CLINICAL STUDY PROTOCOL

A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture

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

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Study Sponsor: Radius Health, Inc. (RADIUS)
201 Broadway, 6th Floor
Cambridge, MA 02139, USA
Tel: 617.551.4700 Fax: 617.551.4701

Sponsor Medical Monitor/Study Safety Officer
Alan Harris, MD
Executive Medical Officer, Radius Health, Inc.
Tel: 617.599.3780. Fax: 617.551.4701.
Email: aharris@radiuspharm.com

Contract Research Organization (CRO):
Nordic Bioscience A/S
Herlev Hovedgade 207
2730 Herlev, Denmark
Tel: +45 4452 5252. Fax: +45 4452 5251

Study Site: Multicenter; international

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## PROTOCOL SYNOPSIS

**Title:** A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture

**Protocol Number:** BA058-05-003

**Phase:** 3

**Test Drug:** Abaloparatide-SC

### Study Objectives:

Please note that the name of BA058 Injection 80 μg has been changed to Abaloparatide-SC, therefore, the name has been changed throughout the document.

The primary objective of this study is to determine the safety and efficacy of Abaloparatide-SC when compared to a matching Placebo for prevention of vertebral fracture in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis. Patients, investigators and independent assessors will be blinded as to treatment for that outcome. The secondary outcomes, also double-blind, of this study are to determine the safety and efficacy of Abaloparatide-SC when compared to Placebo for prevention of non-vertebral fractures and for change in vertical height. Additional key secondary efficacy outcomes include bone mineral density of spine, hip and femoral neck and hypercalcemia when compared to teriparatide (Forteo®, Forsteo®, Eli Lilly and Co.), which will be assessor-blind.

The specific objectives of this study are to:

- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.
- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on lumbar spine, hip, and femoral neck bone mineral density (BMD) in otherwise healthy ambulatory postmenopausal women with severe osteoporosis when compared to teriparatide.
- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of non-vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.
- Determine the overall safety and tolerability of 18 months of treatment with Abaloparatide-SC, and specifically the number of patients with hypercalcemic events, in otherwise healthy ambulatory postmenopausal women with severe osteoporosis when compared to teriparatide and Placebo.
- Provide additional evidence of bone safety through histomorphometric assessment of bone biopsy samples in a randomized subset of patients from the Abaloparatide-SC, Placebo, and teriparatide groups.
- Provide additional evidence of renal safety through radiological assessment by renal CT scan in a subset of patients from selected centers in the Abaloparatide-SC, Placebo, and teriparatide groups.

### Study Population:

#### Inclusion Criteria:

Otherwise healthy ambulatory postmenopausal (≥ 5 years) women from 50 to 85 years of age (inclusive) who meet the study entry criteria and have provided written informed consent are eligible for the study. The women are to have a BMD T-score ≤ -2.5 and > -5.0 at the lumbar spine or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. Postmenopausal women older than 65 who meet the above fracture criteria but have a T-score ≤ -2.0 and > -5.0 may be enrolled. Women older than 65 who do not meet the fracture criteria would be excluded from the study.
criteria may also be enrolled if their T-score is ≤-3.0 and > -5.0.

All patients are to be in good general health as determined by medical history, physical examination (including vital signs) and clinical laboratory testing. Serum calcium, PTH(1-84), serum phosphorus and serum alkaline phosphatase values must be within the normal range during the Screening Period. Serum 25-hydroxy Vitamin D must be above 15 ng/mL and within 3 times the upper normal range to be eligible for enrollment. The resting 12-lead ECG obtained during screening should have no clinically significant abnormality and a QTc (Bazett’s correction) of ≤ 470 msec. Patients with more than four mild or moderate fractures, or any severe fractures, will be excluded from the study. In addition, patients with fewer than 2 evaluable lumbar vertebrae or patients with unevaluable hip BMD will be excluded from the study.

Patients with unexplained elevation of serum alkaline phosphatase, with a history of Paget’s disease, of any cancer within the past 5 years other than basal cell or squamous cancer of the skin, will be ineligible for enrollment. Also, patients with a history of Cushing’s disease, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year are also ineligible for enrollment. Patients who have ever received treatment with a PTH or PTHrP drug will be excluded. Treatment with bisphosphonates, fluoride or strontium in the past 5 years, or treatment with androgens, other anabolic steroids, corticosteroids or selective estrogen receptor modulators within the past 12 months will also exclude patients from enrollment. Patients who had a short course of bisphosphonate treatment (3 months or less) and were intolerant of the treatment may be considered for study participation. Estrogens administered as hormone replacement therapy (HRT), with or without progestins, are not exclusionary. Patients who have participated in a clinical study of any novel unapproved medication in the past 12 months, and received other than placebo, will also be excluded from participation.

The specific inclusion and exclusion criteria are described in Sections 4.2 and 4.3 of the protocol, respectively.

**Study Design and Methodology:**

**Number of Patients**

A total of 2400 patients are planned to be enrolled in the study in approximately 40 medical centers.

**Design**

This is a randomized, double-blind, placebo-controlled, comparative Phase 3, multicenter international study to evaluate the efficacy and safety of Abaloparatide-SC in the prevention of fracture in otherwise healthy ambulatory postmenopausal women with severe osteoporosis.

A total of 2400 eligible patients will be randomized equally to receive one of the following: Abaloparatide-SC, a matching Placebo, or teriparatide 20 μg for 18 months. Study drug will be blinded to patients and medical personnel until the randomization process is completed. Treatment with Abaloparatide-SC or Placebo will remain blinded to all parties throughout the study. As a proprietary prefilled drug and device combination marketed product, teriparatide cannot be repackaged and blinded. Study medication will be self-administered daily by SC injection for a maximum of 18 months. Patients unable to self-administer drug may be injected by a third party after appropriate training of that person by the study site personnel.

The dosages of study medications and the number of patients to be enrolled are shown below:

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Study Medication</th>
<th>Daily Dose (SC)</th>
<th>Duration</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abaloparatide-SC</td>
<td>80 μg</td>
<td>18 months</td>
<td>800</td>
</tr>
<tr>
<td>2</td>
<td>Placebo</td>
<td>--</td>
<td>18 months</td>
<td>800</td>
</tr>
<tr>
<td>3</td>
<td>Teriparatide</td>
<td>20 μg</td>
<td>18 months</td>
<td>800</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>2400</strong></td>
</tr>
</tbody>
</table>

All enrolled patients will also receive Calcium and Vitamin D supplementation from Visit 1 until the end of the Treatment Period; it will be recommended to patients that they also continue these supplements through...
the Follow-up Period.

**Study Visits**

Upon signing of the informed consent at Visit 1, patients will enter a screening and pretreatment period. After eligibility is assessed during the Screening period, a one week Pretreatment period is used to collect more baseline data (Visit 2). Patients will also be trained on self-administration of study drug and on recording of medication usage and local tolerance during this period. The patients will be randomized and receive study drug at Visit 3 (Baseline or Day 1) and patients will return to their study center for safety and efficacy assessments at 1, 3, 6, 9, 12, and 18 months, for a safety and drug resupply visit at Month 15, and at any other time as warranted by safety, efficacy or compliance concerns. A final study visit is planned one month after the last dose of study drug (the Follow-up Period).

The study periods and number of clinic visits are summarized below:

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Duration of Study Period*</th>
<th>Scheduled Visits (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Screening</td>
<td>Up to 2 months</td>
<td>1</td>
</tr>
<tr>
<td>2. Pretreatment</td>
<td>1 week</td>
<td>1</td>
</tr>
<tr>
<td>3. Treatment</td>
<td>18 months</td>
<td>7</td>
</tr>
<tr>
<td>4. Follow-up</td>
<td>1 month</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20 to 21 months</td>
<td>10</td>
</tr>
</tbody>
</table>

*For the purposes of this study one month is equal to 30 days.

**Procedures and Assessments**

**Efficacy**

The primary efficacy endpoint will be the number of Abaloparatide-SC-treated patients showing new vertebral fractures at End-of-Treatment when compared to Placebo. New incident vertebral fractures will be evaluated according to the method of Genant (1). Efficacy assessments will therefore include documentation of the incidence of clinical and radiographic fractures of the lumbar and thoracic spine. Patients will undergo baseline and End-of-Treatment antero-posterior and lateral radiographs of the lumbar and thoracic spine. All radiographs will be viewed and assessed by a blinded, independent assessor (radiologist) on the basis of existing baseline and study-acquired vertebral deformity, and fracture will be assessed according to a set of pre-determined criteria. A second blinded radiologist will review the assessment of the first reviewer for all patient radiographs in which an incident fracture has been identified. In the case of any disagreement, a third consensus assessment will be made to adjudicate the incident fracture. A standardized graded scale of severity of the vertebral deformity will be evaluated according to the method of Genant (1).

Secondary efficacy parameters will also include reduction in the incidence of non-vertebral fractures (wrist, hip, rib, etc.) and reduction in moderate and severe vertebral fractures. Clinical fracture occurring de novo at these anatomical sites during the study will also be assessed and analyzed. Other secondary efficacy endpoints will include changes in BMD of spine, hip, and femoral neck, and wrist from Baseline to End-of-Treatment as assessed by DXA. Patients will undergo BMD assessments at Screening (spine and hip; all patients), at Day 1 (wrist; in a subset of patients), and at Months 6, 12 and 18 (End-of-Treatment) of study participation. Any patient who shows a continuing significant deterioration (>7%) of BMD at spine or hip will have the assessment repeated and, if confirmed, will be discontinued from the study. Patients sustaining a radiologically confirmed incident clinical vertebral or non-vertebral fragility fracture will be informed of the finding and offered the opportunity to remain in or discontinue from the study. Should a patient who experiences an incident clinical vertebral or non-vertebral fragility fracture choose to remain in the study, she will be asked to sign an additional Informed Consent Form explaining the potential risks and benefits of remaining in the study.
Additional secondary endpoints will include change in standing height and changes in serum bone markers across treatment, such as PINP, osteocalcin, and bone-specific alkaline phosphatase. Serum C-telopeptides (CTX), a marker of bone resorption and collagen breakdown, will be measured and reported. Bone markers will be assessed Pretreatment and at Months 6, 12 and 18 (End-of-Treatment). Urine samples will be collected for the measurement of calcium and creatinine to determine the Calcium:Creatinine ratio. The Calcium:Creatinine ratio will be measured at each visit during the Treatment Period. The frequency of hypercalcemia across treatment groups will also be assessed.

Patients who discontinue study participation prematurely will undergo End-of-Treatment and End-of-Study assessments once their discontinuation is confirmed.

Safety

Safety evaluations to be performed will include physical examinations, vital signs, 12-lead ECGs, clinical laboratory tests, and monitoring and recording of adverse events. Specific safety assessments will include post-dose (4 hours) determination of serum calcium, determination of Creatinine Clearance, post-dose ECG assessments at selected visits, and assessments of postural hypotension (60 minutes post-dose) at selected clinic visits.

The incidence and severity of adverse events by dose and duration of exposure and pathological changes in hematology, chemistry and urinalysis data will be recorded and summarized. Changes in physical examination (including height), vital signs, ECG and clinical laboratory tests will be descriptively summarized. Shift frequencies will be summarized for clinical laboratory tests.

Injection sites will be graded to assess local tolerance to study medication.

ECG and safety laboratory assessments will be performed at all scheduled visits and at any unscheduled visit as deemed necessary by the Investigator. QT interval assessments will be performed for all study subjects across the Treatment Period.

Bone biopsy of the iliac crest will be performed in a subset of patients receiving Abaloparatide-SC, Placebo, and teriparatide (up to 100 per group to obtain up to 75 evaluable biopsies per treatment group) between Visits 8 and 9 for assessment of quantitative bone histomorphometry using a duel-labeling procedure. All bone biopsies will be read blinded to treatment at a central specialized facility.

In selected centers, a subset of patients in all the Abaloparatide-SC/Placebo and teriparatide groups will undergo renal CT (obtained through standard abdominal/pelvic CT scan procedures). For patients enrolled prior to the effective date of Version 3 of the protocol, a single renal CT scan will be performed between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. Patients enrolled after the effective date of Version 3 of the protocol will have two renal CT scans, the first between Visit 3 and Visit 4, inclusive, and the second between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. The renal CT scans will be read centrally by a radiologist blinded to treatment to assess the renal parenchyma and collecting system for renal calcification.

Study safety will be monitored by an independent Data Safety Monitoring Board.

Complete details of the study assessments are provided in Section 7.0, in the Schedule of Visits and Procedures (Appendix 14.1) and in the Suggested Schedule of Events and Procedures by Study Visit (Appendix 14.2).

Statistical Considerations:

Sample Size

A sample size of 622 patients per treatment arm provides 90% power at a two-sided alpha of 0.05 to detect a superiority difference of 4% between placebo patients and Abaloparatide-SC-treated patients on vertebral fracture incidence. To ensure an evaluable population of 622 patients, an overall sample size of 800 patients per treatment arm will be recruited. For statistically powered secondary endpoints the sample size will have greater than 90% power at an alpha of 0.05 to detect a 1.15%, 2.45%, and 2.00% difference for spine, hip, and femoral neck BMD, respectively, between Abaloparatide-SC and teriparatide. The study sample size will also
provide more than 90% power to detect differences between Abaloparatide-SC and teriparatide in the number of patients reporting one or more events of hypercalcemia.

Baseline Comparisons
Baseline characteristics, medical history, physical examination, vital signs and ECG, will be summarized using standard descriptive statistics by treatment group. Specific demographic and baseline parameters will be tested for overall agreement across treatment groups using one-way ANOVA or Chi-square tests as appropriate for the type of data.

Efficacy Analyses
The primary efficacy endpoint will be the number of Abaloparatide-SC-treated patients showing new vertebral fractures at End-of-Treatment when compared to Placebo.

Key secondary endpoints that will be statistically analyzed include change in BMD (spine, hip, and femoral neck) and differences in the number of patients reporting one or more events of hypercalcemia from baseline to End-of-Treatment for Abaloparatide-SC when compared to teriparatide. Additional secondary efficacy endpoints will include the change in vertical height in Abaloparatide-SC patients when compared to Placebo and the incidence of Abaloparatide-SC patients with new non-vertebral fractures from baseline to End-of-Treatment when compared to Placebo. Severity of vertebral fractures, fracture incidence over time by treatment group, and new vertebral fractures in teriparatide patients compared to Placebo will also be assessed.

Other efficacy endpoints will include change in wrist BMD in Abaloparatide-SC-treated patients, and changes in serum PINP, bone-specific alkaline phosphatase, osteocalcin, and CTX across treatment.

Population PK/PD Analysis
Samples for measurement of serum levels of abaloparatide will be taken to evaluate population PK effects on demographics, efficacy, and safety.

Safety Analysis
All patients who receive at least one dose of study medication will be included in the safety analysis that will be performed on the following parameters:

- Incidence and severity of AEs; dose and duration of exposure when the AE occurred.
- Pathological changes in hematology, chemistry and urinalysis data based on normal ranges supplied by the clinical laboratory.
- Frequency of hypercalcemia will also be compared across treatment groups.
- Bone histomorphometry as assessed by bone biopsy at End-of-Treatment in a subset of patients randomized to Abaloparatide-SC, Placebo or teriparatide.
- Renal safety as assessed by renal CT scans in a subset of patients in selected centers in all treatment groups.

All AEs collected prior to first injection will be separately summarized in a fashion similar to the TEAEs.
**Treatments Administered:**

Abaloparatide Drug Product for Injection (2.0 mg/mL abaloparatide in 5 mg/mL tri-hydrate sodium acetate and 5mg/mL of phenol (preservative) adjusted at pH 5.1 with acetic acid) will be supplied as a liquid in a 1.5 mL Type 1 glass cartridge and is stored refrigerated at 5 ± 3°C. The multi-dose cartridge is designed to deliver a dose of 80 μg of abaloparatide in 40 μL of fluid or a half dose of 40 μg of abaloparatide in 20 μL of fluid when inserted into the Pen Injector device. Each cartridge contains enough study medication to deliver the required daily dose for 30 days. Patients will be provided with a sufficient number of cartridges to continue on treatment until the next scheduled clinic visit. Study medication should be stored in refrigerated conditions (2-8 ºC) until dispensed for use. In-use storage may be at room temperature, up to 25 ºC for 30 days.

Placebo is formulated similarly but without active abaloparatide and will be similarly supplied as a liquid in a 1.5 mL Type 1 glass cartridge and is stored refrigerated at 5 ± 3°C. The multi-dose cartridge is designed to deliver a dose of Placebo in 40 μL of fluid when inserted into the Pen Injector device. Each cartridge contains enough study medication to deliver the required daily dose for 30 days. Storage and dispensing conditions will match those of active study drug.

Teriparatide (rDNA origin) injection (250 μg/mL) will be supplied in multi-dose disposable pens containing a glass cartridge. Each pen contains enough study medication to deliver the required daily dose for 28 days. Study medication should be stored in refrigerated conditions (2-8 ºC) until dispensed for use. In use storage should also be in refrigerated conditions, 2-8 ºC.

Calcium (500–1000 mg) and Vitamin D (400–800 IU) supplements will be provided at the study site.

**Duration of Subject Participation:**

The maximum total duration of study participation for an individual patient is approximately 20 to 21 months from the initial screening visit to the completion of final study evaluations. Patients will complete screening and study-specific procedures within 1 to 2 months. After completion of the Screening and Pretreatment Periods, patients will be randomized and will receive the first dose of study medication on Day 1 of the Treatment Period. The Treatment Period will be a maximum of 18 months with daily SC dosing. After completion of dosing, patients will enter the Follow-up Period for 1 month. The End-of-Study Visit will be scheduled at the end of the Follow-up Period and patients will be terminated from the study.

**Post-study Treatments and Assessments:**

**Abaloparatide-SC/Placebo Patients**

Abaloparatide-SC/Placebo patients who complete 18 months of study participation and who remain eligible, will be given the opportunity to participate in an Extension Study. The Extension Study will be comprised of standard-of-care osteoporosis management, consisting of treatment with alendronate at a dose of 70 mg once per week for up to 24 months. Patients enrolled in the Extension Study will undergo study related procedures as described in Section 7.0, including BMD and radiologic assessments.

Abaloparatide-SC/Placebo patients who do not participate in the Extension Study will be offered 24 months of alendronate, and will receive standard-of-care management, according to their physician.

**Teriparatide Patients**

There will be no post-study treatments or assessments for patients completing treatment with teriparatide.
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6.1 CONCOMITANT MEDICATIONS

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>°F</td>
<td>Degree Fahrenheit</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>μL</td>
<td>Microliter</td>
</tr>
<tr>
<td>μmol</td>
<td>Micromole</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>BSAP</td>
<td>Bone-specific alkaline phosphatase</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatine phosphokinase</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract research organization</td>
</tr>
<tr>
<td>CTX</td>
<td>C-telopeptides of type 1 collagen crosslinks (serum)</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FRAX</td>
<td>Tool developed by WHO to evaluate fracture risk of patients</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyltranspeptidase</td>
</tr>
<tr>
<td>GLP</td>
<td>Good laboratory practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
</tr>
<tr>
<td>HEENT</td>
<td>Head, eye, ear, nose, and throat</td>
</tr>
<tr>
<td>hPTH1R</td>
<td>Human parathyroid hormone receptor 1</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>IU</td>
<td>International unit</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
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<td>--------------</td>
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<tr>
<td>IVRS</td>
<td>Interactive voice response system</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>L</td>
<td>Liter</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular hemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular hemoglobin  concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeter of mercury</td>
</tr>
<tr>
<td>msec</td>
<td>Millisecond</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximal tolerated dose</td>
</tr>
<tr>
<td>N.P.O.</td>
<td>Nothing by mouth</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observed adverse effect level</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>pg</td>
<td>Picogram</td>
</tr>
<tr>
<td>PINP</td>
<td>N-terminal propeptide of type I procollagen</td>
</tr>
<tr>
<td>PO</td>
<td>By mouth</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>PTHrP</td>
<td>Parathyroid hormone related peptide</td>
</tr>
<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
</tr>
<tr>
<td>PVCs</td>
<td>Premature ventricular complexes</td>
</tr>
<tr>
<td>QT</td>
<td>Total depolarization and repolarization time</td>
</tr>
<tr>
<td>QTc</td>
<td>Total depolarization and repolarization time corrected with heart rate</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>rDNA</td>
<td>Recombinant deoxyribonucleic acid</td>
</tr>
<tr>
<td>rhPTH</td>
<td>Recombinant hPTH</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SERMs</td>
<td>Selective estrogen receptor modulators</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
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</tbody>
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1.0 INTRODUCTION

1.1 Background Information

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue which leads to enhanced fragility and increased risk of fractures (2). The common therapeutic approach is to decrease bone loss with the use of antiresorptive agents such as estrogens, selective estrogen receptor modulators (SERMs) and bisphosphonates (3). However, when osteoporosis is severe, these classes of pharmacological agents provide only a moderate rate of return of bone mass and take a number of years to effect their fracture reduction benefit. A preferable approach is to more rapidly reduce fracture risk by inducing a faster and greater return of bone mass through use of bone anabolic agents. To date, only one class of bone anabolic drugs, PTH and its analogs, has been approved to prevent fractures in postmenopausal women with osteoporosis who are at risk of fracture. PTHrP, and specifically abaloparatide, offers another and potentially better therapeutic option than PTH in this indication and shows particular potential for reversing bone loss at the hip, the site of the most debilitating osteoporotic fractures in elderly women.

