CLINICAL STUDY PROTOCOL

A Randomized, Non-Inferiority, Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Abaloparatide-sMTS for the Treatment of Postmenopausal Women with Osteoporosis

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 BA058-05-021

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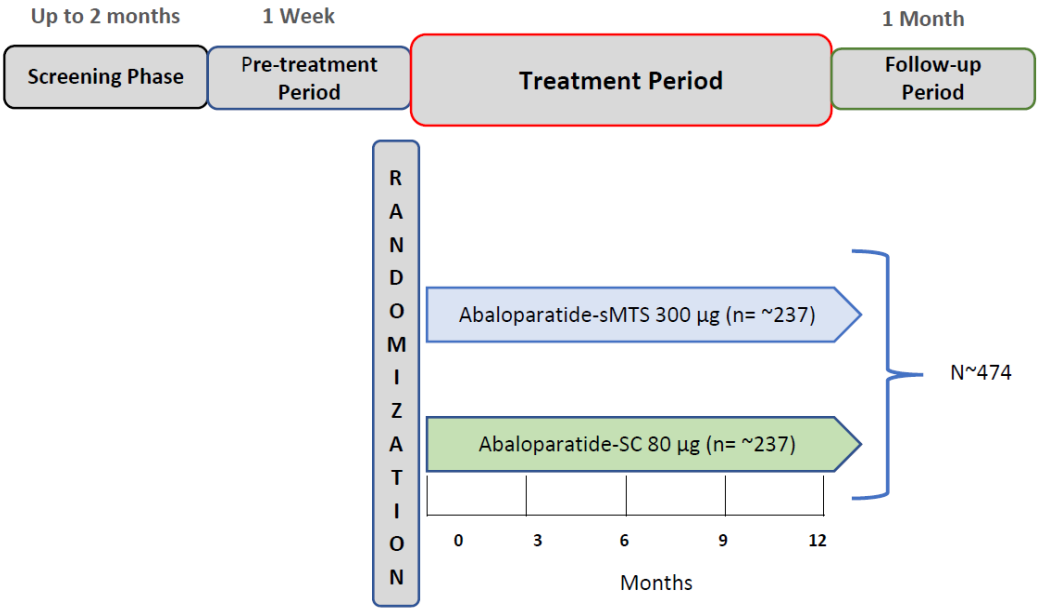
LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMD	Bone mineral density
BUN	Blood urea nitrogen
CI	Confidence interval
CPK	Creatine phosphokinase
CRO	Contract research organization
DXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-treat
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDR	Medical device reports
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MMRM	Mixed-Effect Model Repeated Measures
PAP	Pharmacometric Analysis Plan
PBS	Phosphate buffered saline

Abbreviation	Term
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin time
PTH	Parathyroid hormone
$PTHR_1$	Parathyroid hormone related peptide type 1 receptor
PTHrP	Parathyroid hormone related peptide
PTT	Partial thromboplastin time
Q1, Q3	Interquartile range
R^0	non-G protein-coupled
RBC	Red blood cell
RDA	Recommended daily allowance
RG	G protein-coupled
rhPTH	Parathyroid hormone receptor modulation using teriparatide
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
s-CTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen
SD	Standard deviation
SE	Standard error
sMTS	Solid microstructured transdermal system
SOC	System organ class
s-PINP	Serum procollagen type 1 N propeptide
TEAEs	Treatment-emergent adverse events
TSH	Thyroid stimulating hormone
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
US	United States
WBC	White blood cells
WHO	World Health Organization
$ZnCl_2$	Zinc chloride

SYNOPSIS

Name of Sponsor/Company: Radius Health, Inc. (RADIUS)
Name of Finished Drug-Device: Abaloparatide-solid microstructured transdermal system (sMTS) for intradermal administration
Name of Active Ingredient: Abaloparatide
Title of Study: A Randomized, Non-Inferiority, Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Abaloparatide-sMTS for the Treatment of Postmenopausal Women with Osteoporosis
Phase of development: 3
Study center(s): Approximately 125 study centers globally
Number of subjects (planned): 474 subjects
Principal investigator: To be determined
Objective: To evaluate the non-inferiority of abaloparatide-sMTS 300 µg compared to abaloparatide-subcutaneous (SC) 80 µg based on lumbar spine bone mineral density (BMD) at 12 months and to evaluate the safety and tolerability of abaloparatide-sMTS in the treatment of postmenopausal women with osteoporosis
Design and Methodology: This is a randomized, open-label, non-inferiority, multicenter study of abaloparatide-sMTS compared with abaloparatide-SC for the treatment of postmenopausal women with osteoporosis. The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), and a Treatment Period (12 months), with a final visit 1 month after the last dose of study drug (Follow-Up/End of Study [EOS] visit); 1 month is defined as 30 days in this study. Thus, subjects will participate in the study for up to 16 months. Eligible subjects will be randomized in a 1:1 ratio to either abaloparatide-sMTS or abaloparatide-SC using a permuted block randomization scheme. Both groups of subjects will undergo protocol-specified procedures, including BMD and bone turnover marker assessment. Before the start of treatment, subjects will receive training on study drug administration (defined as abaloparatide-sMTS application or abaloparatide-SC injection). During the study, subjects will record their assessments of patch adhesion each day during the Treatment Period. The subject and Investigator will both assess local tolerance (symptoms [subject] and signs [Investigator] of local skin reactions). The study design is as follows:



Screening Period (up to 2 months):

During the Screening Period, signed informed consent will be obtained, eligibility for study entry assessed, and screening evaluations performed, including baseline lumbar and thoracic spine radiographs, BMD assessments by dual X-ray absorptiometry (DXA) of lumbar spine, total hip, and femoral neck, and baseline laboratory tests. Subjects who do not meet the 25-hydroxyvitamin D entry criterion (25-hydroxyvitamin D < 20 ng/mL) may receive vitamin D supplementation and be retested 1 time. 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. All safety labs should be done within 30 days prior to randomization (Day 1).

Pretreatment Period (1 week):

Following screening evaluations, eligible subjects will enter the Pretreatment Period of the study to ensure that each subject receives the recommended daily allowance (RDA) of calcium and vitamin D from either food intake and/or calcium and vitamin D supplementation for 7 days. For a subject who is currently taking calcium and vitamin D supplements at the time of screening and where the screening lab results meet eligibility criteria, the Principal Investigator should exercise his/her clinical discretion to assess if the RDA has been met. The time spent on calcium and vitamin D supplementation prior to Screening may apply towards the required 7-day duration of the Pretreatment Period.

All 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's Medical Monitor according to the subject's need. Calcium and vitamin D supplementation will continue until the end of the Treatment Period. Subjects will also receive training in the use of the applicator/injector pen for abaloparatide self-administration.

Treatment Period (12 months):

Subjects will be randomized on Day 1 of the Treatment Period. During the Treatment Period, subjects will self-administer study drug once a day for 12 months and visit the study site on Days 1 and 14, and Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12.

Study procedures will include the measurement of lumbar spine, total hip and femoral neck BMD by DXA (Screening, Month 3, Month 6, and Month 12) and collection of serum samples to assess markers of bone turnover (Day 1, Month 1, Month 3, Month 6, and Month 12). Clinical fractures will be assessed at Pre-treatment, Day 1, Month 1, Month 3, Month 6, Month 9, and Month 12. Serum samples for evaluation of calcium levels after study drug administration and anti-drug antibody (ADA) testing will be done at specified visits during the Treatment Period. ADA-positive samples will be tested for cross reactivity to endogenous parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP).

Blood samples for measurement of plasma concentrations of abaloparatide will be taken on Day 1, Day 14, Month 1, Month 3, Month 6, and Month 9. In addition, 1 sample per subject per visit will be collected at the following varying post-injection/application times: >1 hour to 2 hours (Day 1); >30 minutes to 1 hour (Day 14); >3 hours to 4 hours (Month 1); >2 hours to 3 hours (Month 3); >10 minutes to 30 minutes (Month 6) and predose (Month 9). These sample collection times were randomly determined. Subjects will return to the study site at the monthly study visits for drug dispensation.

Follow-Up/EOS Visit:

All subjects will return to the study site for a follow-up visit 1 month after the last dose of study drug. Any subject who shows presence of ADAs at Visit 17 or 1 month following End of Treatment (EOT) will be retested at 6-month intervals post-study until antibody status returns to negative.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

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

1. Healthy ambulatory female from 50 to 85 years of age (inclusive) with postmenopausal osteoporosis
2. Postmenopausal for at least 5 years as demonstrated by a history of amenorrhea for at least 5 years
3. BMD T-score based on the female reference range as assessed by the central imaging vendor of:
   a. Less than or equal to -2.5 and greater than -5.0 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by DXA and
      i. Radiological evidence of 2 or more mild or 1 or more moderate lumbar or thoracic vertebral fractures, or
      ii. History of fragility fracture to the forearm, humerus, sacrum, pelvis, hip, femur, or tibia within the past 5 years
   b. Postmenopausal women older than 65 years who meet the fracture criteria (i or ii) but have a T-score of ≤ -2.0 and > -5.0 may be enrolled
   c. Postmenopausal women older than 65 years who do NOT meet the fracture criteria may be enrolled if they have a BMD T-score ≤ -3.0 and > -5.0 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by DXA
4. In good general health as determined by medical history and physical examination (including vital

signs), has a body mass index of 18.5 to 33 kg/m^2, inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator

5. Serum calcium (albumin-corrected), PTH (1-84), serum phosphorus, alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value and who meets all other entry criteria would be required to have a normal bone-specific alkaline phosphatase in order to be enrolled. Any subject with a TSH value outside of the normal range may be enrolled if their T3 and free T4 values are within the normal range
6. Serum 25-hydroxyvitamin D values must be ≥ 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 pulse rate is ≥ 45 and ≤ 100 beats per minute (taken sitting or supine)
9. No clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells, and platelets, or usual serum biochemistry, 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

Exclusion criteria:

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

General exclusion criteria:

1. History of more than 4 spine fractures, mild or moderate, or any severe fractures based on Genant Semi-quantitative Scoring method on radiographic findings
2. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal BMD, defined as having at least 2 radiologically-evaluable vertebrae within L1–L4 as assessed by the central imaging review of the DXA images.

   Anatomically abnormal vertebrae are excluded if:

   - They are clearly abnormal and non-assessable within the resolution of the system; or
   - There is a more than 1.0 T-score difference between the vertebra in question and adjacent vertebrae
3. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable)
4. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis
5. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine
6. History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism, or malabsorptive

syndromes within the past year

7. 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/minute
8. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin)
9. History of osteosarcoma at any time
10. Hereditary disorders predisposing to osteosarcoma
11. History of nephrolithiasis or urolithiasis within the past 5 years
12. Decrease of 20 mmHg or more in systolic blood pressure or 10 mmHg or more in diastolic blood pressure from supine to standing (5 minutes laying and 3 minutes standing) or any symptomatic hypotension at Screening
13. Application site is compromised by scars, inflammation, or skin conditions that may compromise patch application or drug delivery (nevi, plaques, tattoos, scars, piercing, etc.)
14. Any other medical condition that, in the opinion of the Investigator, renders the subject unable or unlikely to complete the study, would interfere with the interpretation of study data or produce significant risk to the subject

Medication-related exclusion criteria:

15. Known or suspected history of hypersensitivity to any of the test materials or related compounds
16. Prior treatment with PTH- or PTHrP-derived drugs or bone anabolic drugs including abaloparatide, teriparatide, or PTH (1-84)
17. Prior treatment with intravenous bisphosphonates at any time or oral bisphosphonates within the past 3 years. 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
18. Prior treatment with selective estrogen receptor modulators (such as raloxifene or tamoxifen) in the past 6 months. Estrogens administered as hormone replacement therapy, with or without progestins, are not exclusionary
19. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or bone-acting investigational agents at any time
20. Prior treatment with calcitonin or tibolone in the past 6 months
21. Treatment with denosumab within the past 18 months
22. 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
23. Treated with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) in the past 90 days

24. Daily treatment with corticosteroids within the 12 months prior to the Screening Period. Occasional use of low dose 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
25. Participation in another clinical trial with any investigational drug or device within 90 days or 5 half-lives of the investigational drug (if known), whichever is longer, of study drug administration

Lifestyle-related exclusion criteria:

26. Abnormal nutritional status as assessed by the Investigator, vitamin D intake of ≥ 4,000 IU/day, or vitamin A intake of ≥ 10,000 IU/day. Short-term use of high doses of vitamin D to bolster endogenous vitamin D levels for study entry during the Screening Period is not exclusionary
27. 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/device, dosage, and mode of administration:

Abaloparatide-sMTS, 300 µg once per day, transdermal, applied to the thigh for 5 minutes

Duration of Treatment:

12 months

Reference therapy, dosage and mode of administration:

Abaloparatide-SC, 80 µg once per day, injected into the abdomen

Criteria for Evaluation:

Efficacy will be assessed by evaluation of BMD by DXA of the lumbar spine, total hip, and femoral neck; clinical fractures; markers of bone turnover (ie, serum procollagen type 1 N-terminal propeptide [s-PINP] and carboxy-terminal cross-linking telopeptide of type 1 collagen [s-CTX]); and serum calcium.

