for each subject from the time of signing of the informed consent.

6.2.6. Pre-treatment Period (Days -7 to -1)

Subjects who are eligible for the study, on the basis of screening evaluations, will enter the 7-day Pre-treatment period of the study.

- Symptom directed physical examination
- Dispense calcium and vitamin D to ensure that daily intake is 1,200 mg/day and 800 IU/day, respectively, (doses to be determined by the Investigator and agreed upon by the Sponsor Medical Monitor, according to the subject's need)
- A 24-hour urine sample will be collected. Subjects will discard the 1st void and begin a 24-hour urine collection on the day prior to the clinic visit
- AE and concomitant medications review

6.2.7. Treatment Period

During the Treatment Period, subjects will self-administer a single dose of study medication once a day.

At each clinic visit during this period, recent health status will be obtained, the subject diary reviewed, AEs collected and orthostatic blood pressure and vital signs recorded. Laboratory assessments of chemistry, hematology and urinalysis will be obtained at Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/EOT).

Bone turnover marker assessments (s-PINP) will be performed within 1-hour prior to the application of abaloparatide-sMTS on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5/ EOT). Results for these labs will not be required prior to dosing.

6.2.7.1. Visit 3 (Day 1)

The following assessments will be conducted on Day 1:

- Symptom directed physical examination
- Body temperature taken predose; orthostatic blood pressure and vital signs: BP, pulse and respiratory rate taken predose and 1-hour after abaloparatide-sMTS application; pulse rate 15 minutes after abaloparatide-sMTS application
- Weight

- 12-lead ECG, to be taken predose and at 1-hour after abaloparatide-sMTS application. Subjects should be allowed to rest for 5 minutes preceding each ECG
- Urine dipstick test on urine sample taken predose
- Urine drug and alcohol test
- Blood draw for serum chemistry and hematology taken predose
- Blood draw for s-PINP taken up to 1-hour predose
- Blood draw for cAMP at predose and at 30 minutes after abaloparatide-sMTS application
- Training on use of the abaloparatide-sMTS
- Subject self-administers abaloparatide-sMTS under the observation of the Investigator
- Blood draw for serum calcium, albumin and phosphorus at predose and 4 hours after abaloparatide-sMTS application
- PK draw done predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, and 4 hours after abaloparatide-sMTS application
- Collect used abaloparatide-sMTS and swab for measurement of residual drug
- AE and concomitant medication review
- Dispense study medication
- Dispense calcium and vitamin D supplements
- Investigator assessment of signs, and subject assessment of symptoms, of local skin reactions at predose, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1-hour following abaloparatide-sMTS application. For any local skin reactions that persist 1 hour after abaloparatide-sMTS application, evaluations by the subject will continue at 24 hour intervals until the skin irritation has stabilized or resolved.
- Prior to dosing, instruct subject on completion of subject diary, including subject assessment of local skin reactions, patch adhesion, pain, and user errors. This will need to be done daily for 29 days beginning on Visit 3 (Day 1).
- Collection of subject preference for treatment attributes and acceptability (5-point Likert scale) information
- Subject assessment of pain
- Subject assessment of patch adhesion immediately prior to abaloparatide-sMTS removal

6.2.7.2. Visit 4 (Day 15)

The following assessments will be conducted on Day 15:

- Symptom driven physical examination
- Body temperature taken predose; orthostatic blood pressure and vital signs: BP, pulse and respiratory rate taken predose and 1 hour after abaloparatide-sMTS application; pulse rate 15 minutes after abaloparatide-sMTS application
- 12-lead ECG, to be taken predose and at 1 hour after abaloparatide-sMTS application. Subjects should be allowed to rest for 5 minutes preceding each ECG
- Weight
- Urine dipstick test on urine sample taken predose
- Blood draw for serum chemistry and hematology taken predose
- Blood draw for s-PINP within 1 hour prior to application of abaloparatide-sMTS

- Blood draw for serum calcium, albumin and phosphorus at 4 hours after abaloparatide-sMTS application
- Blood draw for cAMP at predose and at 30 minutes after abaloparatide-sMTS application
- PK draw done predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, and 4 hours after abaloparatide-sMTS application
- Subject self-administration of abaloparatide-sMTS
- Collect used abaloparatide-sMTS and swab for measurement of residual drug
- AE and concomitant medication review
- Drug accountability
- Dispense study medication
- Dispense calcium and vitamin D supplements
- Investigator and Subject assessment of local skin reactions predose, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour following abaloparatide-sMTS application. For any administration site reaction, evaluations by the subject will continue at 24 hour intervals until the skin irritation has stabilized or resolved.
- Subject assessment of patch adhesion immediately prior to abaloparatide-sMTS removal
- Subject assessment of pain
- Subject assessment of user error
- Collection of subject preference for treatment attributes, acceptability (5-point Likert scale) and convenience and satisfaction (TSQM9) information
- Review subject diary

