NCT # NCT03710889

STATISTICAL ANALYSIS PLAN

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

Protocol BA058-05-020

Protocol Version and Date: Amendment 2 (5 November 2018)

Name of Test Drug: Abaloparatide-SC

Phase: Phase 3

Methodology: Prospective, Single Arm, Open-Label

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Analysis Plan Date: 05 Mar 2020

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ATC	Anatomical therapeutic chemical
BFR/BS	Bone formation rate
BMD	Bone mineral density
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CSR	Clinical study report
Ct.Po/Ct.Ar	Cortical porosity
CTMS	Clinical trial management system
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ES/BS	Eroded surface
FSH	Follicle-stimulating hormone
IRB	Institutional Review Board
MAR	Mineral apposition rate
MedDRA	Medical dictionary for regulatory activities
MF/BS	Modeling-based formation
MS/BS	Mineralizing surface
msec	Millisecond
oMF/BS	Overflow modeling-based formation
OS/BS	Osteoid surface
O.Th	Osteoid thickness
OV/BV	Osteoid volume
PCS	Potentially clinically significant
pQCT	Peripheral quantitative computed tomography
PR	Time from beginning of P wave (onset of atrial depolarization) to beginning of QRS complex (onset of ventricular depolarization)
PT	Preferred Term
PTH	Parathyroid hormone
PTT	Partial thromboplastin time

Abbreviation	Term
Q1, Q3	Lower and upper quartiles, respectively, of the interquartile range
QT	Total depolarization and repolarization time
QTc	Total depolarization and repolarization time corrected with heart rate
QTcF	Total depolarization and repolarization time corrected with heart rate – Fridericia correction
RmF/BS	Remodeling-based formation
RR	Time elapsed between two successive R-waves of the QRS signal on the electrocardiogram
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SI	Standard international
SOC	System organ class
s-CTX	Carboxy-terminal cross-linking telopeptide of type I collagen
s-PINP	Serum procollagen type 1 N propeptide
TEAE	Treatment emergent adverse event
WHO	World Health Organization
W.Th	Wall thickness

1 BACKGROUND

This statistical analysis plan (SAP) enhances the statistical considerations specified in the protocol for Study BA058-05-020. If considerations are substantially different, they will be identified. Any post-hoc or unplanned analyses, or any significant changes from the planned analysis in this SAP will be clearly identified and described in the clinical study report (CSR).

1.1 Study Objectives

Study objectives are to

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

1.2 Study Design

1.2.1 Synopsis of Study Design

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

There is a sub study at one site to collect pQCT data and extend an additional 3 months of study drug administration for a total of 6 months of treatment.

The study design is presented in **Figure 1**. Full details of the protocol required assessments can be found in the Schedule of Assessments and Procedures (Table 1).