Safety and tolerability will be assessed by treatment-emergent adverse events (TEAEs), vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), electrocardiograms (ECGs), laboratory tests (chemistry, hematology, coagulation, and urinalysis), local tolerance, and presence of ADA. Events of ulcer, eschars, and non-healing wounds at the injection/application site will be evaluated as an adverse event of special interest (AESI). Hypersensitivity will also be evaluated as an AESI.

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 that were assessed by the Investigator to have met any of these conditions will be monitored by the subject every 24 hours until complete resolution.

Endpoints:

Efficacy:

Primary Efficacy Endpoint:

- Percent change from baseline in lumbar spine BMD at 12 months

Secondary Efficacy Endpoints:

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

Additional Efficacy Endpoints:

- Percent change from baseline in lumbar spine BMD at 3 and 6 months
- Percent change from baseline in total hip BMD at 3 and 6 months
- Percent change from baseline in femoral neck BMD at 3 and 6 months

Other Endpoints

- Log ratio of post-baseline over baseline in s-PINP at 1, 3, 6, and 12 months
- Log ratio of post-baseline over baseline in s-CTX at 1, 3, 6, and 12 months
- Plasma concentration of abaloparatide from sparse PK sampling

Safety and Tolerability Endpoints:

TEAEs, vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), ECGs, laboratory tests (chemistry, hematology, coagulation, and urinalysis), local tolerance, presence of ADAs, and AESI.

Sample Size and Power Calculation:

The previous pivotal, Phase 3, multicenter, randomized, open-label, active- and double-blind, placebo-controlled study of abaloparatide-SC (Study BA058-05-003) showed that the placebo-adjusted effect of abaloparatide-SC 80 µg on the percent change from baseline in lumbar spine BMD based on a Mixed-Effect Model Repeated Measures (MMRM) analysis was 9.096% (95% confidence interval (CI): 8.557%, 9.634%) at 12 months. According to the Food and Drug Administration's (FDA) *Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness* (2016), the lower bound of this CI can be considered as the historical treatment effect of abaloparatide-SC versus placebo, M_1 (=8.557%). Based on FDA's recommendation of a clinically meaningful difference of 2.0% between treatment groups, a non-inferiority margin, M_2, is selected at 2.0% to preserve approximately 77% of M_1, the historical treatment effect of abaloparatide-SC.

This preserved effect supports the superiority to placebo because the amount of preserved effect, 6.557% (=77% * M_1), is larger than the placebo-adjusted effect of alendronate 10 mg daily (5.4%; Fosamax® USPI) and of denosumab 60 mg once every 6 months (5.5%; Bolognese 2013) on lumbar spine BMD at 12 months. Furthermore, the placebo-adjusted effect of teriparatide observed in the previous Phase 3 study (Study BA058-05-003) based on an MMRM analysis was 7.841% (95% CI: 7.384%, 8.297%). Thus, the proposed non-inferiority margin leads to 89% (=6.557/7.384) of the effect of teriparatide, another approved anabolic agent.

Non-inferiority of abaloparatide-sMTS to abaloparatide-SC will be concluded if the lower bound of the 2-sided 95% CI for the estimated treatment difference (abaloparatide-sMTS minus abaloparatide-SC) in the percent change from baseline in lumbar spine BMD at 12 months is above -2.0%, using an MMRM analysis.

A sample size of 426 subjects will provide at least 90% power to conclude the non-inferiority of abaloparatide-sMTS 300 µg to abaloparatide-SC 80 µg, assuming a true mean difference of zero percent and a standard deviation of 6.35%. To ensure an analysis size of 426 subjects, an overall sample size of 474 subjects (237 subjects per group) will be randomized, anticipating that approximately 10% of treated subjects may not have both a baseline lumbar spine BMD measurement and at least 1 post-baseline lumbar spine BMD measurement.

Statistical Methods:

Analysis Populations:

The modified Intention-to-Treat (mITT) Population, defined as all randomized subjects who received at least 1 dose of study drug and had a baseline lumbar spine BMD measurement and at least 1 post-baseline lumbar spine BMD measurement, will be the primary population for the analyses of all efficacy endpoints. Supportive analyses of efficacy will be conducted using the Intention-to-Treat (ITT) Population, defined as all subjects randomized into the study, and the Per-Protocol (PP) Population, defined as all subjects in the mITT Population who did not have any critical protocol deviations (as defined in the Statistical Analysis Plan). The primary population for safety analyses will be the Safety Population, defined as all randomized subjects who received at least 1 dose of study drug.

Baseline Comparison:

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

Efficacy Analyses:

The primary hypothesis is that the effect of abaloparatide-sMTS 300 µg on the percent change from baseline in lumbar spine BMD at 12 months is no worse than the effect of abaloparatide-SC 80 µg by a non-inferiority margin of 2.0%. The primary efficacy endpoint will be analyzed using an MMRM model with fixed effects of treatment, DXA instrument manufacturer, visit, and treatment-by-visit interaction, and with baseline lumbar spine BMD as covariate. An unstructured variance-covariance matrix will be used to model the within-subject errors over the visits. The estimated difference (abaloparatide-sMTS minus abaloparatide-SC) and its corresponding 2-sided 95% CI will be derived from the MMRM model. If the lower bound of the 2-sided 95% CI for the between-group difference in mean percent change from baseline in lumbar spine BMD at 12 months is above -2.0%, non-inferiority of abaloparatide-sMTS to abaloparatide-SC will be concluded.

The secondary endpoints of percent changes in BMD at the total hip and the femoral neck at 12 months will be evaluated to support the primary endpoint. These endpoints will be analyzed using the same MMRM model used to analyze the primary efficacy endpoint, with the appropriate baseline BMD as covariate. The estimated differences between abaloparatide-sMTS and abaloparatide-SC and their corresponding 95% CIs will be presented.

The additional efficacy endpoints will be analyzed in a similar fashion as the secondary endpoints.

Plots will be presented for the mean (±standard error [SE]) percent change in BMD of the lumbar spine, total hip, and femoral neck over the 12-month Treatment Period.

Analysis of bone turnover markers, s-PINP and s-CTX, will be based on the ratio of the post-baseline value relative to the baseline value. The transformation of the $\log_e$ ratio of post-baseline versus baseline value will be used to normalize the distributions of the s-PINP and s-CTX parameters. The analysis comparing abaloparatide-sMTS with abaloparatide-SC will use a MMRM model similar to the MMRM model for BMD analysis, with the appropriate baseline bone turnover marker value as a covariate.

Plots will be presented for the geometric mean of the ratio to baseline (±SE) for s-PINP and s-CTX values over time by treatment group.

Subgroup analyses (eg, age, geography, prior fracture, and baseline BMD) may be performed for the percent change from baseline at 12 months in BMD at the lumbar spine, the total hip, and the femoral neck.

Percent changes from baseline in BMD (lumbar spine, total hip, femoral neck) at 12 months will be

analyzed by ADA status and treatment group.

Details of analyses will be described in the Statistical Analysis Plan.

Population Pharmacokinetic (PK) Analyses:

A population PK analysis will be performed on the sparse plasma concentrations of abaloparatide. The analysis plan for the population PK will be described in a separate document.

Safety Analyses:

Safety analysis will be presented descriptively by treatment group and will include the following parameters:

- TEAEs, serious TEAEs, TEAEs by severity, and TEAEs leading to dose interruption, treatment discontinuation, or death
- Changes in vital signs (including orthostatic blood pressure), ECGs, and clinical laboratory (hematology, coagulation, serum chemistry, and urinalysis) tests
- Hypercalcemia and hypercalciuria
- Skin and hypersensitivity AESI
- Investigator and subject assessment of local tolerance
- Presence of ADAs

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

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 April 28, 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 peptide designed to be a potent and selective activator of the PTH/PTH-related protein (PTHrP) type 1 receptor ($PTHR_1$) signaling pathway with 41% homology to PTH[1–34] and 76% homology to human PTHrP[1–34]. Abaloparatide is differentiated from PTH and PTHrP ligands based on its high affinity and >1,000-fold greater selectivity for the G protein-coupled (RG) vs the non-G protein-coupled (R^0) conformation of $PTHR_1$ (Hattersley 2016). Differential $PTHR_1$-RG binding with abaloparatide results in potent and transient intracellular cyclic adenosine monophosphate 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 bone mineral density (BMD) and reducing fracture in individuals with osteoporosis, but with a limited effect on bone resorption and a reduced risk of hypercalcemia.

Abaloparatide 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. The sponsor, in collaboration with 3M, has developed a short wear time transdermal 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 the drug (abaloparatide) and excipient (zinc chloride [$ZnCl_2$]) 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
    - A tray 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 (ie, 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 (World Health Organization [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 has sustained a vertebral fracture, the risk of a subsequent vertebral fracture increases by >300% and the risk of a subsequent hip fracture increases 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 1 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 2003). 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 2014). 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 is 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. Additional 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. Full details of the nonclinical development program for abaloparatide are provided in the Investigator's Brochure.

1.1.2.2. Clinical Studies

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

The abaloparatide-sMTS clinical trial program includes a Phase 1 study with abaloparatide-sMTS administration (BA058-05-015) to select an optimized formulation and dose for abaloparatide-sMTS to be used in the Phase 3 study.

Additional details for these clinical studies can be found in the most recent Investigator's Brochure.

1.1.2.2.1. Abaloparatide-SC

In the pivotal Phase 3 study (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 and well tolerated 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 (Study BA058-05-005), subjects who were in the abaloparatide-SC or placebo arms were transitioned to oral alendronate 70 mg weekly. Subjects who received 18 months of abaloparatide-SC followed by 6 months of alendronate experienced no new morphometric vertebral fractures from Study BA058-05-005 baseline and continued to have statistically significant reductions in nonvertebral, major osteoporotic, and clinical fractures when compared to subjects who previously received 18 months of placebo followed by 6 months of alendronate. These results validate the osteoporosis treatment paradigm of build (with an anabolic agent) and then maintain and consolidate gains (with an 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 adverse events (AEs) were comparable between subjects previously treated with abaloparatide-SC and the previous placebo group. The incidences of cardiovascular AEs, including serious adverse events (SAEs), were similar between groups.

There have been no cases of osteosarcoma, osteonecrosis of the jaw, or atypical femoral fracture in the entire abaloparatide-SC clinical development program. In nonclinical 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 one Phase 2 study, including an abaloparatide-sMTS phosphate buffered saline (PBS) formulation (abaloparatide-sMTS PBS) and an optimized formulation (abaloparatide $ZnCl_2$·HCl).

The abaloparatide-sMTS PBS formulation has similar abaloparatide maximum concentration, but lower abaloparatide area under the concentration-time curve (AUC) than the reference abaloparatide-SC 80 µg treatment. This abaloparatide-sMTS formulation was evaluated in 3 completed Phase 1 studies in healthy postmenopausal women, Studies BA058-05-004, BA058-05-006, and BA058-05-008. These studies were conducted to evaluate the pharmacokinetics (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. The results from this study with the abaloparatide-sMTS PBS formulation did not support the selection of this abaloparatide-sMTS 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 to select an optimized formulation and dose for abaloparatide-sMTS to be used in the Phase 3 study. From the PK data in this clinical study, abaloparatide-sMTS Formulation W-1 (abaloparatide $ZnCl_2$·HCl) 300 µg applied to the thigh for 5 minutes was selected for further clinical development.