6.2.7.3. Visit 5 / End of Treatment (Day 29)

The following assessments will be conducted on Day 29:

- Symptom driven physical examination
- 12-lead ECG, to be taken predose and at 1 hour after abaloparatide-sMTS application. Subjects should be allowed to rest for 5 minutes preceding each ECG
- Body temperature taken predose; orthostatic blood pressure and vital signs: BP, pulse and respiratory rate taken predose and 1 hour after abaloparatide-sMTS application; pulse rate taken 15 minutes after abaloparatide-sMTS application
- Weight
- Urine dipstick test on urine sample taken predose
- Blood draw for serum chemistry and hematology taken predose
- Subject self-administration of abaloparatide-sMTS
- Blood draw for serum calcium, albumin and phosphorus at 4 hours after abaloparatide-sMTS application
- Blood draw for cAMP at predose and at 30 minutes after abaloparatide-sMTS application
- PK draw done predose and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours and 4 hours after abaloparatide-sMTS application.
- Collect used abaloparatide-sMTS and swab for measurement of residual drug
- AE and concomitant medication review
- Drug accountability

- Bone turnover markers (s-PINP) taken within 1 hour prior to abaloparatide-sMTS application
- Investigator and subject assessment of local skin reactions predose, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour following study drug administration. For any administration site reaction, evaluations by the subject will continue at 24 hour intervals until the skin irritation has stabilized or resolved.
- Subject assessment of patch adhesion immediately prior to abaloparatide-sMTS removal
- Subject assessment of pain
- Subject assessment of user error
- Collection of subject preference for treatment attributes, acceptability (5-point Likert scale) and convenience and satisfaction (TSQM9) information
- Review subject diary

6.2.8. Visit 6/Follow up (Day 36)

Visit 6/ Follow up (Day 36) can be completed as a clinic visit or remotely through a phone call by the study staff. The following are the study assessments for Visit 6:

- Assessment of local tolerance post EOT visit for subjects with ongoing signs or symptoms of local skin reactions
- AE and concomitant medication review

6.2.9. 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.

6.3. Vital Signs and Physical Examinations

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

A comprehensive 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 orthostatic blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiratory rate. These will be assessed following a 5 minute rest (seated or supine). At visits when study drug is administered at the site, vital sign assessments will be collected before the dose of study drug and 1 hour after abaloparatide-sMTS application for blood pressure, pulse and respiratory rate. Seated or supine and standing blood pressure measurements will be performed at each visit during the Treatment Period. In addition, pulse rate will be collected 15 minutes after abaloparatide-sMTS application. Temperature will only be collected predose.

6.4. 12-Lead Electrocardiogram

A standard, 12 lead ECG will be performed. Two hard copies of the ECG should be printed and signed by the Investigator at the site; the first copy will be kept in the subject's medical chart and the second copy will be kept in the study file for retrospective collection by the Sponsor, if necessary. Any abnormalities should be noted and clinical relevance should be documented. An ECG will be recorded immediately prior to dosing and at 1 hour after abaloparatide-sMTS application on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 (Visit 5). Additional ECGs may be performed as clinically indicated.

6.5. Laboratory Evaluations

6.5.1. Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be collected at time points indicated in the SOA in Table 1. All clinical laboratory blood and 24 hour urine samples will be sent to the local laboratory for analysis and testing. A list of study clinical laboratory tests is in Table 2.

Although the Screening Period is 60 days, all enrolled subjects must have the following safety laboratory results reported within 30 days prior to Day 1 (Visit 3): hematology, serum chemistry (including calcium and phosphorus), urinalysis, PTH (intact), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and serum pregnancy. These laboratory tests must be repeated for subjects who were screened more than 30 days prior to Day 1 (first day of treatment).

Subjects are required to fast for 8 hours prior to any safety laboratory assessments at Screening and on Days 1, 15 and 29. Subjects are allowed to continue water consumption during these times.