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

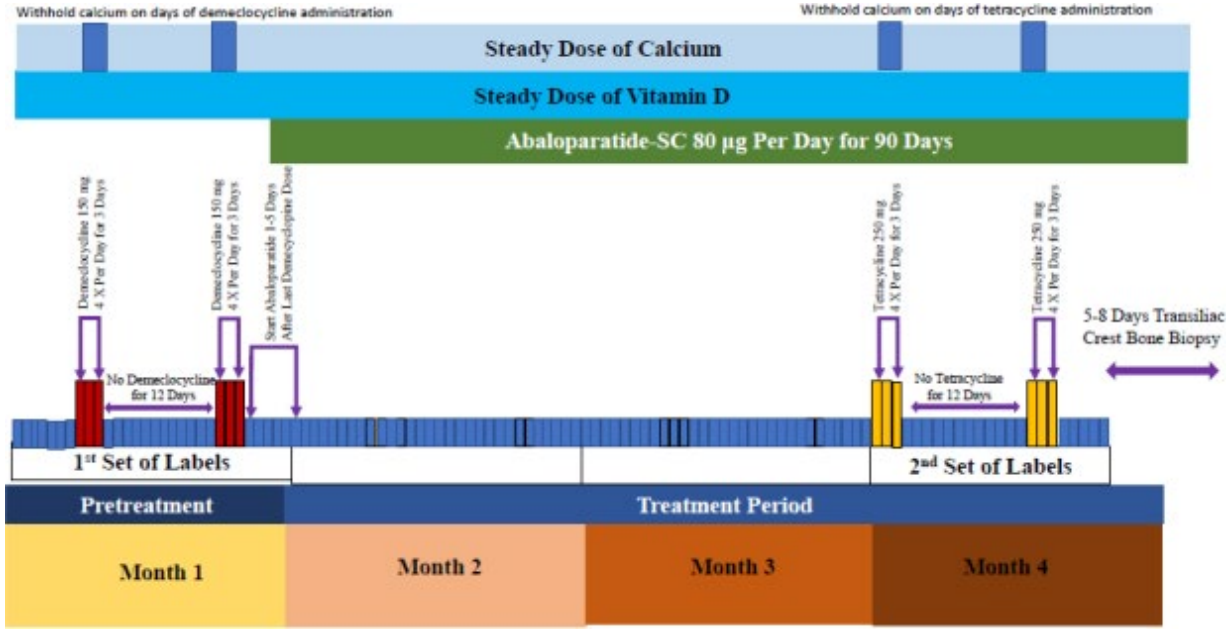

Table 1: Schedule of Assessments

Procedure	Visit 1 **Screening (30 Days)**	Visit 2 (±4 days) **Pre-treatment**	Visit 3 (+4 days) **Day 1**	Visit 4 (±4 days) **Month 1**	Visit 5 (±4 days) **Month 3**	Visit 6 (±7 days) **Month 4**
Informed consent	X					
Verification of entry criteria	X	X				
Review of medical history[a]	X	X	X	X	X	X
Physical examination[b]	X					
Symptom directed physical examination		X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X
Weight and height measurements[d]	X		X	X	X	X
12-lead Electrocardiogram[e]	X		X		X	X
Urinalysis (dipstick)[f]	X		X	X	X	
Chemistry blood collection[g]	X		X	X	X	
Hematology blood collection	X		X	X	X	
Coagulation (Prothrombin time and PTT) blood collection	X				X	
PTH (1-84)	X				X	
25-hydroxyvitamin D level	X					

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pre-treatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±7 days) Month 4
1,25-dihydroxy vitamin D level	X					
FSH	X					
Thyroid stimulating hormone	X					
Injection training for subjects		X				
Dispense calcium and vitamin D supplements[n]	X	X	X	X		
Study medication (abaloparatide) administration			Daily abaloparatide administration until and including the day of bone biopsy			
Demeclocycline (dispense and administration)		X[h]				
Tetracycline (dispense and administration)				X[i]		
Transiliac crest bone biopsy[j]					X	
Serum markers of bone metabolism (PINP and CTX)			X	X	X	
AP and lateral lumbar and thoracic spine radiographs	X					
Clinical assessment of new fractures[k]		X	X	X	X	X
Collect blood for immunogenicity testing			X		X	
BMD of lumbar spine, total hip, and femoral neck	X				X	

Procedure	Visit 1 Screening (30 Days)	Visit 2 (±4 days) Pre-treatment	Visit 3 (+4 days) Day 1	Visit 4 (±4 days) Month 1	Visit 5 (±4 days) Month 3	Visit 6 (±7 days) Month 4
Investigator assessment of local tolerance (dermal reactions assessment)			X	X	X	
Subject diary review[l]			X	X	X	
Document AEs and concomitant medications[m]	At any time, question subject at each visit					
Drug supply/resupply/accountability		X	X	X	X	

[a] Including alcohol and tobacco use assessment.

Error! Reference source not found. A complete physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal, and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in physical examinations not present at screening should be reported as AEs.

Error! Reference source not found. Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiratory rate. These will be assessed following a 5-minute rest (seated or supine) and before blood sample collection. At visits when study drug is administered at the site, vital sign assessments will be collected before the dose of study drug. Only blood pressure, pulse rate, and respiration rate are to be recorded one hour post-dose. Supine and standing blood pressure measurements will be performed at each visit during the Treatment Period.

Error! Reference source not found. Height is to be measured in the standing position with shoes off using a medical stadiometer.

Error! Reference source not found. An ECG will be recorded immediately prior to dosing and one hour post-dose during the Treatment Period.