Full details of the results of clinical trials conducted with abaloparatide-SC and abaloparatide-sMTS are provided in the Investigator's Brochure.

1.2. Study Rationale

The purpose of this study is to evaluate the comparability of abaloparatide-sMTS 300 µg based on lumbar spine BMD non-inferiority compared to abaloparatide-SC 80 µg at 12 months and to evaluate the safety and tolerability of abaloparatide-sMTS in the treatment of postmenopausal women with osteoporosis. The transdermal method of administration for abaloparatide may be preferred to an SC method by some subjects and may reduce a barrier for anabolic therapy.

1.3. Dose Rationale

The approved dose of abaloparatide-SC in the US for the treatment of postmenopausal women at high risk for fracture is 80 µg per day; this will be used as the comparator for the 300 µg abaloparatide-sMTS for the present study.

BA058-05-015 was a Phase 1 study initiated to select an optimized formulation and dose for abaloparatide-sMTS to be used in this study. From the PK data, it was determined that

abaloparatide-sMTS Formulation W-1 (abaloparatide $ZnCl_2$·HCl) 300 µg applied to the thigh for 5 minutes provided a single-patch administration option with a similar PK profile (slow absorption with a similar time of maximum concentration 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 is expected to provide an acceptable safety profile for this Phase 3 non-inferiority BMD study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives and Primary Endpoint

The objective of this study is to evaluate the non-inferiority of abaloparatide-sMTS 300 µg compared to abaloparatide-SC 80 µg based on lumbar spine BMD at 12 months and to evaluate the safety and tolerability of abaloparatide-sMTS in the treatment of postmenopausal women with osteoporosis.

The primary efficacy endpoint is the percent change from baseline in lumbar spine BMD at 12 months.

2.2. Secondary Endpoints

Secondary Efficacy Endpoints:

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

Additional Efficacy Endpoints:

- Percent change from baseline in lumbar spine BMD at 3 and 6 months
- Percent change from baseline in total hip BMD at 3 and 6 months
- Percent change from baseline in femoral neck BMD at 3 and 6 months

Other Endpoints

- Log ratio of post-baseline over baseline in serum procollagen type 1 N propeptide (s-PINP) at 1, 3, 6, and 12 months
- Log ratio of post-baseline over baseline in serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) at 1, 3, 6, and 12 months
- Plasma concentration of abaloparatide from sparse PK sampling

Safety and Tolerability Endpoints:

Treatment-emergent AEs (TEAEs), AEs of special interest (AESI), vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate), electrocardiograms (ECGs), laboratory tests (chemistry, hematology, coagulation, and urinalysis), local tolerance, and presence of anti-drug antibodies (ADAs)

3. STUDY DESIGN

3.1. Description of the Study Design

This is a randomized, open-label, non-inferiority, multicenter study of abaloparatide-sMTS compared with abaloparatide-SC for the treatment of women with postmenopausal osteoporosis. An overview of the design of the study is presented in Figure 1.

The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), and a Treatment Period (12 months) with a final visit 1 month after the last dose of study drug (Follow-Up/End of Study [EOS] visit); 1 month is defined as 30 days in this study. Thus, subjects will participate in the study for up to 16 months.

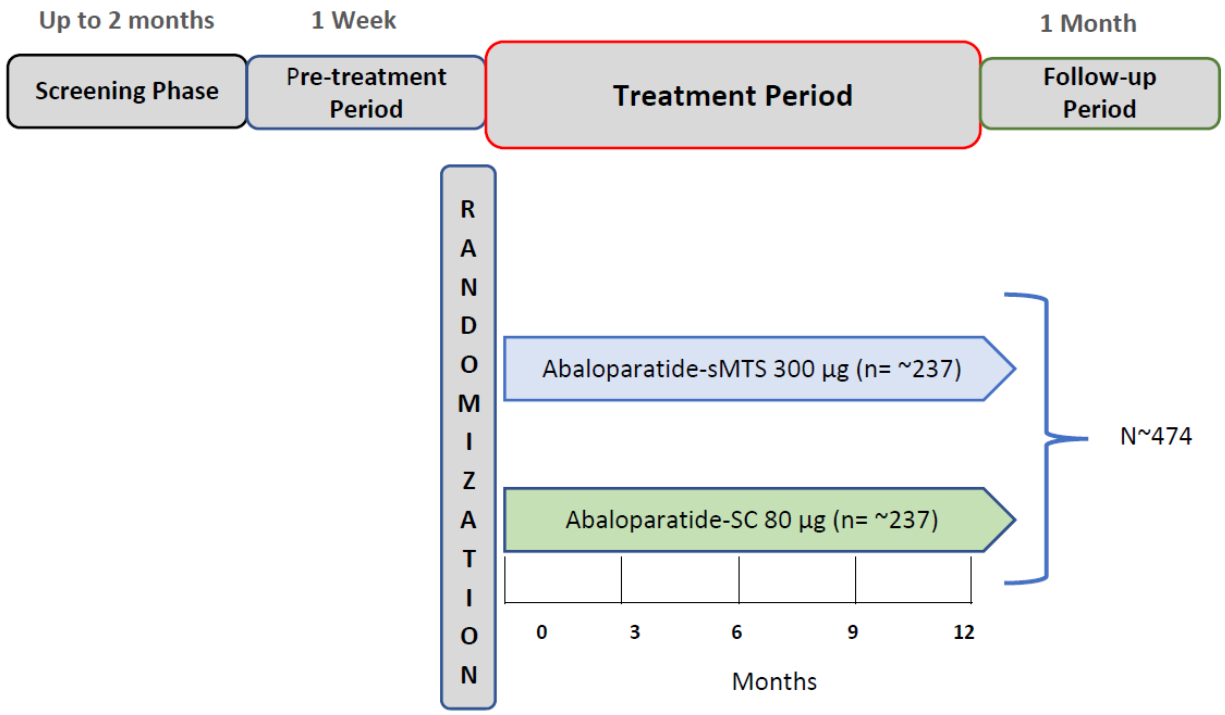
Subjects will be randomized on Day 1 of the Treatment Period. During the Treatment Period, subjects will self-administer study drug once a day for 12 months and visit the study site on Days 1 and 14 and Months 1, 2, 3, 4, 5, 6, ,7 8, 9, 10, 11, and 12.

Eligible subjects will be randomized in a 1:1 ratio to either abaloparatide-sMTS or abaloparatide-SC using a permuted block randomization scheme. Both groups of subjects will undergo protocol-specified procedures, including BMD and bone turnover marker assessment.

All 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's Medical Monitor according to the subject's need.

All subjects will undergo safety, BMD, bone turnover markers, and fracture assessments at regular intervals according to the Schedule of Assessments and Procedures (Table 1).

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 are screened and excluded from this study will be recorded in the electronic Case Report Form (eCRF) with the reason why they were screen failures.

4.1. Inclusion Criteria

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

1. Healthy ambulatory female from 50 to 85 years of age (inclusive) with postmenopausal osteoporosis
2. Postmenopausal for at least 5 years as demonstrated by a history of amenorrhea for at least 5 years
3. BMD T-score based on the female reference range as assessed by the central imaging vendor of:
    a. Less than or equal to -2.5 and greater than -5.0 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by dual energy X-ray absorptiometry (DXA) and
        i. Radiological evidence of 2 or more mild or 1 or more moderate lumbar or thoracic vertebral fractures, or

ii. History of fragility fracture to the forearm, humerus, sacrum, pelvis, hip, femur, or tibia within the past 5 years

b. Postmenopausal women older than 65 years who meet the fracture criteria (i or ii) but have a T-score of ≤ -2.0 and > -5.0 may be enrolled

c. Postmenopausal women older than 65 years who do NOT meet the fracture criteria may be enrolled if they have a BMD T-score ≤ -3.0 and >-5 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by DXA

4. In good general health as determined by medical history and physical examination (including vital signs), has a body mass index of 18.5 to 33 kg/m^2, inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator
5. Serum calcium (albumin-corrected), PTH (1-84), serum phosphorus, alkaline phosphatase, and thyroid stimulating hormone (TSH) values all within the normal range during the Screening Period. Any subject with an elevated alkaline phosphatase value and who meets all other entry criteria would be required to have a normal bone-specific alkaline phosphatase in order to be enrolled. Any subject with a TSH value outside of the normal range may be enrolled if their T3 and free T4 values are within the normal range
6. Serum 25-hydroxyvitamin D values must be ≥ 20 ng/mL
7. Resting 12-lead ECG 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 pulse rate is ≥ 45 and ≤ 100 beats per minute (taken sitting or supine)
9. Has no clinically significant abnormality of serum hemoglobin, hematocrit, white blood cells, and platelets, or usual serum biochemistry, 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 (ICF)

4.2. Exclusion Criteria

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

General exclusion criteria:

1. History of more than 4 spine fractures, mild or moderate, or any severe fractures based on Genant Semi-quantitative Scoring method on radiographic findings
2. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal BMD, defined as having at least 2 radiologically-evaluable vertebrae within L1–L4 as assessed by the central imaging review of the DXA images

   Anatomically abnormal vertebrae are excluded if:

   - They are clearly abnormal and non-assessable within the resolution of the system; or

- There is a more than 1.0 T-score difference between the vertebra in question and adjacent vertebrae

3. Unevaluable hip BMD or subjects who have undergone bilateral hip replacement (unilateral hip replacement is acceptable)
4. History of bone disorders (eg, Paget's disease) other than postmenopausal osteoporosis
5. History of prior external beam or implant radiation therapy involving the skeleton, other than radioiodine
6. History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism, or malabsorptive syndromes within the past year
7. 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/minute
8. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin)
9. History of osteosarcoma at any time
10. Hereditary disorders predisposing to osteosarcoma
11. History of nephrolithiasis or urolithiasis within the past 5 years
12. Decrease of 20 mmHg or more in systolic blood pressure or 10 mmHg or more in diastolic blood pressure from supine to standing (5 minutes laying and 3 minutes standing) or any symptomatic hypotension at Screening
13. Application site is compromised by scars, inflammation, or skin conditions that may compromise uniformity of patch application or drug delivery (nevi, plaques, tattoos, scars, piercing, etc)
14. Any other medical condition, that, in the opinion of the Investigator, renders the subject unable or unlikely to complete the study, would interfere with the interpretation of study data, or produce significant risk to the subject

Medication-related exclusion criteria:

15. Known history of hypersensitivity to any of the test materials or related compounds
16. Prior treatment with PTH- or PTHrP-derived drugs or bone anabolic drugs including abaloparatide, teriparatide, or PTH (1-84)
17. Prior treatment with intravenous bisphosphonates at any time or oral bisphosphonates within the past 3 years. 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
18. Prior treatment with selective estrogen receptor modulators (such as raloxifene or tamoxifen) in the past 6 months. Estrogens administered as hormone replacement therapy, with or without progestins, are not exclusionary

19. Treatment with fluoride or strontium in the past 5 years or prior treatment with gallium nitrate or bone-acting investigational agents at any time
20. Prior treatment with calcitonin or tibolone in the past 6 months
21. Treatment with denosumab within the past 18 months
22. 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
23. Treated with anabolic steroids or calcineurin inhibitors (cyclosporin, tacrolimus) in the past 90 days
24. Daily treatment with corticosteroids within the 12 months prior to the Screening Period. Occasional use of low dose 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
25. Participation in another clinical trial with any investigational drug or device within 90 days or 5 half-lives of the investigational drug (if known), whichever is longer, of study drug administration

Lifestyle-related exclusion criteria:

26. Abnormal nutritional status as assessed by the Investigator, vitamin D intake of ≥ 4,000 IU/day, or vitamin A intake of ≥ 10,000 IU/day. Short-term use of high doses of vitamin D to bolster endogenous vitamin D levels for study entry during the Screening Period is not exclusionary
27. 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.