Human parathyroid hormone (hPTH) is a naturally occurring 84-amino acid hormone and is primarily a regulator of calcium homeostasis (4). 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-dihydroxy Vitamin D production. In turn, hPTH levels are tightly regulated by Calcium and Vitamin D levels. When present at high doses or when administered in a continuous manner, hPTH has a catabolic effect on the skeleton through its ability to activate and increase osteoclast number which leads to increased serum calcium levels and decreased bone mass in humans (5). However, when given intermittently at low doses, hPTH has a well-documented anabolic effect on bone, and can increase bone mineral density (BMD) in a number of intact animal models as well as in osteoporotic patients (6).

The 34-amino acid terminal fragment of hPTH, known as hPTH(1-34), appears to contain the full biological activity of native PTH(1-84) with regard to restoration of bone (7). Teriparatide (Forteo®/Forsteo®; Eli Lilly and Co., Indianapolis, Indiana), a recombinant human PTH (rhPTH(1-34)), was approved by FDA in 2002 as a new therapy for osteoporosis. Teriparatide can stimulate bone formation, increase bone mass and reduce the risk of fractures in both animals and humans (8).

Human PTH-related peptide (hPTHrP) is a member of the PTH family that is secreted endogenously and which is partially homologous with the sequence of hPTH at the amino-terminus, where 8 of the first 13 amino acids are identical in both peptides (9). Different to hPTH, PTHrP is produced by osteoblasts (10) and, like hPTH, hPTHrP is also involved in calcium homeostasis (9) but to a lesser degree than PTH. PTHrP has also been shown to have an important role in normal skeletal development (11), and has been shown to restore bone mass in people when administered in an intermittent pattern (12). When administered daily for three months by subcutaneous injection to women with severe postmenopausal osteoporosis, PTHrP(1-36) in a dose of 6.6 μg/kg (approximately 400 μg/day) increased lumbar spine BMD by 4.7%, a value that was statistically different from placebo (1.4%). In
addition, there was no associated hypercalcemia reported and no evidence of bone resorption when assessed by changes in serum markers of bone resorption (12).

Abaloparatide is a 34-amino acid analog of hPTHrP, with molecular modifications of specific amino acids. Abaloparatide is expected to have similar or greater efficacy in restoring BMD in individuals with osteoporosis than hPTH(1-34), but with less risk of causing hypercalcemia. Initial in vitro and in vivo studies identified abaloparatide as displaying such properties (13-16). Clinical evaluations have shown abaloparatide to be well tolerated and to have significant positive effect on bone formation.

1.2 Drug under Study

As noted above, abaloparatide is an analog of the first 34 amino acids of hPTHrP(1-34). abaloparatide was originally discovered and developed by the Beaufour-Ipsen Pharma Group (Ipsen) under the names BIM44058 and BIM44058C. Radius Health, Inc. (hereafter referred to as RADIUS) acquired the license for the compound and is developing abaloparatide to treat postmenopausal women with osteoporosis who are at high risk of fracture.

Nonclinical pharmacology and toxicology studies have demonstrated that abaloparatide is a potent and selective agonist of the human parathyroid hormone receptor 1 (hPTH1R). It has significantly less calcium mobilizing activity at higher doses than the native hormone and is a potent anabolic agent capable of fully restoring BMD in ovariectomized, osteopenic rats.

Results from safety pharmacology studies indicate that abaloparatide is generally safe. The subcutaneous bioavailability was estimated to be 33% after administration of a single dose of 10 μg/kg in rats. Tachycardia and hypotension were observed in dogs following both intravenous and subcutaneous administrations, however such effects have not been observed in other species or in human studies. Minor pharmacological effects (increased bone formation, transient slightly higher blood total calcium levels after dosing) were observed at low doses in the toxicology studies. The No Observed Adverse Effect Level (NOAEL) was 15, 25 and 25 μg/kg/day in rats in the 4-, 13, and 26-week studies, respectively, and 100, 50 and ≤ 10 μg/kg/day in monkeys in the 4-, 13- and 39-week studies, respectively. No local clinical signs or microscopic findings were noted at the injection sites in rats and monkeys treated daily in the toxicity studies. In the 39-week study, minimal to moderate mineralization of lung and kidney was observed at all doses evaluated, ranging from 7- to 70-times the present human dose. There were slight but progressive and occasionally significant changes in blood parameters. Significant hypercalcemia associated with premortem morbidity was also observed. The repeated-dose studies revealed the presence of specific antibodies against abaloparatide in a proportion of animals tested, particularly following longer term exposure at higher doses, and more commonly in monkeys than in rats. The presence of antibodies did not appear to neutralize the therapeutic effect of abaloparatide.

As required by US FDA regulatory guidelines, a carcinogenicity study is currently ongoing in Fischer 344 rats, which is the recommended model for drugs intended to treat osteoporosis. The study, 670364, entitled “A 2-year Subcutaneous Carcinogenicity Study of BA058 in the Fischer 344 Albino Rat” was initiated in January 2011. PTH(1-34) is being used as a positive control in the experiment, as treatment with rhPTH 1-34 in this model has previously been associated with the development of bone neoplasms including...
osteosarcomas. In this on-going study, necropsies in animals that have died prior to
scheduled sacrifice revealed, as expected, findings of osteosarcomas in rats in both the
PTH(1-34) and abaloparatide arms at all doses. This finding was expected, based on
previously published results with rhPTH 1-34, and rhPTH 1-84 in this animal model. For
this nonclinical experiment, abaloparatide and PTH (1-34) are administered to juvenile rats,
are provided for nearly a lifetime of daily exposures, and are dosed daily at 3 to 22 times the
equivalent human exposure. To date, there has been no established link in the published
literature between the osteosarcomas found in this susceptible Fischer 344 study model with
other PTH-like therapies and the occurrence of clinical events in humans. There have been
no cases of osteosarcoma observed in human subjects treated with abaloparatide.

To date, Abaloparatide-SC has been studied in single and multiple dose Phase 1 clinical trials
in which Abaloparatide-SC was evaluated in healthy male and female subjects. In addition, a
Phase 2 dose finding clinical study was performed in postmenopausal women with
osteoporosis to evaluate a range of doses of Abaloparatide-SC.

The Phase 1 program involved 3 studies, a single-dose PK and bioavailability clinical trial
(Study 2-52-52127-001) that enrolled healthy male and female subjects > 55 years of age, a
repeated dose 7-day PK/PD study (Study BA058-05-001) that enrolled 39 healthy
postmenopausal women from 50 to 73 years of age, and Study BA058-05-001B, a second
repeated dose 7-day PK/PD study that investigated a new liquid formulation of
Abaloparatide-SC presented as a prefilled multi-dose cartridge for use in a pen injector
device. The single exposure PK study investigated subcutaneous doses of 5 μg to 120 μg.
The single exposure study determined that Abaloparatide-SC was well-tolerated up to 80 μg,
was 100% bioavailable, had approximately dose-proportional kinetics, and had a half-life of
approximately 2.25 hours. The repeated dose studies determined that Abaloparatide-SC was
well-tolerated up to 100 μg, had limited hypercalcemic effect, induced early changes in bone
formation markers and that 100 μg was the maximal tolerated dose. Cardiac safety
monitoring was conducted for all subjects in all Abaloparatide-SC Phase 1 studies and no
clinically significant findings were identified.

A Phase 2 dose-finding clinical trial (Study BA058-05-002) was conducted in four countries
(the United States, Argentina, India, and the United Kingdom) to evaluate the safety and
efficacy of Abaloparatide-SC in women with osteoporosis (T-score ≤ -2.5). This was a
randomized, placebo- and comparator-controlled, parallel group dose-finding study of
Abaloparatide-SC to evaluate the effects of daily SC injections of abaloparatide for six
months in 225 postmenopausal women with osteoporosis, subsequently extended to 12
months in a subset of patients. Following enrollment, patients underwent a 4-week
Pretreatment Period of Calcium and Vitamin D supplementation and instruction in study
medication self-administration, at the end of which patients were randomized to daily SC
self-administration of placebo, abaloparatide 20 μg, 40 μg, 80 μg or teriparatide.

The study was powered for change from baseline in primary study endpoints: BMD (spine)
by DXA, and change in anabolic bone markers (serum PINP, BSAP, and osteocalcin). Other
anatomical sites were also assessed by DXA for change in BMD and additional anabolic and
resorptive bone markers were also assessed. Routine clinical and laboratory safety
assessments were employed with additional monitoring of cardiac safety, serum calcium
levels and local tolerance assessment by patient diary. Two hundred and seventy patients were enrolled into pretreatment, 222 patients were randomized and 221 received study drug. One hundred and eighty-seven patients completed treatment and 155 patients were evaluable as the Per Protocol Population. The age of the study population ranged from 54 to 84 years old (mean 65) and mean spinal T-score at screening was -2.9.

Mean percent changes in total analyzable BMD of the spine at Week 24 increased with abaloparatide dose (1.4%, 3.5%, 4.9%, and 6.7% in the placebo, Abaloparatide-SC 20 μg, Abaloparatide-SC 40 μg, and Abaloparatide-SC 80 μg groups, respectively) for the Per Protocol Population. The test for a linear trend (dose response) was statistically significant (p<0.001). Mean percent change in the teriparatide group at this visit was 6.0%. The anabolic bone markers showed a similar statistically significant dose response.

Treatment emergent adverse events (TEAEs) were reported in 164 (74%) of the 221 patients through the End-of-Study visit (Week 28) and were similar in number and profile across all treatment groups. Treatment emergent and unrelated serious adverse events of bronchitis, ovarian cancer, and diverticulitis were reported in 3 patients (1%) overall in the placebo, 20 μg and 80 μg groups, respectively. There were also no clinically significant changes on intensive cardiac safety assessments conducted in approximately 30% of patients.

Serum calcium levels were measured pre- and post-dose (4 hours) at multiple times through the study and were higher throughout the study in the teriparatide study group. Episodes of hypercalcemia (both above normal at any time or above the alert value) post-dose were more common in teriparatide patients. Overall, 27% of patients treated with Abaloparatide-SC 80 μg and 53% of patients treated with teriparatide had a serum calcium level above normal (≥ 10.2 mg/mL) on one or more occasions. The percentages of patients with post-dose calcium values of ≥10.2 mg/mL were 17% and 48% in the Abaloparatide-SC 80 μg and teriparatide groups, respectively. In addition, 18% of patients treated with Abaloparatide-SC 80 μg and 40% of patients treated with teriparatide had a clinically significant elevation of serum calcium level (≥10.5 mg/mL) on one or more occasions, while the corresponding results for post-dose calcium values of ≥10.5 mg/mL were 11% and 40%, respectively.

Low titer anti-drug antibodies were reported in 16 abaloparatide treated patients after 6 months of abaloparatide treatment. Of the 16 positive patients, 2 were in the Abaloparatide-SC 20 μg group, 8 were in the Abaloparatide-SC 40 μg group and 6 were in the Abaloparatide-SC 80 μg group. There were no associated safety events and no attenuation of treatment efficacy. One antibody-positive patient in the Abaloparatide-SC 40 μg group was found to have evidence of neutralizing activity at 24 weeks. The patient did not appear to have any attenuation of drug efficacy, having a 9.3% gain in total analyzable spine BMD at the Week 24 assessment.

Fifty-five patients continued into a second 6 months of treatment with their original treatment assignment; 48 of these patients completed the additional treatment period. BMD continued to show time-dependent and dose-dependent increases. At the end of study, final spinal BMD was approximately 50% greater in the Abaloparatide-SC 80 μg dose group than teriparatide and hip and femoral neck BMD were approximately 100% greater than teriparatide. The second six months of treatment did not uncover additional safety
considerations; the overall percent of patients experiencing a TEAE over 48 weeks of study treatment was 81% as compared to 74% in the 24-week study exposure. One additional unrelated SAE of bilateral crural hernia was reported in the second 24 weeks of study conduct in the Abaloparatide-SC 80 μg group.

In conclusion, this study demonstrated that abaloparatide induces a substantial positive dose- and time-dependent change in BMD at both spine and hip in women with osteoporosis and achieves this benefit safely and with substantially less hypercalcemic effect than teriparatide.

Across the studies conducted with abaloparatide, abaloparatide-related AEs were generally mild and did not require discontinuation of treatment. The most common AEs observed in patients were influenza, nasopharyngitis, bronchitis, headache, hypercalciuria, back pain and arthralgia. Occasional events of changes in orthostatic blood pressure were noted but were mild or moderate and did not appear to be dose related. Reported local tolerance reactions were generally mild and resolved quickly, with redness being the most commonly reported symptom. Elevated calcium levels were observed in a subset of patients to a lesser degree than that observed in patients treated with teriparatide.

According to the FDA-approved labeling for teriparatide, AEs reported in clinical trials were usually mild and generally did not require discontinuation of therapy. The most commonly reported adverse events were pain, arthralgia, rhinitis, asthenia, nausea, dizziness, headache, hypertension, cough increased, pharyngitis, constipation, dyspepsia, and diarrhea. Transient episodes of symptomatic orthostatic hypotension were observed infrequently. In addition, teriparatide caused osteosarcomas in long-term toxicology studies in rats but the clinical relevance of this finding is unknown.

For additional details on potential AEs and precautions with the use of abaloparatide, please refer to the Investigator’s Brochure.

**1.3 Study Rationale and Selection of Doses**

**1.3.1 Study Rationale**

This study is designed as a randomized, double-blind, placebo-controlled, comparative Phase 3 study of Abaloparatide-SC in the treatment of postmenopausal women with severe osteoporosis and at risk of fracture. The purpose of the study is to evaluate the efficacy and safety of Abaloparatide-SC in the prevention of fracture in otherwise healthy ambulatory postmenopausal women with severe osteoporosis. The dose chosen for this study is based on the safety and pharmacodynamic information derived in study BA058-05-002 according to predetermined criteria provided in the protocol. The population to be studied is the recommended and intended population for treatment, postmenopausal women with severe osteoporosis (17-19). Daily SC doses of Abaloparatide-SC 80 μg, Placebo or teriparatide 20 μg will be self-administered for 18 months (78 weeks) to patients randomized equally to one of 3 treatment groups.
1.3.2 Study Design and Rationale for Placebo

This study is designed as a randomized, double-blind, parallel-group, clinical trial. There will be 3 treatment arms, one of which will be Abaloparatide-SC 80 μg, one of which will be a placebo to Abaloparatide-SC 80 μg, the study drug, and one of which will be teriparatide 20 μg. Therefore, 2 of 3 patients treated will receive an active treatment. All subjects, regardless of treatment assignment, will receive Calcium and Vitamin D supplements during the Pretreatment and Treatment Periods.

The study will be blinded up to the time of randomization and assignment of the patient to treatment. On opening of the assigned treatment, although patients and study personnel will remain blinded to Abaloparatide-SC or Placebo, it will become apparent to them whether a Abaloparatide-SC-based treatment or teriparatide has been assigned. An independent blinded evaluator will review all study radiographs. A second blinded evaluator will confirm all findings. A Data Safety Monitoring Board (DSMB) will monitor study safety.

The total period of placebo exposure and therefore of potential delay of specific treatment is 18 months. Placebo is the usual and recommended comparator for studies in this indication. While the indication infers the prevention of fractures with treatment, the actual benefit is a reduction in fracture incidence in women at risk. It is calculated that while fractures may occur in patients both on active treatment and Placebo, it is estimated that treatment will result in a relative reduction of fracture risk of approximately 60% over 18 months.

In the RADIUS Phase 2 study (Study BA058-05-002), patients randomized to placebo and supplemented with Calcium and Vitamin D over their 6-12 months of study participation demonstrated no overall reduction in spinal or hip BMD and reported no fractures while on study treatment.

In addition, all blinded Abaloparatide-SC/Placebo patients who complete the study will be offered the chance to enroll in an Extension Study, in which they will receive standard of care osteoporosis management, including alendronate treatment, as appropriate, according to their physician.

1.3.3 Study Population

The study population in this protocol is the population recommended by Regulatory Authorities (17-19) for the clinical evaluation of PTH and PTH-like drugs in this indication: postmenopausal women (50 to 85 years of age) who are more than 5 years post menopause and whose menopause has been confirmed by an elevated serum FSH and a BMD T-score of ≤-2.5 (2.5 SD below the population norm) and > -5.0 at the lumbar spine or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. However, postmenopausal women older than 65 who meet the above fracture criteria but have a T-score ≤-2.0 and > -5.0 may be enrolled. In addition, women older than 65 who do not meet the fracture criteria may also be enrolled if their T-score is ≤-3.0 and > -5.0. Women
who are intolerant of bisphosphonates as outlined in exclusion criterion #17 (Section 4.3) and meet the above criteria will also be allowed to enroll.

Based on midpoint demographics of the proposed study population, the anticipated 10-year fracture rate in Study BA058-05-003 is estimated to fall within the recommended ranges in the relevant guideline (CPMP/EWP/552/95 Rev.2) when calculated using the FRAX assessment tool (http://www.shef.ac.uk/FRAX/).

A sample size of 622 patients per treatment arm provides 90% power at a two-sided alpha of 0.05 to detect a difference of 4% between treatments, assuming a vertebral fracture rate of 7% in placebo patients and 3% in Abaloparatide-SC for injection-treated patients when the large scale approximation of the binomial method is employed. This superiority assessment infers a relative risk reduction of 57% and presupposes the availability of a pretreatment and post-treatment radiological assessment. To ensure a per protocol population of 622 patients, an overall sample size of 800 patients per treatment arm will be recruited, anticipating that approximately 20% of patients may not have a second evaluable X-ray film available for analysis. Prior studies have demonstrated that approximately 20% of enrolled patients drop out over the lengthy period of the study and a further proportion (10%) fail to provide an evaluable End-of-Treatment X-ray, therefore a sample size of 800 patients per arm is proposed.

1.3.4 Selection of Endpoints

Bone remodeling is a constant process in the adult human skeleton and maintains the integrity of the skeleton through a process of replacing old bone (resorption) with new bone formation (anabolism). Both cortical and trabecular bone are involved in this process which needs to be in balance to maintain normal bone density and strength (20). In childhood, the balance favors bone formation and, with aging, the process favors the resorptive component, causing bone loss. Assessments of this balance of formation and resorption can be performed over the long-term by quantitative imaging of bone density. Consequences of bone loss are commonly observed as fracture in a severe osteoporotic population. An improvement in bone quality and quantity can reduce the risk of existing and incidental fracture. Therefore, while earlier studies have demonstrated the benefit of abaloparatide for improvement in BMD in postmenopausal women, this study will assess the relative efficacy and safety of Abaloparatide-SC 80 μg for prevention of new fractures in the same population but among the cohort of patients with a history of fracture, or those who are at an increased risk of fracture. While all new fractures will be assessed, the relative short duration of treatment anticipated with abaloparatide is unlikely to yield definitive evidence of fracture prevention benefit at all anatomical sites; therefore the study is designed to identify a statistically significant benefit on radiographically defined vertebral fracture. Non-vertebral fractures will be assessed as a secondary efficacy endpoint as will BMD changes by DXA at spine, hip and femoral neck as additional indices of bone anabolic benefit.

In addition to BMD by DXA, bone formation and resorption markers will also be assessed over time (21). The rise in the markers of bone formation indicates
restoration of lost bone, in particular the lost microarchitecture that places osteoporotic women at an increased risk for fracture. Increases in the principal markers of bone formation: N-terminal propeptide of type I procollagen (PINP), osteocalcin, and bone-specific alkaline phosphatase (BSAP) are accepted predictors of BMD change (21,22). Serum C-telopeptides (CTX), a marker of bone resorption and collagen breakdown, will also be measured in this study. Markers of anabolic effect and resorptive effect have become valuable tools in the management of osteoporosis since they can provide early information on potential treatment efficacy (23).

1.3.5 Selection of Dose

The abaloparatide dose to be studied in this Phase 3 trial has been previously studied in the Phase 1 and Phase 2 clinical trials. The dose chosen for this study is based on the safety and pharmacodynamic information derived in study BA058-05-002 according to predetermined criteria provided in the protocol. The 80 μg dose was the maximum efficacy dose in the abaloparatide Phase 2 clinical program, was well tolerated (refer to Section 1.2) and demonstrated a significant increase in mean lumbar spine and mean femoral neck BMD when compared to Placebo. This beneficial effect was achieved safely and with substantially less hypercalcemia than teriparatide. Doses of up to 120 μg have been studied in the Phase 1 program and 100 μg has been determined to be the maximum tolerated dose, due to patients experiencing an increase in nausea and one discontinuation due to vomiting at the 120 μg dose.