Error! Reference source not found. All routine urinalysis will be performed on a sample freshly voided during the visit and sent to a central lab for microscopy if test is positive for micro-organisms via dipstick.

Error! Reference source not found. Serum chemistry will be measured predose at Visits 3, 4, and 5.

Error! Reference source not found. Eighteen days before Day 1 of the Treatment Period (Visit 3), subjects who remain eligible for study participation will begin the first bone biopsy labeling procedure with administration of 150 mg demeclocycline 4 times daily for 3 days followed by a 12-day intermission, and then demeclocycline for 3 additional days at the same dose.

Error! Reference source not found. Approximately 23 to 26 days before Month 3 (Visit 5), subjects will begin the second bone biopsy labeling procedure with administration of 250 mg tetracycline 4 times daily for 3 days followed by a 12-day intermission, and then tetracycline for 3 additional days at the same dose.

Error! Reference source not found. Transiliac crest bone biopsy 5-8 days after last tetracycline dose. Sponsor Medical Monitor will decide if included in Early Termination Visit.

Error! Reference source not found. If the subject reports that a fracture has occurred, remind the subject to bring X-rays and any medical reports of the fracture to the next clinic visit. Documentation must be obtained on all new fractures that occur during the study. This documentation should be maintained in the source documents.

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

[m] AEs and SAEs will be recorded on the case report forms starting from the time of subject entry into the Screening Period (Visit 1) of the study (signed informed consent) until 30 days after the last dose of study medication. All AEs will be followed until resolution or stabilization. Any SAEs that occur at any time after completion of the study, which are considered by the Investigator to be related to study treatment, must be reported to the Sponsor or its designee.

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

1.2.2 Randomization Methodology

This is a single arm study, and randomization is not used. i.e., not applicable.

1.2.3 Unblinding

This is an open-label study, and there is no blinding of study medication. i.e., not applicable.

1.2.4 Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1.

1.2.5 Study Endpoints

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

2 SUBJECT ANALYSIS POPULATIONS

2.1 Population Definitions

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

2.2 Protocol Deviations

As documented in the BA058-05-020 Medical Monitoring Plan, the definitions/classifications of protocol deviations are as defined in [redacted] document CTM002-SOP (Managing Protocol Deviations; Effective Date: 05 Sep 2017). A protocol devation is any intentional, unintentional change or non-compliance with the current IRB/IEC and Competent Authority approved protocol procedures or requirements per ICH/GCP guidelines. A deviation may result from the action or inaction of the subject, Investigator or site staff.

Subjects with protocol deviations will be identified and recorded by the clinical trial vendor [redacted] using their Clinical Trial Management System (CTMS). The list of protocol deviations and protocol violations will be reviewed by the clinical team on a regular basis throughout the study. At the end of the study, a list of the protocol deviations/violations will be generated from the CTMS and included in the clinical study report (CSR).

3 GENERAL STATISTICAL METHODS

3.1 Sample Size Planned and Specified in the Protocol

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

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

3.2 General Methods

Continuous variables will be summarized with the following descriptive statistics: number of observations, (arithmetic) mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum. If the number of subjects is 1, the standard deviation will be left blank. Categorical data will be summarized with frequencies for each category and corresponding percentages.

All data listings that contain an evaluation date will contain a relative study day. Screening, pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

In listings, data will be presented with the same precision as the original data. Derived data may be rounded to 1 decimal place greater than the original data for presentation purposes.

Frequency percentages will be presented with 1 decimal.

For all summaries, the mean and median will be presented to 1 decimal place greater than the original data, standard deviation (SD) to 2 greater than the original data, and the minimum and maximum will be presented to the same number of decimal places as the original data.

The summaries will include:

- data from subjects participating in the main study (i.e., subjects with planned treatment duration of 3 months, plus 1 month after the last dose of study medication); and
- data up to Month 4 for subjects participating in the sub-study (i.e., subjects with planned treatment duration of 6 months, plus 1 month after the last dose of study medication).

All subject data (from the main study and the sub-study) will be presented in listings.

3.3 Computing Environment

All descriptive and statistical analyses will be performed using SAS statistical software Version 9.4, or later version. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug Global March 2018 B3).