Subjects who withdraw consent prior to being randomized into the study will be recorded as having failed the eligibility criterion for study consent (signed ICF is no longer valid at the time of randomization).

The Investigator may consider terminating study drug and/or discontinuing subjects from the study for the following reasons:

- Continuing significant deterioration from baseline (≥7%) of BMD at spine or hip (after confirmation of the finding)

- Hypercalcemia, hypercalciuria, or excessive skin reactions as described in Section 4.7
- Severe hypersensitivity to abaloparatide or test materials
- Refusal of treatment
- Inability to complete study procedures
- Lost to follow-up
- SAEs (as described in Section 7.1.2)
- A complex of AEs or laboratory abnormalities which, in the judgment of the Investigator, justifies treatment cessation
- Serious intercurrent illness
- Noncompliance
- Protocol deviations
- Administrative reasons
- Incident vertebral or nonvertebral 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 is to be recorded in the source documents and on the eCRF. All subjects withdrawn prior to completing 12 months of study drug treatment should be encouraged to complete study procedures scheduled for the Month 12/End of Treatment (EOT) visit as soon as possible, and to return in 1 month for a Follow-up visit (EOS Visit). All AEs should be followed as described in Section 7. Subjects who discontinue prematurely or are withdrawn from the study will not be replaced. For early terminations that occur on or after the day of study drug initiation, every effort should be made to document the subject's outcome, regardless of cause. Whenever a subject is discontinued prematurely, the Sponsor's 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, according to 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, which are part of the study drug protocol, should be adhered to and not be changed other than for medical necessity (Section 4.7). The supplements should be taken in the evening with or without food or as otherwise 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 study entry and every effort should be made to maintain a stable dose during study participation.

The occasional use of over-the-counter medications at approved doses (eg, ibuprofen or acetaminophen) for headache or minor discomfort is allowed. Subjects should not take any other medications, including over-the-counter medications, herbal medications, or mega-doses of vitamins during the study, without prior approval of the Investigator.

If it becomes necessary for a subject to take any other medication during the study, the specific medication(s) and indication(s) must be discussed with the Investigator. All concomitant medications taken during the 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 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) or Independent Ethics Committee (IEC) and will provide the reason(s) for the termination or suspension.

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

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

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

4.7. Temporary Suspension of Treatment

The Investigator has the right to suspend treatment with study drug for up to 14 continuous days. Subjects can miss up to 28 cumulative days of dosing without withdrawal of the subject from the study. Reasons for temporary suspension of treatment may include a medical reason unrelated to an AE (eg, a planned procedure) or important social or administrative events. The reason for the suspension of treatment is to be documented and source verified during monitoring visits.

When treatment is restarted, the subject should resume treatment with the next scheduled dose and continue until the scheduled EOT.

Subjects who develop hypercalcemia or hypercalciuria during the study are to have treatment with calcium and vitamin D temporarily suspended as described below. The Investigator should contact the sponsor for any planned suspension of treatment or if suspension of treatment is contemplated.

4.7.1. Treatment Algorithm in Subjects who Develop Hypercalcemia

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

For any predose serum calcium (albumin-corrected) value which is ≥ 0.3 to 1.0 mg/dL, corresponding to ≥ 0.08 to 0.25 mmol/L, above the ULN (inclusive), confirm hypercalcemia by drawing a new serum sample as soon as possible after the result is received (Figure 2).

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

Treatment can be restarted if other causes of hypercalcemia are excluded after consultation with the Sponsor. Treatment with study drug should not be suspended for greater than 14 days. If the subject continues in the study (with calcium and vitamin D supplements) and has a repeat episode of a predose serum calcium (albumin-corrected) value ≥ 0.3 to 1.0 mg/dL (corresponding to ≥ 0.08 to 0.25 mmol/L) above the ULN, repeat testing of the predose serum calcium (albumin-corrected).

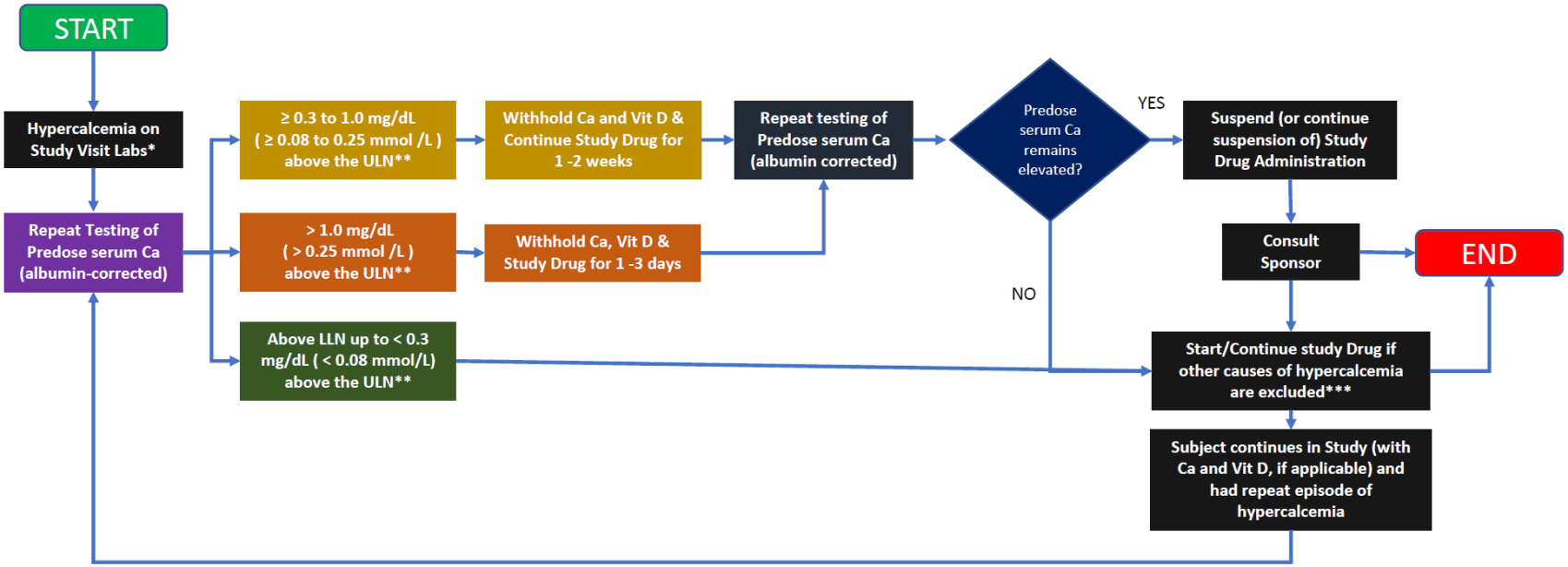
- If the subject's serum calcium (albumin-corrected) value again returns to normal when not taking calcium and vitamin D supplements, the subject may continue in the study without calcium and vitamin D supplements.

- If the retest is still elevated, contact the Sponsor's medical monitor to assess whether the subject is to be discontinued from the study.

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

- Discontinue calcium and vitamin D supplements and discontinue the study drug as soon as the result is received. Confirm hypercalcemia by drawing a new serum sample as soon as possible.
- If the result of the retest remains >1.0 mg/dL above ULN, perform a second retest after 3 days without calcium and vitamin D supplements and study drug.
  - If the second retest is normal, the subject may continue in the study and resume study drug, including the calcium and vitamin D supplements.
  - If the second retest is still elevated, contact the sponsor medical monitor to assess whether the subject is to be discontinued from the study.
- If the subject continues in the study and has a repeat episode of serum calcium >1.0 mg/dL above ULN, contact the Sponsor's medical monitor to assess whether the subject is to be discontinued from the study.

Figure 2: Treatment Algorithm in Subjects who Develop Hypercalcemia



* For any predose serum calcium (albumin-corrected) >1.0 mg/dL (>0.25 mmol/L) above the upper limit of normal (ULN), immediately discontinue calcium, vitamin D, and study drug

** ULN, lower limit of normal (LLN), and normal ranges are determined per the central laboratory

*** If applicable, also consider restarting/continuing vitamin D and calcium supplementation after consultation with the Sponsor

4.7.2. Treatment Algorithm in Subjects who Develop Hypercalciuria

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

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

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

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

4.7.3. Treatment Algorithm for Subjects who develop Excessive Skin Irritation

Excessive skin irritation is defined as any severe assessment of irritation signs (Section 6.6.3.1) or symptoms (Section 6.6.3.2) on the 4-point scale or any lesions in the skin AESI as assessed by the Investigator (ie, eschar, ulcer ,or non-healing wound). Per the Investigator's discretion, the subject may be temporarily discontinued from study therapy. The Investigator should practice clinical judgment when determining when to resume study therapy (ie, resolution of excessive skin irritation). If sensitization is suspected, the Investigator should contact the Sponsor for further instructions and evaluation.

5. STUDY DRUG ADMINISTRATION AND MANAGEMENT

In this study, study drug administration is defined as abaloparatide-sMTS application or abaloparatide-SC injection.

5.1. Study Drugs

All study drugs are for investigational use only and are to be used only within the context of this study; administration of treatment is to be carried out as described in Section 5.4. Abaloparatide-sMTS patches and abaloparatide-SC cartridges for administration of study drugs will be supplied to the study site by the Sponsor.

5.1.1. Abaloparatide-sMTS

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

5.1.2. Abaloparatide-SC

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

5.1.3. Calcium and Vitamin D Supplements

Calcium and vitamin D supplements will be sourced locally by the site and provided to the subjects at the expense of the Sponsor.

5.2. Medical Devices

The medical devices provided for use in this study include an abaloparatide prefilled pen for SC injection and an abaloparatide-sMTS for transdermal administration. The instructions for use of these medical devices are provided in the Pharmacy Manual and also included with the study drug.

5.2.1. Abaloparatide-sMTS

Abaloparatide-sMTS is a drug device combination product consisting of the drug (abaloparatide:$ZnCl_2$ in 1:2:2 molar ratio, HCl < 0.1%) coated onto the sMTS array and contained within the following packaging system:

- The primary packaging components with delivery functions include:
  - An array patch for adhering the drug formulation-coated sMTS array to the skin
  - A tray that holds and protects the coated array patch and inserts it into an applicator
- The primary packaging components with protective functions include:
  - 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 (ie, 5-minutes).

5.2.2. Abaloparatide-SC

Abaloparatide-SC is supplied in a single-patient-use prefilled pen that delivers 80 μg of abaloparatide as an SC injection into the periumbilical region of the abdomen and is marketed in the US as TYMLOS®.

5.3. Packaging, Labeling, and Storage

5.3.1. Packaging and Labeling

Abaloparatide-sMTS arrays and abaloparatide-SC cartridges will be supplied separately to the study site by the Sponsor. Abaloparatide-sMTS applicators for transdermal application and abaloparatide pens for SC injection will also be supplied. All packaging operations will be performed in accordance with Good Manufacturing Practices.

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

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

5.3.2. Storage

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

5.3.2.1. Abaloparatide-sMTS

Prior to study drug being dispensed to a subject, abaloparatide-sMTS must be kept in a secure, limited-access storage area at 2° to 8°C (36° to 46°F).

Subjects should remove abaloparatide-sMTS from refrigerated storage approximately 1 hour prior to administration. Abaloparatide-sMTS patches used during the study site visits will be carefully placed in a supplied container using minimal manipulation and will be frozen for returning to the manufacturer for further inspection and analysis together with residual drug swabs. Refer to the Pharmacy Manual for additional details.

5.3.2.2. Abaloparatide-SC

Prior to study drug being dispensed to a subject, abaloparatide-SC must be kept in a secure, limited-access storage area at 2° to 8°C (36° to 46°F).

After the abaloparatide-SC injection pen is used for the first time, the pen may be stored for 30 days at room temperature, 20°C to 25°C (68°F to 77°F). Unused pens should be refrigerated until initial use. Additional instructions will be provided to sites in the Pharmacy Manual.