Table 2: Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis (dipstick)[a]**	**Additional Tests**
Hemoglobin	Sodium	pH	PTH (intact) [b]
Hematocrit	Potassium	Glucose	25-hydroxyvitamin D[b]
White blood cell count with differential in absolute counts	Chloride	Protein	1,25-dihydroxyvitamin D[b]
Red blood cell count	Inorganic phosphorus	Ketones	Urine Drug and Alcohol Tests
Mean corpuscular volume	Albumin	Bilirubin	24 hour urine collection
Mean corpuscular hemoglobin concentration	Total protein	Blood	
Mean corpuscular hemoglobin	Glucose	Urobilinogen	Estradiol[b]
Platelet count	Blood urea nitrogen	Specific gravity	TSH[b]
Coagulation test	Creatinine	Nitrite	FSH[b]
	Uric acid	Leukocytes	Serum pregnancy test[b]

Hematology	Serum Chemistry	Urinalysis (dipstick)[a]	Additional Tests
PT[b]	Aspartate aminotransferase		s-PINP
PTT[b]	Alanine aminotransferase		cAMP
	Gamma-glutamyltranspeptidase		
	Creatine phosphokinase		
	Alkaline phosphatase		
	Total bilirubin		
	Lactate dehydrogenase		
	Total Cholesterol		
	Triglycerides		
	Total calcium		

a) Clinic only, if required by investigator send to central lab for microscopy
b) Only required at Screening

Serum calcium, phosphorus and albumin will be measured predose from the standard chemistry panel on Day 1, Day 15 and Day 29, and from a separate blood draw at 4 hours after abaloparatide-sMTS application on Day 1, Day 15, and Day 29. Blood draw for cAMP will be done predose and 30 minutes after sMTS application at Day 1, Day 15 and Day 29.

In the event of medically significant, unexplained, or abnormal clinical laboratory test values, the test(s) should be repeated and followed up until the results have returned to within the normal range or an adequate explanation for the abnormality is found. Clinically significant changes in laboratory tests that occur during the course of the study are to be reported as AEs unless included as part of a reported diagnosis (see Section 7).

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

6.5.2. Serum Markers of Bone Metabolism

Blood samples will be taken within 1 hour predose to measure serum procollagen type I N-terminal propeptide (s-PINP), a marker of bone formation on Day 1 (Visit 3), Day 15 (Visit 4) and Day 29 / EOT (Visit 5).

6.5.3. 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.

6.6. Imaging Procedures

6.6.1. Dual Energy X-ray Absorptiometry (DXA)

Subjects will have areal bone density measurements taken via DXA of the lumbar spine, total hip, femoral neck, at Screening. Lumbar spine scans must include L1 through L4. Hip scans will include the entire proximal femur to about 2 cm below the lesser trochanter. If a DXA is available that was taken in the previous 12 months and meets the above criteria, it can be used in place of taking a new scan.

6.6.2. Local Tolerance

Assessment of local tolerance will consist of evaluation of signs (Section 6.6.2.1) and symptoms (Section 6.6.2.2) of local skin reactions.

6.6.2.1. Investigator assessment of signs of local tolerance

The investigator's assessment of local tolerance will consist of evaluation of signs of local skin reactions, which must be performed by a physician or trained evaluator at designated study visits. During each clinic visit, as indicated in Table 1, the application site will be evaluated prior to the application of abaloparatide-sMTS, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour after abaloparatide-sMTS application.

Investigators will assess each of the 12 signs of local skin reaction using a 4-point scale: 0-none, 1-mild, 2-moderate, 3-severe. The 12 signs for local skin reactions are as follows: erythema, edema, vesiculation, glazed appearance, erosions, crusting, hyperpigmentation, hypopigmentation, scarring, atrophy, bruising, and bleeding.

If severe local skin reactions occur, investigators may contact the Sponsor for further instructions.

For any severe administration site reaction, the subject will be instructed to continue evaluations of the application site at 24 hour intervals until the skin irritation has stabilized or resolved. Any ongoing treatment-emergent local skin reactions noted on Day 29 will continue to be assessed at 24 hour intervals until resolved or stabilized.

6.6.2.2. Subject assessment of symptoms of local tolerance

Study subjects will be instructed to perform a daily self-assessment of symptoms of local skin reaction. The application site will be evaluated prior to study drug administration, 5 minutes after application (ie, immediately upon removal of abaloparatide-sMTS), and 1 hour following abaloparatide-sMTS application on the day of clinic visits, and between visits beginning Day 1 up until the scheduled Day 29 or EOT visit.

The 5 symptoms of pain, itching, burning, tenderness and swelling will be assessed using a 4-point scale: 0-none, 1-mild, 2-moderate, 3-severe. If the subject has severe, or worsening, local skin reactions or any local skin reactions that have not resolved within the last 48 hours, they should contact the investigator for further instructions; local skin reactions may then be monitored by the subject every 24 hours until complete resolution.