Abaloparatide-SC 80 μg per day will be dosed by SC self-administered injection. In addition, a matching Placebo comparator will be employed in one treatment arm and teriparatide will be employed as a reference drug and comparator for secondary efficacy and safety outcomes. All enrolled patients will also receive Calcium (500-1000 mg) and Vitamin D (400-800 IU) supplementation, or a dose to be determined by the Investigator and agreed by the Sponsor Medical Monitor, according to the patient’s need, from the Pretreatment Period until the end of the Treatment Period; it will be recommended to patients that they continue these supplements through the Follow-up Period. The treatment regimens are summarized in the table in Section 3.1.
2.0 STUDY OBJECTIVES

The primary objective of this study is to determine the safety and efficacy of Abaloparatide-SC when compared to Placebo for prevention of vertebral fracture in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis. The secondary objectives of this study are to determine the safety and efficacy of Abaloparatide-SC when compared to Placebo for prevention of non-vertebral fractures and for additional secondary efficacy outcomes (bone mineral density of spine, hip and femoral neck) and safety (hypercalcemia) when compared to teriparatide (Eli Lilly and Co.) in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis.

The specific objectives of this study are to:

- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.

- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on lumbar spine, total hip, and femoral neck bone mineral density (BMD) in otherwise healthy ambulatory postmenopausal women with severe osteoporosis when compared to teriparatide.

- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of non-vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.

- Determine the overall safety and tolerability of 18 months of treatment with Abaloparatide-SC, and specifically the number of patients with hypercalcemic events, in otherwise healthy postmenopausal women with severe osteoporosis when compared to teriparatide and Placebo.

- Provide additional evidence of bone safety through histomorphometric assessment of bone biopsy samples in a subset of patients from the Abaloparatide-SC, Placebo, and teriparatide groups.

Provide additional evidence of renal safety through radiological assessment by renal CT scan in a subset of patients from selected centers in the Abaloparatide-SC, Placebo, and teriparatide groups.
3.0 INVESTIGATIONAL PLAN

3.1 Overall Design and Study Plan

This is a randomized, double-blind, placebo-controlled, comparative Phase 3, multicenter, international study to evaluate the efficacy and safety of Abaloparatide-SC in the prevention of fracture in otherwise healthy ambulatory postmenopausal women with severe osteoporosis. Women who are postmenopausal for \( \geq 5 \) years and are 50 years old to 85 years old (inclusive) with a bone mineral density T-score \( \leq -2.5 \) and \( > -5.0 \) at the lumbar spine or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years may be enrolled. Postmenopausal women older than 65 who meet the above fracture criteria but have a T-score \( \leq -2.0 \) and \( > -5.0 \) may be enrolled. Women older than 65 who do not meet the fracture criteria may also be enrolled if their T-score is \( \leq -3.0 \) and \( > -5.0 \).

The study consists of a Screening Period (up to 2 months), a Pretreatment Period (1 week), a Treatment Period (18 months) and a Follow-up Period (1 month). The duration and number of scheduled visits for each study period, and the study medications being administered in each study period are summarized in the table below.

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Duration of Study Period*</th>
<th>Scheduled Visits (#)</th>
<th>Active Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Screening</td>
<td>Up to 2 months</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2. Pretreatment</td>
<td>1 week</td>
<td>1</td>
<td>Calcium, Vitamin D</td>
</tr>
<tr>
<td>3. Treatment</td>
<td>18 months</td>
<td>7</td>
<td>Calcium, Vitamin D, Study Medication</td>
</tr>
<tr>
<td>4. Follow-up</td>
<td>1 month</td>
<td>1</td>
<td>Calcium, Vitamin D</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20 to 21 months</strong></td>
<td><strong>10</strong></td>
<td></td>
</tr>
</tbody>
</table>

*For the purposes of this study one month is equal to 30 days

The total duration of study participation for an individual patient is approximately 20 to 21 months from the initial screening visit to final study evaluations. The total duration of dosing with active medication (or placebo) is 18 months.

For subjects randomized to Abaloparatide-SC/Placebo, who remain eligible, and who agree to participate, the 18-month treatment study will be followed by an Extension Study, administered as a separate protocol. The Extension Study will be comprised of standard-of-care osteoporosis management including up to 24 months of treatment with alendronate at a dose of 70 mg per week. Patients, for whom alendronate is not appropriate, will receive an alternative treatment for osteoporosis as determined to be appropriate by their study doctor. Subjects enrolled in the Extension Study will undergo study related procedures as described in Section 7.0, including BMD and radiologic assessments.

Patients who received Abaloparatide-SC/Placebo in Study BA058-05-003 and do not participate in the Extension Study will be offered up to 24 months of treatment with
alendronate. Patients will receive standard-of-care management during this period, according to their physician.

Blinded Placebo or abaloparatide patients who experience a clinical fracture during the BA058-05-003 study will be given the opportunity to receive treatment with alendronate for up to 24 months. Patients will receive standard-of-care management including assessment of BMD during this period, according to their physician.

During the Screening Period, informed consent is obtained, eligibility for study entry is assessed and screening evaluations are performed, including baseline radiographic and DXA (hip and spine) assessments and baseline (routine) safety laboratory tests including serum biochemistry and hematology, and ECG.

Patients who are eligible for the study on the basis of screening evaluations will enter the Pretreatment Period of the study and will have baseline assessments of 1,25-dihydroxy Vitamin D, serum markers of bone metabolism and abaloparatide serum antibody levels. Patients will be given daily Calcium and Vitamin D supplements, which will continue until the end of the Treatment Period; it will be recommended to patients that they continue these supplements through the Follow-up Period.

Patients who do not meet the Vitamin D entry criterion at Visit 1 may receive Vitamin D supplementation and be retested. Similarly, patients with minor elevations of PTH may be retested after Vitamin D supplementation. All patients enrolled following retesting must have safety labs reported within 30 days of randomization.

In addition, patients will undergo training in self-injection with the device to be employed for administration of Abaloparatide-SC or Placebo. Patients subsequently randomized to treatment with teriparatide will be trained to use the teriparatide pen on Day 1 prior to the first injection. Patients with medically significant abnormalities, or any patient who experiences a serious adverse event during the Screening or Pretreatment Periods, will be excluded from further study participation and treatment. At the end of the Pretreatment Period, all patients who continue to meet the eligibility criteria for the study will enter the Treatment Period.

Patients who remain eligible for study participation will be randomized on Day 1 to treatment with one of the 3 treatment regimens shown below.
Treatment will be blinded to patients and investigators until the time of randomization and assignment of treatment. Blinding will be maintained between Abaloparatide-SC and Placebo, but not with regard to teriparatide.

During the Treatment Period, patients will self-administer a single subcutaneous dose of study medication once a day. Study procedures during this study period will include the collection of x-rays and DXA scans to evaluate fractures and of serum samples to assess serum markers of bone formation and resorption. A subset of patients in the Abaloparatide-SC, Placebo, and teriparatide treatment groups (up to 100 per group to obtain up to 75 evaluable biopsies per treatment group) will be asked to undergo a bone biopsy at the end of the Treatment Period. In addition, in selected centers, patients in the Abaloparatide-SC/Placebo and teriparatide groups who enrolled prior to the effective date of Version 3 of the protocol will be asked to undergo a renal CT scan (obtained through standard abdominal/pelvic CT scan procedures). For patients enrolled prior to the effective date of Version 3 of the Protocol, a single CT scan will be performed at the End Treatment Visit (Visit 9). Patients in selected centers after the effective date of Version 3 of the protocol will be asked to undergo two renal CT scans, the first prior to treatment (Visit 3), and the second at the End-of-Treatment Visit (Visit 9). Serum samples for evaluation of study medication levels and anti-abaloparatide antibody formation will be drawn at specified visits during the Treatment Period. Monitoring for adverse events, concomitant medications and other safety assessments will be conducted throughout the course of the study (from Visit 2 through End-of-Study).

During the month after the last dose of study medication has been administered (Follow-up Period), it will be recommended to patients that they continue to take Calcium and Vitamin D supplements until they return for an End-of-Study Visit during which final clinical evaluations are performed. Patients eligible to continue in the Extension Study will not undergo the End-of-Study Visit and will transition into the Extension Study during the Follow-up Period.

The maximum duration of study participation for an individual patient is estimated as 21 months from the initial screening visit to the End-of-Study Visit. Ten to 11 clinical visits are planned during the study; additional visits may be scheduled for clinical laboratory retesting or to obtain protocol-specified evaluations, if required.
Visit windows are allowed for flexibility in scheduling of study visits. For initial visits which are scheduled at shorter intervals, a \( \pm 1 \) or \( \pm 3 \) day window is allowed. For visits later in the study, which occur at longer intervals, a \( \pm 7 \) day window is allowed.

A brief summary of each study period is provided below. For a summary of the study assessments to be performed, refer to Section 7.0 (Study Assessments) and to the Schedule of Visits and Procedures (Appendix 14.1). A more detailed description of the study procedures on a by-visit basis is provided in Appendix 14.2 (Suggested Schedule of Events and Procedures by Study Visit). A suggested order of procedure conduct is also provided in this schedule.

3.1.1 Screening Period

The purpose of the Screening Period is to verify that the patient’s medical history and current status are consistent with the inclusion and exclusion criteria (refer to Sections 4.2 and 4.3, respectively), to ascertain the patient’s willingness to participate in the study, to obtain written informed consent and to establish baselines for the physical and laboratory parameters to be followed for the duration of the study. Patients will undergo baseline radiographic (lumbar and thoracic spine) and DXA (hip and lumbar spine) evaluations. One clinic visit (Visit 1) is scheduled during the Screening Period, but the required examinations may be performed on different days during the period, if needed.

Prior to entering the Screening Period, each potential study participant will have a preliminary assessment of inclusion/exclusion criteria by the investigator. A complete description of the study will provided to each potential participant and written informed consent will be obtained. After informed consent is obtained, the patient is entered into the Screening Period and procedures are conducted according to the Schedule of Visits and Procedures (refer to Appendix 14.1). Data should be recorded for patients who fail to complete screening or fail to meet study eligibility criteria, including the reason for failure. Patients who meet the study requirements based upon the Screening Period assessments will enter the Pretreatment Period.

If laboratory tests are delayed, or if a test needs to be repeated, two months (60 days) will be allowed for completion of screening procedures. Patients who do not meet the Vitamin D entry criterion may receive Vitamin D supplementation and be retested, as may patients with minor elevations of PTH. All patients enrolled following retesting and extended screening must have safety labs within 30 days of randomization.

3.1.2 Pretreatment Period

During the Pretreatment Period, one visit (Visit 2) is scheduled. Patients will have baseline evaluations performed as outlined in the Schedule of Visits and Procedures (Appendix 14.1).

Patients will undergo baseline efficacy labs. This study visit is to be scheduled within 7 days prior to the anticipated first day of treatment to allow confirmation of clinical laboratory test results and continued eligibility. Patients who have experienced a
serious adverse event during the Pretreatment Period will be terminated from the study.

Patients will undergo training on self-injection with the abaloparatide pen injector device in anticipation of treatment assignment. Teriparatide is a marketed treatment; therefore, if the patient is subsequently randomized to teriparatide, training will be done with the teriparatide pen after randomization but before the first injection on Day 1 (Visit 3). In addition, patients will be provided with daily Calcium (500–1000 mg) and Vitamin D (400–800 IU) supplementation, or a dose to be determined by Investigator, according to the patient’s need, which will be continued until the end of the Treatment Period; it will be recommended to patients that they continue these supplements through the Follow-up Period. Patients will be instructed to take the supplements during the evening with or without food or as otherwise instructed by the Investigator. Only the daily doses of Calcium and Vitamin D identified in the study protocol and determined by the Investigator may be taken during the study. Any patient unable to take the preparation of Calcium and Vitamin D supplied may be recommended a different preparation of Calcium and Vitamin D by the Investigator as long as the same daily dose of both Calcium and Vitamin D is administered.

On completion of the Pretreatment period, eligible patients will enter the Treatment Period.

3.1.3 Treatment Period

The Treatment Period starts on Day 1 and continues for 18 months. Patients are randomized to treatment on Day 1 and begin treatment the same day. A subset of 300 patients per group will have a wrist DXA scan, which will occur after randomization to study drug and can occur anytime up to 24 hours after the first injection. Those patients who are randomized to treatment with teriparatide will be trained with the teriparatide pen prior to the first injection on Day 1.

A total of 7 assessment clinic visits are scheduled during the Treatment Period (Visits 3-9), with an additional drug resupply and safety visit at Month 15 (Visit V8R). The final Treatment Period visit will be scheduled to occur one day after the last dose of study medication. Treatment will be daily, by self-injection. During the first 30 days of treatment patients will record drug dose, site of injection and any local reactions in a patient diary card. Local tolerance will again be assessed during a second 30-day period. This second diary will be provided to the patient either at the Month 9 (Visit 7) or will be forwarded later by mail, as appropriate, for completion by the patient during the 30 days of treatment in Month 11 of treatment. The diary will be collected and reviewed with the patient for treatment compliance and adverse events at the Month 1 (Visit 4) and Month 12 (Visit 8) visits. The patient will also maintain a diary throughout the study to summarize all study drug administration on a weekly basis.

Study patients will continue Calcium and Vitamin D supplementation during the Treatment Period.
Safety will be assessed at each study visit during the Treatment Period. Efficacy assessments will include one evaluation by x-ray after 18 months of treatment (End-of-Treatment, Visit 9) and evaluations of BMD by DXA after 6, 12 and 18 months of treatment (Visits 6, 8 and 9). Serum markers of bone metabolism, abaloparatide antibody and abaloparatide serum levels will also be measured during the Treatment Period. Additionally, a subset of patients treated with Abaloparatide-SC, Placebo and teriparatide (up to 100 per group to obtain up to 75 evaluable biopsies per treatment group) will consent and have a bone biopsy performed between Visit 8 and the End-of-Treatment visit (Visit 9). Patients in selected centers in the Abaloparatide-SC, Placebo and teriparatide groups who enrolled prior to the effective date of Version 3 of the protocol will be asked to undergo a single renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. Patients in selected centers enrolled after the effective date of Version 3 of the protocol will be asked to undergo two renal CT scans (obtained through standard abdominal/pelvic CT scan procedures), the first prior to treatment (Visit 3 and Visit 4, inclusive) and the second between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10, inclusive). Procedures are to be performed according to the Schedule of Visits and Procedures (Appendix 14.1).

In addition, at Visit 9, in patients who received Abaloparatide-SC/Placebo, the possibility of participating in the Extension Study will be discussed.

Patients who discontinue from the study prior to completing the Treatment Period will have all End-of-Treatment Visit evaluations performed as close to the time a patient is permanently discontinued from treatment as possible. If possible, an End-of-Study Visit should also be scheduled one month after the last dose of study medication was administered.

3.1.4 Follow-up Period

The Follow-up Period is the one month interval after the last dose of study medication during which patients are followed for adverse events, including clinically significant laboratory abnormalities. At the end of the Follow-up Period, patients will return to the clinic to undergo final study assessments (End-of-Study Visit; Visit 10). Patients will be recommended to continue their Calcium and Vitamin D supplements until the End-of-Study Visit (Visit 10).

Any clinically significant adverse events occurring during the Follow-up Period will be assessed and recorded at the End-of-Study Visit. Any adverse event or clinical laboratory abnormality recorded at this final visit will be monitored until it has resolved or has become chronic or stable.

Abaloparatide-SC/Placebo patients who complete 18 months of treatment and remain eligible will be given the opportunity to participate in an Extension Study. If patients elect to enroll in the Extension study, they will undergo the End-of-Study Visit (Visit 10), which will serve as the Day 1 Visit in the Extension Study.
Patients who received Abaloparatide-SC/Placebo and who do not participate in the Extension study will be offered 24 months of treatment with alendronate. These patients will receive standard-of-care management, according to their physician, during this period.

4.0 SELECTION OF STUDY POPULATION

4.1 Number of Subjects

A sufficient number of otherwise healthy postmenopausal women aged 50 to 85 with osteoporosis will be screened so that 2400 eligible patients qualify for the study and are randomized.

For the purposes of this study, osteoporosis is defined as a BMD that is 2.5 standard deviations or more below the norm of the adult female population. Postmenopausal women older than 65 who meet the fracture criteria but have a T-score ≤ -2.0 and > -5.0 may be enrolled. Additionally, women older than 65 who do not meet the fracture criteria may also be enrolled if their T-score is ≤ -3.0 and > -5.0.

The specific inclusion and exclusion criteria for enrolling patients in this study are presented below in Sections 4.2 and 4.3, respectively. Exceptions to these criteria should occur infrequently and should be discussed in advance and approved by the Sponsor Medical Monitor. If the exception is agreed upon (rare) and a patient is allowed to participate, the Sponsor Medical Monitor will send confirmation to the study site acknowledging the exception. The confirmation form or letter must be kept with the study records.

Minor variations from the normal range in clinical laboratory test results (hematology, chemistry, and urinalysis) are acceptable if they are determined to be not medically significant by the Investigator in that they do not compromise patient safety or the assessment of efficacy and are documented as such. Any unexpected clinically significant abnormality that would exclude the patient from participation in the study may be retested. If the parameter is normal on retest, the patient may be included in the study.

Patients who previously screened for this study cannot be rescreened and entered into the study other than subsequent to an amendment of eligibility criteria.

4.2 Inclusion Criteria

Patients must meet all of the following criteria to be eligible to participate in this study.

1. The patient is a healthy ambulatory postmenopausal woman from 50 to 85 years of age (inclusive) with osteoporosis.

2. The patient has been postmenopausal for at least 5 years. Postmenopausal status will be established by a history of amenorrhea for at least 5 years and by an elevated serum follicle-stimulating hormone (FSH) value of ≥ 30 IU/L.

3. The patient has a bone mineral density T-score ≤ -2.5 and > -5.0 at the lumbar spine (L1-L4) or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or
thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. Postmenopausal women older than 65 who meet the above fracture criteria but have a T-score ≤ -2.0 and > -5.0 may be enrolled. Women older than 65 who do not meet the fracture criteria may be enrolled if their T-score is ≤ -3.0 and > -5.0.

4. The patient is in good general health as determined by medical history and physical examination (including vital signs), has a body mass index (BMI) of 18.5 to 33 (Appendix 14.3), inclusive, and is without evidence of clinically significant abnormality in the opinion of the Investigator.

5. Any required concomitant medications which are not excluded in Section 6.0 may be continued through the study. Every effort should be made to maintain the medication at a stable dose throughout the study, subject to the Investigator’s medical judgment.

6. The patient has serum calcium (albumin-corrected), PTH (1-84), serum phosphorus and alkaline phosphatase values all within the normal range during the Screening Period. Patients with minor elevations or reductions in serum calcium may be enrolled if serum ionized calcium is normal. Any patient with an elevated alkaline phosphatase value, and who meets all other entry criteria, would be required to have a normal bone-specific alkaline phosphatase result to be enrolled.

7. The patient has serum 25-hydroxy Vitamin D values above 15 ng/mL and within 3 times the upper normal range.

8. The patient’s resting 12-lead electrocardiogram obtained during screening shows no clinically significant abnormality and a QTc ≤ 470 msec (Bazett’s correction).

9. The patient’s systolic blood pressure is ≥ 100 and ≤ 155 mmHg, diastolic blood pressure is ≥ 40 and ≤ 95 mmHg, and heart rate is ≥ 45 and ≤ 100 bpm (sitting or supine).

10. The patient has no clinically significant abnormality of serum hemoglobin, hematocrit, WBC and platelets, or usual serum biochemistry: electrolytes, renal function, liver function and serum proteins.

11. The patient has read, understood, and signed the written informed consent form.

4.3 Exclusion Criteria

Patients with any of the following characteristics are not eligible to participate in the study.

General exclusion criteria:

1. History of more than 4 spine fractures, mild or moderate, or any severe fractures.

2. Presence of abnormalities of the lumbar spine that would prohibit assessment of spinal bone mineral density, defined as having at least 2 radiologically evaluable vertebrae within L1-L4.

3. Unevaluable hip BMD or patients who have undergone bilateral hip replacement (unilateral hip replacement is acceptable).
4. History of bone disorders (e.g., Paget’s disease) other than postmenopausal osteoporosis.
5. Unexplained elevation of serum alkaline phosphatase.
6. History of radiotherapy (radiation therapy), other than radioiodine.
7. History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances to a degree that would interfere with the interpretation of study data or compromise the safety of the patient.
8. History of Cushing’s disease, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year.
9. History of significantly impaired renal function (serum creatinine >177 μmol/L or >2.0 mg/dL). If the serum creatinine is > 1.5 and ≤ 2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must be ≥ 37 mL/min.
10. History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin).
11. History of osteosarcoma at any time.
12. History of nephrolithiasis or urolithiasis within the past five years.
13. 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 lying and 3 minutes standing) and/or any symptomatic hypotension at screening (24,25).
14. Patients known to be positive for Hepatitis B, Hepatitis C, HIV-1 or HIV-2. Testing is not required in the absence of clinical signs and symptoms suggestive of HIV infection or acute or chronic hepatitis.

Medication-related exclusion criteria:

15. Known history of hypersensitivity to any of the test materials or related compounds.
16. Prior treatment with PTH or PTHrP drugs, including abaloparatide.
17. Prior treatment with bisphosphonates*, fluoride or strontium in the past five years or prior treatment with gallium nitrate, or with as yet unapproved bone-acting investigational agents at any time (26).
   (*Patients who had a short course of bisphosphonate treatment (3 months or less) and were intolerant of the treatment are not excluded from study participation.)
18. Prior treatment with denosumab, calcitonin, SERMs (such as raloxifene or tamoxifen), tibolone, or anabolic steroids in the past 12 months. Estrogens administered as hormone replacement therapy (HRT), with or without progestins, are not exclusionary.
19. Treatment with anticonvulsants that affect Vitamin D metabolism (phenobarbital, phenytoin, carbamazepin or primidone) or with chronic heparin within the 6 months prior to the Screening Period.