5.4. Study Drug Administration

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

5.4.1. Abaloparatide-sMTS

Prior to the administration of abaloparatide-sMTS, the application site will be prepped, cleaned with an alcohol wipe, left to air dry for a couple of minutes, and examined in order to assure that the area is not compromised.

Before loading the abaloparatide-sMTS into the patch holder of the applicator, the subjects should check the abaloparatide-sMTS patch for any damages. If damaged, the abaloparatide-sMTS patch should be replaced with a new one. In addition, subjects should also be instructed to place the damaged abaloparatide-sMTS in a container that was provided and to bring this together with any used and unused patches at the next site visit. Please refer to the Pharmacy Manual for further details.

5.4.2. Abaloparatide-SC

Before use of abaloparatide-SC, subjects will perform a priming procedure after loading a new cartridge into the pen. Instructions for this procedure will be provided in a Pharmacy Manual. The contents of the medication cartridge will be inspected before each injection. If the cartridge contents are not clear and not colorless or if the cartridge contains visible particles, that cartridge will not be used and a new cartridge will be chosen.

5.5. Treatment Assignment

All subjects who sign informed consent for the study will be assigned a unique 6-digit subject ID which will be used to identify subjects throughout the study and on the eCRFs. [redacted]

[redacted]

Subjects who met the study's eligibility criteria and have successfully completed the Screening and Pretreatment Periods, will be assigned sequentially to a randomized treatment group on Day 1 of the Treatment Period. Subjects will only receive 1 subject ID at the time of screening and therefore, will not receive a new identifier at randomization.

Prior to study start, the Sponsor's statistician will be responsible for overseeing the preparation of the master randomization scheme that will be used to package study drug into kits and for the Interactive Response Technology (IRT).

5.6. Dosing and Administration

On Day 1, subjects will be trained by study personnel how to self-administer study drug with the abaloparatide-SC injection pen or the abaloparatide-sMTS applicator. If a subject requires assistance with study drug administration, an individual (eg, primary caregiver) who has been trained by study personnel may provide such assistance. Subjects are to be instructed to self-administer at home in a location where they have the ability to sit or lie down.

Subjects will self-administer a single daily dose of 80 µg of abaloparatide-SC or 300 µg of abaloparatide-sMTS during the Treatment Period beginning on Day 1 and until Month 12 or the EOT visit.

The first self-administration of abaloparatide-sMTS or abaloparatide-SC will occur at the study site on Day 1 under observation. On the days of study site visits, study drug **must be administered at the study site** to accommodate pre-administration and post-administration procedures.

The subject should self-administer study drug while in a sitting or lying position. The subject should remain in that position for approximately 5 minutes.

At any visit during which study drug is administered, the subject is to remain under observation for a minimum of 60 minutes. When scheduled (see Table 1), an orthostatic blood pressure measurement will be taken 60 minutes after administration. On the days when blood sampling is required after study drug administration, the subject is to remain in the vicinity of the study site for the blood collections scheduled up to 4 hours after study drug administration.

Subjects will also be provided with written instructions on how to use abaloparatide-SC and abaloparatide-sMTS. Study drug should be administered at approximately the same time each day; morning administration is suggested. If a dose is missed, the dose should be administered as soon as possible up to 12 hours after the missed dose schedule. Anytime thereafter, the dose should be skipped and study drug should be administered at the next scheduled time on the following day.

All abaloparatide-SC doses are to be given in the periumbilical region, rotating the site of injection each day. All abaloparatide-sMTS doses are to be applied on the thigh for 5 minutes. If it is deemed medically necessary for the study drug to be administered at an anatomic site other than what is required per protocol, the alternate site of study drug application/injection is to be recorded and the reason for change documented in the medical chart in the source documents as a protocol deviation.

Subjects will be dispensed abaloparatide-SC pens each month and will be instructed to use a new abaloparatide-SC injection pen after each 30-day period. A new set of abaloparatide-sMTS patches will be provided after each 30-day period. At each study site visit during the Treatment Period, the used and unused abaloparatide-SC injection pens and sMTS patches should be returned. All returned study drug should either be destroyed at the study site following that site's local procedures or sent to a depot identified by the Sponsor.

5.7. Treatment Compliance

To ensure treatment compliance, the Investigator or designee will supervise all study drug administration that occurs at the site. At each study visit, the Investigator or designee will review subject compliance with study drug administration and remind the subject of study drug dosing requirements.

For abaloparatide-SC, subject compliance will be ascertained by using the data entered on the subject diaries and the measurement of residual volume of study drug in the cartridge.

Similarly, subject compliance for abaloparatide-sMTS will be ascertained by using the data entered on the subject diaries and total used and unused patches returned at each study visit.

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

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the Investigator should contact the Sponsor's medical monitor to discuss possible discontinuation of the subject from the study.

5.8. Drug Accountability

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

- Abaloparatide-sMTS patches/abaloparatide-SC pens received
- Abaloparatide-sMTS patches/abaloparatide-SC pens dispensed to the subjects
- Abaloparatide-sMTS patches/abaloparatide-SC pens returned by the subjects
- Abaloparatide-sMTS patches/abaloparatide-SC pens returned to Sponsor/designee or destroyed at the site

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

6. STUDY PROCEDURES AND SCHEDULE

6.1. Study Procedures

6.1.1. Study-Specific Procedures

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

6.2. Study Schedule

Study assessments are to be performed according to the Schedule of Events (Table 1). There is a ± 4-day window for each study site visit.

The study will consist of a Screening Period (up to 2 months), a Pretreatment Period (1 week), a Treatment Period (12 months), and a post treatment Follow-Up Period (1 month). For the purpose of this study, 1 month is equal to 30 days.

During the Treatment Period, subjects will self-administer study drug once a day for 12 months and visit the study site as follows:

- Study drug administration, study procedures, and assessments: Day 1, Day 14, Month 1, Month 3, Month 6, Month 9, and Month 12
- Study drug administration and assessments: Month 2, Month 4, Month 5, Month 7, Month 8, Month 10, and Month 11

6.2.1. Schedule of Assessments and Procedures

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

Table 1: Schedule of Assessments and Procedures

Procedure / *Visit*	*Study Day/ Month (Mo.):*	1 Screen	2 Pre-TX	3 Day 1	4 Day 14	5 Mo. 1	6 Mo. 2	7 Mo. 3	8 Mo. 4	9 Mo. 5	10 Mo. 6	11 Mo. 7	12 Mo. 8	13 Mo. 9	14 Mo. 10	15 Mo. 11	16 Mo. 12/ EOT	17 Follow-up/ EOS[21]
Visit Window (Days)		N/A	N/A	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4
Duration		Up to 2 mo.	1 week	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Informed consent		X																
Verification of entry criteria		X	X															
Physical examination[1]		X																
Review of medical history[2]		X																
Symptom-directed physical examination			X	X		X		X			X			X			X	X
Vital signs[3]		X	X	X		X		X			X			X			X	X
Weight measurement		X		X		X					X						X	
Height measurement[4]		X	X	X		X		X			X			X			X	X
Electrocardiogram[5]		X		X													X	X
Urinalysis (dipstick)[6]		X		X		X					X						X	
Chemistry blood collection[7]		X		X		X					X						X	
Hematology blood collection[7]		X		X		X					X						X	
Coagulation (PT and PTT) blood collection[7]		X															X	
PTH(1–84) [7]		X															X	
25-hydroxyvitamin D level[7]		X															X	
1,25-dihydroxyvitamin D level				X													X	
Estradiol, FSH		X																
Thyroid stimulating hormone[8]		X																
Study drug assignment via IRT				X														
Subject training for study drug administration				X														

Procedure	*Visit*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Study Day/ Month (Mo.):	Screen	Pre-TX	Day 1	Day 14	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo. 5	Mo. 6	Mo. 7	Mo. 8	Mo. 9	Mo. 10	Mo. 11	Mo. 12/ EOT	Follow -up/ EOS[21]
Visit Window (Days)		N/A	N/A	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4
Duration		Up to 2 mo.	1 week	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Calcium and vitamin D supplements			← Daily Administration →															
Study Drug administration				← Daily Administration →														
Serum markers of bone metabolism (s-PINP and s-CTX)				X		X		X			X						X	
Lumbar and thoracic spine radiographs[9]		X																
Serum calcium and albumin[10]		X		X		X		X			X			X				
24-hour urine collection (for calcium:creatinine and creatinine clearance)[11]				X				X										
Symptom-driven spinal radiologic assessment			← At any Time →															
Clinical assessment of new fractures[12]			X	X		X		X			X			X			X	
BMD of lumbar spine, total hip and femoral neck by DXA[13]		X						X			X						X	
ADA testing[14]				X	X	X		X			X			X			X	X
Assessment of local tolerance[15]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of patch adhesion[16]				← Daily Assessment →														
Subject diary review[17]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Document AEs and concomitant medication[18]		← At Any Time, Question Subjects at Every Visit →																
Dispense study drug				X		X	X	X	X	X	X	X	X	X	X	X		
Sparse PK sampling[19]				X	X	X		X			X			X				

Procedure	*Visit*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	Study Day/ Month (Mo.):	Screen	Pre-TX	Day 1	Day 14	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo. 5	Mo. 6	Mo. 7	Mo. 8	Mo. 9	Mo. 10	Mo. 11	Mo. 12/ EOT	Follow -up/ EOS[21]
Visit Window (Days)		N/A	N/A	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4
Duration		Up to 2 mo.	1 week	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Collect used patch and swab for abaloparatide-sMTS[20]				X	X	X		X			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 in 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 study drug administration at each study visit. All blood pressure assessments will be orthostatic.
4. Height is to be measured in the standing position using a medical stadiometer.
5. ECGs are to be performed predose and also at 1 hour after study drug administration on Day 1 and Month 12.
6. All routine urinalysis will be performed on a sample freshly voided during the visit and sent to a central lab for microscopy if test is positive for micro-organisms via dipstick.
7. Screening labs may be analyzed either at a local laboratory or sent to the central laboratory; central laboratory testing must be performed at all other study visits. Blood draws to be done prior to dosing during the treatment period.
8. Any subject with a TSH value outside of the normal range may have T3 and free T4 tested, with results within the normal range in order to be enrolled.
9. X-ray results will be evaluated by a qualified evaluator at the site, with prevalent fractures assessed using the Genant-semiquantitative scoring method.
10. Serum calcium and albumin will be measured predose from the standard chemistry panel on Screening, Day 1, Month 1 and Month 6 and from a separate blood draw predose at Month 3 and Month 9 and at 4 hours postdose at Month 1. Albumin corrected serum calcium will be reported using the serum calcium and albumin results on the following visits: Screening, Day 1, Month 1, Month 3, Month 6 and Month 9.
11. A 24-hour urine collection will be collected at Day 1 and Month 3 and will be used for urinary calcium and urinary creatinine measurements. Subjects will discard the 1st void and begin a 24-hour urine collection on the day prior to the study site visit.
12. Spine radiographs at screening will be assessed locally. If the subject reports that a fracture has occurred, remind the subject to bring X-rays and any medical reports of the fracture to the next study site visit. Documentation must be obtained on all new fractures that occur during the study. This documentation should be maintained in the source documents.
13. Each DXA for a given subject should be performed on the same machine, and if available, preferably by the same technician and will be assessed by a central imaging laboratory. For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken up to 35 days prior to the beginning of the Screening Period may be used to enroll a subject in the study if the BMD T-score criteria in Section 6.2.5 are met.
14. Samples for ADA will be drawn prior to treatment on Day 1, Day 14, Month 1, Month 3, Month 6, Month 9, Month 12/EOT, and 1 month following the last dose of study drug. All subjects who remain antibody positive will continue to be followed for ADA testing every 6 months until the result is negative.
15. Investigators will perform an assessment of the injection/application site at each study site visit prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1- hour following study drug administration. Signs of local tolerance will be assessed using a 4-point scale described in Section 6.6.3.1. The subject will maintain a diary of their daily assessment of local tolerance; the application/administration site will be evaluated prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration daily from Day 1 to the Month 12/EOT visit. Symptoms of local tolerance will be assessed using a 4-point scale described in Section 6.6.3.2.

