STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP634-102
Protocol Title:	A Phase 1, Open-label, Randomized, Cross-over Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single Dose of rhPTH(1-84) Administered Subcutaneously in Japanese Healthy Subjects Compared with Matched Non-Hispanic, Caucasian Healthy Adult Subjects and to Assess Dose Proportionality of 3 Doses of rhPTH(1-84) in the Japanese Subjects
Drug:	rhPTH(1-84)
Sponsor:	Shire 300 Shire Way Lexington, MA 02421 USA
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ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	anatomical therapeutic class
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CRC	clinical research center
CV	coefficient of variation
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PCI	potentially clinically important
PD	pharmacodynamic
PK	pharmacokinetic
PTH	parathyroid hormone
QTcB	QT Interval Corrected for Heart Rate using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
rhPTH(1-84)	recombinant human parathyroid hormone (1-84 amino acids)
RR	a time interval on an ECG trace starting at the peak of one R wave to the peak of the next R wave
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic, pharmacodynamics and safety data as described in the study protocol dated 29 Jan 2017 incorporating the most recent amendment 1 (dated 21 Mar 2017). Specifications for tables, figures, and listings are contained in a separate document. Statistical analyses for pharmacokinetic/pharmacodynamic data are included in the SAP, as appropriate.

2. STUDY DESIGN

2.1 General Study Design

This study is a Phase 1, open-label, randomized, cross-over, single-center study to evaluate the PK and PD profiles and safety and tolerability of rhPTH(1-84) administered in healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian, healthy adult volunteer subjects. The non-Hispanic, Caucasian volunteers will receive a single dose of 100µg rhPTH(1- 84). The Japanese subjects will receive 3 single doses of rhPTH(1-84). On Day 1 the subjects of Japanese descent will receive a single SC injection of 100µg. On Days 4 and 7 the subjects of Japanese descent will be randomized to receive a single SC injection of either 25µg or 50µg such that all of these subjects are exposed to the 3 dose strengths over a 7-day period to further characterize the PK profile in that group. A total of 24 subjects will be enrolled: 12 non-Hispanic, Caucasian subjects and 12 subjects of Japanese descent (1:1 male: female). Non-Hispanic, Caucasian subjects will be matched to Japanese subjects based on sex, age (±7 years), and body mass index (±15%).

All subjects will receive a single dose of 100µg rhPTH(1-84) administered by SC injection in the mid-thigh with the Haselmeier injector pen on Day 1. In addition, the subjects of Japanese descent will also receive single dose injections of 25µg and 50µg rhPTH(1-84) administered by SC injection in the mid-thigh to characterize the PK profile over a range of doses. There will be a minimum of 72 hours (maximum 73 hours) washout between doses for the volunteers of Japanese descent. The study duration will comprise of a 28-day screening period, 1 treatment period for the non-Hispanic, Caucasian group (Days 1 and 2); 1 treatment period for the volunteers of Japanese descent (Days 1-8), and a follow-up visit (30±2 days) after the last dose of investigation drug is administered for all subjects. The total number of nights subjects will be expected to stay at the clinical research center (CRC) is 2 for the non-Hispanic, Caucasian group and 8 for the volunteers of Japanese descent. The maximal total duration of study participation is 62 days for a non-Hispanic, Caucasian subject and 68 days for the volunteers of Japanese descent, if the maximum screening, treatment and follow-up visit durations are used.

Screening will occur within 28 days of the first dose. Subjects will be admitted to the CRC on Day -1.

Treatment Period:

- On Day 1, all study subjects will receive rhPTH(1-84) as a single 100µg SC injection in the mid-thigh.
- On Day 4, and Day 7, all subjects of Japanese descent will receive rhPTH(1-84) as a single SC injection in the mid-thigh of either 25µg or 50µg depending upon randomization assignment. Administration of rhPTH(1-84) in subjects of Japanese descent in the mid-thigh should be randomized locally so that an equal number of subjects receive the first dose in the right thigh and an equal number in the left thigh. Subsequent doses should be administered in the opposing thigh to the last dose.