20. Daily treatment with oral, intranasal or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of corticosteroids (for seasonal allergies or asthma) is not exclusionary.

21. Exposure to general anesthesia within the 12 weeks prior to the Screening Period.

22. Exposure to an investigational drug within the 12 months prior to the Screening Period.

**Lifestyle-related exclusion criteria:**

23. Abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption, significant recent weight change), Vitamin D intake of \( \geq 4,000 \) IU/day or Vitamin A intake of \( \geq 10,000 \) IU/day\(^1\).

24. Patient is known to abuse alcohol or use illegal drugs within 12 months of the Screening Period.

### 4.4 Withdrawal of Patients from the Study

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

The Investigator must withdraw patients 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 or hypercalciuria as described in Sections 4.5.1 and 4.5.2;
- Treatment-related SAEs;
- Severe hypersensitivity to abaloparatide or teriparatide;
- Refusal of treatment;
- Inability to complete study procedures;
- Lost to follow-up.

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

- WHO Grade 3 or 4 adverse events [Refer to Appendix 14.4];
- A complex of adverse events which, in the judgment of the Investigator justifies treatment cessation;
- Serious intercurrent illness;

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\(^1\) Vitamin D given during the pretreatment period to treat vitamin D deficiency is permissible.
Patients will be offered the opportunity to discontinue from the study for the following reasons after site consultation with the Study Medical Monitor:

- Incident vertebral or non-vertebral fragility fracture

Patients treated with Abaloparatide-SC/Placebo who withdraw due to incident clinical vertebral or non-vertebral fragility fracture will be offered standard-of-care treatment with alendronate for up to 24 months. Should a patient who experiences a clinical vertebral or non-vertebral fragility fracture choose to remain in the study, they will be asked to sign an additional Informed Consent Form further explaining the potential risks and benefits of remaining in the study.

If a patient is withdrawn or discontinued from the study, the reason for withdrawal from the study is to be recorded in the source documents and on the case report form. All patients withdrawn prior to completing the study should be encouraged to complete study procedures scheduled for the End-of-Treatment and End-of-Study Visits. The End-of-Treatment procedures should be conducted as close to the time a patient is permanently discontinued from treatment. If possible, the End-of-Study Visit should be scheduled one month after the last dose of study medication was administered. All adverse events should be followed as described in Section 8.2.

### 4.5 Temporary Suspension of Treatment

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

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

If the treatment suspension is due to a medical emergency and study medication needs to be unblinded, please refer to Section 5.6 for the procedures to be followed.

**Response to Hypercalcemia or Hypercalciuria**

Patients who develop hypercalcemia or hypercalciuria during the study are to have treatment with study medication reduced or study medication temporarily suspended as described below.
4.5.1 Treatment Suspension due to Hypercalcemia

For any pre-dose serum calcium (albumin-corrected) value which is \( \geq 0.3 \) to 1.0 mg/dL, corresponding to \( \geq 0.08 \) to 0.25 mmol/L, above the upper limit of normal (ULN) (inclusive), confirm hypercalcemia by drawing a new serum sample as soon as the result is received:

- If the result of the retest remains within this range, discontinue Calcium and Vitamin D supplements for 7 days and perform a second retest. The patient is to continue study medication administration during this interval.
  - If the second retest is normal, the patient may continue on study and resume Calcium and Vitamin D supplements.
  - If the second retest is still elevated and the patient is receiving Abaloparatide-SC/Placebo, the patient continues on study with a dose reduction for abaloparatide from 80 μg to 40 μg, but without Calcium and Vitamin D supplements.
  - If the second retest is still elevated and the patient is receiving teriparatide, the patient is to be discontinued from the study.

- If the patient continues in the study (with Calcium and Vitamin D supplements) and has a repeat episode of a pre-dose serum calcium value \( \geq 0.3 \) to 1.0 mg/dL, corresponding to \( \geq 0.08 \) to 0.25 mmol/L, above the ULN (inclusive), repeat the above assessment.
  - If the patient again returns to normal when not taking Calcium and Vitamin D supplements, the patient may continue in the study without Calcium and Vitamin D supplements.
  - If the hypercalcemia is confirmed in the absence of Calcium and Vitamin D supplements and the patient is receiving Abaloparatide-SC/Placebo, the patient continues on study with a dose reduction for abaloparatide from 80 μg to 40 μg, but without Calcium and Vitamin D supplements.
  - If the hypercalcemia is confirmed in the absence of Calcium and Vitamin D supplements and the patient is receiving teriparatide, the patient is to be discontinued from the study.

- If a Abaloparatide-SC/Placebo patient continues on the study at the reduced dose of 40 μg (without Calcium and Vitamin D supplements) and has another episode of a pre-dose serum calcium value \( \geq 0.3 \) to 1.0 mg/dL, corresponding to \( \geq 0.08 \) to 0.25 mmol/L, above the ULN (inclusive), perform a retest.
  - If the retest is normal, the patient may continue on study at the reduced dose (without Calcium and Vitamin D supplements).
  - If the retest is still elevated, the patient is to be discontinued from the study.
For any pre-dose serum calcium value >1.0 mg/dL, corresponding to >0.25 mmol/L, above ULN:

- Discontinue Calcium and Vitamin D supplements and discontinue the study medication 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 medication.
  - If the second retest is normal, the patient may continue on study and resume study medication and Calcium and Vitamin D supplements.
  - If the second retest remains elevated (≥0.3 mg/dL above ULN, or ≥ 0.08 mmol/L) and the patient is receiving Abaloparatide-SC/Placebo, the patient continues on study with a dose reduction for abaloparatide from 80 μg to 40 μg, but without Calcium and Vitamin D supplements.
  - If the second retest remains elevated (≥0.3 mg/dL above ULN) and the patient is receiving teriparatide, the patient is to be discontinued from the study.

- If a Abaloparatide-SC/Placebo patient continues on the study at the reduced dose of 40 μg (without Calcium and Vitamin D supplements) and has another episode of a pre-dose serum calcium value ≥0.3 mg/dL above the ULN, perform a retest.
  - If the retest is normal, the patient may continue on study at the reduced dose (without Calcium and Vitamin D supplements).
  - If the retest is still elevated, the patient is to be discontinued from the study.

If the patient continues in the study and has a repeat episode of pre-dose serum calcium >1.0 mg/dL above ULN, the patient is to be discontinued from the study.

4.5.2 Treatment Suspension due to Hypercalciuria

For a Calcium:Creatinine ratio >0.4 mg/mg, corresponding to >1.131 mmol/mmol, check the patient’s pre-dose serum calcium and apply the algorithm outlined in Section 4.5.1 if Calcium is elevated.

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

- Discontinue Calcium and Vitamin D supplements and recheck urine Calcium:Creatinine values after 7 days.
  - If the urine Calcium:Creatine ratio continues to be >0.4 mg/mg in the presence of normal serum calcium, the patient may continue in the study under medical supervision.
If the urine Calcium:Creatine ratio returns to normal, the patient may restart Calcium and Vitamin D supplements and continue in the study.

If the patient restarts the Calcium and Vitamin D supplements and hypercalciuria returns, Calcium and Vitamin D supplementation should be terminated. The patient may continue in the study under medical supervision, and resuming Calcium and Vitamin D supplementation may be considered if deemed appropriate by the investigator.

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

4.6 Replacement of Patients

Patients who have been randomized into the study and subsequently withdraw or drop out of the study will not be replaced.
5.0 STUDY TREATMENTS

5.1 Study Medications

All study medications are for investigational use only and are to be used only within the context of this study. The Sponsor will supply all study medications.

5.1.1 Abaloparatide-SC, Placebo and Teriparatide

Abaloparatide-SC, Placebo and teriparatide will be supplied by the Sponsor. Pen devices and needles for administration of study medications also will be supplied to the study sites.

Abaloparatide-SC: Each multi-dose cartridge contains 2 mg/mL abaloparatide (free base) in 5 mg/mL tri-hydrate sodium acetate and 5 mg/mL of phenol (preservative) adjusted at pH 5.1 with acetic acid. Abaloparatide-SC is supplied as a liquid in a 1.5 mL Type 1 glass cartridge and is stored refrigerated at 5 ± 3°C. The multi-dose cartridge is designed to deliver a dose of 80 μg of abaloparatide in 40 μL of fluid when inserted into the Pen Injector device. The pen is also capable of delivering a half dose of abaloparatide, or 40 μg of abaloparatide in 20 μL of fluid, with appropriate manual adjustment. When in use, multi-dose cartridges of Abaloparatide-SC can be stored for up to 30 days at room temperature. When used with the supplied pen and needles, each cartridge may be used to deliver study medication at the required daily dose for 30 days. Patients will be provided with a sufficient number of cartridges to continue on treatment until the next scheduled return to the study site.

Placebo: Placebo is formulated similarly but without active abaloparatide and is similarly supplied as a liquid in a 1.5 mL Type 1 glass cartridge and is stored refrigerated at 5 ± 3°C. The multi-dose cartridge is designed to deliver a dose of Placebo in 40 μL of fluid when inserted into the Pen Injector device. The pen is also capable of delivering a half dose of Placebo, or 40 μg of abaloparatide in 20 μL of fluid, with appropriate manual adjustment. When in use, multi-dose cartridges of Placebo can be stored for up to 30 days at room temperature. When used with the supplied pen and needles, each cartridge may be used to deliver study medication at the required daily dose for 30 days. Patients will be provided with a sufficient number of cartridges to continue on treatment until the next scheduled return to the study site.

Teriparatide (rDNA origin) injection (250 μg/mL) will be supplied in multi-dose disposable pens containing a glass cartridge. Each pen contains enough study medication to deliver the required daily dose for 28 days. Patients will be provided with a sufficient number of pens to continue on treatment until the next scheduled return to the study site.

5.1.2 Calcium and Vitamin D Supplements

Calcium and Vitamin D supplements will be provided by the sites.

5.2 Packaging, Labeling and Storage

5.2.1 Packaging

Abaloparatide-SC and Placebo will be supplied and packaged as identical cartridges and pens. The study will not be blinded with regard to teriparatide which is supplied from marketed product; however, because teriparatide will be supplied to the site in identical outer packaging as Abaloparatide-SC and Placebo, the site will remain blinded until treatment is
assigned, the package is opened, and its contents are dispensed. 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.

5.2.2 Labeling

Each study medication kit will be labeled with an identifying kit number. In addition, each kit will be labeled with a caution statement and other information required by local Regulatory Authorities.

Calcium and Vitamin D supplements will not be relabeled for the study.

5.2.3 Storage

All study medications (abaloparatide, Placebo, teriparatide) must be kept in a secure, limited-access storage area at 2°C to 8°C (36°F to 46°F) until dispensed for use to a study patient or until returned to the Sponsor. Once dispensed, Abaloparatide-SC or Placebo is stable for 30 days at room temperature. When more than one cartridge of abaloparatide or Placebo is dispensed for 30 days of use each, it is recommended that the cartridges not in use be kept refrigerated until required.

The teriparatide pen should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) at all times.

Calcium and Vitamin D supplements may be stored at room temperature.

5.3 Treatment Assignment

All patients who are screened for the study will be assigned a unique 7 digit patient number which will be used to identify patients throughout the study and on the CRFs. Patient numbers will be assigned as follows:

XXX YYYY, where:

- XXX represents the study site number;
- YYYYY represents the patient ID number

Patients who meet all inclusion criteria and none of the exclusion criteria and successfully complete the Screening and Pretreatment Periods of the study will be assigned sequentially to a randomized treatment group on Day 1 of the Treatment Period. Patients will only receive one study ID at the time of screening and therefore will not receive a new identifier at randomization. During the randomization call, sites will enter the kit number assigned to the subject into the IVRS system. The IVRS system will record the site number, the subject number and the kit/randomization number within the system. Information regarding treatment assignment will reside within the IVRS system, as part of the study blinding.

Study medication kits will be assigned sequential numbers beginning with 001. The study medication kit number assigned to an eligible patient will be recorded in the source
documents, on the appropriate page of the CRF, and reported to the IVRS system as described above. Once a kit has been assigned, it may not be reused.

The Sponsor statistician will be responsible for overseeing the preparation of the master randomization scheme that will be used to package study medication into kits and for the IVRS system.

5.4 Study Medication Administration

Patients will self-administer study medication on a daily basis during the Treatment Period. The first self-administration is to occur at the study site under observation. On the days of clinic visits, study medication must be administered in the clinic to accommodate pre-injection and post-injection procedures; study personnel may administer the study medication.

Patients will be trained by study personnel during the Pretreatment Period to self-inject study medication with the Abaloparatide-SC/Placebo cartridge and pen device. Those patients who are subsequently randomized to teriparatide treatment on Day 1 will be trained in the use of the teriparatide pen on Day 1. If a patient requires assistance with study medication administration, an individual (e.g., a family member) who has been trained by study personnel may provide assistance.

Patients will be instructed by the study site to inspect the contents of their study medication device before each injection. If the cartridge or pen contents are not clear and colorless, or if the contents contain particles, the patients will be instructed not to use that cartridge or pen and to contact the study site for further guidance.

Injections should be administered in the morning and preferably at the same time each day. All injections are to be given in the periumbilical region, rotating the exact site of injection each day. If it is deemed medically necessary by the investigator for an injection to be administered at a site other than the abdomen, the alternate site of injection is to be recorded and the reason for the change documented in the medical chart.

On the first day of study medication administration, the patient should self-inject while in a sitting or lying position at the study site and remain in that position for approximately 5 minutes. The patient is to remain under observation for a minimum of 60 minutes. An orthostatic blood pressure measurement will be taken 60 minutes after the injection. On the days when blood sampling is required after study medication injection, the patient is to remain in the vicinity of the clinic for the blood collections scheduled up to 4 hours post-injection.

Abaloparatide-SC and Placebo will be supplied in cartridges, each containing enough study medication to deliver the required daily dose for 30 days. Patients are to be instructed to change cartridges after 30 days, regardless of how much medication is left in the initial cartridge. Teriparatide will be supplied as a pre-filled pen, each with enough study medication for 28 days. Patients will be instructed to use a new pen after each 28-day period. At each clinic visit during the Treatment Period, the used Abaloparatide-SC or Placebo cartridges, but not pen, or the used teriparatide pens should be returned and a sufficient
number of new cartridges or teriparatide pens are to be provided to last until the next clinic visit or as needed to replenish drug supply. Compliance, adverse events, and use of concomitant medications should be reviewed upon drug re-supply.

5.5 Treatment Compliance

In order to evaluate the safety, efficacy and tolerance of Abaloparatide-SC, it is critical that patients comply with the treatment regimen to which they were randomized and honor the schedule of visits and procedures required by the study. Patient compliance will be ascertained by three methods: patient diaries, cartridge accountability, and site-assessment of remaining drug content of returned cartridges.

The location, date and time that each dose of study medication was administered will be recorded in a patient diary for the first 30 days of treatment for review at the Month 1 (Visit 4), and for the 30 days of Month 11 for review at the Month 12 (Visit 8) study visit, and entered in the appropriate case report form. Weekly summaries of study drug administration will also be maintained by the patient throughout the study. All doses of study medication are to be self-administered or administered by an individual trained in giving the injection (e.g., a family member). Study personnel may administer the injection on days of clinic visits.

If a patient does not take all study medication (Abaloparatide-SC, Placebo, teriparatide, Calcium and Vitamin D supplements), the reason for the missed dosing is to be recorded in source documents and on the appropriate case report form. During the Follow-up Period, it is recommended that patients continue taking the Calcium and Vitamin D supplements, but treatment compliance will not be assessed during this post-treatment period.

The residual volume of returned cartridges will be measured by the height of the fluid column and recorded in source documents and on the appropriate case report form by the site personnel when the cartridge is returned by the patient.

5.6 Unblinding of Study Medication

5.6.1 Medical Emergency

Breaking the study blind for a patient should be done only in the event of a medical emergency where the identity of study medication is necessary to appropriately treat the patient. The Investigator may unblind the patient as to study medication through the IVRS system. The IVRS system will automatically document and record any such unblinding and notify the Sponsor Medical Monitor and the Study Safety Officer of the unblinding. In addition, the Sponsor Medical Monitor and the Study Safety Officer also have the ability to unblind the study medication in a medical emergency.

If the Investigator determines that the medical event that resulted in unblinding of the study medication is not treatment related (relationship is documented as “none”; see Section 8.3 for definitions of relationship), the patient may continue treatment and participation in the study, providing no more than 14 days has elapsed since the last dose of study medication (refer to Section 4.5 for details regarding temporary suspension of treatment).
If the patient discontinues from further treatment with study medication, they should undergo the End-of-Treatment and End-of-Study procedures as outlined in Section 7.0 and the Schedule of Visits and Procedures (Appendix 14.1).
6.0 CONCOMITANT MEDICATIONS

6.1 Concomitant Medications

Calcium (500-1000 mg/day) and Vitamin D (400-800 IU/day) supplements, or a dose to be
determined by Investigator according to the patient’s need, are required to be administered
daily from the Pretreatment Period until the end of the Treatment Period. It is recommended
that patients continue taking these supplements through the Follow-up Period. The doses and
schedule of Calcium and Vitamin D supplements, which are part of the study medication
protocol, should be adhered to and not be changed other than for medical necessity (Section
3.1.2). 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 patient
must be on a stable dose at study entry and every effort should be made to maintain a stable
dose during study participation.

The occasional use of over-the-counter medications at approved doses (e.g., ibuprofen or
acetaminophen) for headache or minor discomfort is allowed. These are to be recorded on
the appropriate case report form. Patients 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 patient to take any other medication during the study, the
specific medication(s) and indication(s) must be discussed with the Investigator. All
concomitant medications taken during the course of the study must be recorded in the
patient’s medical record or source document and transcribed into the case report form.

6.2 Prohibited Medications

Patients cannot take any medications, including over-the-counter, non-prescription
medication, with the exception of those noted in Section 6.1, within 72 hours prior to dosing
on Day 1.

As outlined in the exclusion criteria (Section 4.3), patients who have been treated with
bisphosphonates, fluoride or strontium in the past five years or received prior treatment with
gallium nitrate, or with as yet unapproved bone-acting investigational agents at any time are
to be excluded from study participation. Patients treated with a short course of
bisphosphonates (3 months or less) who were intolerant of the treatment may be considered
for study participation.

Estrogens given as HRT are allowed at entry into the study but cannot be initiated during the
study except for local low dose vaginal estrogen.

In addition, patients are ineligible for the study if they have received general anesthesia
within 12 weeks or have an abnormal nutritional status (abnormal diets, excessive or unusual
vitamin or herbal intakes, malabsorption).
Occasional short term (≤ 3 months) use of corticosteroids for seasonal allergies or asthma is not prohibited.

Patients who require chronic treatment with either an anticonvulsant (phenobarbital, phenytoin, carbamazepin or primidone), or with heparin will be discontinued.
7.0 STUDY ASSESSMENTS

The study protocol will consist of a Screening Period, a Pretreatment Period, a Treatment Period and a Follow-up Period. During the Screening Period, patients will be assessed to establish study eligibility and to collect baseline measurements.

In the Pretreatment Period, patients will undergo baseline efficacy labs, receive training in the techniques of self-injection with the Abaloparatide-SC/Placebo pen device, receive diary training and begin taking Calcium and Vitamin D supplements.

The Treatment Period will begin with randomization. Patients randomized to teriparatide treatment will be trained in the use of the teriparatide pen on Day 1. During the Treatment Period, patients will continue to take Calcium and Vitamin D supplements and will self-administer the assigned study medication. Safety, efficacy and pharmacodynamic evaluations will be performed.

During the Follow-up Period (the one month interval after the completion of study treatment) it is recommended that patients continue the daily supplementation of Calcium and Vitamin D. This will culminate in an End-of-Study Visit where final study evaluations are performed and the patient is terminated from the study.

The assessments performed at each study visit are displayed in the Schedule of Visits and Procedures in Appendix 14.1. Appendix 14.2 provides a more detailed schedule of the study procedures by study visit with a suggested order of procedure conduct. Day 1 is defined as the first date that study medication is administered. All days prior to this point are designated with a ‘minus’ sign (e.g., Day –2, Day –1).

Exact procedures for centrifuging, storage, and shipping of laboratory samples will be detailed in a separate document. The actual time of each sample collection will be recorded in the case report form.

Study-specific assessments are to be conducted only after the patient has provided written informed consent to participate in this study. The study assessments are described in more detail in Section 7.1 below.

7.1 Clinical Procedures/Assessments

7.1.1 Informed Consent

Signed informed consent is obtained before any study-specific procedures are performed.

7.1.2 Medical History

A complete medical history and review of body systems along with demographic data will be obtained for all patients during the Screening Period. Data to be recorded in the case report form include the patient’s gender, race, date of birth, tobacco use history, alcohol and caffeine use, and use at any time of hormone replacement therapy. Prior fracture history will also be recorded.
7.1.3 Physical Examination

A complete physical examination (general appearance, head/ears/eyes/nose/throat [HEENT], lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, and extremities) will be performed during the Screening Period and at the End-of-Treatment. Any treatment-related findings should be followed up at the final study visit during the Follow-up Period (Visit 10).