16. Patch adhesion will be assessed by the subject immediately prior to abaloparatide-sMTS patch removal each day during the Treatment Period.
17. The subject diary will be reviewed by study personnel at each study visit to ensure subject compliance.
18. AEs and SAEs will be recorded on the eCRF starting from the signing of the informed consent until 30 days after the last dose of study drug. 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.
19. Blood samples for measurement of plasma concentrations of abaloparatide will be taken at Day 1, Day 14, Month 1, Month 3, Month 6, and Month 9. One sample per subject per visit will be collected at 1 of the following varying post-injection/application times: 1 hour to 2 hours (Day 1); 30 minutes to 1 hour (Day 14); 3 hours to 4 hours (Month 1); 2 hours to 3 hours (Month 3); 10 minutes to 30 minutes (Month 6) and predose (Month 9). The date and time of injection/patch application and the date and time of PK blood sample collection will be recorded on the CRF.
20. Used patches from the study site visits (Day 1, Day 14, Months 1, 3, 6, and 9) including the swab used will be placed in separate vials and shipped to 3M.
21. Follow-up/ EOS visit is 1 month (±4 days) after the Month 12/EOT Visit.

ADA = Anti-drug antibody; AE=adverse event; BMD=bone mineral density; DXA=dual energy X-ray absorptiometry; eCRF = Electronic case report form; EOS = End of study; EOT = End of treatment; FSH=follicle-stimulating hormone; IRT=Interactive Response Technology; NA=not applicable; PK = Pharmacokinetic; Pre-TX = Pretreatment; PT=prothrombin time; PTH=parathyroid hormone; PTT=partial thromboplastin time; SAEs = Serious adverse events; s-CTX=serum carboxy-terminal cross-linking telopeptide of type 1; sMTS=solid microstructured transdermal system; s-PINP=serum procollagen type 1 N peptide; TSH = Thyroid stimulating hormone.

6.2.2. Informed Consent Process

Each subject must sign and date a study-specific 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 or IEC, must be used. The Investigator or designee must record the date when the ICF was signed in the subject's source document.

6.2.3. Assigning Subject Numbers

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

6.2.4. Subject and Disease Characteristics

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

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

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

6.2.5. Screening Period (Visit 1)

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

- Physical examination
- Review of medical history, including alcohol, tobacco, and drug use
- Review of concomitant medications
- Height
- Weight
- ECG
- Orthostatic blood pressure and vital signs
- Lumbar and thoracic spine radiographs (anteroposterior and lateral) assessed locally (the radiology report should be retained as the source document)
- BMD assessments of lumbar spine, total hip, and femoral neck by DXA assessed by a central imaging laboratory
- Laboratory testing of serum chemistry, hematology, coagulation, and urine dipstick
- PTH and 25-hydroxyvitamin D level
- Estradiol, FSH, and TSH level

For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken up to 35 days prior to the beginning of the Screening Period may be used to enroll a subject in the study if the following criteria for BMD T-score based on the female reference range are met:

a. Less than or equal to -2.5 and greater than -5.0 at the lumbar spine (L1–L4) or hip (femoral neck or total hip) by dual energy X-ray absorptiometry (DXA) and
    i. Radiological evidence of 2 or more mild or 1 or more moderate lumbar or thoracic vertebral fractures, or
    ii. History of fragility fracture to the forearm, humerus, sacrum, pelvis, hip, femur, or tibia within the past 5 years
b. Postmenopausal women older than 65 years who meet the fracture criteria (i or ii) but have a T-score of ≤ -2.0 and > -5.0 may be enrolled
c. Postmenopausal women older than 65 years who do NOT meet the fracture criteria may be enrolled if they have a BMD T-score ≤ -3.0 and >-5 at the lumbar spine (L1-L4) or hip (femoral neck or total hip) by DXA

Screening labs may be performed either at a local laboratory or the central laboratory. Subjects who do not meet the 25-hydroxyvitamin D entry criterion (25-hydroxyvitamin D is less than 20 ng/mL) may receive vitamin D supplementation and be retested once during the Screening Period. Any subject with a TSH value outside of the normal range may be enrolled if their T3 and free T4 values are within the normal range. Subjects whose other 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 for the out of range laboratory test. All safety labs should be done within 30 days prior to randomization (Day 1).

All AEs, including SAEs, will be recorded for each subject from the time of signing of the ICF and up to 30 days after the last dose of study drug.

6.2.6. Pretreatment Period (Visit 2)

Following screening evaluations, eligible subjects will enter the Pretreatment Period of the study to ensure that each subject receives the recommended daily allowance (RDA) of calcium and vitamin D from either food intake and/or calcium and vitamin D supplementation for 7 days. For a subject who is currently taking calcium and vitamin D supplements at the time of screening and where the screening lab results meet eligibility criteria, the Principal Investigator should exercise his/her clinical discretion to assess if the RDA has been met. The time spent on calcium and vitamin D supplementation prior to Screening may apply towards the required 7-day duration of the Pretreatment Period.

All subjects will be provided calcium and vitamin D supplements to ensure that their daily intake is 1,200 mg/day and 800 IU/day, respectively (or doses determined by the Investigator and agreed by the Sponsor's Medical Monitor, according to the subject's need). Calcium and vitamin D supplementation will continue until the end of the Treatment Period.

After verification of entry criteria, AEs and concomitant medications will be recorded and the following procedures will be performed:

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

6.2.7. Treatment Period

Subjects who remain eligible for study participation will be randomly allocated to a treatment group through the IRT, using a 1:1 randomization ratio on Day 1 to receive treatment with either abaloparatide-SC 80 µg per day or daily 300 µg abaloparatide-sMTS administration. During the Treatment Period, subjects will self-administer a single dose of study drug once a day. Subjects will also take calcium and vitamin D each day during the Treatment Period, as directed by the Investigator.

Subjects will be randomized on Day 1 of the Treatment Period. During the Treatment Period, subjects will self-administer study drug once a day for 12 months and visit the study site as shown in Table 1.

At each study site visit during this period, as indicated in Table 1, recent health status will be obtained, the diary reviewed, AEs collected, and orthostatic blood pressure and vital signs performed. Laboratory assessments of chemistry, hematology, and urinalysis will be obtained at Day 1, Month 1, Month 6, and Month 12 and a 24-hour urine collection will start on the day prior to Day 1 and on the day prior to the Month 3 visit. Clinical assessments for fracture will be performed at the pretreatment visit and at Day 1 and Months 1, 3, 6, 9, and 12. Source documentation (imaging report and/or film along with other supporting documentation as appropriate) will be collected from each site to confirm fracture.

Subjects will have BMD assessed by DXA at the lumbar spine, total hip, and femoral neck at Screening and Months 3, 6, and 12. All DXA assessments will be performed by a central imaging laboratory. Bone turnover marker assessments (s-PINP and s-CTX) will be performed on Day 1 and Months 1, 3, 6, and 12.

6.2.7.1. Visit 3 (Day 1)

- 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 study site visit
- Symptom-driven physical exam, including assessment for potential vertebral fracture
- Collect sample for ADA testing (predose)
- ECG (predose and 1 hour after study drug administration)
- Orthostatic blood pressure and vital signs
- Height
- Weight
- Laboratory testing of serum chemistry, hematology, and urine dipstick
- Serum calcium and albumin (taken predose as part of serum chemistry)
- 1-25 dihydroxyvitamin D
- Dispense study drug
- PK draw between >1 hour to 2 hours after study drug administration
- Clinical assessment of new fractures
- AE and concomitant medication review
- Bone turnover markers (s-PINP and s-CTX)
- Randomization and study drug (abaloparatide-SC or abaloparatide-sMTS) will be assigned through the IRT
- Training for medication self-administration (subjects will be trained on both routes of administration)

- First dose of study drug will be administered by the subject in clinic
- Investigator assessment of signs of local tolerance prior to application of study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour following study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Collection of used abaloparatide-sMTS and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.2. Visit 4 (Day 14)

- AE and concomitant medication review
- Self-administer study drug
- Collect sample for ADA testing (predose)
- PK draw between >30 minutes and 1 hour after study drug administration
- Review subject diary
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance, in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Collection of used abaloparatide-sMTS and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.3. Visit 5 (Month 1)

- Symptom-driven physical exam, including assessment for potential vertebral fracture
- Orthostatic blood pressure and vital signs
- Height
- Weight
- Laboratory testing of serum chemistry, hematology, and urine dipstick
- Dispense study drug
- Self-administration of study drug
- Collect sample for ADA testing (predose)
- Serum calcium and albumin (taken predose as part of serum chemistry and 4 hours after study drug administration)
- PK draw between >3 hours to 4 hours after study drug administration
- Clinical assessment of new fractures

- AE and concomitant medication review
- Bone turnover markers (s-PINP and s-CTX)
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Review subject diary
- Collection of used abaloparatide-sMTS and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.4. Visit 6 (Month 2)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Provide subject with supplies for collecting a 24-hour urine sample (the sample is to be collected on the day prior to the Month 3 visit)

6.2.7.5. Visit 7 (Month 3)

- A 24-hour urine sample will be collected. Subject will discard the 1st void and begin a 24-hour urine collection on the day prior to the study site visit
- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Orthostatic blood pressure and vital signs
- Height
- BMD assessments of lumbar spine, total hip, and femoral neck by DXA
- Bone turnover markers (s-PINP and s-CTX)
- Collect sample for ADA testing (predose)
- Dispense study drug
- Self-administration of study drug
- Serum calcium and albumin (predose)

- PK draw between >2 hours to 3 hours after study drug administration
- Clinical assessment of new fractures
- AE and concomitant medication review
- Review subject diary
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Collection of used abaloparatide-sMTS patch and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.6. Visit 8 (Month 4)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.7. Visit 9 (Month 5)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.8. Visit 10 (Month 6)

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Height
- Weight
- Orthostatic blood pressure and vital signs
- Dispense study drug
- Self-administration of study drug
- Laboratory testing of serum chemistry, hematology, and urine dipstick
- Serum calcium and albumin (taken predose as part of serum chemistry)
- PK draw between 10 minutes to 30 minutes after study drug administration
- BMD assessments of lumbar spine, total hip, and femoral neck by DXA
- Bone turnover markers (s-PINP and s-CTX)
- Collect sample for ADA testing (predose)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Review subject diary
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Collection of used abaloparatide-sMTS patch and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.9. Visit 11 (Month 7)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.10. Visit 12 (Month 8)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.11. Visit 13 (Month 9)

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Orthostatic blood pressure and vital signs
- Height
- Dispense study drug
- Self-administration of study drug
- Serum albumin (predose)
- PK draw predose
- Collect sample for ADA testing (predose)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Review subject diary
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal
- Collection of used abaloparatide-sMTS patch and swab for residual drug testing (for subjects randomized to the abaloparatide-sMTS treatment arm)

6.2.7.12. Visit 14 (Month 10)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug

- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.13. Visit 15 (Month 11)

- AE and concomitant medication review
- Review subject diary
- Dispense study drug
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration
- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Instruct subject on completion of diary, including daily assessment of local tolerance in between visits
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.7.14. Visit 16 (Month 12)/EOT Visit

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Collect sample for ADA testing
- ECG (predose and 1 hour after study drug administration)
- Weight
- Height
- Orthostatic blood pressure and vital signs
- PTH, 25-hydroxy vitamin D, and 1,25-dihydroxyvitamin D level
- Laboratory testing of serum biochemistry, hematology, coagulation and urine dipstick
- BMD assessments of lumbar spine, total hip, and femoral neck by DXA
- Bone turnover markers (s-PINP and s-CTX)
- Clinical assessment of new fractures
- AE and concomitant medication review
- Review subject diary
- Self-administration of study drug
- Investigator assessment of signs of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and at 1 hour after study drug administration

- Subject assessment of symptoms of local tolerance prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration
- Subject assessment of patch adhesion (if applicable) immediately prior to patch removal

6.2.8. Visit 17/Safety Follow-up/EOS Visit

- Symptom-directed physical examination, including assessment for potential vertebral fracture
- Record vital signs
- Height
- ECG
- Collect sample for ADA testing. Any subject who show presence of antibodies at EOT will be retested at 6-month intervals post study until antibody status return to negative
- AE and concomitant medication review

6.2.9. Unscheduled Visit

If the subject returns to the study site 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 complete physical examination (review of all body systems), height, weight, and vital signs assessment will be performed at Screening.