Assessments

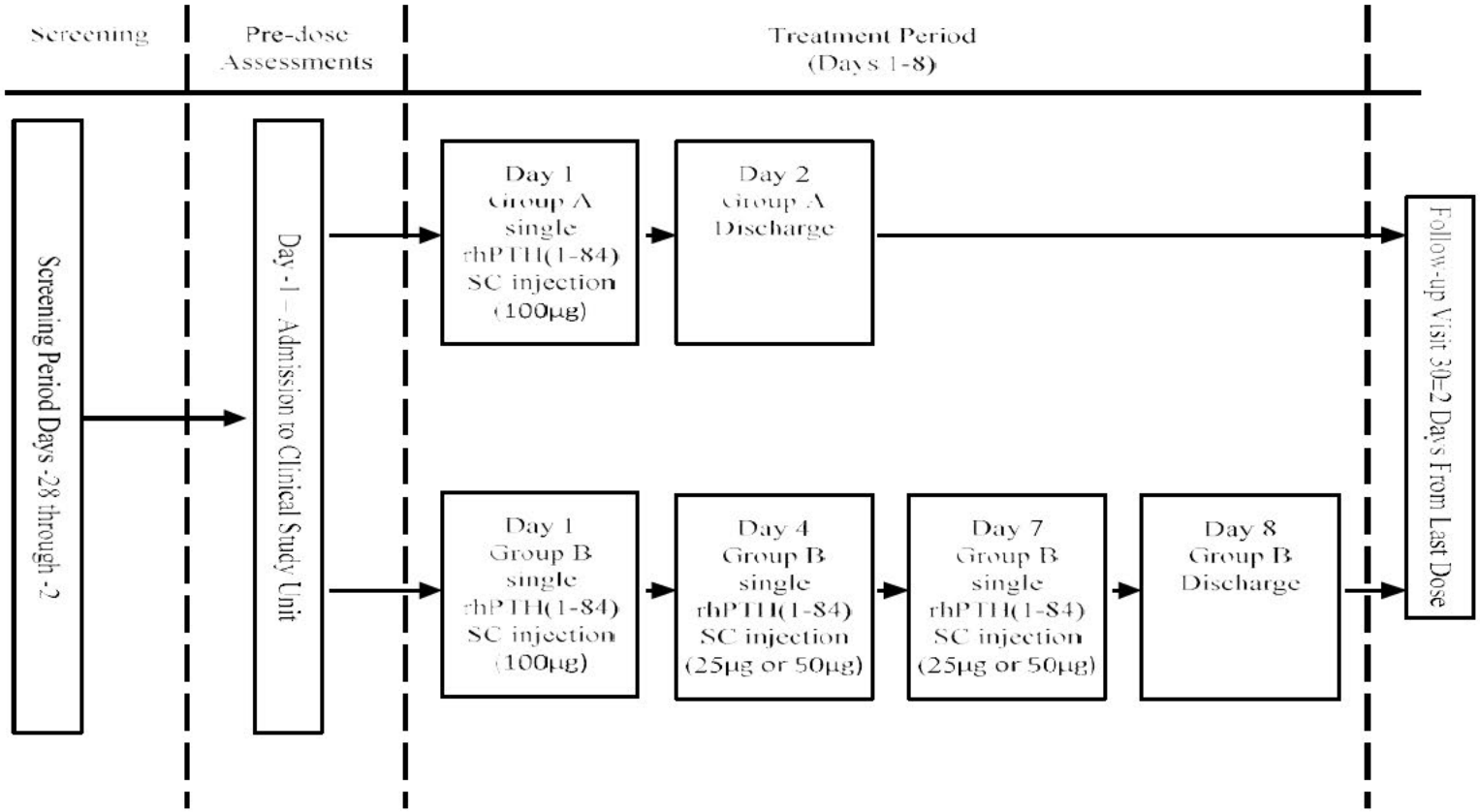
- Serial blood samples for PK analysis will be collected on Day 1 (and Day 4 and Day 7 for the subjects of Japanese descent) for the determination of parathyroid hormone (PTH) concentrations at pre-dose and up to 24 hours post dose. These blood samples will be collected according to the Schedule of Assessments.
- Serial blood samples for PD analysis will be collected on Day 1 (and Day 4 and Day 7 for the subjects of Japanese descent) at pre-dose and up to 24 hours post dose for the determination of serum calcium, phosphate, and albumin concentrations.
- Safety and tolerability will be determined through assessment of treatment-emergent adverse events (TEAEs) from Day 1 time of dose up to the follow-up visit and vital signs, electrocardiogram (ECG) findings, and clinical laboratory evaluations on Day 1 pre-dose and up to 24 hours post dose for the non-Hispanic, Caucasian subjects and Day 1 pre-dose and up to 24 hours post last dose (Day 8) for the subjects of Japanese descent.
- Additional blood samples for safety purposes will be collected for assessment of anti-PTH antibodies.