Interim or symptom-directed physical examinations may be performed at other times at the discretion of the Investigator, if necessary, to evaluate adverse events or clinical laboratory abnormalities.

7.1.4 Vital Signs, Weight and Height

Vital signs (orthostatic blood pressure, body temperature (°C) and respiration rate (breaths/minute)) are to be measured and recorded at each study visit.

All blood pressure assessments will be conducted as orthostatic measurements. Blood pressure (mmHg; measured in the same arm each visit) and pulse rate (bpm) will be measured after five minutes in the supine position. Immediately following this measurement blood pressure will be measured again after three minutes in the standing position. At Treatment Visits 3, 4, 5, 6, 7, and 8, orthostatic blood pressure will be measured prior to injection and again 60 minutes after injection.

Height (cm) will be measured at Visit 1, 2 and 9. Height will be measured in the standing position at the Pretreatment and End-of-Treatment visits using a medical stadiometer and standardized procedures each time.

Weight (kg) will be measured at Visits 1, 8, 9 and 10.

7.1.5 Electrocardiogram

Twelve-lead supine electrocardiograms (ECGs) will be performed according to the Schedule of Visits and Procedures. The following ECG parameters will be recorded: rhythm, heart rate, PR interval, QRS duration and QT/QTc. ECGs will be performed during the Screening Period (Visit 1), the Treatment Period (Visits 3-9), and the Follow-up Period (Visit 10). At Treatment Visits 3, 4, 5, 6, 7, and 8, ECGs will be measured prior to injection and again 1 hour after injection. More than one ECG may be performed per time-point.

7.1.6 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory. Prior to starting the study, the Sponsor (or its designee) will provide each Investigator with copies of the appropriate laboratory certifications and normal ranges for all laboratory parameters to be performed by that laboratory.

Routine clinical laboratory tests will be assessed during the Screening, Pretreatment and Treatment Periods until the End-of-Treatment Visit (Visit 9). Bone-specific laboratory tests (serum calcium, PTH(1-84), and 25-hydroxy Vitamin D) will be
conducted during the Screening and Treatment Periods as outlined in Appendix 14.1. Once eligibility has been confirmed, anabolic (PINP, osteocalcin, and BSAP) and resorptive bone marker (CTX) and 1,25-dihydroxy Vitamin D will be measured during the Pretreatment and Treatment Periods as outlined in Appendix 14.1. Urine Calcium:Creatinine ratio will be determined during the Treatment Period at Visits 3, 4, 5, 6, 7, 8, and 9. Creatinine Clearance also will be determined during the Treatment Period at Visits 3, 4, 5, 6, 7, 8, and 9. Serum calcium will be measured at treatment Visits 1 and 3, 4, 5, 6, 7, 8, and 9. Four hour post-dose serum calcium will be measured at treatment Visits 3, 4, 5, 6, 7, and 8. Hypercalcemia and hypercalciuria are to be evaluated as described in Sections 4.5.1 and 4.5.2, respectively. In addition, all clinically significant laboratory abnormalities indicating an adverse event will be followed up by repeat testing and further investigated according to the judgment of the Investigator.

Clinical laboratory evaluations are to be performed according to the Schedule of Visits and Procedures (Appendix 14.1). Specific tests to be run are described below.

Note: blood and urinalysis samples are to be obtained under fasting conditions (N.P.O. for 8 hours; water is acceptable) in the morning of each scheduled study visit prior to injection of the study medication with the exception of blood samples for abaloparatide post-injection drug levels and 4-hour post-injection calcium levels. For the 24-hour urine collection, patients will be instructed to begin the collection by discarding the first morning void (~6 a.m.) the day prior to the scheduled clinic visit and to then collect their urine for 24 hours. A final void is to be collected at the end of the 24-hour period and the urine collection transported to the clinic by the patient. Routine urinalyses are to be performed using samples freshly voided during the clinic visit.

**Hematology:**
- Hemoglobin
- Hematocrit
- WBC count with differential in absolute counts
- RBC count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular hemoglobin (MCH)
- Platelet count

**Coagulation**
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)

**Chemistry**
- Sodium
- Potassium
- Chloride
- Inorganic phosphorus
- Albumin
- Total protein
- Glucose
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyltranspeptidase (GGT)
- Creatine phosphokinase (CPK)
- Alkaline phosphatase
- Total bilirubin
- Lactate dehydrogenase (LDH)
- Cholesterol
- Triglycerides
- Total calcium

**Vitamin D**
- 1, 25-dihydroxy Vitamin D level
- 25-hydroxy Vitamin D level

**Urine**
- Calcium
- Creatinine

**Urinalysis**
- pH
- Glucose
- Protein
- Ketones
- Bilirubin
- Blood
- Urobilinogen
- Specific gravity
- Nitrite
- Leukocytes

Urine microscopic examination will be done, if positive findings noted on dipstick.

**Endocrine Tests**
- PTH(1-84)
- *Serum FSH
- *Serum estradiol

* Only performed during Screening Period.

7.1.7  Serum Markers of Bone Metabolism

Blood samples will be taken to measure efficacy-related markers of bone metabolism during the Pretreatment Period and at specified visits during the Treatment Period in a subset of 600 patients (approximately 200 per treatment group).
The following markers of bone formation will be measured:

- Serum N-terminal propeptide of type I procollagen (PINP)
- Serum bone-specific alkaline phosphatase (BSAP)
- Serum osteocalcin

The following marker of bone resorption and collagen breakdown will be measured:

- Serum C-telopeptides of type 1 collagen crosslinks (CTX)

7.1.8 Clinical and Radiologic Evaluation of Fractures

To be eligible for randomization and entry into the Treatment Period, patients must have radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. Women older than 65 who do not meet the fracture criteria may also be enrolled if their T-score is ≤ -3.0 and > -5.0.

All patients will have x-rays taken to document fractures of the spine, lumbar and thoracic vertebrae. Patients will undergo antero-posterior and lateral radiographs of the lumbar and thoracic spines during the Screening Period and at the End-of-Treatment visit. However, in the event that qualifying lumbar or thoracic vertebral x-rays have been obtained as a consequence of routine patient care within 3 months prior to the Screening visit and comply with the study x-ray procedures, such x-rays may be used for assessment of eligibility.

Patients will also be clinically evaluated for non-vertebral fractures (wrist, hip, rib, etc.) which occur de novo during the Treatment Period.

All radiographs will be viewed and assessed centrally by a blinded, independent assessor (radiologist) on the basis of existing baseline and study-acquired vertebral deformity, and fracture will be assessed according to the severity scale of Genant (1). A second blinded radiologist will confirm the assessment of the first reviewer for all patient radiographs in which an incident fracture has been identified. In the case of any disagreement, a third consensus assessment will be made to adjudicate the incident fracture. A standardized graded scale of severity of the vertebral deformity will be provided for this assessment.

Fractures identified during the study will not be recorded as AEs unless the patient is hospitalized, the fracture is complicated, or the Investigator considers the fracture to be unrelated to the patient’s underlying osteoporosis. All fractures will be identified and evaluated as part of the disease assessment and will be documented in the case report forms and source documents.

7.1.9 Bone Mineral Density

To be eligible for randomization and entry into the Treatment Period, each patient must have a BMD T-score ≤ -2.5 and > -5.0 at the lumbar spine or hip by dual energy
x-ray absorptiometry (DXA) and will be reported based on gm/cm² (Appendix 14.5). Postmenopausal women older than 65 who meet the fracture criteria but have a T-score ≤ -2.0 and > -5.0 may be enrolled as well as women older than 65 who do not meet the fracture criteria but who do have a T-score ≤ -3.0 and > -5.0.

All patients will have BMD measurements taken via DXA during the Screening (Visit 1; spine, hip) and Treatment Day 1 (Visit 3; forearm in a subset) and during the Treatment Period (Visits 6, 8 and 9). However, in the event that qualifying BMD scans have been obtained as a consequence of routine patient care within 3 months prior to the Screening visit and comply with the study DXA procedures, such scans may be used for assessment of eligibility and need not be redone at Screening.

The initial DXA will be performed during the Screening Period and will be used to determine eligibility for participation in the study in conjunction with the radiological evaluations of fractures. The DXA is to be performed on the hip (femoral neck) and spine (L1-L4) at this visit and a qualifying T-score from either location can be used to determine eligibility. The spinal DXA is to be taken in the postero-anterior projection with any subsequent spinal DXA to be taken in the same projection. Patients who meet the entry criterion for BMD who satisfy all other eligibility criteria, and who have no exclusionary findings, will then be enrolled. On Day 1, a subset of 300 patients per group will have a wrist DXA scan. BMD measurements by DXA will be repeated at the lumbar spine (L1-L4), hip, and wrist during the Treatment Period (Visits 6, 8 and 9).

Details regarding the procedures for the conduct and processing of DXA scans will be provided in separate instruction manual. Patient eligibility will be determined based on local analysis of the BMD scan at the study site. The Central Imaging CRO will subsequently confirm the acceptability of each DXA scan with the study sites. If any scan is unacceptable for technical or other reasons, a repeat scan must be completed as soon as possible. Investigators will be blinded to the results of all follow-up DXA scan results throughout the study unless a safety issue is identified by the independent radiologist.

If the independent radiologist identifies any patient who shows a continuing significant deterioration from baseline (>7%) of BMD at spine or hip during the study, the study physician will be notified, the assessment will be repeated and, if confirmed, the patient will be discontinued from the study. The study physician will make this determination on the basis of the centrally read DXA relative to the baseline measurement in consultation with the Sponsor Medical Monitor. All such instances will be communicated to the DSMB.

7.1.10 Quantitative Bone Histomorphometry Assessment

In a subset of patients receiving Abaloparatide-SC, Placebo and teriparatide (up to 100 per group to obtain up to 75 evaluable biopsies per treatment group), bone biopsy of the iliac crest will be performed between Visit 8 and the End-of-Treatment Visit (Visit 9) for assessment of quantitative bone histomorphometry using a dual-labeling procedure. Details regarding the procedures for the conduct and processing of the
bone biopsy will be provided in separate instruction manual. All bone biopsies will be read at a central specialized facility. A separate consent form will be obtained for those patients agreeing to undergo the biopsy procedure and additional clinic visits will be scheduled, as required, to prepare for the bone biopsy procedure between Visit 8 and Visit 9.

7.1.11 Renal assessment by CT Scan

In selected centers, a subset of patients in the Abaloparatide-SC/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. Patients in selected centers enrolled after the effective date of Version 3 of the protocol, will be asked to undergo two renal CT scans, the first prior to treatment (between Visit 3 and Visit 4, inclusive), and the second between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. The renal CT scans will assess the renal parenchyma and collecting system for renal calcification. Details regarding the procedures for the conduct and processing of renal CT scans will be provided in separate instruction manual. A separate consent form will be obtained for patients participating in the procedure.

7.1.12 Abaloparatide Serum Level and Antibody Assessments

Samples for measurement of serum levels of abaloparatide will be taken at Visits 3, 4, 5, 6, 8 and 9 during the Treatment Period as part of a Population PK assessment. One peak level is to be drawn per patient per visit at the following varying post-injection times: 10 minutes to 30 minutes; 30 minutes to 1 hour; 1 hour to 2 hours; 2 hours to 3 hours; 3 hours to 4 hours. These draw times are to be randomized across Visits 3, 4, 5, 6, and 8. At the End-of-Treatment (Visit 9), only a trough level will be measured. Patients randomized to teriparatide will not have samples drawn for abaloparatide serum levels.

Samples for anti-abaloparatide antibody assessment will be obtained at Visits 3 (Day 1), 4, 5, 6, 8 and 9 during the Treatment Period. Any patients who show presence of antibodies at End-of-Treatment (Visit 9), will have additional time points tested to determine the time-course of antibody positivity. These subjects will be retested at 6 months and 12 months post-study if considered medically necessary.

7.1.13 Local Tolerance

Assessment of local tolerance will consist of a self-evaluation by the patient of any dermal reaction to study medication injection during the first 30 days of study treatment for review at the Month 1 (Visit 4), and for the 30 days of Month 11 for review at the Month 12 (Visit 8) study visit, and entered in the appropriate case report form. This second diary will be dispensed at the Month 9 (Visit 7) or forwarded to the patient by mail, as appropriate. Each injection site will be graded twice, 1 hour and 24 hours after the injection was performed and information will be recorded by the patient into the patient diary. In addition, at each study visit during the Treatment
Period, the Investigator will review and assess the injection sites for any evidence of dermal reaction.

Each injection site will be graded according to the following skin reaction scale.

**Redness**
- 0 = none
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible, less than 1 inch (2.54 cm) in diameter
- 3 = definite erythema, extensive, greater than 1 inch (2.54 cm) in diameter

**Swelling**
- 0 = none
- 1 = minimal swelling, without elevation
- 2 = definite swelling, readily visible; elevation less than 1 inch (2.54 cm) in diameter
- 3 = definite swelling, extensive, greater than 1 inch (2.54 cm) in diameter

**Pain**
- 0 = none
- 1 = minimal pain
- 2 = moderate pain, similar to a paper cut
- 3 = severe pain, similar to a bee sting or greater

**Tenderness**
- 0 = none
- 1 = minimal tenderness to touch
- 2 = moderate tenderness, no withdrawal to touch
- 3 = severe tenderness, withdraws to touch

Any injection site reaction with a grade of 3 will continue to be evaluated and recorded in the diary by the patient at 24 hour intervals until the symptom or sign has resolved. If any reactions are severe or persistent at any time during the Study, the patient will be instructed to contact the Investigator.

**7.1.14 Patient Diaries**

As noted above in Section 7.1.13, a diary to record study drug administration and local tolerance will be maintained by patients during two 30-day periods of the study.

The first diary will be provided on Day 1 (the first day of study treatment) for the patient to record the date, time and site of study medication injection and to assess local tolerance using the scale described in Section 7.1.13. Patients will record the required information daily during the first 30 days of the Treatment Period and at the Month 1 (Visit 4) clinic visit study personnel will review the diary with the patient. The Investigator will assess the information recorded by the patient for adverse events. The second diary will be dispensed at the Month 9 (Visit 7) or later mailed to the patient, as appropriate, for completion by the patient for the 30 days of Month 11. The diary will be collected and reviewed at the Month 12 (Visit 8) visit. The diary data will be entered into the CRF, and any abnormality or adverse event will be followed up with the patient.
In addition, a diary summarizing all study drug administration will also be completed by the patient on a weekly basis. The weekly diary will be maintained by the patient throughout the study and will be reviewed at each visit.

7.1.15 Activity and Diet

Patients who qualify for enrollment in the study will have no restrictions placed on their usual level of activity or on their usual diet.
8.0 ADVERSE EVENTS AND SAFETY EVALUATION

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

8.1 Definitions, Documentation, and Reporting

8.1.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

8.1.2 Serious Adverse Event Definition

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions.
- Is a congenital anomaly/birth defect. This includes any anomaly detected at or after birth, or any anomaly that results in fetal loss.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.
Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms “serious” and “severe” since they are not synonymous. The term “severe” is often used to describe the intensity (synonym: severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject’s life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.2 Monitoring of Adverse Events and Period of Observation

All AEs will be monitored until they are resolved or have become chronic or stable. AEs will be recorded on the case report forms starting from the time of patient entry into the Pretreatment Period (Visit 2) of the study until 30 days after the last dose of study medication. SAEs will be collected up to 30 days after the last dose of study medication. 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.

8.3 Procedures for Recording and Reporting AEs and SAEs

All adverse events spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded in the source document and on the appropriate page of the case report form. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded on the appropriate pages of the case report form. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All SAEs that occur during the course of the study, as defined by the protocol, must be reported by the Investigator to the Study Safety Officer by completing and transmitting the SAE Form within one working day from the point in time when the Investigator becomes aware of the SAE. In addition, all SAEs including all deaths, which occur up to and including 30 days after administration of the last dose of study drug, must be reported to the Study Safety Officer within one working day. All SAEs and deaths must be reported whether or not considered causally related to the study drug. SAE forms will be provided to the study site. The information collected will include a minimum of the following: subject number, a narrative description of the event, and an assessment by the Investigator as to the intensity of the event, and relatedness to study drug. Follow-up information on the SAE may be requested by the CRO, the Study Safety Officer or the Sponsor Medical Monitor. Contact information for reporting SAEs to the Study Safety Officer is provided on the SAE form.
Study Safety Officer Contact Information

PLEASE SEE SERIOUS ADVERSE EVENT REPORTING FORM FOR DETAILED REPORTING OF SAEs, INCLUDING CONTACT INFORMATION (e.g., FAX, EMAIL OR TELEPHONE CONTACT NUMBERS)

It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all serious adverse drug reactions involving risk to human subjects in accordance with the requirements of the IRB/IEC. An unexpected event is one that is not reported in the Investigator’s Brochure.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial or before study drug was given are not to be considered AEs unless they occur at a time other than the planned date.

Fractures identified during the study are not to be recorded as AEs unless the patient is hospitalized, the fracture is complicated, or the Investigator considers the fracture to be unrelated to the patient’s underlying osteoporosis. All fractures will be identified and evaluated as part of the disease assessment and will be documented in the case report forms and source documents.

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

Intensity for each AE will be defined according to the following criteria:

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Awareness of sign or symptom, but easily tolerated.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Discomfort enough to cause interference with normal daily activities.</td>
</tr>
<tr>
<td>Severe</td>
<td>Inability to perform normal daily activities</td>
</tr>
</tbody>
</table>

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 administration will be determined by the Investigator according to the following criteria:

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>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.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>The current state of knowledge indicates that a relationship to study drug is unlikely or the temporal relationship is such that study drug would not have had any reasonable association with</td>
</tr>
</tbody>
</table>
the observed event.

Possible
A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject’s clinical state or other modes of therapy administered to the subject.

Probable
A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject’s clinical state or other modes of therapy administered to the subject.

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

8.4 Rules for Suspension of the Study
The study will be immediately suspended and no additional doses of study medication will be administered if one or more patients develop any of the following serious adverse events deemed to be possibly or probably attributable to study medication by the Investigator and/or Sponsor Medical Monitor, based upon close temporal relationship or other factors:

- Death,
- Serious anaphylaxis characterized by severe angioedema, hypotension, shock, bronchospasm, hypoxia or respiratory distress,
- New development or discovery of osteosarcoma in humans.

The study will be suspended pending review and discussion of all appropriate study data with local Regulatory Authorities. The study will not be restarted until all parties have agreed to the course of action to be taken, the IRBs and Regulatory Authorities have been notified, and IRB approval is confirmed.
9.0 STATISTICAL PROCEDURES

The purpose of this section is to outline prospectively the types of analyses and presentations of data that will answer the study objectives outlined in the protocol, and to explain how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

The primary objective of this study is to determine the safety and efficacy of Abaloparatide-SC when compared to a matching placebo (Placebo) for prevention of vertebral fracture in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis. The secondary objectives of this study are to determine the safety and efficacy of Abaloparatide-SC when compared to Placebo for prevention of non-vertebral fractures and change in vertical height. Additional secondary efficacy outcomes include BMD (spine, hip and femoral neck) and safety (hypercalcemia) when compared to teriparatide in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis.

The specific objectives of this study are to:

- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.
- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on lumbar spine, hip, and femoral neck bone mineral density (BMD) in otherwise healthy ambulatory postmenopausal women with severe osteoporosis when compared to teriparatide.
- Determine the comparative efficacy of 18 months of treatment with Abaloparatide-SC on reduction of non-vertebral fracture incidence in otherwise healthy ambulatory postmenopausal women at risk of fracture from severe osteoporosis when compared with Placebo.
- Determine the overall safety and tolerability of 18 months of treatment with Abaloparatide-SC, and specifically the number of patients with hypercalcemic events, in otherwise healthy postmenopausal women with severe osteoporosis when compared to teriparatide and Placebo.
- Provide additional evidence of bone safety through histomorphometric assessment of bone biopsy samples in a subset of patients from the Abaloparatide-SC, Placebo, and teriparatide groups.
- Provide additional evidence of renal safety through radiological assessment by renal CT scan in a subset of patients from selected centers in the Abaloparatide-SC, Placebo and teriparatide groups.

9.1 Sample Size

A sample size of 622 patients per treatment arm provides 90% power at a two-sided alpha of 0.05 to detect a difference of 4% between treatments, assuming a vertebral fracture rate of 7% in placebo patients and 3% in Abaloparatide-SC-treated patients when the large scale
approximation of the binomial method is employed. This superiority assessment infers a relative risk reduction of 57% and presupposes the availability of a pretreatment and post-treatment radiological assessment. This population analysis would therefore be considered a modified ITT and will constitute the primary analysis population for this study. To ensure an analysis size of 622 patients, an overall sample size of 800 patients per treatment arm will be recruited, anticipating that approximately 20% of patients may not have a second evaluable X-ray film available for analysis. Should the projected fracture rate of 7% in placebo patients not be achieved, the sample size retains greater than 90% power at an alpha of 0.05 to detect a 4% difference between treatments based on placebo fracture incidence of 6% or 5%.