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

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

Vital signs include orthostatic blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiratory rate. These will be assessed at the time points indicated in Table 1 following a 5-minute rest (seated or supine) and before blood sample collection. At visits when study drug is administered at the site, vital sign assessments will be collected before the dose of study drug; blood pressure will be measured both supine and standing.

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 1 hour after study drug administration on Day 1 and at Month 12; additional ECGs will be collected at screening and at follow-up.

Additional ECGs may be performed as clinically indicated and reported as an AE if results show clinical significance as assessed by the Investigator.

6.5. Laboratory Evaluations

6.5.1. Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be collected at time points indicated in the Schedule of Assessments and Procedures in Table 1. Screening labs may be analyzed by either a local laboratory or by the central laboratory; all subsequent laboratory tests will be sent to a central laboratory for analysis and testing. A list of study clinical laboratory tests is in Table 2.

Table 2: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (dipstick)	Additional Tests
Hemoglobin	Sodium	pH	PTH (1–84)
Hematocrit	Potassium	Glucose	25-hydroxyvitamin D 1,25-dihydroxy vitamin D
WBC count with differential in absolute counts	Chloride	Protein	Estradiol, FSH, TSH, T3, and free T4
RBC count	Inorganic phosphorus	Ketones	Bone-specific alkaline phosphatase[d]
MCV	Albumin	Bilirubin	
MCHC	Total protein	Blood	
MCH	Glucose	Urobilinogen	
Platelet count	BUN	Specific gravity	
Coagulation (PT and PTT)	Creatinine	Nitrite	
	Uric acid	Leukocytes	
	AST		
	ALT		
	GGT		
	CPK		
	Alkaline phosphatase		
	Total bilirubin		
	LDH		
	Total cholesterol		
	Triglycerides		
	Total calcium		

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CPK = Creatine phosphokinase; FSH = Follicle-stimulating hormone; GGT = Gamma-glutamyltranspeptidase; LDH = Lactate dehydrogenase; MCH = Mean corpuscular hemoglobin; MCHC = Mean corpuscular hemoglobin concentration; MCV = Mean corpuscular volume; PT = Prothombin time; PTH = Parathyroid hormone; PTT = Partial thromboplastin time; RBC = Red blood cell; TSH = Thyroid stimulating hormone; WBC = White blood cell.

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

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

6.5.2. Serum Markers of Bone Metabolism

Blood samples will be taken to measure efficacy-related markers of bone metabolism within 1 hour predose at Day 1, Month 1, Month 3, Month 6, and Month 12/EOT. s-PINP and s-CTX will be measured in all subjects.

6.5.3. Anti-Drug Antibody Testing

Serum samples for ADA testing will be collected predose at Day 1, Day 14, Month 1, Month 3, Month 6, Month 9, Month 12, and 30 days following the last dose of study drug. Samples should be taken prior to in-office administration to prevent interference with the ADA assay. Samples will be tested for the presence of binding ADAs, including determination of antibody titer. Any positive samples will be tested for the potential to neutralize abaloparatide in a cell-based assay. Additionally, positive samples will be tested for cross reactivity to endogenous PTH and PTHrP. Any subject who show presences of antibodies at EOT will be retested at 6-month intervals post-study until antibody status returns to negative.

6.5.4. Specimen Preparation, Handling, and Storage

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

6.6. Imaging Procedures

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

6.6.1. Dual Energy X-ray Absorptiometry

All subjects will have areal BMD measurements taken via DXA of the lumbar spine, total hip, and femoral neck at Screening, Month 3, Month 6, and Month 12. Lumbar spine scans must include L1 through L4. Hip scans will include the entire proximal femur to about 2 cm below the lesser trochanter. For hip scans, the same side should be used for all scans at all visits measured. If a subject fractures the hip being examined during the study, no further scans of the hip will be acquired.

For screening purposes, DXA scans of the lumbar spine, total hip, and femoral neck taken up to 35 days prior to the beginning of the Screening Period may be used to enroll a subject in the study if the BMD T score criteria in Section 6.2.5 are met.

6.6.2. Clinical and Radiologic Evaluation of Fractures

All subjects will have X-rays taken to document fractures of the lumbar and thoracic vertebrae at Screening to confirm entry criteria; the X-rays will be read locally. Radiographs of the lateral thoracic and lumbar spine will include coverage of T3 to S1. The lateral spine radiographs will be assessed locally for prevalent and incident vertebral fractures using the Genant Semi-quantitative scoring method (Genant et al, 1993)

- Grade 0: Normal (approximately <20% reduction in anterior, middle, or posterior height)

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

Subjects will be clinically evaluated for vertebral and nonvertebral fractures (wrist, hip, rib, etc.) which occur during the study. Should a clinical fracture occur, X-ray images and reports associated with the fracture must be obtained and maintained in the subject's medical record.

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

6.6.3. Local Tolerance

Assessment of local tolerance will consist of evaluation of signs (Section 6.6.3.1) and symptoms (Section 6.6.3.2) of local skin reactions. If the subject has severe, worsening,s or non-resolving local skin reactions within the past 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. If sensitization is suspected, the Investigator should contact the Sponsor for further instructions and evaluation.

6.6.3.1. 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 during study site visits. At each study site visit, as indicated in Table 1, the application/administration site will be evaluated prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour after study drug administration.

Investigators will assess each of the 12 signs of local skin reaction using a 4-point scale: 0-none, 1-mild, 2-moderate, and 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 should contact the Sponsor for further instructions. If sensitization is suspected, the Investigator should contact the Sponsor for further instructions and evaluation.

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 at Month 12 will continue to be assessed at 24-hour intervals until resolved or stabilized.

Study sites will have access to a dermatology consultant for severe local skin reactions.

Events of ulcer, eschars, and non-healing wounds at the injection/application site will be evaluated as an AESI (ie, skin AESI).

6.6.3.2. Subject Assessment of Symptoms of Local Tolerance

Study subjects will be instructed to perform a daily self-assessment of symptoms of local skin irritation. The application/administration site will be evaluated prior to study drug administration, 5 minutes after study drug administration (ie, immediately after patch removal for subjects receiving abaloparatide-sMTS), and 1 hour following study drug administration beginning on Day 1 up until the scheduled Month 12 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, and 3-severe. To aid in this assessment, a laminated pictograph with morphologic descriptions of the associated application site reactions in the 4-point scale will be provided.

6.6.4. Residual Drug

The clinical site will collect the used abaloparatide-sMTS at the study site visits. The used abaloparatide-sMTS will be placed in a glass vial labelled with the subject ID and study visit (ie, Day 1, Month 1, etc) by the clinical site and then shipped to the manufacture for residual drug evaluation. Upon removal of the abaloparatide-sMTS, the skin surface will be swabbed and the collected swabs will be placed in a separate glass vial labelled with the subject ID and study visit and then shipped by the clinical site to the manufacturer following the same procedure as for the used abaloparatide-sMTS. Please refer to the Pharmacy Manual for additional details.

6.6.5. Assessment of Patch Adhesion

The abaloparatide-sMTS patch is to be assessed by the subject for adhesion every day during the Treatment Period. Adhesion scores will be scored according to the following scoring system:

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)

6.7. Discontinuation from the Study

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

Any subject who demonstrates decreases in BMD ≥7% from baseline of this study at the lumbar spine or total hip will have the assessment repeated and, if confirmed, will be notified by the Investigator and may be withdrawn from the study. Subjects sustaining a radiologically confirmed incident vertebral or nonvertebral fracture will be informed of the finding and will be counseled as to treatment options and may discontinue or choose to remain on the study.

Subjects who decide they do not wish to participate in the study further should be encouraged to return for the assessments indicated for the Month 12/EOT Visit and 1 month later for the Follow-up/EOS Visit in the Schedule of Assessments and Procedures (Table 1). If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, email, and letter) should be made to contact them to obtain final follow-up information.

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/IECs 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 by the sponsor 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 30 days after last dose of investigational product. At any time after 30 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 source documents and the eCRF. The Investigator will assess the relationship of all AEs to the study drug. For information on the safety profile obtained to date for abaloparatide, please refer to the Investigator's Brochure.

7.1.1. Adverse Events

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

AEs could include but are not limited to the following:

- 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. The Application Site Skin Adverse Event form should be completed and sent by the clinical site. Events of ulcer, eschars, and non-healing wounds at the application site will be evaluated as an AESI (Section 7.1.3.1). 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

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 1 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 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. Adverse Events of Special Interest

An AESI is an AE that is designated to be of special medical or scientific interest to the Sponsor. All AEs suspected to be included within the Skin or Hypersensitivity AESIs should be reported promptly, following the reporting procedure for AEs or SAEs as appropriate.

7.1.3.1. Skin Adverse Event of Special Interest

Included in the Skin AESI are abaloparatide-sMTS or abaloparatide-SC administration site skin reactions that are assessed by the local Investigator to be any of the following:

1. Eschars
2. Ulcers
3. Non-healing wounds

A pictograph including a description of the morphologic features of these skin reactions will be provided to aid in this assessment. The clinical site should take serial photographs of these skin reactions until complete resolution. These photographs are to be transmitted by the clinical site through the imaging portal. Refer to the Imaging Manual for further details. In addition, the Application Site Skin AE form should be completed and sent by the clinical site.

Study sites will have access to a dermatology consultant for severe local skin reactions.

7.1.3.2. Hypersensitivity Adverse Event of Special Interest

Included in the Hypersensitivity AESI are AEs experienced following abaloparatide-sMTS or abaloparatide-SC administration, generally occurring as immune-mediated responses. Specific AEs included in the Hypersensitivity AESI will be detailed in the Statistical Analysis Plan (SAP). Investigators should evaluate and treat subjects experiencing an event suspected as a hypersensitivity reaction as appropriate.

7.1.4. Recording an Adverse Event

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

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

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

For both serious and non-serious AEs, the Investigator must determine the intensity of the event and the relationship of the event to study drug administration (abaloparatide-SC and abaloparatide-sMTS). 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.
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 drug 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.

7.1.4.1. 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), 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 serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the abaloparatide-sMTS device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Study Reference Manual, 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 subjects, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. Termination will occur not later than 5 working days after the Investigator and the Sponsor makes this determination and not later than 15 working days after 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.

7.1.4.2. Medical Device Reporting for Abaloparatide-SC

Sites will report medical device reports (MDRs) that reasonably suggest that abaloparatide-SC may have caused or contributed to a death or serious injury or has malfunctioned and the malfunction of the device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur, including events occurring as a result of device failure, malfunction, improper or inadequate design, manufacture, labeling, or user error.

A serious injury is an injury or illness that:

- Is life threatening
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

If the Investigator learns of any MDR after a subject has been discharged from the study, and such incident is reasonably related to abaloparatide-SC, the Investigator will promptly notify RADIUS.

7.1.5. Serious Adverse Event Reporting

Any SAEs that occur during the study from the time the subject signs the ICF until 30 days after the last dose of study drug must be reported within 24 hours of first awareness of the event by entering data in the clinical trial eCRF. SAEs (initial reports and follow-up information) must be

reported by the Investigator using the SAE reporting form; the form must be completed and emailed to PV@radiuspharm.com.

Treatment-related SAEs will be followed until resolution or stabilization. The reference safety information for this study is included in the Investigator's Brochure which will be provided under separate cover to all investigators.

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

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

7.1.6. Device Reporting

Abaloparatide-sMTS and abaloparatide-SC are drug-device combination products. 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 7.1.4.1) and MDR events that occur with abaloparatide-SC (Section 7.1.4.2).

Any UADEs that occur during the study with abaloparatide-sMTS or MDR reportable events with abaloparatide-SC, from the time the subject signs the ICF until 30 days after the last dose of study drug, must be reported within 24 hours of first awareness that the event meets the definition of a reportable incident by entering data in the clinical trial eCRF. Treatment-related UADEs and MDRs will be followed until resolution or stabilization, the condition is otherwise explained, or until the subject is lost to follow-up. SAEs (initial reports and follow-up information) must be reported by the Investigator using the SAE reporting form; the form must be completed and emailed to PV@radiuspharm.com.