Follow-up

- A post treatment follow-up visit will be completed 30 (±2) days after the last dose of investigational product for each subject.

Figure 1 Study Design Flow Chart

This study is an open-label study to evaluate the PK and PD profiles, safety, and tolerability of single doses of rhPTH(1-84) in healthy adult subjects of Japanese descent (Group B) and matched healthy, adult non-Hispanic, Caucasian subjects (Group A). Group A and Group B need not be dosed at the same time.



2.2 Randomization

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting at 0001.

For eligible subjects, the subject number will be the identifying number used throughout the CRF.

The actual dose (either 25µg or 50µg) given to Group B (subjects of Japanese descent) on Day 4 and Day 7 is determined by a randomization schedule. The randomization schedule was produced by Shire Biostatistics. Japanese subjects will be randomized to receive either 25µg on Day 4 and 50µg on Day 7, or 50µg on Day 4 and 25µg on Day 7 in a 1:1 ratio.

Administration of rhPTH(1-84) in subjects of Japanese descent in the mid-thigh should be randomized locally so that an equal number of subjects receive the first dose in the right thigh and an equal number in the left thigh. Subsequent doses should be administered in the opposing thigh to the last dose.

2.3 Blinding

This is an open-label study, and, as such, there are no special handling considerations for blinded data.

2.4 Schedule of Assessments

Table 1 Schedule of Assessments

Visit	Screening	Predose assessments	Treatment Period								Follow-up[h]
Study Day	**–28 to -02**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Demography and medical/medication history	X										
Physical examination[a]	X			X							X
Vital signs (BP, temperature and pulse)[a,b,g]	X	X	X	X		X[j]	X[j]		X[j]	X[j]	X
Height and weight[c]	X	X									
Serum PTH	X	X									
Triplicate Electrocardiogram (12-lead)[a,g]	X		X	X		X[j]	X[j]		X[j]	X[j]	X
Biochemistry, hematology, and urinalysis[a]	X	X	X	X		X[j]	X[j]		X[j]	X[j]	X
HIV, HBsAg, and HCV antibodies	X										

Table 1 Schedule of Assessments

Visit	Screening	Predose assessments	Treatment Period								Follow-up[h]
Study Day	**–28 to -02**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Pregnancy test (females only)[a,d]	X	X		X						X[j]	X
Urine drug and alcohol screening[e]	X	X									
Randomization			X[j]								
Investigational drug administration[k]			X			X[j]			X[j]		
Pharmacodynamic blood sampling[f,g]			X	X		X[j]	X[j]		X[j]	X[j]	
Anti-PTH antibody sampling[g]			X								X[a]
Pharmacokinetic blood sampling[g]			X	X		X[j]	X[j]		X[j]	X[j]	
Check-in to the CRC		X									
Discharge from the CRC				X[i]						X[j]	
Adverse events/serious adverse events[a]	X	X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[l]
Concomitant medication[a]	X	X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X

BP=blood pressure; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PTH=parathyroid hormone

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[b] Vital signs will be obtained while subject is supine on study days noted. Temperature will only be taken at screening and predose on Day 1.

[c] Height will be recorded at the screening visit only.

[d] FSH (follicle stimulating hormone) is required at screening for all females. Serum β-hCG testing at timepoints indicated for all female subjects.

[e] Drugs of abuse at screening and drugs of abuse and alcohol on Day -1.