6.6.3. Residual Drug

Residual drug evaluation from abaloparatide-sMTS which was applied and removed at the site will be conducted by 3M. The clinical site will collect only the abaloparatide-sMTS at Day 1, Day 15 and Day 29 and ship the used abaloparatide-sMTS to 3M. The abaloparatide-sMTS will be placed into a glass vial and labelled with subject number and visit number by clinic staff. Upon removal of the abaloparatide-sMTS, the skin surface will be swabbed to measure residual drug and the collected swabs will be shipped by the clinical site to 3M. Refer to the pharmacy manual for additional details.

6.6.4. Assessment of Patch Adhesion

The patch is to be assessed by the subject for adhesion immediately prior to the removal of abaloparatide-sMTS at each day during the treatment period. Adhesion scores will be scored according to the following scoring system and recorded in the subject diary:

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off skin without falling off)
4 = 0% adhered – patch detached (patch completely off the skin)

6.6.5. Assessment of Subject Reported Outcomes

The proposed study will be the first to generate user experience data for abaloparatide in the context of a clinical study. Discontinuation rates are particularly high with available osteoporosis therapies regardless of the mode of intake. Abaloparatide will be the first osteoporosis treatment delivered through a patch and could have potential to improve compliance. Previous studies have suggested that microneedle patches have a greater acceptability when compared with the traditional intramuscular hypodermic injections (Norman 2014) and may be ideal for subject adherence as they do not stimulate nerves that are associated with pain (Ita 2015). The additional endpoint assessment will determine whether the abaloparatide-sMTS is well tolerated with minimal impact on subject reported outcomes and improved adherence.

Acceptability-Given the low acceptability of osteoporosis medications and subject perception of benefit/risk, an evaluation of acceptability will be carried out. There is currently no specific instrument with psychometric validation for "acceptability." Studies including teriparatide have provided a single question "Is this medication acceptable to you." (Rouphael 2017). General acceptability will be measured using a 5-point Likert-like scale. One being the least acceptable/negative experience to 5 being the most acceptable/positive experience. Acceptability will be assessed after abaloparatide-sMTS application on Day 1, Day 15 and Day 29.

Question posed directly to the subject:

- *"On a scale of 1 (least acceptable/negative experience) to 5 (most acceptable/positive experience), how would you rate this treatment."*

Subject preference of treatment attributes-While some subject reported outcomes may be treatment related, subjects' preference regarding osteoporosis treatment is likely to impact their perception of the treatment and their behavior. As such subject preference and value for drug attributes will be measured after abaloparatide-sMTS application on Days 1, 15, and 29. The data collected will help identify which factors may affect subjects' perspectives on risk/benefits. Further, which subject types may be more likely to find treatment acceptable based on value they place on various attributes.

Question posed directly to the subject:

- *"Which attributes of the treatment do you find most favorable for you?"*

- *"Which attributes of the treatment do you find least favorable?"*

Treatment Satisfaction Questionnaire for Medication (TSQM)-Treatment satisfaction will be measured with the psychometrically validated treatment satisfaction questionnaire for medication short form (TSQM-9). TSQM has been previously used in osteoporosis studies (Palacios 2015) to assess satisfaction in post-menopausal women with osteoporosis (POSSIBLE US Study). TSQM is associated with discontinuation rates (Bharmal 2009). The 9-item questionnaire contains 3 domains: effectiveness, convenience, and global satisfaction. While the side effect domain is not included, any unpleasant experiences with a medication are likely to be captured in the TSQM global satisfaction items. As a result, the TSQM-9 allows for subjects to weigh the pros and cons of medication and the less favourable aspects of subjects' experiences with their medications would be captured. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain. Score can be calculated overall or for each domain. Only the convenience and global satisfaction domain will be assessed for the current study as effectiveness evaluation is not relevant given the short follow-up time. Measurements will be done after abaloparatide-sMTS application on Day 15 and 29. See appendix for the questionnaire.

6.7. Discontinuation from the Study

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

6.7.1. Withdrawal of Consent

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

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

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up. The Sponsor may retain and continue to use any data collected before consent was withdrawn.

6.7.2. Early Study Termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

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

7. ADVERSE EVENT AND SERIOUS ADVERSE EVENT DOCUMENTATION

PLEASE SEE THE STUDY OPERATIONS MANUAL FOR DETAILED INSTRUCTIONS ON REPORTING OF SAEs, INCLUDING EMERGENCY CONTACT INFORMATION (eg, FAX, EMAIL OR TELEPHONE CONTACT NUMBERS)

7.1. Evaluation of Safety

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and is mandated by Regulatory Agencies worldwide. All clinical studies sponsored by RADIUS will be conducted in accordance with Standard Operating Procedures 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 signing the informed consent until 7 days after last dose of investigational product. At any time after 7 days from the last dose of study treatment, the investigator may report any SAE that he/she believes is possibly related to study treatment. 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 the relationship of all AEs to the study drug.