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

7.1.7. Follow-up of Adverse Events

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

7.1.8. Abuse, Misuse, Overdose, or Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor whether or not they result in an AE/SAE. Any TEAEs/treatment-emergent SAEs associated with abuse, misuse, overdose, or medication error should be reported as TEAEs or treatment-emergent SAEs as appropriate (Section 7.1.3 and Section 7.1.4).

- Abuse – Persistent or sporadic intentional excessive use of investigational medicinal product which is accompanied by harmful physical or psychological effects
- Misuse – Intentional and inappropriate use of investigational medicinal product other than as directed or indicated at any dose
- Overdose – Intentional or unintentional injection/application of a dose of abaloparatide at least 2 times higher than the protocol-specified dose

- Medication Error – A mistake made in prescribing, dispensing, administration, and/or use of the investigational medicinal product. Cases of subjects missing doses of the study drug are not considered reportable as medication errors.

In the event of an overdose the Investigator should contact the Medical Monitor immediately and closely monitor the subject for TEAEs/treatment-emergent SAEs and laboratory abnormalities. No specific treatment is recommended; the Investigator will use clinical judgment to treat any overdose.

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

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

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

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. The contact may be by phone or email.

7.2. Study Completion and Post-Study Treatment

The Investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study due to an AE 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 the scheduled EOS visit would have occurred.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical and Analytical Plans

A comprehensive SAP and a Pharmacometric Analysis Plan (PAP) will be completed and approved prior to database lock. All statistical tests will be 2-sided with a significance level of 5%, unless otherwise specified.

8.2. Statistical Hypotheses

The objective of this study is to evaluate the non-inferiority of abaloparatide-sMTS 300 µg compared to abaloparatide-SC 80 µg based on lumbar spine BMD at 12 months and to evaluate the safety and tolerability of abaloparatide-sMTS in the treatment of postmenopausal women with osteoporosis.

8.3. Analysis Datasets

8.3.1. Populations for Analyses

Four subject populations will be defined as follows:

- Intention-to-Treat (ITT) Population

  The ITT Population consists of all subjects randomized into this study.

- Modified Intention-to-Treat (mITT) Population

  The mITT Population includes all randomized subjects who received at least 1 dose of study drug and had a baseline lumbar spine BMD measurement and at least 1 post-baseline lumbar spine BMD measurement.

- Safety Population

  The Safety Population consists of all randomized subjects who received at least 1 dose of study drug.

- Per-Protocol (PP) Population

  The PP Population consists of all mITT subjects who did not have any critical protocol deviations. The criteria for the exclusion from the PP population will be defined in the SAP prior to database lock and treatment unblinding.

The mITT population will be the primary population for the analyses of all efficacy endpoints. Supportive analyses will be conducted on the ITT and PP populations. The primary population for all safety analyses will be the Safety population.

8.4. Description of Statistical Methods

8.4.1. General Approach

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

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

8.4.2. Analysis of the Primary Efficacy Endpoint(s)

The primary hypothesis is that the effect of abaloparatide-sMTS 300 µg worn 5 minutes on the thigh on the percent change from baseline in lumbar spine BMD at 12 months is no worse than the effect of abaloparatide-SC 80 µg by a non-inferiority margin of 2.0%. The primary efficacy endpoint will be analyzed using an Mixed-Effect Model Repeated Measures (MMRM) model with fixed effects of treatment, DXA instrument manufacturer, visit, and treatment-by-visit interaction and with baseline lumbar spine BMD as covariate. An unstructured variance-covariance matrix will be used to model the within-subject errors over the visits. The estimated difference (abaloparatide-sMTS minus abaloparatide-SC) and its corresponding 2-sided 95% confidence interval (CI) will be derived from the MMRM model. If the lower bound of the 2-sided 95% CI for the between-group difference in mean percent change from baseline in lumbar spine BMD at 12 months is above -2.0%, non-inferiority of abaloparatide-sMTS to abaloparatide-SC will be concluded.

8.4.3. Analysis of Secondary Endpoint(s)

The secondary efficacy endpoints of percent changes in BMD at the total hip and the femoral neck at 12 months will be evaluated to support the primary endpoint. These endpoints will be analyzed using the same MMRM model used to analyze the primary efficacy endpoint, with the appropriate baseline BMD as covariate. The estimated differences between abaloparatide-sMTS and abaloparatide-SC and their corresponding 95% CIs will be presented.

The additional efficacy endpoints of percent changes in BMD at the lumbar spine, total hip, and femoral neck at 3 and 6 months will be analyzed in a similar fashion as the secondary endpoints.

Plots will be presented for the mean (±standard error [SE]) percent change in BMD of the lumbar spine, total hip, femoral neck over the 12-month Treatment Period.

Analysis of bone turnover markers, s-PINP and s-CTX, will be based on the ratio of the post-baseline value relative to the baseline value. The transformation of the $\log_e$ ratio of post-baseline versus baseline value will be used to normalize the distributions of the s-PINP and s-CTX parameters. The analysis comparing abaloparatide-sMTS with abaloparatide-SC will use a MMRM model similar to the MMRM model for BMD analysis, with the appropriate baseline bone turnover marker value as covariate.

Plots will be presented for the geometric mean (±SE) of the ratio to baseline and mean (±SE) percent change from baseline for s-PINP and s-CTX values over time by treatment group.

Subgroup analyses (eg, age, geography, prior fracture, and baseline BMD) may be performed for the percent change from baseline in BMD at the lumbar spine, the total hip, and the femoral neck.

Percent changes from baseline in BMD (lumbar spine, total hip, and femoral neck) at 12 months will be analyzed by ADA status and treatment group.

Details of analyses will be described in the SAP.

8.4.4. Safety Analyses

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

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

All AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) version 22.0. The number and percent of subjects who experienced TEAEs will be summarized by MedDRA system organ class (SOC), preferred term, and treatment group. Summaries will also be provided for severe TEAEs, severe related TEAEs, serious TEAEs, serious related TEAEs, TEAEs leading to dose interruption, TEAEs leading to study withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and TEAEs by maximum severity (mild, moderate, severe); similar summaries will be provided for the Skin AESI and for Hypersensitivity AESI. A summary will also be provided for the most common (≥ 5% in any treatment group) TEAEs.

TEAEs leading to dose interruption and TEAEs leading to study withdrawal will be summarized. The AE eCRFs collect only information on AEs leading to study drug withdrawal and that will be summarized as stated in the SAP.

All AEs collected prior to the first dose of study drug will be provided in a by-subject listing.

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

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

The serum antibody assessment will be categorized by 3 outcomes: negative, positive for ADAs, or positive for the presence of neutralizing antibodies. The number (%) of subjects in each of these 3 categories will be summarized at Month 12 by treatment group.

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

8.4.5. PK Analysis

A PK analysis will be performed on the sparse plasma concentrations of abaloparatide as described in the PAP.

Blood samples for PK analysis will be collected using a 5 mL K3 EDTA w/ 0.1 mg/mL aprotinin tube at the time points described in the Schedule of Assessments.

8.4.6. Adherence and Retention Analyses

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

8.4.7. Baseline Descriptive Statistics

Medical history, physical examination, demographics, and baseline characteristics will be summarized and presented by treatment group and overall. Medical history will be presented by MedDRA SOC and 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.

8.4.8. Interim Analyses

There are no interim analyses planned for this study.

8.4.9. Additional Subgroup Analyses

Subgroup analysis (eg, age, geography, prior fracture, and baseline BMD) on the primary efficacy endpoint may be performed and will be described in the SAP.

8.4.10. Multiple Comparison/Multiplicity

No adjustments for multiple comparisons will be made.

8.4.11. Tabulation of Individual Response Data

Individual efficacy and safety data will be tabulated as appropriate.

8.4.12. Exploratory Analyses

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

8.5. Sample Size Calculation

The previous pivotal, Phase 3, multicenter, randomized, open-label active- and placebo-controlled study of abaloparatide-SC (Study BA058-05-003) showed that the placebo-adjusted effect of abaloparatide-SC 80 µg on the percent change from baseline in lumbar spine BMD based on a MMRM analysis was 9.096% (95% CI: 8.557%, 9.634%) at 12 months. According to Food and Drug Administration's (FDA) *Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness* (2016), the lower bound of this CI can be considered as the historical treatment effect of abaloparatide-SC versus placebo, M_1 (=8.557%). Based on FDA's recommendation of a clinically meaningful difference of 2.0% between treatment groups, a non-

inferiority margin, M_2, is selected at 2.0% to preserve approximately 77% of M_1, the historical treatment effect of abaloparatide-SC.

This preserved effect supports the superiority to placebo because the amount of preserved effect, 6.557% (=77% * M_1), is larger than the placebo-adjusted effect of alendronate 10 mg daily (5.4%; Fosamax® USPI) and of denosumab 60 mg once every 6 months (5.5%; Bolognese 2013) on lumbar spine BMD at 12 months. Furthermore, the placebo-adjusted effect of teriparatide observed in the previous Phase 3 study (Study BA058-05-003) based on an MMRM analysis was 7.841% (95% CI: 7.384%, 8.297%). Thus, the proposed non-inferiority margin leads to 89% (=6.557/7.384) of the effect of teriparatide, another market-approved anabolic agent.

Non-inferiority of abaloparatide-sMTS to abaloparatide-SC will be concluded if the lower bound of the 2-sided 95% CI for the estimated treatment difference (abaloparatide-sMTS minus abaloparatide-SC) in the percent change from baseline in lumbar spine BMD at 12 months is above -2.0%, using an MMRM analysis.

A sample size of 426 subjects will provide at least 90% power to conclude the non-inferiority of abaloparatide-sMTS 300 µg to abaloparatide-SC 80 µg, assuming a true mean difference of zero percent and a standard deviation of 6.35%. To ensure an analysis size of 426 subjects, an overall sample size of 474 subjects (237 subjects per group) will be randomized, anticipating that approximately 10% of treated subjects may not have both a baseline lumbar spine BMD measurement and at least 1 post-baseline lumbar spine BMD measurement.

8.6. Measures to Minimize Bias

Not applicable.

8.7. Enrollment/Randomization/Masking Procedures

This is an open-label study; thus, subjects and investigators will not be blinded to treatment assignment. However, the central imaging laboratory responsible for measuring BMD will be blinded to treatment assignment throughout the study.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Ethical Considerations

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

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21CFR Part 312, 21 CFR Part 314 and ICH GCP E6.

The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, 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 the Sponsor 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, and 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 the Sponsor 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. The Sponsor 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 the Sponsor's medical monitor to discuss the planned course of action. If possible, contact should be made before the implementation of any changes. Any departures from the 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 the sponsor's quality assurance group, and inspection by the regulatory agencies. The records must also be available for inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The Investigator

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

9.5. Subject and Data Confidentiality

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subject by unique subject ID numbers assigned to each subject. As required by federal regulations, the Investigator will allow the Sponsor 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/electronic health records and the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation, for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act 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 the Sponsor 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 the Sponsor.

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 the Sponsor. These samples could be used for retrospective biomarker research, isotype analysis on anti-drug-antibodies, including analysis of clinical response or 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 the Sponsor.

9.7. Data Quality Assurance

The Sponsor 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. The Sponsor 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 the

Sponsor' designee. External data will be incorporated into Study Data Tabulation Model datasets by the Sponsor' designee for the Sponsor' 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 the Sponsor, 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 the Sponsor, 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

The Sponsor 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 the Sponsor or its designee. Study site monitoring will be done by personal visits from a representative of the Sponsor 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.

Risk-based monitoring will also be done via remote monitoring of the study data to identify trends based on predefined risks for the study. Refer to the Risk-Based Monitoring Plan for further details.

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.

The Sponsor 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 for 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 AE 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 and 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.

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

9.10. Study Records Retention

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

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 the sponsor 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 the Sponsor.

10. LITERATURE REFERENCES

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