[f] Pharmacodynamic blood sampling assessments will include serum calcium and phosphate.
[g] See Table 2 and Table 3 for detailed collection time points.
[h] There will be a follow-up visit approximately 30 ±2 days following the last dose of investigational product.
[i] Non-Hispanic, Caucasian subjects only.
[j] Subjects of Japanese descent only.
[k] There must be a minimum washout period of 72 hours (maximum 73 hours) from dose to dose for the volunteers of Japanese descent.
[l] SAEs will be followed to resolution

Table 2 Detailed Schedule of Assessments (non-Hispanic, Caucasian Subjects)

Study Day	**Day 1**																		**Day 2**
Hour (relative to dosing time)	**Pre Dose 1**	**Pre Dose 2**	**0**	**10m**	**20m**	**30m**	**45m**	**1h**	**1.25h**	**1.5h**	**2h**	**2.5h**	**3h**	**4h**	**6h**	**8h**	**12h**	**16h**	**24h**
Physical examination[a]																			X
Vital signs (BP, temperature and pulse)[a,b]		X[e]						X						X		X			X
Triplicate Electrocardiogram (12-lead)[a,c]		X[e]																	X
Biochemistry, hematology, and urinalysis[a]		X[e]																	X
Serum β-hCG Pregnancy test (females only)[a]																			X
Investigational drug administration			X																
Pharmacodynamic blood sampling[d]		X[e]												X		X	X		X
Anti-PTH antibody sampling		X[e]																	
Pharmacokinetic blood sampling	X[f]	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic, PTH=parathyroid hormone

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[b] Vital signs will be obtained while subject is supine at times noted. Temperature only to be obtained at screening and at predose on Day 1.

[c] Electrocardiograms will be performed in triplicate at each timepoint.

[d] Pharmacodynamic blood sampling assessments will include serum calcium and phosphate and must be drawn before PK samples at the same timepoint.

[e] These assessments should be performed within 30 minutes prior to dose administration. The urine collection may be the first void of the day [providing that it is predose] but may be outside the 30 minute window if necessary.

[f] These assessments should be performed within 90 (±30) minutes prior to dose administration.

Table 3 Detailed Schedule of Assessments (Subjects of Japanese Descent)

Study Day	**Days 1, 4 and 7**																	**Days 2, 5 and 8**
Hour (relative to dosing time)	**Pre-dose 1**	**Pre-dose 2**	**0**	**10m**	**20m**	**30m**	**45m**	**1h**	**1.25h**	**1.5h**	**2h**	**2.5h**	**3h**	**4h**	**6h**	**8h**	**12h**	**16h**	**24h**
Physical examination[a]																			X[h]
Vital signs (BP, temperature and pulse)[a,b]		X[e]						X						X		X			X
Triplicate Electrocardiogram (12-lead)[a,c]		X[e]																	X
Biochemistry, hematology, and urinalysis[a]		X[e]																	X
Serum β-hCG Pregnancy test (females only)[a]																			X[h]
Investigational drug administration			X																
Pharmacodynamic blood sampling[d]		X[e]												X		X	X		X
Anti-PTH antibody sampling		X[e]																	
Pharmacokinetic blood sampling	X[f]	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BP=blood pressure; ECG=electrocardiogram; PK=pharmacokinetic, PTH=parathyroid hormone

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[b] Vital signs will be obtained while subject is supine at times noted. Temperature only to be obtained at screening and at predose on Day 1.

[c] Electrocardiograms will be performed in triplicate at each timepoint.

[d] Pharmacodynamic blood sampling assessments will include serum calcium and phosphate and must be drawn before PK samples at the same timepoint.

[e] These assessments should be performed within 30 minutes prior to dose administration. The urine collection may be the first void of the day [providing that it is predose] but may be outside the 30 minute window if necessary. Anti-PTH antibody sampling on Day 1 only, not on Day 4 and 7.

[f] These assessments should be performed within 90 (±30) minutes prior to dose administration.

[h] Serum β-hCG Pregnancy test (females only) and physical exam on Day 8 at discharge only.

2.5 Determination of Sample Size

No formal calculations were performed to determine sample size for this study. The sample size is based on feasibility and is similar to that of comparable studies.