7.1.1. Adverse Event

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

AEs could 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
- Clinically significant 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.

When possible, a clinical diagnosis for the study assessment should be provided rather than the abnormal test result alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the

abnormal study assessment itself should be listed as the AE (eg, bacteria in urine or decreased hemoglobin).

Determination of clinical significance must be made by the Investigator.

All skin reactions at the application site reported by the subject and investigator, expected or unexpected, and regardless of severity will be reported as AEs and should include reference to the application site. Events of ulcer, eschars, and non-healing wounds at the application site will be evaluated as an adverse event of special interest (Skin AESI). Skin AEs that occur at other locations of the body should be reported as AEs as appropriate but are not to be recorded/entered using phrases such as 'at the application site', 'involving the application site', etc., to ensure the phrase 'application site' is used exclusively for the sites of study drug administration.

7.1.2. Serious Adverse Event (SAE)

An 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.
- Hospitalization or prolongation of existing hospitalization.
- 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 subject hospitalization, or the development of drug dependency or drug abuse.

All AEs of osteosarcoma will be reported as SAEs.

All treatment related AEs/SAEs noted on the follow-up visit 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), or until the subject is lost to follow-up.

7.1.3. Recording an Adverse Event

All AEs/SAEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be recorded in the source document and 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.

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 study drug or device, defined as 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 administration is unlikely or the temporal relationship is such that study drug administration 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. The AE will be determined to be device-related if it is identified to have had a probable or possible causal relationship to the investigational device.

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

An adverse device effect is defined as any adverse event that may or may not be related to the investigational abaloparatide-sMTS device and should be reported as an AE (Section 7.1.1), and includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, malfunction, use error or from intentional misuse of the investigational medical device.

An unanticipated adverse device effect (UADE) is defined as any SAE on health or safety or any life-threatening problem or death caused by, or associated with, the abaloparatide-sMTS device, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator and the Sponsor will immediately conduct an evaluation of any UADE occurring with abaloparatide-sMTS. The results of the evaluation will be reported to the IRB within 10 days of the Investigator and/or the Sponsor becoming aware of the event. If it is determined by the Investigator and the Sponsor to present an unreasonable risk to study participants, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. Termination will occur not later than 5 working days after the Investigator and the Sponsor makes this determination, and not later than 15 working days after first receiving notice of the event. The Investigator and the Sponsor will not resume an investigation terminated under these conditions without an additional IRB approval.

7.1.4. Serious Adverse Event Reporting

Any SAEs that occur during the study from the time the subject signs the ICF until 7 days after the last dose of study medication must be reported within 24 hours of first awareness of the event by completing and faxing the SAE Form and entering data in the clinical trial eCRF. In addition, all SAEs including all deaths which occur up to and including 7 days after administration of the last dose of study drug, must be reported to the Medical Monitor within 1 working day. SAE forms will be provided to the clinical study site. The reference safety information for this study is included in the IB, which will be provided under separate cover to all investigators.

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

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

7.1.5. Device Reporting

Abaloparatide-sMTS is a drug-device combination product. In order to fulfil regulatory reporting obligations worldwide the investigator is responsible for the detection and documentation of events meeting the definition of UADEs that occur with abaloparatide-sMTS (Section 7.1.3.1).

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

The investigator will comply with the applicable local regulatory requirements relating to the reporting to the IRB.

7.1.6. Follow-up of Adverse Events

All treatment-related AEs will be followed with appropriate medical management until resolved or stabilized, or the subject is lost to follow-up. UADEs will be followed until their medical outcome is determined, with periodic written reports about the status provided to the study Sponsor.

7.1.7. Overdose

An overdose of abaloparatide-sMTS is the intentional or unintentional application of a dose of abaloparatide that is greater than intended, such as using multiple patches on the same day. Overdoses must be reported to the Sponsor whether or not they result in an AE/SAE. In the event of an overdose the Investigator should contact the Medical Monitor immediately and closely monitor the subject for AEs and laboratory abnormalities. No specific treatment is recommended; the investigator will use clinical judgment to treat any overdose.

7.1.8. Regulatory Agency, Institutional Review Board, and Site Reporting

The sponsor and/or the clinical contract research organization are responsible for notifying the relevant regulatory authorities/ IRBs of related, unexpected SAEs.

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

7.2. Study Completion and Post-Study Treatment

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

7.3. Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his scheduled Visit 6/follow-up visit would have occurred.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and Analytical Plans

A comprehensive Statistical Analysis Plan (SAP) and a Pharmacometric Analysis Plan will be completed and approved prior to database lock.