3.4 Baseline Definitions

Unless otherwise specified, the baseline value is defined as the last value obtained prior to the first dose of study medication.

3.5 Data Pooling

Data from all sites will be pooled together for all analyses unless otherwise

specified.

3.6 Adjustments for Covariates

No adjustment for covariates will be made in any of the planned analyses for study endpoints.

3.7 Multiple Comparisons

Not applicable.

3.8 Subgroups

Not applicable.

3.9 Withdrawals, Dropouts, Loss to Follow-up

Data from subjects who do not complete the study, or who are lost to follow-up will be included in data listings and in summary tables, as appropriate.

3.10 Missing, Unused, and Spurious Data

Unless otherwise specified, there will be no imputation of data.

In the event that incorrect data are discovered after database lock, the impact of such incorrect data will be assessed and a determination will be made as to whether the data need to be corrected in the database (and subsequently in the analysis). In cases where it is decided that the data need to be corrected, the decision will be documented and the documentation will be saved in the Trial Master File.

All available data will be included in data listings.

3.11 Visit Windows

Unless otherwise specified, data will not be analyzed using visit windows; instead, the nominal visit will be used.

3.12 Interim Analyses

There are no interim analyses planned for this study.

4 STUDY ANALYSES

Unless otherwise specified, all summary tables described in this section will be presented for the Safety Population.

4.1 Subject Disposition

Subject disposition will include the number of subjects enrolled, included in the safety population and reasons for exclusion from the safety population, included in the bone-biopsy population and reasons for exclusion from the bone-biopsy population, completed treatment, discontinued treatment with reasons for treatment discontinuation, completed the study, discontinued study with primary reasons for not completing the study.

A by-subject data listing of treatment completion and study completion information, including the primary reasons for treatment discontinuation and for study withdrawal, as recorded in the eCRF, will be presented.

4.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized. Age, height, weight, body mass index (BMI), total hip T-score, total hip BMD, femoral neck T-score, femoral neck BMD, lumbar spine T-score, and lumbar spine BMD will be summarized using descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum). The number and percentage of subjects in each age (<65 years, 65 to <75, >=75), gender, ethnicity, race and total hip/lumbar spine/femoral neck T-score category (> -2.5 to <= -2.0; > -3.0 to <= -2.5; and <= -3.0) will also be presented.

The number and percentage of subjects in each substance use category (tobacco history, alcohol use, use of other substances) and with prevalent clinical fracture will also be presented.

Medical history will be presented by MedDRA system organ class (SOC) and preferred term (PT) summarizing the proportion of subjects who have a condition noted.

All subject data collected for demographics and baseline characteristics will be presented in data listings.

4.3 Extent of Exposure and Compliance

Study drug exposure and compliance will be calculated using the data recorded on the Visit Day Study Medication Injection, the Injected Medication Accountability Log, and the End of Treatment eCRF pages as follows:

- Duration of Exposure (days)
  = date of last study medication – date of first study medication + 1
  Note: The date of last study medication will be obtained from the End of Treatment eCRF. If the date of last study medication is missing, the last available date of study medication on the Visit Day Study Medication Injection eCRF will be used.
- Number of Doses Delivered
  = duration of exposure - number of missed doses per subject diary
- Compliance (%)
  = (Number of doses delivered / Duration of exposure) x 100%

For demeclocycline and tetracycline, the number of doses delivered will be calculated as

- Number of Tablets Dispensed - Number of Tablets Returned.

Descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum) will be used to summarize duration of exposure, number of doses delivered, and compliance.

4.4 Concomitant Medication

Concomitant medications will be coded using the WHO Drug Dictionary. The number (and percentage) of subjects taking medications will be tabulated by Anatomical Therapeutic Chemical (ATC) class and preferred term (PT).

The tabulations will include concomitant medications taken from the date of the first dose of study medication (Day 1) until 30 days after the last dose of study medication. Medications that did not end prior to the first dose of study medication will be included in the summary.

Prior medications (those with start date prior to the first dose of study medication) will also be summarized by ATC and PT.

All recorded prior and concomitant medications will be presented in a by-subject listing.