A total of 24 subjects will be enrolled: 12 non-Hispanic, Caucasian subjects and 12 subjects of Japanese descent (1:1 male: female). Non-Hispanic, Caucasian subjects will be matched to Japanese subjects based on sex, age (±7 years), and body mass index (±15%).

2.6 Multiplicity Adjustments for Type I Error Control

Not applicable, as the statistical analyses are for exploratory rather than confirmatory purposes.

3. OBJECTIVES

3.1 Primary Objective

- To compare the PK profile of recombinant human parathyroid hormone (rhPTH[1-84]), administered as a single SC dose of 100µg, between healthy adult volunteer subjects of Japanese descent and matched, non-Hispanic, healthy, adult Caucasian subjects.

3.2 Secondary Objectives

- To assess the dose proportionality of the selected PK parameters of rhPTH(1-84) in healthy adult volunteer subjects of Japanese descent when exposed to single SC doses of rhPTH(1-84) at 25µg, 50µg, and 100µg.
- To compare the PD profile (serum calcium and phosphate concentration levels vs time) of a 100µg SC injection of rhPTH(1-84) in healthy adult volunteer subjects of Japanese descent and matched, non- Hispanic, healthy, adult Caucasian, subjects.
- To assess the PD profile (serum calcium and phosphate concentration levels vs time) of a 25µg and 50µg SC injection of rhPTH(1-84) in healthy adult volunteer subjects of Japanese descent.
- To assess the safety and tolerability of single SC doses of 25µg, 50µg, and 100µg of rhPTH(1-84) in healthy adult volunteer subjects of Japanese descent.
- To evaluate the safety and tolerability of a 100µg SC injection of rhPTH(1-84) in matched, non-Hispanic, healthy, adult volunteer Caucasian subjects.

3.3 Exploratory Objective

- To evaluate the PK similarity of rhPTH(1-84) administered as a single SC dose at 25µg and 50µg between healthy adult volunteer subjects of Japanese descent and matched, non-Hispanic, healthy, adult Caucasian subjects using dose-normalized PK data.

4. SUBJECT POPULATION SETS

4.1 Enrolled Set

The Enrolled Set consists of all subjects who sign the informed consent form and meet the study inclusion/exclusion criteria.

4.2 Safety Analysis Set

The Safety Set consists of all subjects who have received at least 1 dose of investigational product.

4.3 Pharmacokinetic Set

The Pharmacokinetic Set consists of all subjects who have received at least 1 dose of investigational product and have at least 1 evaluable post dose PK concentration value.

4.4 Pharmacodynamic Set

The Pharmacodynamic Set consists of all subjects who have received at least 1 dose of investigational product and have at least 1 evaluable post dose PD concentration value.

5. SUBJECT DISPOSITION

Final subject numbers will be presented for subjects that had been re-screened.

The number of subjects included in each subject set (i.e., Enrolled, Safety, Pharmacokinetic, and Pharmacodynamic) will be summarized by ethnic group (Japanese or Non-Hispanic Caucasian) and treatment sequence. Details of randomization assignments for randomized subjects will be listed.

Additionally, the number and percentage of subjects who either completed or prematurely discontinued during the study will be presented. Reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) by ethnic group and treatment sequence for the Enrolled Set. Details of reasons for discontinuation for all subjects who prematurely discontinued during the study will be listed.

For Japanese subjects, the number and percentage of subjects in each subject set, and who either completed each treatment period or prematurely discontinued during each treatment period including reasons will also be summarized by rhPTH(1-84) dose. Discontinuations will be attributed to the last dose that the subject received prior to discontinuation.

6. PROTOCOL DEVIATIONS

All protocol deviation data will be listed for the Enrolled Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by ethnic group and treatment sequence, for the Safety Analysis Set. For Japanese subjects, demographic and baseline characteristics will also be summarized by rhPTH(1-84) dose for the Safety Analysis Set.

The following demographic characteristics will be summarized in the following order in the tables: age, sex, ethnicity and race. Other baseline characteristics including weight, height and BMI will be summarized.

BMI will be calculated locally at screening for eligibility using the formula below:

$$\text{BMI} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

A listing will be created to show all the demographic and baseline characteristics for the Safety Analysis Set.