8.2. Statistical Hypotheses

The primary objective of this study is to evaluate the ability of subjects to self-administer 300 µg abaloparatide sMTS over a period of 29 days based on pharmacokinetic (PK) and pharmacodynamic (PD) markers.

No formal statistical tests will be conducted for any of the study endpoints.

8.3. Analysis Datasets

8.3.1. Population for Analysis

The primary population for all safety analyses will be the Safety Population, which will be defined as all subjects who received at least 1 dose of study medication.

The primary population for PK analyses will be the Pharmacokinetic (PK) Analysis Population, which will include all subjects in the Safety Population who have sufficient evaluable plasma concentrations to reliably estimate 1 or more PK parameters.

8.4. Description of Statistical Methods

8.4.1. 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, unless otherwise specified.

8.4.2. Analysis of the Primary Endpoint

The primary population for the analysis of the PK parameters will be the PK Analysis Population.

Individual plasma concentrations of abaloparatide will be listed and summarized by visit and sampling time. Concentration data will be summarized at each nominal time point with the following descriptive statistics: number of subjects, mean, SD, coefficient of variation (CV%), median, minimum, and maximum. Individual plasma concentrations will be plotted vs nominal sampling time on linear-linear and log-linear scales by visit. Spaghetti plots of abaloparatide plasma concentrations will also be prepared.

The following PK parameters will be derived:

Parameters	Description
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration-time curve from time zero to infinity
C_{max}	Maximum observed plasma concentration
t_{max}	Time of maximum observed plasma concentration
$t_{1/2}$	Apparent terminal phase half-life
λ_z	Elimination rate constant

All plasma PK parameter calculations will be performed using actual time (or nominal time, when actual time is not available) calculated relative to the time of study drug administration. PK parameters will be determined using non-compartmental methods based on individual plasma concentration-time data for abaloparatide. Individual plasma PK parameters will be listed and summarized by visit. PK parameters will be summarized with the following descriptive statistics: number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean (Geo Mean), and coefficient of variation of the geometric mean (Geo Mean CV%).

Comparisons between the abaloparatide PK parameter values on Day 15 and on Day 29 vs Day 1 (based on natural log (ln)-transformed AUC_{0-inf}, AUC_{0-t}, and C_{max}) will be conducted. Point estimates and 90% CIs for the difference in PK parameter values between visits will be obtained. Further details will be described in the Pharmacometric Analysis Plan.

8.4.3. Analysis of Secondary Endpoints

The primary population for the analysis of the secondary endpoints will be the Safety Population, unless otherwise specified.

Pharmacodynamic endpoints

The change from baseline, percentage change from baseline and ratio of post-baseline value to baseline value in s-PINP will be summarized descriptively by visit, together with the 90% CI.

The actual values change from baseline values, and the percentage change from baseline values for serum calcium (albumin-corrected), serum phosphorus, and cAMP will be summarized using descriptive statistics by visit and timepoint.

Local Tolerance

Local tolerance is defined as the assessment of signs (investigator) or symptoms (subject) of local skin reactions. For the investigator assessment of signs of local skin reactions, the number (%) of subjects in each response category of the 4-point scale will be provided per visit and timepoint. The maximum severity of reaction scores will be similarly summarized for each response category by visit.

For the subject assessment of symptoms of local skin reactions, the mean of the local tolerance scores across the entire treatment period and at the Follow-Up visit will be calculated for each response category of the 4-point scale per subject by timepoint. The mean local tolerance score will be summarized using descriptive statistics by response category and timepoint. Frequency counts (and percentages) for the maximum severity of reaction scores for each response category by timepoint will be presented.

In addition, the subject assessment of symptoms of local skin reactions collected at the clinic visits will be separately summarized, with the number (%) of subjects in each response category of the 4-point scale provided per visit and timepoint. The maximum severity of reaction scores collected at the clinical visits will be similarly summarized for each response category by visit.

Subject Reported Outcomes:

- TSQM9- Global Satisfaction and Convenience Domains
  - Mean TSQM-9 score (±standard error [SE]) for each domain will be tabulated for Day 15 and Day 29 for the subjects who completed the study
  - Association between improvement in convenience and satisfaction score (TSQM9) and adherence (definition of adherence will be provided in the SAP)
- 5-point Likert-like scale of acceptability will be tabulated and summarized
  - Mean score (±SE) will be tabulated for Day 1, 15, and 29
  - Association between improvement in acceptability and adherence will be assessed
- Subject Preference for treatment attributes will be summarized
  - Pending data availability, association between subject preference for treatment attributes and subsequent acceptability and satisfaction will be evaluated separately for: outcome (effectiveness/safety) and other attributes (duration, frequency of use, mode of intake).