For statistically-powered secondary endpoint assessments, the sample size will have more than 90% power (n=275) at a two-sided alpha of 0.05 to detect a 1.15 percent difference between abaloparatide and teriparatide for spinal BMD based on a superiority hypothesis. Similarly, for total analyzable hip BMD, the sample size will provide more than 90% power (n=25) at a two-sided alpha of 0.05 to detect a 2.45 percent difference between abaloparatide and teriparatide treatment effect and to detect a 2.00 percent difference between abaloparatide and teriparatide for femoral neck BMD (n=125) based on the same hypothesis.

For differences in the number of patients in the abaloparatide and teriparatide treatment groups reporting one or more events of hypercalcemia, both above the upper limit of normal and at a value of 0.3 mg/mL above the upper limit of normal, the medically significant elevation, the study sample size will also provide more than 90% power to detect such a difference using a two-sided alpha of 0.05.

Additional and other secondary endpoints will also be satisfied by these study sizes and will be included in the details provided in the Statistical Analysis Plan (SAP).

9.2 Randomization, Stratification and Blinding

Patients who have signed informed consent, completed the Screening and Pretreatment Periods, and are eligible for the study will be equally randomized into the three treatment groups on Day 1 of the Treatment Period. A balanced randomized block assignment will be utilized to ensure that an approximately equal number of patients are assigned to each treatment group after a pre-specified block size has been achieved.

The Population PK sample timings will be randomized across visits for each patient.

Subsets of the population will be asked to undergo bone biopsies, renal CT scans, DXAs to assess wrist BMD. A subset of patients will also be randomized for assessment of serum bone markers in such a manner to ensure equal representation across the treatment groups throughout the study. In selected centers, a subset of patients in the Abaloparatide-SC/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. Patients in selected centers enrolled after the effective date of Version 3 of the protocol will be asked to undergo two renal CT scans, the first prior to treatment (between Visit 3 and Visit 4, inclusive), and the second between the
End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. The renal CT scans will assess the renal parenchyma and collecting system for renal calcification using an exploratory semi-quantitative approach.

No stratification is planned in this study. However, adjustments for fracture history and regional effects may be considered.

Abaloparatide-SC and Placebo study medications will be prepared in a blinded fashion. The study will not be blinded with regard to teriparatide which is supplied from marketed product; however, because teriparatide will be supplied to the site in identical outer packaging as Abaloparatide-SC and Placebo, the site will remain blinded until treatment is assigned, the package is opened, and its contents are dispensed. Therefore, teriparatide will not be blinded in use relative to Abaloparatide-SC or Placebo.

9.3 Populations for Analysis

All analyses and data summaries will be presented for the Intent-to-Treat (ITT) or Safety Population. In addition key selected endpoints will also be analyzed for the mITT and Per Protocol Populations.

9.3.1 ITT (Safety) Population

The Safety Population is comprised of all patients who receive one or more doses of study medication.

9.3.2 Modified Intent-to-Treat Population

The Modified ITT Population includes all patients with Pretreatment and End-of-Treatment evaluable radiologic assessments.

9.3.3 Per Protocol Population

The Per-Protocol (PP) population includes subjects in the mITT population who complied with treatment and did not have any protocol violations.

A protocol violation is defined as a deviation from basic requirements of the study protocol, including inclusion and exclusion criteria, concomitant medication restrictions, or any other protocol requirements that result in a significant added risk to the study subject or has an impact on the quality of the data collected or the outcome of the study.

A protocol deviation is defined as a deviation from the protocol that does not impose added risk to the study design or the study subject. The criteria for the determination of the evaluability of subjects will be defined in the Statistical Analysis Plan.

Data will be reviewed in a blinded fashion and the population defined prior to database lock and unblinding.
9.4 Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in the data listings and tabulations. Where appropriate, imputations of values for missing data for primary and secondary efficacy analyses will be performed as specified in the Statistical Analysis Plan. All data recorded on the CRF will be included in the data listings that will accompany the clinical study report.

9.5 Statistical Methods

9.5.1 Baseline Comparisons

Baseline characteristics, medical history, physical examination, vital signs and ECG, will be summarized using standard descriptive statistics by treatment group. Specific demographic and baseline parameters will be tested for overall agreement (uniformity across treatment groups) using one-way ANOVA or Chi-square tests as appropriate for the type of data and specified in the Statistical Analysis Plan.

9.5.2 Efficacy Analysis

The primary efficacy endpoint will be the number of Abaloparatide-SC-treated patients showing new vertebral fractures at End-of-Treatment when compared to Placebo. New incident vertebral fractures will be evaluated according to the method of Genant (1). This analysis will be performed using a Fisher’s Exact test on the modified intent to treat population.

Secondary efficacy endpoints will be analyzed using a Fisher’s Exact test (categorical variables) or analyses of covariance employing the baseline measure as the covariate (continuous variable) on the modified intent to treat population unless otherwise noted below. For continuous variables, analyses will be performed on the last available assessment for each variable.

A hierarchical approach to secondary analyses will be employed. The variables within the hierarchy will include non-vertebral fractures; and spine, hip and femoral neck BMD. Full details of the inferential analysis and the hierarchy will be provided in the Statistical Analysis Plan.

Additional non-hierarchical analyses will be employed on the following efficacy parameters:

- The change in vertical height in patients treated with Abaloparatide-SC when compared to Placebo.
- The difference in severity of incident vertebral fractures in Abaloparatide-SC-treated patients at End-of-Treatment when compared to Placebo. The analysis will employ a Chi-Square approach as severity is assessed in multiple grades.
- A Cox proportional hazard model will be used to calculate the relative risk of a new non-vertebral fractures by treatment group. A Kaplan-Meir plot will be generated to display the time to first non-vertebral fracture. Data will be censored at the time of study termination for those not experiencing a fracture.
The number of teriparatide-treated patients showing new vertebral fractures at End-of-Treatment when compared to Placebo. New incident vertebral fractures will be evaluated according to the method of Genant (1). This analysis will be performed using a Fisher’s Exact test on the modified intent to treat population.

The change in distal 1/3 radius BMD from baseline to End-of-Treatment in Abaloparatide-SC-treated patients when compared to Placebo.

The changes in serum PINP, bone-specific alkaline phosphatase, osteocalcin and CTX across treatment.

Analyses of continuous variables (e.g., change in BMD and height) will be analyzed using the Safety Population with last observations carried forward as noted in Section 9.4. In addition, patients who have a dose adjustment and continue on the study at a reduced dose, will be presented in a data listing.

All specified endpoints will be summarized by treatment groups and study period using standard descriptive statistics (N, mean, SD, median, minimum, maximum). Changes in serum markers of bone metabolism (PINP, bone-specific alkaline phosphatase, osteocalcin, and CTX) will be analyzed using a mixed model with factors for baseline value, treatment (treatment groups), time (study period) and their interaction.

A population PK/PD analysis will be performed on samples for measurement of serum levels of abaloparatide. The PK/PD analyses and exposure response modeling will be described in a separate Statistical Analysis Plan and report and will generally follow the guidance provided by FDA (Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), April 2003).

Additional exploratory analyses will be presented as either pre-planned or post-hoc to complement the overall understanding of study results.

9.5.3 Safety Analysis

A secondary endpoint of the study is the difference in number of patients with hypercalcemia in Abaloparatide-SC-treated patients at End-of-Treatment when compared to teriparatide will be assessed via a Fisher’s Exact test. The test will be performed separately to compare Abaloparatide-SC to teriparatide and Abaloparatide-SC to Placebo, but only the comparison to teriparatide will be considered a secondary endpoint.

All patients who receive at least one dose of study medication will be included in the safety analysis that will be performed on the following parameters:
12. Safety

Incidence and severity of AEs. Dose and duration of exposure when the AE occurred will also be recorded.

Pathological changes in hematology, chemistry and urinalysis data based on normal ranges supplied by the clinical laboratory.

Incidence of hypercalcemia across treatment groups

Bone histomorphometry as assessed by bone biopsy at End-of-Treatment in a subset of Abaloparatide-SC, Placebo and teriparatide patients.

Renal safety as assessed by serum and urine creatinine (all patients) and renal CT scan (subset of patients) in all treatment groups.

Safety assessments for changes in physical examination, vital signs (systolic and diastolic blood pressure plus heart rate), ECG (normal and abnormal), and laboratory tests will be descriptively summarized by group and selected study periods. Clinical symptomatology associated with blood pressure changes will be recorded for subsequent analysis. In addition laboratory tests will be classified as low range, normal range, or high range and shift frequencies summarized between the Screening Period and the End-of-Treatment Visit. Concomitant medication classes will be coded employing the WHO drug dictionary and summarized by number and percent of patients using each class and preferred drug term by treatment group. All treatment emergent adverse events will be coded for body system, preferred term, and lowest level term using MedDRA and the number (%) patients experiencing each type of adverse event will be summarized by treatment group, duration of exposure, relationship to treatment, and severity. All serious adverse events (SAE) and adverse events leading to study discontinuation will be listed and the number (%) patients presented by treatment group.

All adverse events collected prior to the first injection will be separately summarized in a fashion similar to the treatment emergent adverse events.

9.5.4 Interim Analysis

No interim analyses are planned for this study.

9.5.5 Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations from the original statistical analysis plan will be provided in the final clinical study report.

9.6 Data Oversight

9.6.1 Central Review of Radiographs and DXA Scans

All radiographs will be viewed and assessed by a blinded, independent assessor (radiologist) on the basis of existing baseline and study-acquired vertebral deformity, and fracture will be assessed according to a set of pre-determined criteria. A second blinded radiologist will review the assessment of the first reviewer for all patient
radiographs in which an incident fracture has been identified. In the case of any disagreement, a third consensus assessment will be made to adjudicate the incident fracture. All study DXA scans will also be evaluated centrally by a blinded independent reviewer. The primary objective of the independent review is to provide an objective, unbiased evaluation of the critical eligibility criteria at screening and during the course of the study to provide objective efficacy data to determine the treatment benefit as demonstrated on the pertinent radiologic and clinical data associated with this study. Finally, all renal CT scans will also be evaluated centrally by a blinded independent reviewer and confirmed by a second reviewer to ensure unbiased assessment of the renal parenchyma and collecting system.

9.6.2 Data Safety Monitoring Board

The DSMB will be responsible for overseeing study safety during the course of the trial.
10.0 ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

This study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) (27) and the appropriate regulatory requirements. The Investigator will be thoroughly familiar with the appropriate use of the study medication as described in the protocol and the Investigator’s Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. The Investigator/institution should establish master files at the beginning of the study which will be maintained and updated during the study and retained thereafter according to the appropriate regulations.

10.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (28). The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study can only be conducted at study sites where IRB/IEC approval has been obtained. The protocol, informed consent form, Investigator’s Brochure, advertisements (if applicable), and all other forms of information given to subjects will be provided to the IRB/IEC by the Investigator. In addition, reports on the progress of the study will be submitted to the IRB/IEC by the Investigator at the appropriate intervals.

10.3 Subject Information and Informed Consent

Each subject (or a legally authorized representative) must give written informed consent prior to any study-specific procedures being conducted. It is the responsibility of the Investigator to ensure written informed consent is obtained from each subject participating in this study after an explanation of the objectives, methods, discomforts and potential risks of the study has been provided. The Investigator (or study personnel) must also explain to each subject that he/she is free to refuse participation in the study or to withdraw from it at any time. Each subject will also be told that his/her records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available.

The informed consent form must be in accordance with the Declaration of Helsinki, ICH and GCP guidelines, and be approved by the Sponsor and the IRB/IEC. State or local laws may require additional information. Each subject (or his/her legally authorized representative) must sign and be given a copy of the informed consent form. Each subject’s signed informed consent form must be maintained by the Investigator and be readily available for review by the Sponsor (or its designee) or the Regulatory Authorities.

10.4 Protocol Compliance

The Investigator will conduct this study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC and the appropriate Regulatory Authority(ies). Changes to the protocol should not be made without agreement of the Sponsor Medical Monitor. All changes to the protocol will require IRB/IEC approval prior to implementation, except when necessary to eliminate an immediate hazard to study...
subjects or when the change involves only logistical or administrative aspects of the study (e.g., change in Sponsor Medical Monitor or telephone number). The IRB/IEC may provide, if applicable regulations permit, expedited review and approval/favorable opinion for minor changes in ongoing studies. The Sponsor will submit all protocol changes to the appropriate Regulatory Authority in accordance with the governing regulations.

In situations requiring a departure from the protocol, the Investigator or other physician in attendance will contact the Sponsor Medical Monitor by telephone, email or fax. If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the Sponsor Medical Monitor must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The case report form and source document will describe any departure from the protocol and the circumstances requiring it.

### 10.5 Case Report Form Completion

Paper and/or electronic case report forms (eCRFs) will be developed to collect information obtained during this study. It is the Investigator’s responsibility to ensure that CRFs are completed for each subject enrolled in this study and for the accuracy, completeness, legibility and timeliness of the data reported in each CRF. Data for subjects who are screened but not enrolled into the study because they do not meet study criteria or do not complete all screening procedures, should be recorded in the CRF.

CRFs or eCRFs will be completed and any corrections of data will be made according to procedures provided by the Sponsor (or designee).

### 10.6 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, work sheets, subjects’ diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, ECG printouts, and/or x-rays.

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents.

### 10.7 Study Monitoring

The Sponsor (or its designee) will ensure that the study is monitored in accordance with ICH-GCP Guidelines. Monitoring is the act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, Good Clinical Practice, and the applicable regulatory requirements and that the study data are accurate, complete and verifiable from source data. All study documentation and other source data will be made available to the Sponsor (or its designee), the IRB and to Regulatory Authorities for inspection upon request.
10.8 On-Site Audits

Representatives of the IRB or the Sponsor (or designee) may visit the study site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records including source documents, CRFs, and other study documents. Direct access to these study records must be guaranteed by the Investigator, who must provide support for these activities at all times.

Similar auditing procedures may also be conducted by agents of any Regulatory Authority reviewing the results of this study. The Investigator/institution should immediately notify the Sponsor if they have been contacted by a Regulatory Authority concerning an upcoming inspection.

10.9 Drug Accountability

Accountability for the study medication at the study site is the responsibility of the Investigator. The Investigator will ensure that the study medication is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the study medication accountability responsibilities to a pharmacist or other appropriately trained individual.

Study medication accountability records indicating the delivery date to the study site, inventory at the study site and dispensing/use will be maintained. These records will adequately document that the study medications were dispensed and returned as specified in the protocol and according to the randomization scheme. Accountability records for all study medications will include dates, quantities, batch/lot numbers, kit numbers, cartridge numbers, and patient numbers. The Sponsor (or its designee) will review study medication accountability records at the study site on an ongoing basis during the study. All used and unused supplies must be inventoried, accounted for, and returned to the Sponsor (or its designee). Records of disposal must be maintained with the study records.

10.10 Record Retention

The Investigator will maintain all study records according to ICH/GCP and applicable regulatory requirements. Essential documents must be retained for two years after the final marketing approval in an ICH region or at least two years have elapsed since the discontinuation of clinical development of the study medication. It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution or medical practice.

The Investigator/institution will take measures to prevent accidental or premature destruction of these documents. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.
10.11 Study Termination

This study may be terminated at any time, if in the opinion of the Sponsor, the Investigator or the DSMB, there is sufficient reasonable cause. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Failure of enrollment
- Administrative reasons
- Plans to modify, suspend or discontinue the development of the study drug.

In addition, individual study sites may be terminated from study participation for reasons including, but not limited to the following:

- Failure to enter subjects at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Incomplete and/or non-evaluable data.

In all cases, the terminating parties will provide written notification documenting the reason for study termination to all the relevant parties.

Should the study or an individual site be prematurely closed, all study materials (completed, partially completed, and blank CRFs, study drug, etc.) must be returned to the Sponsor (or its designee).

10.12 Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.
11.0 USE OF INFORMATION AND PUBLICATION OF STUDY FINDINGS

11.1 Use of Information

All information regarding abaloparatide supplied by the Sponsor (or its designee) to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without prior consent from the Sponsor.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of abaloparatide. This information may be disclosed as deemed necessary by the Sponsor to other clinical investigators, other pharmaceutical companies, and to Regulatory Authorities. To allow for the use of the information derived from this study and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor (or its designee) with complete study results and all data developed in this study and to allow direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection.

11.2 Publication

Results of this study may not be published prior to the completion of this study and completion of the formal clinical study report and other required regulatory reports and documents.

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. A pre-publication manuscript must be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

The Investigator shall comply with the policy of the Sponsor regarding confidential or proprietary information in any such paper and agrees to withhold publication of same for an additional 60 days in order to permit the Sponsor to obtain patent or other proprietary rights protection, if the Sponsor deems it necessary.
12.0 INVESTIGATOR AGREEMENT

To be completed by the Investigator

I have read Protocol BA058-05-003: A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture.

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

The signature below constitutes my agreement to the contents of this protocol.

_________________________    ______________________
Signature of Principal Investigator   Date

_________________________
Principal Investigator (print)

_________________________
Signature of Sponsor’s Medical Officer (where applicable)

_________________________    ______________________
Alan Harris, MD   Date
13.0 REFERENCES


14.0 APPENDICES
14.1 Schedule of Visits and Procedures

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Screening</th>
<th>Pretreatment</th>
<th>Treatment</th>
<th>Follow-up</th>
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<td>Procedure</td>
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<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Study Day/Month</td>
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<td>Visit Window (Days)</td>
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- **Visit:**
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  - 2
  - 3
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  - 5
  - 6
  - 7
  - 8 (V)
  - 8 (R)
  - 9
  - 10

- **Procedure:**

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<th>Study Day/Month</th>
<th>Visit Window (Days)</th>
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<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
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<td>Quantitative Bone Histomorphometric Assessment (biopsy in subset of patients)</td>
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<td>Calcium and Vitamin D supplements</td>
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<td>Local tolerance (dermal reactions) assessment</td>
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<tr>
<td>Document adverse events and concomitant medications</td>
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<td>At any time; question patients at study visits</td>
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<td>Drug resupply</td>
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<td>Discuss possible participation in the Extension Study with Abaloparatide-SC/Placebo patients</td>
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**Daily Administration:**
- Injection training for patients
- Study medication kit assignment via IVRS
- Study medication administration
- Local tolerance (dermal reactions) assessment
- Patient diary review
- Document adverse events and concomitant medications
- Drug resupply
- Discuss possible participation in the Extension Study with Abaloparatide-SC/Placebo patients
14.1 Schedule of Visits and Procedures (continued)

1. Interim or symptom directed physical examinations may be conducted at other time points to assess adverse events or clinical laboratory abnormalities.

2. Vital signs (orthostatic blood pressure, pulse rate, body temperature, and respiration rate) are to be recorded at each study visit. Height is to be measured at Visits 1, 2 and 9. Height will be measured at Visits 2 and 9 in the standing position using a medical stadiometer.

3. Study medication injections are to be administered under supervision in the study clinic during scheduled clinic visits. Assessments of orthostatic blood pressure will be done pre-dose and 60 minutes post-dose at Visits 3, 4, 5, 6, 7, and 8.

4. ECGs are to be obtained pre-dose and 1 hour post-dose on Visits 3, 4, 5, 6, 7, and 8.

5. On days of 24-hour urine collection, routine urinalysis will be performed on a sample freshly voided during the clinic visit.

6. These blood and urine samples are to be obtained under fasting conditions (N.P.O. for 8 hours; water is acceptable) in the morning of each scheduled study visit. They are to be collected prior to injection of the study medication during the Treatment Period.

7. Includes blood samples for PINP, bone-specific alkaline phosphatase, serum osteocalcin and CTX (subset of 600 patients).

8. Any patients who show presence of antibodies at End-of-Treatment (Visit 9) will have these additional time points tested to determine first occurrence of antibody positivity.

9. One peak level is to be drawn per patient per visit at the following varying post-injection times: 10 minutes to 30 minutes; 30 minutes to 1 hour; 1 hour to 2 hours; 2 hours to 3 hours; 3 hours to 4 hours. These draw times are to be randomized across Visits 3, 4, 5, 6, and 8. At the End-of-Treatment (Visit 9), only a trough level will be measured. No abaloparatide serum levels will be drawn for patients randomized to teriparatide.

10. These samples are to be drawn post-injection; the patient no longer needs to be fasting. The patient is to remain near the clinic for the post-injection blood collections.

11. DXA is to be performed initially on the hip (femoral neck) and spine (L1-L4) during the Screening visit. A DXA of the wrist should be performed in a subset of patients on Day 1. Each DXA for a given patient must be performed on the same machine, preferably by the same technician.

12. DXA is to be performed initially on the hip (femoral neck) and spine (L1-L4) during the Screening visit. A DXA of the wrist should be performed in a subset of patients on Day 1. Each DXA for a given patient must be performed on the same machine, preferably by the same technician.

13. In selected centers, a subset of patients in the Abaloparatide-SC/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. Patients in selected centers enrolled after the effective date of Version 3 of the protocol, will be asked to undergo two renal CT scans (obtained through standard abdominal/pelvic CT scan procedures), the first prior to treatment (between Visit 3 and Visit 4, inclusive), and the second between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive.

14. Patients who agree to undergo the quantitative bone histomorphometric assessment will have additional clinic visits scheduled, as required, to prepare for the bone biopsy performed between Visit 8 and the End-of-Treatment visit (Visit 9).