4.5 Analyses of the Primary Endpoint

The primary endpoint is the change from baseline to 3 months in MS/BS in the cancellous envelope. Paired t-tests will be used to compare the differences in dynamic indices between the two time-points using the Bone-Biopsy Population. If the normality assumption of the efficacy data is not satisfied at the 0.01 significance level with Shapiro–Wilk test and if visual inspection of the data deems it necessary, the Wilcoxon signed-rank test will be used to assess changes from baseline. No adjustments for multiplicity will be made. A two-sided p-value < 0.05 will be considered statistically significant. The actual values and change from baseline values will be summarized with descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum) by visit, together with 95% CI for the mean.

4.6 Analyses of Secondary Endpoints

4.6.1 Change from baseline to 3 months in MS/BS in the endocortical, intracortical, and periosteal envelopes

The same analyses described in Section 4.5 will be used.

4.6.2 Change from baseline to 3 months in MAR in the cancellous, endocortical, intracortical, and periosteal envelopes

The same analyses described in Section 4.5 will be used.

4.6.3 Change from baseline to 3 months in BFR/BS in the cancellous, endocortical, intracortical, and periosteal envelopes

The same analyses described in Section 4.5 will be used.

4.6.4 Structural index (Ct.Po/Ct.Ar) in the intracortical envelope at Month 3

The actual values will be summarized with descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum), together with 95% CI for the mean.

4.6.5 Static indices in the relevant bone envelopes (cancellous, endocortical, intracortical, and periosteal) at Month 3

The following study endpoints will be summarized with descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum), together with 95% CI for the mean.

- OV/BV
- OS/BS
- O.Th
- W.Th
- ES/BS

4.6.6 Change from baseline to 3 months in special histomorphometric variables in the relevant bone envelopes (cancellous, endocortical, intracortical, and periosteal)

Decriptive statistics (number of subjects, mean, SD, median, interquartiale range (Q1, Q3), minimum and maximum) will be provided for the following endpoints.

- RmF/BS
- MF/BS
- oMF/BS

4.6.7 Change in s-PINP and s-CTX from baseline to 1 and 3 months

The actual values, change from baseline values, percentage change from baseline values, geometric mean, geometric mean (SE) of ratio (post-baseline value to baseline value) in s-PINP and s-CTX will be summarized descriptively by visit, together with the 95% CI of the mean, for both the Bone-Biopsy and the Safety populations.

4.6.8 Correlations of tissue-based indices of bone formation and bone resorption with s-PINP and s-CTX

Linear regression analyses will be used to assess the relationships between tissue-based indices of bone formation and bone resorption and changes in bone turnover markers at each visit, including

- Changes in MS/BS in each envelope (cancellous, endocortical, intracortical, and periosteal) at Month 3 to changes in s-PINP at Months 1 and 3
- Changes in BFR/BS in each envelope (cancellous, endocortical, intracortical, and periosteal) at Month 3 to changes in s-PINP at Months 1 and 3
- Changes in intracortical MS/BS at Month 3 to changes in s-CTX at Months 1 and 3,
- Changes in intracortical BFR/BS at Month 3 to changes in s-CTX at Months 1 and 3,
- MS/BS in each envelope (cancellous, endocortical, intracortical, and periosteal) at Month 3 to s-PINP at Months 1 and 3

- BFR/BS in each envelope (cancellous, endocortical, intracortical, and periosteal) at Month 3 to s-PINP at Months 1 and 3
- Intracortical MS/BS at Month 3 to s-CTX at Months 1 and 3
- Intracortical BFR/BS at Month 3 to s-CTX at Months 1 and 3
- ES/BS in each envelope (cancellous, endocortical, intracortical, and periosteal) at Month 3 to s-CTX at Months 1 and 3
- Cortical porosity at Month 3 to s-CTX at Months 1 and 3

The analyses include scatter plots, Spearman's rank correlation coefficient, and slopes of simple regression models, together with corresponding 95% CI of Spearman's correlation coefficient using the Bone-Biopsy population.

4.7 Safety Analyses

All safety analyses will be conducted using the Safety population. Unless otherwise specified, no formal statistical hypothesis testing will be performed for safety endpoints, and the presentations will be based on descriptive summaries.