Patch Adhesion Score:

Frequency counts (and percentages) for the patch adhesion score collected at each clinic visit will be summarized by visit, along with the best adhesion score (ie, lowest patch adhesion score per subject) and the worst adhesion score (ie, highest patch adhesion score per subject).

The mean of the patch adhesion scores collected from Day 1 to Day 29 will be calculated for each subject. The mean patch adhesion score will be summarized using descriptive statistics for the entire treatment period. The mean of each subject's best adhesion score and worst adhesion score will also be summarized.

Abaloparatide-sMTS Released Dose

Descriptive statistics will be provided to summarize the abaloparatide-sMTS released dose, the percentage of released dose to nominal dose, the percentage of release dose to initial abaloparatide-sMTS content, the residual drug amount from abaloparatide-sMTS, the residual drug amount from abaloparatide-sMTS, and the residual drug amount from abaloparatide-sMTS and swab, by visit.

Details of analyses will be described in the SAP.

8.4.4. Safety Analyses

All 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 the current version of MedDRA available at the time of study start. The number and percent of subjects who experienced treatment-emergent AEs (TEAEs) will be summarized by MedDRA system organ class (SOC) and preferred term. Summaries will also be provided for severe TEAEs, severe related TEAEs, serious TEAEs, serious related TEAEs, TEAEs leading to study withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and TEAEs by maximum severity (mild, moderate, severe). A summary will also be provided most common (≥ 5%) TEAEs.

Summaries will be provided for Skin and Hypersensitivity AESIs for TEAEs by SOC and preferred term, severe TEAEs, severe related TEAEs, serious TEAEs, serious related TEAEs, TEAEs leading to study withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and TEAEs by maximum severity (mild, moderate, severe). A summary will also be provided most common (≥ 5%) TEAEs for each AESI.

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

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

Descriptive statistics for laboratory data (including albumin corrected serum calcium, phosphorus and cAMP), vital signs (including orthostatic BP), and ECGs will be provided by visit and time point (when applicable). 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 World Health Organization (WHO) Drug Dictionary and summarized by number and percentage of subject using each class and preferred drug term.

8.4.5. Adherence and Retention Analyses

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

8.4.6. 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 preferred term, summarizing the proportion of subject who have a condition noted. Results from the baseline physical examination will be summarized by body system as recorded in the eCRF.

8.4.7. Interim Analyses

There are no interim analyses planned for this study.

8.4.8. Additional Subgroup Analyses

Subgroup analysis may be performed and will be described in the SAP.

8.4.9. Multiple Comparison/Multiplicity

No formal statistical tests will be performed, and hence no adjustments for multiple comparisons will be made.

8.4.10. Tabulation of Individual Response Data

Individual efficacy and safety data will be tabulated as appropriate.

8.4.11. Exploratory Analyses

Additional exploratory analyses may be presented as either planned (and described in the SAP) or post-hoc to complement the overall understanding of study results.

8.5. Sample Size Calculation

This is a hypothesis generating study and the sample size is based on previous clinical trial experience without a formal power calculation.

8.6. Measures to Minimize Bias

Not applicable.

8.7. Enrollment/Randomization/Masking Procedures

Treatment will not be blinded.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Ethical Considerations

This clinical study will be conducted in accordance with the current version of International Conference on Harmonization (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, 21CFR 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.

9.2. Subject Information and Informed Consent

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

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

9.3. Investigator Compliance

No modifications to the protocol should be made except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. RADIUS will submit all protocol modifications as amendments to the required regulatory authorities.

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

9.4. Access to Records

The Investigator must make the office and/or hospital records of subjects enrolled in this study available for review by site monitors at the time of each monitoring visit, audit by RADIUS 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 (Food and Drug Administration and others). The Investigator must

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

9.5. Subject and Data Confidentiality

To maintain subject confidentiality, all eCRFs, study reports and communications relating to the study will identify subject by unique subject ID numbers assigned to each subject. 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/source data documents and the review of the data collection process. The Food and Drug Administration (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 study subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of RADIUS.

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

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

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

9.7. Data Quality Assurance

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

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study subject. Study data for each enrolled subject will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. RADIUS will have read-only access to all data upon entry in the EDC application. Study assessment data generated by contracted 3rd party vendors will be obtained via external data transfers (outside the EDC application) and reconciled against confirmatory data contained in the EDC system by RADIUS'

designee. External data will be incorporated into Study Data Tabulation Model (SDTM) datasets by RADIUS' designee for RADIUS' use.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study eCRF data will be made in the eCRF and documented in an audit trail, which will be maintained within the clinical database. Changes to external data will be handled exclusively by the 3rd party vendor responsible for the data.