15. Calcium and Vitamin D supplements begin at the Pretreatment Period visit and continue until the end of the Treatment Period; it will be recommended to patients that they continue these supplements through the Follow-up visit. A supply of supplements is provided for each patient. At each study visit, the patient’s supply is to be assessed and the patient resupplied as necessary. Drug usage reconciliation is to be performed when a new supply is provided.

16. All patients will be trained on the use of the Abaloparatide-SC/Placebo cartridge/pen delivery device at Visit 2; patients who are subsequently randomized to receive teriparatide will be trained on the use of the teriparatide pen at Visit 3.

17. The Investigator is to review and assess the injection sites at each Treatment Period visit.

18. Diaries will be provided to patients to record information regarding study medication injections (date/time/site of injection; local tolerance) for the first 30 days of treatment and for 30 days prior to Month 12 (Visit 8). In addition, the patient will also maintain a diary throughout the study to summarize all study drug administration on a weekly basis. The diaries are to be reviewed with the patient at each study visit.
14.2 Suggested Schedule of Events and Procedures by Study Visit

The purpose of this guide is to provide more detailed instructions for the study procedures listed in Appendix 14.1. This guide presents the procedures in a suggested sequence of performance at each study visit. Further information may be found within the protocol and in other study reference manuals (e.g., ECG, clinical lab sample processing).

Of note:

- During the Treatment Period, on the days of clinic visits, study medication must be injected at the clinic to accommodate pre-injection and post-injection procedures; study personnel may administer the study medication on those days.
- Pre-injection procedures include assessments of the patient, vital signs, ECG, and pre-injection blood/urinalysis collections.
- Pre-injection blood and urinalysis samples are to be obtained under fasting conditions (N.P.O. for 8 hours; water is acceptable) in the morning of each scheduled study visit; post-injection blood samples do not require fasting.
- BMD Scans: Always use the same study-validated machine; preferably the same technician.
- The 24-hour urine collection will be started at home the day before the clinic visit where the collection is required. Patients will be instructed to discard the first morning void and begin the collection at least 24 hours before their clinic visit the following day. They will collect all urine for 24 hours with a final void before coming to the clinic. Routine urinalyses are to be performed using samples freshly voided during the clinic visit.
- Pen devices and needles for administration of study medications will be provided. abaloparatide and Placebo will be supplied in cartridges, each containing enough study medication to deliver the required daily dose for 30 days. Patients are to be instructed to change to a new cartridge after 30 days, regardless of how much medication is left in the cartridge. At each clinic visit, the used abaloparatide or Placebo cartridges, but not pen, are to be returned and a sufficient number of new cartridges to last until the next clinic visit are to be provided. Teriparatide will be supplied as pre-filled pens, each with enough medication for 28 days. At each clinic visit, the used teriparatide pens should be returned and a sufficient number of new pens provided to last until the next clinic visit.
- Patients will be instructed to take the Calcium and Vitamin D supplements daily (in the evening with or without food or as otherwise instructed by the Investigator) until they are discharged from the study. This is required until the End-of-Treatment. During the Follow-up Period it is recommended that they continue the supplements.
- Patients will be approached at Visit 8 regarding participation in the quantitative bone histomorphometric evaluations. Patients who consent to this assessment will undergo a bone biopsy between Visit 8 and Visit 9. Additional clinic visits will be scheduled to complete all necessary preparations for the procedure.
Definitions of Common Procedures:
The terms used in the by-visit schedule that follows are further defined below.

Recent Health Status (document any changes from last visit)
- Question patient regarding any new health issues
- Question patient regarding any new adverse events
- Question patient regarding any new concomitant medications
- Question patient regarding any new issues related to ability to continue with study

Vital Signs and Weight
- **Orthostatic Blood pressure** (mmHg) (measured in same arm each time/each visit) is measured after five minutes in the supine position followed immediately by a measurement taken after 3 minutes in the standing position. There is a ± 10 minute window for blood pressure assessments
- **Pulse rate** (beats/minute) is taken after approximately five minutes in the supine position
- **Respiration rate** (breaths/minute)
- **Body temperature** (°C)
- **Weight** (kg)

Height
- At Visits 2 and 9 standing measurements (cm) are to be performed using the same medical stadiometer and standardized procedures each time.

ECG
- Twelve-lead supine electrocardiogram
- Print hard copy for reading by qualified study personnel
- There is a ± 10 minute window for ECG assessments

24 Hour Urine Collection
- Patient to discard first morning void (suggest 6 a.m.) on day before clinic visit
- Patient to collect urine for approximately 24 hours
- Patient to collect final void at end of collection and bring collection to clinic.
- Process for calcium and creatinine

Urinalysis
- Obtain under fasting conditions (N.P.O. except water for 8 hours)
- Routine urinalysis is to be performed using a sample freshly voided during the clinic visit.

Review study medication injection procedures with patient
- Injections should be given daily, preferably at the same time each morning
- Injections are to be given in the periumbilical region, rotating the exact site of injection each day to minimize discomfort
- If medically necessary for an injection to be administered at a site other than the abdomen, the alternate site is to be recorded and the reason is to be documented in the medical chart
- Patients are to self-inject study medication; if the patient is unable to self-inject, she may be assisted by a competent companion (e.g., family member) trained to use the injection devices
- Study personnel may administer the study medication at clinic visits

Scheduling and instructions for next clinic visit
- Schedule visit
- Remind patient of any fasting requirements
- Provide urine collection instructions as necessary
- Remind patient that injections are to be administered at the clinic during Treatment Period study visits

Vitamins and Calcium Supplements
- Calcium and Vitamin D supplements begin during the Pretreatment Period and continue until the end of the Treatment Period. Only those supplements supplied as part of study medication may be used and are to be used at the daily recommended dose (see Section 3.1.2).
- Supplements should be taken in the evening, with or without food as instructed by the Investigator.
- Recommend to patients that they continue these supplements through the Follow-up Visit.
- Dispense the initial supply of supplements for each patient at Visit 2.
- At each study visit, assess the patient’s supply and resupply as necessary.
- Drug usage reconciliation is to be performed when a new supply is provided.
## SCREENING PERIOD

<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 1 Screening Visit | Up to 2 months before Visit 2 | Written informed consent  
  - Must be obtained before any study-specific procedure is performed  
  Review of entrance criteria  
  Medical history and concomitant medications  
  Physical exam  
  *Vital Signs and Weight and Height (stadiometer not necessary)  
  *ECG  
  Urinalysis – dipstick: fasting conditions (N.P.O. except water for 8 hours)  
  Blood Collection: fasting conditions (N.P.O. except water for 8 hours)  
  - Chemistry  
  - Hematology  
  - Coagulation (PT and PTT)  
  - FSH and serum estradiol  
  - PTH(1-84)  
  - 25-hydroxy Vitamin D level  
  Clinical and Radiologic Fracture Evaluations  
  - Obtain antero-posterior and lateral radiographs of the lumbar and thoracic spine  
  - Document any non-vertebral fractures  
  Bone Mineral Density DXA  
  - Perform hip (femoral neck) and spine (L1-L4) DXA  
  *Scheduling and Instructions for next Clinic Visit  
  Screen Failures:  
  - Data for patients who do not successfully complete screening procedures or do not meet study eligibility requirements should be entered into the eCRF, including the reason for failure. |

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures*
### PRETREATMENT PERIOD

<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 2 | -7 to -1 | *Recent Health Status  
- Document any changes from Visit 1 including changes in medical history, including any new adverse events or concomitant medications  
*Vital Signs  
*Height (cm): standing height measurement with medical stadiometer  
Blood Collection: fasting conditions (N.P.O. except water for 8 hours)  
- 1,25-dihydroxy Vitamin D levels  
- Serum markers of bone metabolism  
  - PINP  
  - bone-specific alkaline phosphatase  
  - serum osteocalcin  
  - serum CTX  
Calcium and Vitamin D Supplements  
- Dispense supply of Calcium and Vitamin D supplements  
- Instruct patient to take daily until they are discharged from the study  
*Training in Self-Injection  
- Instruct patient in use of the abaloparatide/Placebo device  
- If patient is unable to self-inject, train competent companion (e.g., family member) to use the injection device  
*Scheduling and Instructions for next Clinic Visit |

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures
## TREATMENT PERIOD

<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 3</td>
<td>1 (± 1 day)</td>
<td>*Recent Health Status&lt;br&gt;  - Document any changes from last visit&lt;br&gt;  Patient Review&lt;br&gt;  - Review Calcium and Vitamin D supplement usage.&lt;br&gt;  - Record deviations in dosing or any AEs in source documents and CRFs.&lt;br&gt;  - Dispense study medication diary card for recording of date, time, site of injection and local tolerance on a daily basis.&lt;br&gt;  - Dispense weekly patient diary.</td>
</tr>
</tbody>
</table>

### BEFORE STUDY MEDICATION ADMINISTRATION

*Vital Signs<br>  *ECG<br>  *24 Hour Urine Collection and Urinalysis<br>  Study medication kit assignment via IVRS:  
  - Call IVRS system: provide patient screening number and DOB<br>  Blood Collection  
    - Chemistry<br>  - Abaloparatide antibody sample (if a abaloparatide treatment is assigned)<br>  Bone Mineral Density DXA in a subset of patients<br>  Renal CT Scan  
    - Perform renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) on patients who consented to this procedure. In selected centers, patients in the Abaloparatide-SC/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10). Patients in selected centers enrolled after the effective date of Version 3 of the protocol, will be asked to undergo renal two CT scans, the first prior to treatment (between Visit 3 and Visit 4, inclusive), and the second between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10).

### STUDY MEDICATION ADMINISTRATION

*Review study medication injection procedures with patient<br>  Patients randomized to teriparatide are to be trained in injection procedures<br>  Observe/Assist patient with injection  
  - patient should self-inject while in a sitting or lying position  
  - patient should remain in that position for approx. 5 min.<br>  Observe patient in clinic for a minimum of 60 minutes<br>  Provide patient with study medication: 1 pen and cartridges for abaloparatide or Placebo; prefilled pen(s) for teriparatide.

### AFTER STUDY MEDICATION ADMINISTRATION

*Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)<br>  *ECGs - 1 hour post-injection<br>  Blood Collection: non-fasting  
  - Abaloparatide peak drug levels (at randomized time). Only draw for patients randomized to abaloparatide, Placebo
<table>
<thead>
<tr>
<th>Calcium (4 hours post-injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local tolerance assessment</strong></td>
</tr>
<tr>
<td>• Remind patients to assess dermal reactions 1 and 24 hours post-injection</td>
</tr>
<tr>
<td>• Investigator to review diary and assess injection sites</td>
</tr>
<tr>
<td><strong>Calcium and Vitamin D Supplements</strong></td>
</tr>
<tr>
<td>• Assess patient’s supply of Calcium and Vitamin D supplements; resupply as necessary</td>
</tr>
<tr>
<td>• Instruct patient to take daily until they are discharged from the study</td>
</tr>
</tbody>
</table>

*Scheduling and Instructions for next Clinic Visit*

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures*
### TREATMENT PERIOD

<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
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</thead>
<tbody>
<tr>
<td>Visit 4</td>
<td>Month 1</td>
<td>*Recent Health Status</td>
</tr>
<tr>
<td></td>
<td>(± 3 days)</td>
<td>• Document any changes from last visit</td>
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<tr>
<td></td>
<td></td>
<td>Patient Review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Review Calcium and Vitamin D supplement usage</td>
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<tr>
<td></td>
<td></td>
<td>• Review diaries of study medication usage/injection site reactions</td>
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<tr>
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<td></td>
<td>• Record dosing deviations or any AEs in source documents and CRFs</td>
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<tr>
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<td></td>
<td>Calcium and Vitamin D Supplements</td>
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<tr>
<td></td>
<td></td>
<td>• Assess and resupply patient’s Calcium and Vitamin D supplements</td>
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<td>• Instruct patient to take daily until they are discharged from the study</td>
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<td>Local tolerance assessment</td>
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<td></td>
<td></td>
<td>• Investigator to review and assess injection sites</td>
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<td></td>
<td><strong>BEFORE STUDY MEDICATION ADMINISTRATION</strong></td>
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<td></td>
<td></td>
<td>*Vital Signs</td>
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<td></td>
<td></td>
<td>*ECG</td>
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<tr>
<td></td>
<td></td>
<td>Blood Collection: fasting conditions (N.P.O. except water for 8 hours)</td>
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<tr>
<td></td>
<td></td>
<td>• Chemistry</td>
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<tr>
<td></td>
<td></td>
<td>• Hematology</td>
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<tr>
<td></td>
<td></td>
<td>• 25-hydroxy Vitamin D level</td>
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<tr>
<td></td>
<td></td>
<td>• 1,25-dihydroxy Vitamin D levels</td>
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<td></td>
<td></td>
<td><strong>STUDY MEDICATION ADMINISTRATION</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Review study medication injection procedures with patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Assist with drug injection as necessary</td>
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<tr>
<td></td>
<td></td>
<td>Teriparatide: collect used pen; supply new pre-filled pens as necessary</td>
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<td></td>
<td></td>
<td><strong>AFTER STUDY MEDICATION ADMINISTRATION</strong></td>
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<tr>
<td></td>
<td></td>
<td>*Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)</td>
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<td></td>
<td></td>
<td>*ECGs - (60 minutes post-injection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood Collection: non-fasting</td>
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<tr>
<td></td>
<td></td>
<td>Abaloparatide peak drug levels (at randomized time). Only draw for patients randomized to abaloparatide, Placebo</td>
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<tr>
<td></td>
<td></td>
<td>Calcium (4 hours post-injection)</td>
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<tr>
<td></td>
<td></td>
<td>*Scheduling and Instructions for next Clinic Visit</td>
</tr>
</tbody>
</table>

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures*
### VISIT 5  
**After 3 Months of Treatment**  

<table>
<thead>
<tr>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Month 3 (± 7 days) | *Recent Health Status*  
- Document any changes from last visit  
  
*Patient Review*  
- Review Calcium and Vitamin D supplement usage  
- Review study medication usage/injection site reactions  
- Review weekly patient diary  
- Record dosing deviations or any AEs in source documents and CRFs  
- Dispense weekly patient diary, if needed  

*Calcium and Vitamin D Supplements*  
- Assess and resupply patient’s Calcium and Vitamin D supplements  
- Instruct patient to take daily until they are discharged from the study  

*Local tolerance assessment*  
- Investigator to review and assess injection sites  

### BEFORE STUDY MEDICATION ADMINISTRATION

*Vital Signs*  

*ECG*  

**Blood Collection:** fasting conditions (N.P.O. except water for 8 hours)*  
- Chemistry  
- Hematology  

*24 Hour Urine Collection and Urinalysis*  

### STUDY MEDICATION ADMINISTRATION

*Review study medication injection procedures with patient*  
- Assist with drug injection as necessary  
- Abaloparatide or Placebo: collect used cartridges; supply new cartridges as necessary  
- Teriparatide: collect used pen; supply new pre-filled pens as necessary

### AFTER STUDY MEDICATION ADMINISTRATION

*Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)*  

*ECGs - (60 minutes post-injection)*  

**Blood Collection:** non-fasting  
- Abaloparatide peak drug levels (at randomized time). Only draw for patients randomized to abaloparatide, Placebo  
- Calcium (4 hours post-injection)  

Scheduling and Instructions for next Clinic Visit

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures*
<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 6 | Month 6 (± 7 days) | *Recent Health Status  
- Document any changes from last visit |
|       |           | Patient Review  
- Review Calcium and Vitamin D supplement usage  
- Review study medication usage/injection site reactions  
- Review weekly patient diary  
- Record dosing deviations or any AEs in source documents and CRFs.  
- Dispense weekly patient diary, if needed |
|       |           | Calcium and Vitamin D Supplements  
- Assess and resupply patient’s Calcium and Vitamin D supplements  
- Instruct patient to take daily until they are discharged from the study |
|       |           | Local tolerance assessment  
- Investigator to review and assess injection sites |
|       |           | BEFORE STUDY MEDICATION ADMINISTRATION  
*Vital Signs  
*ECG  
Blood Collection: fasting conditions (N.P.O. except water for 8 hours)  
- Chemistry  
- Hematology  
- PTH(1-84)  
- 25-hydroxy Vitamin D levels  
- 1, 25-dihydroxy Vitamin D levels  
- Serum markers of bone metabolism:  
  o PINP  
  o bone-specific alkaline phosphatase  
  o serum osteocalcin  
  o serum CTX  
*24 Hour Urine Collection and Urinalysis |
|       |           | STUDY MEDICATION ADMINISTRATION  
- Review study medication injection procedures with patient  
- Assist with drug injection as necessary  
- Abaloparatide or Placebo: collect used cartridges; supply new cartridges as necessary  
- Teriparatide: collect used pen; supply new pre-filled pens as necessary |
|       |           | AFTER STUDY MEDICATION ADMINISTRATION  
*Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)  
*ECGs - (60 minutes post-injection)  
Blood Collection: non-fasting  
- Abaloparatide peak drug levels (at randomized time). Only draw for patients randomized to abaloparatide, Placebo  
- Calcium (4 hours post-injection)  
Bone Mineral Density  
- Perform hip (femoral neck), spine (L1-L4) and radius DXA. |
|       |           | *Scheduling and Instructions for next Clinic Visit |

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures.
## TREATMENT PERIOD

<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 7 After 9 Months of Treatment | Month 9 (± 7 days) | *Recent Health Status  
  - Document any changes from last visit  
  Patient Review  
  - Review Calcium and Vitamin D supplement usage  
  - Review study medication usage/injection site reactions  
  - Review weekly patient diary  
  - Record dosing deviations or any AEs in source documents and CRFs.  
  - Dispense study medication diary card for recording of date, time, site of injection and local tolerance on a daily basis for the 30 days of Month 11. The diary can also be sent later to the patients by post.  
  - Dispense weekly patient diary, if needed  
  Calcium and Vitamin D Supplements  
  - Assess and resupply patient’s Calcium and Vitamin D supplements  
  - Instruct patient to take daily until they are discharged from the study  
  Local tolerance assessment  
  - Investigator to review and assess injection sites  
  **BEFORE STUDY MEDICATION ADMINISTRATION**  
  *Vital Signs  
  *ECG  
  Blood Collection: fasting conditions (N.P.O. except water for 8 hours)  
  - Chemistry  
  - Hematology  
  *24 Hour Urine Collection and Urinalysis  
  **STUDY MEDICATION ADMINISTRATION**  
  - *Review study medication injection procedures with patient  
  - Assist with drug injection as necessary  
  - Abaloparatide or Placebo: collect used cartridges; supply new cartridges as necessary  
  - Teriparatide: collect used pens; supply new pre-filled pens as necessary  
  **AFTER STUDY MEDICATION ADMINISTRATION**  
  *Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)  
  *ECGs - (60 minutes post-injection)  
  Blood Collection: non-fasting  
  - Calcium (4 hours post-injection)  
  *Scheduling and Instructions for next Clinic Visit  

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures.*
<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 8 | Month 12 (± 7 days) | *Recent Health Status  
  - Document any changes from last visit  
  Patient Review  
  - Review Calcium and Vitamin D supplement usage  
  - Review diaries of study medication usage/injection site reactions  
  - Dispense weekly patient diary, if needed  
  Calcium and Vitamin D Supplements  
  - Assess and resupply patient’s Calcium and Vitamin D supplements  
  - Instruct patient to take daily until they are discharged from the study  
  Local tolerance assessment  
  - Investigator to review and assess injection sites  
  **BEFORE STUDY MEDICATION ADMINISTRATION**  
  - Vital Signs and Weight  
  - ECG  
  Blood Collection: fasting conditions (N.P.O. except water for 8 hours)  
  - Chemistry  
  - Hematology  
  - PTH(1-84)  
  - 25-hydroxy Vitamin D levels  
  - 1, 25-dihydroxy Vitamin D levels  
  - Serum markers of bone metabolism  
    - PINP  
    - bone-specific alkaline phosphatase  
    - serum osteocalcin  
    - serum CTX  
  - 24 Hour Urine Collection and Urinalysis  
  **STUDY MEDICATION ADMINISTRATION**  
  - Review study medication injection procedures with patient  
  - Assist with drug injection as necessary  
  - Abaloparatide or Placebo: collect used cartridges; supply new cartridges as necessary  
  - Teriparatide: collect used pens; supply new pre-filled pens as necessary  
  **AFTER STUDY MEDICATION ADMINISTRATION**  
  - Vital Signs - Repeat orthostatic blood pressure (60 minutes post-injection)  
  - ECGs - (60 minutes post-injection)  
  Blood Collection: non-fasting  
  - Abaloparatide peak drug levels (at randomized time). Only draw for patients randomized to abaloparatide, Placebo  
  - Calcium (4 hours post-injection)  
  Bone Mineral Density  
  - Perform hip (femoral neck), spine (L1-L4) and radius DXA  
  **Quantitative Bone Histomorphologic Assessment:**  
  - Discuss with patient and sign informed consent  
  - Schedule visits to prepare for biopsy (between Visit 8 and Visit 9)  
  *Scheduling and Instructions for next Clinic Visit  