4.7.1 Adverse Events

Analyses of AEs will be performed for those events that are considered to be treatment-emergent adverse events (TEAEs). A TEAE is defined as any AE that was absent (i.e., had not occurred) prior to the start of study drug and which occurs on or after the date of the first dose of study drug and within 30 days of the last dose of study drug, or any AE that started during the study period(s) prior to the start of study drug and worsened in severity after the start of study drug within 30 days of the last dose of study drug.

In any tabulation of adverse events, a subject contributes only once to the count for a given SOC or PT. For summaries by severity, a subject with multiple occurrences of an AE will be represented under the most severe occurrence. For summaries by relationship to study drug, a subject with multiple occurrences of an AE will be represented under the most related occurrence.

The number (%) of subjects with TEAEs will be summarized by SOC and PT. This analysis will also be performed for the following types of AEs: most common (≥5%) TEAEs, severe TEAEs, serious TEAEs (SAEs), TEAEs leading to study drug withdrawal, drug-related TEAEs (with probable or possible relationship to study drug), and AEs that are not treatment-emergent.

The number (%) of subjects with TEAEs will also be summarized by PT in order of decreasing frequency.

The number (%) of subjects with TEAEs by SOC and PT will also be tabulated by maximum severity (mild, moderate, or severe). A similar tabulation will be presented by relationship (related or not related) to study drug.

Subject listings will be provided for all AEs by SOC and PT. Listings will also be produced for AEs with outcome of deaths, severe AEs, SAEs, and AEs leading to study drug withdrawal.

4.7.2 Investigator Assessment of Local Tolerance

For each symptom (redness, swelling, pain, tenderness), descriptive statistics (number of subjects, mean, SD, median, interquartile range, minimum and maximum) will be used to summarize 4-point scale scores (0=None, 1=Mild, 2=Moderate,3=Severe) by visit and timepoint. The maximum severity of each symptom of local skin reaction per subject will be summarized with the number (%) of subjects in each response category by visit. The maximum severity of each symptom of local skin reaction per subject will also be summarized with the number (%) of subjects in each response category by timepoint (including any post dose timepoint).

In addition, for each symptom, the number (%) of subjects in each response category (none, mild, moderate, and severe) will be provided per visit and timepoint. The maximum severity of symptom scores will be similarly summarized for each response category by visit and by timepoint, respectively.

All local tolerance assessment scores will be presented in a listing.

4.7.3 Laboratory Data

Clinical laboratory values will be provided in standard international (SI) units by the central laboratory.

Summaries of laboratory data using descriptive statistics by study visit will be presented based on the SI units, including absolute results and changes from baseline. This includes serum chemistry, hematology, coagulation, urinalysis, and additional tests. In the event of repeat or unscheduled assessments prior to Day 1, the last non-missing value prior to Day 1 will be used to represent the Screening laboratory assessment. Results from other repeat or unscheduled visits will not be included in this summary.

Shift analyses of laboratory data from baseline to each post-baseline visit will be performed. Results for laboratory data will be presented by category (above normal limit, within normal limit, below normal limit). For shift tables, subjects who are missing either assessment will not be included in the percentage calculation (numerator or denominator). In addition, shift analyses of laboratory data from baseline to the worst post-baseline value will be provided. Results from repeat or unscheduled visits will be included in the shift analyses as applicable.

All laboratory data, including repeated values and results from unscheduled visits, will be presented in data listings, with indication of higher or lower than the associated normal range of each laboratory test.

4.7.4 Vital Signs

Vital signs data will be summarized by visit (and timepoint if applicable). Descriptive statistics will be provided for the observed value and the change from baseline values.Results from repeat or unscheduled visits will not be included in this summary.

All vital signs data will be presented for each subject in a data listing.