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

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

9.8. Monitoring

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

9.9. Data Collection and Management Responsibilities

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

RADIUS or its designee 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 subject for which they are responsible.

An eCRF will be completed for each subject who receives at least 1 dose of study drug. Nominal data, limited to demographics and the reason for screen failure, will be collected for all subjects who sign an ICF but are not randomized, although additional data will be collected if a screen failure experiences an adverse event during while being screened. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, attributability, 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, the date and time of log in, the date and time of data entry and/or any change or correction to previously entered data, as well as the reason for any data change. The Investigator must provide formal approval of all the information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the Investigator is responsible.

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

9.10. Study Records Retention

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

9.11. Publication and Data Sharing Policy

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

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

10. LITERATURE REFERENCES

Barrett-Connor E, Wade SW, Do TP, et al. Osteoporos Int (2012) 23: 733.

Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes. 2009;**7**: 36.

Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1999; 14(5): 821-828.

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

Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. Endocr Rev. 1993;14:690–709.

Ebeling PR. Osteoporosis in men. New Engl J Med. 2008;358:1474-1482.

Ensrud KE, Blackwell TL, Cawthon PM, et al. Degree of Trauma Differs for Major Osteoporotic Fracture Events in Older Men Versus Older Women. J Bone Miner Res. 2016; 31(1): 204-207.

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;157:141-49.

International Osteoporosis Foundation. Osteoporosis in men. 2014; accessed via http://www.iofbonehealth.org/WOD/2014/thematic-report/WOD14-Report.pdf

Ita, K. Transdermal Delivery of Drugs with Microneedles-Potential and Challenges. Pharmaceutics. 2015; 7(3): 90-105.

Kanis JA, OBJ O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35(2): 375-382.

Khosla S, Amin S, Orwoll E. Osteoporosis in men. Endocrine Rev. 2008;29:441-464.

Li G, Thabane L, Papaioannou A, Adachi JD. Comparison between frailty index of deficit accumulation and fracture risk assessment tool (FRAX) in prediction of risk of fractures. Bone. 2015; 77: 107-114.

Li G, Ioannidis G, Pickard L, et al. Frailty index of deficit accumulation and falls: data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort. BMC Musculoskelet Disord. 2014; 15: 185.

Lindsay R, Silverman SL, Cooper C, MD; et al. Risk of New Vertebral Fracture in the Year Following a Fracture. JAMA. 2001;285(3):320-323. doi:10.1001/jama.285.3.320

Litwic A, Lekarz, Warwick D, Denniston E. Distal radius fracture: Cinderella of the osteoporotic fractures. Orthop Muscul Syst. 2014; 3:162-8.

Makino M, Takagi H, Sugiyama H, Kobayashi T, Kasahara Y. Effects of abaloparatide on the expression of bone resorption and formation-related factors in osteoblastic cells; a comparison

with teriparatide. Annual Meeting of the American Society for Bone and Mineral Research 2015; MO0121.

Mannstadt M, Juppner H, Gardella TJ. Receptors for PTH and PTHrP: Their biological importance and functional properties. Am J Physiol. 1999; 277:F665-F675

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. J Am Med Assoc. 2016;316:722-733.

Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Stat Med. 1998; 17:873-890.

Norman JJ, Arya JM, McClain MA, Frew PM, Meltzer MI, Prausnitz MR. (2014). Microneedle patches: usability and acceptability for self-vaccination against influenza. Vaccine. 2014;32(16): 1856-1862.

Palacios S, Agodoa I, Bonnick S, et al. Treatment satisfaction in postmenopausal women suboptimally adherent to bisphosphonates who transitioned to denosumab compared with risedronate or ibandronate. J Clin Endocrinol Metab. 2015; 100(3): E487-492.

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

Robinson, CM, Royds M, Abraham A, McQueen MM, Court-Brown CM, Christie J. Refractures in patients at least forty-five years old. a prospective analysis of twenty-two thousand and sixty patients. J Bone Joint Surg Am. 2002; **84-a(**9): 1528-1533.

Rouphael NG, Paine M, Mosley r, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. Lancet. 2017; 390(10095): 649-658.

Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med. 2005;353:595-603.

Suzuki N, Ogikubo O, Hansson T. The course of the acute vertebral body fragility fracture: its effect on pain, disability and quality of life during 12 months. Eur Spine J. 2008; 17(10): 1380-1390.

World Health Organization (WHO). Assessment of osteoporosis at the primary health care level. Summary of a WHO Scientific Group 2007 [16 Feb 2017]. Available from: www.who.int/chp/topics/rhuematicrheumatic/en/index.html

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