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures.
<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
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</thead>
<tbody>
<tr>
<td>Visit V8R After 15</td>
<td>Month 15 (± 7 days)</td>
<td>*Recent Health Status</td>
</tr>
<tr>
<td>Months of Treatment</td>
<td></td>
<td>• Document any changes from last visit</td>
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<tr>
<td></td>
<td></td>
<td>Patient Review</td>
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<tr>
<td></td>
<td></td>
<td>• Review Calcium and Vitamin D supplement usage</td>
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<tr>
<td></td>
<td></td>
<td>• Review diaries of study medication usage/injection site reactions</td>
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<td></td>
<td>• Dispense weekly patient diary, if needed</td>
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<tr>
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<td></td>
<td>Calcium and Vitamin D Supplements</td>
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<td></td>
<td></td>
<td>• Assess and resupply patient’s Calcium and Vitamin D supplements</td>
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<td>• Instruct patient to take daily until they are discharged from the study</td>
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<tr>
<td></td>
<td></td>
<td>Drug resupply</td>
</tr>
<tr>
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<td></td>
<td>• Abaloparatide or Placebo: collect used cartridges; supply new cartridges as necessary</td>
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<tr>
<td></td>
<td></td>
<td>• Teriparatide: collect used pens; supply new pre-filled pens as necessary</td>
</tr>
</tbody>
</table>

*Scheduling and Instructions for next Clinic Visit

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures.
<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
</table>
| Visit 9  
End-of-Treatment Visit | Month 18  
(± 14 days)  
(one day after the last dose of study drug) | **Physical Examination**  
*Recent Health Status*  
- Document any changes from last visit  
**Patient Review**  
- Review Calcium and Vitamin D supplement usage  
- Review study medication usage/injection site reactions  
- Review weekly patient diary  
- Dispense weekly patient diary, if needed  
- Record dosing deviations or any AEs in source documents and CRFs.  
**Calcium and Vitamin D Supplements**  
- Assess and resupply patient’s Calcium and Vitamin D supplements  
- Instruct patient to take daily until they are discharged from the study  
**Local tolerance assessment**  
- Investigator to review and assess injection sites  
**Vital Signs and Weight**  
*Height (cm):* standing measurement with medical stadiometer  
**ECG**  
**Blood Collection:** fasting conditions (N.P.O. except water for 8 hours)  
- Chemistry  
- Hematology  
- Coagulation (PT and PTT)  
- PTH(1-84)  
- 25-hydroxy Vitamin D levels  
- 1, 25-dihydroxy Vitamin D levels  
- Serum markers of bone metabolism  
  - PINP  
  - bone-specific alkaline phosphatase  
  - serum osteocalcin  
  - serum CTX  
- Abaloparatide trough drug levels (only for patients randomized to abaloparatide, Placebo)  
- Abaloparatide antibody levels  
**24 Hour Urine Collection and Urinalysis**  
**There is no study medication administration**  
- Collect used study medication pens and cartridges  
**Clinical and Radiologic Fracture Evaluations**  
- Obtain antero-posterior and lateral radiographs of the lumbar and thoracic vertebrae  
- Document any non-vertebral fractures  
**Bone Mineral Density**  
- Perform spine (L1-L4), hip, and wrist (in subset of patients) DXA.  
**Renal CT Scan**  
- Perform renal CT scan (obtained through standard abdominal/pelvic CT scan procedures) on patients who consented to this procedure between the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive. In selected centers, patients in the Abaloparatide-SC/Placebo and teriparatide groups enrolled prior to the effective date of Version 3 of the protocol, will be asked to undergo a single renal CT scan between the End-of-Treatment Visit (Visit 9) and
Patients in selected centers enrolled after the effective date of Version 3 of the protocol, will be asked to undergo renal two CT scans, the first prior to treatment (between Visit 3 and Visit 4, inclusive), and the second at the End-of-Treatment Visit (Visit 9) and the End-of-Study Visit (Visit 10), inclusive.

- Discuss possibility of participation in the Extension Study with Abaloparatide-SC/Placebo patients.
- Discuss continuing treatment options with qualified patients

*Scheduling and Instructions for next Clinic Visit

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures
<table>
<thead>
<tr>
<th>VISIT</th>
<th>STUDY DAY</th>
<th>ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 10</td>
<td>Month 19</td>
<td>*Recent Health Status</td>
</tr>
<tr>
<td>Final Study</td>
<td>(± 3 days)</td>
<td>• Document any changes from last visit</td>
</tr>
<tr>
<td>Visit</td>
<td></td>
<td>Calcium and Vitamin D Supplements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Collect any leftover supplements</td>
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<tr>
<td></td>
<td></td>
<td>• Review weekly patient diary</td>
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<td></td>
<td>*Vital Signs and Weight</td>
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<tr>
<td></td>
<td></td>
<td>*ECG</td>
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<tr>
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<td></td>
<td>Discharge patient from study</td>
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<td>• Patient is terminated from the study unless</td>
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<tr>
<td></td>
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<td>abnormal clinical laboratory tests or adverse</td>
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<td></td>
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<td>events require further follow-up</td>
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<td></td>
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<td>• Discuss continuing treatment options with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>qualified patients</td>
</tr>
</tbody>
</table>

*Refer to “Definitions of Common Procedures” for more detailed information regarding these procedures.
14.3 **Body Mass Index Table**

A BMI of 18.5 to 33, inclusive, is required for study participation.

<table>
<thead>
<tr>
<th>Height (inches)</th>
<th>Body Weight (pounds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
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<td>90</td>
<td>93</td>
</tr>
</tbody>
</table>

### 14.4 Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (x10^9/L)</td>
<td>4</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>WNL</td>
<td>75.0 - normal</td>
<td>50.0 - 74.9</td>
<td>25.0 - 49.9</td>
<td>&lt; 25.0</td>
</tr>
<tr>
<td>Haemoglobin (g/dL); (mmol/L)</td>
<td>WNL</td>
<td>100.0 - normal;</td>
<td>80.0 - 99.0;</td>
<td>65.0 - 79.0;</td>
<td>&lt; 65.0</td>
</tr>
<tr>
<td>Granulocytes/ Bands (x10^9/L)</td>
<td>2</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Lymphocytes (x10^9/L)</td>
<td>2</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>WNL</td>
<td>0.99 - 0.75 x N</td>
<td>0.74 - 0.50 x N</td>
<td>0.49 - 0.25 x N</td>
<td>&lt; 0.25 x N</td>
</tr>
<tr>
<td>Prothrombin time(quick)</td>
<td>WNL</td>
<td>1.01 - 1.25 x N</td>
<td>1.26 - 1.50 x N</td>
<td>1.51 - 2.00 x N</td>
<td>&gt; 2.00 x N</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>WNL</td>
<td>1.01 - 1.66 x N</td>
<td>1.67 - 2.33 x N</td>
<td>2.34 - 3.00 x N</td>
<td>&gt; 3.00 x N</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia (mmol/L)</td>
<td>&lt; 6.4</td>
<td>6.4 - 8.9</td>
<td>9.0 - 13.9</td>
<td>14.0 - 27.8</td>
<td>&gt; 27.8 or ketoacidosis</td>
</tr>
<tr>
<td>Hypoglycaemia (mmol/L)</td>
<td>&gt; 3.6</td>
<td>3.6 - 3.1</td>
<td>3.0 - 2.3</td>
<td>2.2 - 1.7</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Amylase</td>
<td>WNL</td>
<td>&lt; 1.5 x N</td>
<td>1.5 - 2.0 x N</td>
<td>2.1 - 5.0 N</td>
<td>&gt; 5.0 x N</td>
</tr>
<tr>
<td>Hypercalcemia (mmol/L)</td>
<td>&lt; 2.65</td>
<td>2.65 - 2.88</td>
<td>2.89 - 3.13</td>
<td>3.14 - 3.36</td>
<td>&gt; 3.37</td>
</tr>
<tr>
<td>Hypocalcaemia (mmol/L)</td>
<td>&gt; 2.10</td>
<td>2.10 - 1.94</td>
<td>1.93 - 1.74</td>
<td>1.73 - 1.52</td>
<td>&lt; 1.51</td>
</tr>
<tr>
<td>Hypomagnesaemia (mmol/L)</td>
<td>&gt; 0.58</td>
<td>0.58 - 0.48</td>
<td>0.47 - 0.36</td>
<td>0.35 - 0.24</td>
<td>&lt; 0.23</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>none</td>
<td>able to eat reasonable intake</td>
<td>intake significantly decreased but can eat</td>
<td>no significant intake</td>
<td>—</td>
</tr>
<tr>
<td>Vomiting</td>
<td>none</td>
<td>1 episode in 24 hrs</td>
<td>2 - 5 episodes in 24 hrs</td>
<td>6 - 10 episodes in 24 hrs</td>
<td>&gt; 10 episodes in 24 hrs or requiring parenteral support</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>none</td>
<td>increase of 2 - 3 stools/day over pre-Rx</td>
<td>increase of 4 – 6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>increase of 7 - 9 stools/day, or incontinence, or severe cramping</td>
<td>increase of &gt; 10 stools/day or grossly bloody diarrhoea, or need for parenteral support</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>none</td>
<td>painless ulcers, erythema, or mild soreness</td>
<td>painful erythema, oedema, or ulcers but can eat solids</td>
<td>painful erythema, oedema, or ulcers and cannot eat solids</td>
<td>requires parenteral or enteral support for alimentation</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (N = 17 μmol/L)</td>
<td>WNL</td>
<td>-----</td>
<td>&lt; 1.5 x N</td>
<td>1.5 - 3.0 x N</td>
<td>&gt; 3.0 x N</td>
</tr>
<tr>
<td>Category</td>
<td>Toxicity (units)</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>---------------</td>
</tr>
<tr>
<td>Transaminase (SGOT, SGPT)</td>
<td>WNL</td>
<td>2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x N</td>
<td>&gt; 20.0 x N</td>
</tr>
<tr>
<td>Alkaline phosphatase or</td>
<td>WNL</td>
<td>&lt; 2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x N</td>
<td>&gt; 20.0 x N</td>
</tr>
<tr>
<td>5-nucleotidase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver- clinical</td>
<td>No change from baseline</td>
<td>-----</td>
<td>-----</td>
<td>precoma</td>
<td>hepatic coma</td>
</tr>
<tr>
<td>Kidney, bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>WNL</td>
<td>&lt; 1.5 x N</td>
<td>1.5 - 3.0 x N</td>
<td>3.1 - 6.0 x N</td>
<td>&gt; 6.0 x N</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>No change</td>
<td>1 (+) or</td>
<td>2 - 3 (+) or</td>
<td>4 (+) or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 0.3 g% or 3 g/L</td>
<td>0.3-1.0 g% or 3-10 g/L</td>
<td>&gt; 1.0 g% or &gt;10g/L</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>Negative</td>
<td>microscopic only</td>
<td>gross,</td>
<td>gross and clots</td>
<td>bladder irrigation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>no clots no Rx needed</td>
<td>no clots no Rx needed</td>
<td></td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>&lt; 5.0 %</td>
<td>5.0 - 9.9 %</td>
<td>10.0 - 19.9 %</td>
<td>20.00%</td>
<td>-----</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>none or no change</td>
<td>asymptomatic, with abnormality in PFTs</td>
<td>dyspnoea on significant exertion</td>
<td>dyspnoea at normal level of activity</td>
<td>dyspnoea at rest</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>none</td>
<td>asymptomatic, transient, requiring no therapy</td>
<td>recurrent or persistent, no therapy required</td>
<td>requires treatment</td>
<td>requires monitoring; or hypotension, or ventricular tachycardia or fibrillation</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>none</td>
<td>asymptomatic, decline of resting ejection fraction by less than 20% of baseline value</td>
<td>asymptomatic, decline of resting ejection fraction by more than 20% of baseline value</td>
<td>mild CHF, responsive to therapy</td>
<td>severe or refractory CHF</td>
</tr>
<tr>
<td>Cardiac ischaemia</td>
<td>none</td>
<td>non-specific T-wave flattening</td>
<td>asymptomatic, ST and T wave changes suggesting ischaemia</td>
<td>angina without evidence of infarction</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>Cardiac- pericardial</td>
<td>none</td>
<td>asymptomatic effusion, no intervention required</td>
<td>pericarditis (rub, chest pain, ECG changes)</td>
<td>symptomatic effusion; drainage required</td>
<td>tamponade; drainage urgently required</td>
</tr>
<tr>
<td>Hypertension</td>
<td>none or no change</td>
<td>asymptomatic, transient increase by greater than 20 mmHg (D) or to &gt; 150/100 if previously WNL</td>
<td>recurrent or persistent increase by greater than 20 mmHg (D) or to &gt; 150/100 if previously WNL</td>
<td>requires therapy</td>
<td>hypertensive crisis</td>
</tr>
<tr>
<td>Hypotension</td>
<td>none or no change</td>
<td>changes requiring no therapy (including transient orthostatic hypotension)</td>
<td>requires fluid replacement or other therapy but not hospitalisation</td>
<td>requires therapy and hospitalisation; resolves within 48 hrs of stopping the agent</td>
<td>requires therapy and hospitalisation for &gt; 48 hrs after stopping the agent</td>
</tr>
<tr>
<td>Category</td>
<td>Toxicity (units)</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
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<tr>
<td>Neurologic</td>
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<tr>
<td>Neuro: sensory</td>
<td>none or no change</td>
<td>mild paraesthesias; loss of deep tendon reflexes</td>
<td>mild or moderate objective sensory loss; moderate paraesthesias</td>
<td>severe objective sensory loss or paraesthesias that interfere with function</td>
<td>-----</td>
</tr>
<tr>
<td>Neuro: motor</td>
<td>none or no change</td>
<td>subjective weakness; no objective findings</td>
<td>mild objective weakness without significant impairment of function</td>
<td>objective weakness with impairment of function</td>
<td>paralysis</td>
</tr>
<tr>
<td>Neuro: cortical</td>
<td>none</td>
<td>mild somnolence or agitation</td>
<td>moderate somnolence or agitation</td>
<td>severe somnolence, (&gt;50 % waking hours), agitation, confusion, disorientation or hallucinations</td>
<td>coma, seizures, toxic psychosis</td>
</tr>
<tr>
<td>Neuro: cerebellar</td>
<td>none</td>
<td>slight incoordination, dysdiadochokinesia</td>
<td>intention tremor, dysmetria, slurred speech, nystagmus</td>
<td>locomotor ataxia</td>
<td>cerebellar necrosis</td>
</tr>
<tr>
<td>Neuro: mood</td>
<td>no change</td>
<td>mild anxiety or depression</td>
<td>moderate anxiety or depression</td>
<td>severe anxiety or depression</td>
<td>suicidal ideation</td>
</tr>
<tr>
<td>Neuro: headache</td>
<td>none</td>
<td>mild</td>
<td>moderate or severe but transient</td>
<td>unrelenting and severe</td>
<td>-----</td>
</tr>
<tr>
<td>Neuro: constipation</td>
<td>none or no change</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td>ileus &gt; 96 hrs</td>
</tr>
<tr>
<td>Neuro: hearing</td>
<td>none or no change</td>
<td>asymptomatic, hearing loss on audiometry only</td>
<td>tinnitus</td>
<td>hearing loss interfering with function but correctable with hearing aid</td>
<td>deafness not correctable</td>
</tr>
<tr>
<td>Neuro: vision</td>
<td>none or no change</td>
<td>-----</td>
<td>-----</td>
<td>symptomatic subtotal loss of vision</td>
<td>blindness</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pain</td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td>reg, narcotics</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Skin</td>
<td>none or no change</td>
<td>scattered macular or papular eruption or erythema that is asymptomatic</td>
<td>scattered macular or papular eruption or erythema with pruritus or other associated symptoms</td>
<td>generalised symptomatic macular, papular or vesicular eruption</td>
<td>exfoliative dermatitis or ulcerating dermatitis</td>
</tr>
<tr>
<td>Alopecia</td>
<td>no loss</td>
<td>mild hair loss</td>
<td>pronounced or total hair loss</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Category</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>Allergy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>analogous to Karnofsky index (WHO grading)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Chills</td>
<td>analogous to fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>analogous to weight gain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>analogous to weight loss</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
14.5 Eligibility Reference Guide for DXA

Radius BA05805003
ELIGIBILITY QUICK REFERENCE GUIDE FOR DXA

ELIGIBILITY CRITERIA

Otherwise healthy ambulatory postmenopausal (≥ 5 years) women from 50 to 85 years of age (inclusive) who meet the study entry criteria and have provided written informed consent are eligible for the study.

The women are to have a bone mineral density T-score ≤ -2.5 and > -5.0 at the lumbar spine (L1-L4) or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial fracture within the past 5 years. Or postmenopausal women older than 65 who meet the above fracture criteria but have a T-score ≤ -2.0 and > -5.0 may be enrolled. Or women older than 65 who do not meet the fracture criteria may be enrolled if their T-score is ≤ -3.0 and > -5.0. Please see the following T-Score and BMD reference values:

Women between 50 and 85 years of age with T-score ≤ -2.5 and > -5.0 who meet the above fracture criteria

<table>
<thead>
<tr>
<th>DXA Manufacturer</th>
<th>T-Score</th>
<th>Lumbar Spine BMD (g/cm²)</th>
<th>Femoral Neck BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hologic</td>
<td>-2.5</td>
<td>0.772</td>
<td>0.558</td>
</tr>
<tr>
<td></td>
<td>-3.0</td>
<td>0.717</td>
<td>0.498</td>
</tr>
<tr>
<td></td>
<td>-3.5</td>
<td>0.662</td>
<td>0.438</td>
</tr>
<tr>
<td></td>
<td>-4.0</td>
<td>0.607</td>
<td>0.378</td>
</tr>
<tr>
<td></td>
<td>-4.5</td>
<td>0.552</td>
<td>0.318</td>
</tr>
<tr>
<td></td>
<td>-5.0</td>
<td>0.497</td>
<td>0.258</td>
</tr>
<tr>
<td>Lunar Prodigy</td>
<td>-2.5</td>
<td>0.880</td>
<td>0.691</td>
</tr>
<tr>
<td></td>
<td>-3.0</td>
<td>0.820</td>
<td>0.622</td>
</tr>
<tr>
<td></td>
<td>-3.5</td>
<td>0.760</td>
<td>0.552</td>
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<td>-4.0</td>
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<td>-4.5</td>
<td>0.640</td>
<td>0.413</td>
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<td></td>
<td>-5.0</td>
<td>0.580</td>
<td>0.344</td>
</tr>
</tbody>
</table>
### ELIGIBILITY QUICK REFERENCE GUIDE FOR DXA

**Women older than 65 and up to 85 years of age with T-score ≤ -2.0 and > -5.0 who meet the above fracture criteria**

<table>
<thead>
<tr>
<th>DXA Manufacturer</th>
<th>T-Score</th>
<th>Lumbar Spine BMD (g/cm²)</th>
<th>Femoral Neck BMD (g/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hologic</strong></td>
<td>-2.0</td>
<td>0.827</td>
<td>0.618</td>
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<tr>
<td></td>
<td>-2.5</td>
<td>0.772</td>
<td>0.558</td>
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<tr>
<td></td>
<td>-3.0</td>
<td>0.717</td>
<td>0.498</td>
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<tr>
<td></td>
<td>-3.5</td>
<td>0.662</td>
<td>0.438</td>
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<td>-4.0</td>
<td>0.607</td>
<td>0.378</td>
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<td>-4.5</td>
<td>0.552</td>
<td>0.318</td>
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<td></td>
<td>-5.0</td>
<td>0.497</td>
<td>0.258</td>
</tr>
<tr>
<td><strong>Lunar Prodigy</strong></td>
<td>-2.0</td>
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<td>0.761</td>
</tr>
<tr>
<td></td>
<td>-2.5</td>
<td>0.880</td>
<td>0.691</td>
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<tr>
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<td>-3.0</td>
<td>0.820</td>
<td>0.622</td>
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<td>0.580</td>
<td>0.344</td>
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</tbody>
</table>

**Women older than 65 and up to 85 years of age - who do not meet the above fracture criteria with T-score ≤ -3.0 and > -5.0**

<table>
<thead>
<tr>
<th>DXA Manufacturer</th>
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<th>Lumbar Spine BMD (g/cm²)</th>
<th>Femoral Neck BMD (g/cm²)</th>
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14.6 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate
laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be
respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a
research protocol. The protocol should contain a statement of the ethical considerations involved and should
indicate how the principles in this Declaration have been addressed. The protocol should include information
regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects
and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the
research study. The protocol should describe arrangements for post-study access by study subjects to
interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research
ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and
any other undue influence. It must take into consideration the laws and regulations of the country or countries in
which the research is to be performed as well as applicable international norms and standards but these must not
be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The
committee must have the right to monitor ongoing studies. The researcher must provide monitoring information
to the committee, especially information about any serious adverse events. No change to the protocol may be
made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate
scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a
competent and appropriately qualified physician or other health care professional. The responsibility for the
protection of research subjects must always rest with the physician or other health care professional and never the
research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the
research is responsive to the health needs and priorities of this population or community and if there is a
reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of
predictable risks and burdens to the individuals and communities involved in the research in comparison with
foreseeable benefits to them and to other individuals or communities affected by the condition under
investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the
risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately
stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of
positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective
outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be
appropriate to consult family members or community leaders, no competent individual may be enrolled in a
research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their
personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed
of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the
researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other
relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the
study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the
specific information needs of individual potential subjects as well as to the methods used to deliver the
information. After ensuring that the potential subject has understood the information, the physician or another
appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably
in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.