Criteria for determining vital signs values that are considered potentially clinically significant (PCS) are listed below:

Vital Sign	Criterion
Body Temperature (ºC)	≥ 39.0
Heart Rate (bpm)	> 100 > 130 < 45
Supine Systolic BP (mmHg)	> 155 < 80
Supine Diastolic BP (mmHg)	> 100
Standing Systolic BP (mmHg)	> 155 < 80
Standing Diastolic BP (mmHg)	> 100

The number (and percentage) of subjects who have PCS values after the first dose of study drug, but did not have PCS values at baseline, will be presented. For the calculation of the percentages of subjects, the denominator will be based on the number of subjects who had no PCS values at baseline and had at least one post-baseline assessment for the specific vital sign parameter of interest. The numerator will be based on the number of subjects from the denominator who had at least one PCS value post-baseline for the specific vital sign parameter of interest. All vital signs data, including repeat and unscheduled assessments, will be included in determining the incidence of PCS vital sign values. A listing of subjects with any PCS vital sign values will be provided.

4.7.4.1 Orthostatic Hypotension

The number (%) of subjects experiencing orthostatic hypotension will be summarized by visit and time point. Orthostatic hypotension will be defined as a decrease in systolic blood pressure (SBP) of ≥ 20 mmHg from seated or supine to standing or in diastolic blood pressure (DBP) of ≥ 10 mmHg from seated or supine to standing. All blood pressure data, including repeat and unscheduled assessments, will be included in determining the incidence of orthostatic hypotension. If a subject has multiple results on the vital signs at a particular visit and time point, the last non-missing value at that visit/time point will be used for this summary.

A listing of subjects who experienced orthostatic hypotension will be provided.

4.7.4.2 Heart Rate

The number (%) of subjects experiencing heart rate increase from pre-dose to post-dose and the number of occurrences per subject will be summarized with various threshold values (ranging from >5 bpm to >40 bpm, with threshold values increasing by 5 bpm). The median, minimum and maximum heart rate increase (in bpm) will be provided per threshold value. The number of

occurrences will be summarized using the median, minimum and maximum values. All heart rate data, including repeat and unscheduled assessments, will be included in determining the increase from pre-dose in this summary.

4.7.5 Electrocardiogram

Descriptive statistics will be provided to summarize ECG parameters and changes from baseline by visit and time point. The ECG parameters include heart rate (bpm), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), and QTcF (Fridericia) (msec). Results from repeat or unscheduled visits will not be included in this summary.

The number (%) of subjects experiencing heart rate increase from pre-dose to post-dose and the number of occurrences per subject will be summarized with various threshold values (ranging from >5 bpm to >40 bpm, with threshold values increasing by 5 bpm). The median, minimum and maximum heart rate increase (in bpm) will be provided per threshold value. The number of occurrences will be summarized using the median, minimum and maximum values. All ECG heart rate data, including repeat and unscheduled assessments, will be included in determining the increase from pre-dose in this summary.

Incidence of change from baseline in QTcF >=30 msec and >=60 msec by visit and time point will be provided. The number and percentage of subjects with post-baseline QTcF > 500 msec and change from baseline >= 60 msec in QTcF by visit and time point will be presented.

Shifts from baseline (<=450 msec and >450 msec, <=480 msec and >480 msec; <=500 msec and >500 msec) in QTcF by visit and time point will be provided.

Listings of subjects satisfying each of the above criteria will be provided.

4.7.6 Clinical Fractures

The number and percentage of subjects with any post-baseline clinical fracture will be presented, together with the fracture location.

4.7.7 Anti-abaloparatide Antibodies

As per Radius deviation report QE-003032 approved 27-Feb-2020, the collected immunogenicity samples will not be tested as part of this study.

5 CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The following changes from the protocol-specified analyses are included in this SAP:

1. Sectioin 4.6.8 states that correlations between the tissue-based indices of bone formation and bone resorption with the bone turnover markers (s-PINP and s-CTX) will be evaluated using Spearman's rank correlation coefficient, instead of Pearson's correlation coefficient, due to the expected non-linear relationship between variables.
2. Section 4.7.4 provides criteria for potentially clinically significant (PCS) vital signs values with corresponding analyses.
3. Section 4.7.4.1 gives the definition for othostatic hypotension and the analysis of this parameter.

4. Section 4.7.5 describes summaries for QTcF notable values, change from baseline values, and shifts from baseline values.
5. Section 4.7.7 states that the collected immunogenicity samples will not be tested as part of this study.

All other statements in this SAP are enhancements to the statistical considerations described in the protocol.

References

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

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