Medical history will be listed for the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

A summary table showing number of subjects exposed to each dose will be produced by visit and ethnic group for the Safety Analysis Set.

A listing will be created by subject number and visit giving the date and time of dose administration, for the Safety Analysis Set.

8.2 Measurement of Treatment Compliance

Since this is a Phase 1 study in which the study medication is administered at the Clinical Research Center (CRC), no summary of treatment compliance will be produced.

9. PRIOR AND CONCOMITANT MEDICATION

Version WHODRUG 2017MAR01 DDE (B2 format) will be used to classify prior and concomitant medications by preferred term. Medications will also be coded by the Anatomical Therapeutic Chemical (ATC) classification system.

Medications starting within 30 days before the first dose of investigational product and up to the end of the follow-up period will be collected on the CRF.

Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product. Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date after the date of the first dose of investigational product.

Concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication by preferred term, by ethnic group and rhPTH(1-84) dose for the Safety Analysis Set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once.

Concomitant medications will be assigned to the dose(s) with which they are concomitant. A medication is concomitant with a dose of rhPTH(1-84) if the subject received that medication any time between the time when that dose of rhPTH(1-84) was received and when the next dose of rhPTH(1-84) was received, or in the case of the last dose, until the end of the follow-up period. Therefore, a medication may be concomitant with more than one dose.

All prior and concomitant medication will be listed.

10. EFFICACY ANALYSES

No efficacy analysis will be performed for this study.

10.1 Primary Efficacy Endpoint(s) and Analysis

Not applicable.

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

Not applicable.

10.3 Other Secondary Efficacy Endpoint(s) and Analysis

Not applicable.

10.4 Exploratory Efficacy Endpoint(s) and Analyses

Not applicable.

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Analysis Set. Safety variables include AEs and TEAEs, clinical laboratory variables, vital signs, and ECG variables. For clinical laboratory and vital sign variables, the last value collected before the dose administration will be used as baseline for all analyses of that safety variable in the respective dose interval. Thus there will be a different baseline for each dose for the Japanese subjects.

Follow-up visits will be summarized under the 100µg dose, regardless of which sequence the subject was randomized to, or which doses they had received.

11.1 Adverse Events

Adverse events will be coded using Version 20.0 or newer of MedDRA.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if it has a start date/time on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity or intensity on or after the date/time of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. An AE that occurs after follow-up visit will not be counted as a TEAE. However, any SAE that occurs after the follow-up visit and is considered related should be counted as a TEAE.

Adverse events will be allocated to a dose by assigning them to the last dose taken at the time of the onset of the AE.

An overall summary of the number of subjects with TEAEs will be presented by ethnic group and dose at onset, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation of investigational product, severe TEAEs, and deaths.

The number and percentage of subjects reporting TEAEs for each ethnic group and dose at onset will be tabulated by system organ class (SOC) and preferred term; and by SOC, preferred term, and maximum severity. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe occurrence for the summarization by severity. Serious TEAEs and TEAEs leading to discontinuation of investigational product will be summarized by SOC, preferred term, ethnic group and dose at onset.

Listings will be produced for all AEs (including pre-treatment AEs), SAEs, AEs considered related to investigational product, AEs leading to discontinuation of investigational product, and deaths.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented by ethnic group and dose for the following clinical laboratory variables.

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell count – total and differential (WBC), total neutrophils (absolute), eosinophils (absolute), monocytes (absolute), basophils(absolute), lymphocytes (absolute).

Biochemistry Sodium, phosphorus, β-hCG[b], potassium, total protein, magnesium, glucose, total CO_2 (Bicarbonate), PTH[c], blood urea nitrogen, albumin, FSH[b], creatinine, aspartate transaminase (AST), calcium, alanine transaminase (ALT), chloride, gamma glutamyl transferase (GGT), thyroid stimulating hormone (TSH) [a], alkaline phosphatase (ALP), thyroxine (T_4 total)[a], total bilirubin, triiodothyronine (T_3)[a], uric acid.

CO_2=carbon dioxide; FSH= follicle stimulating hormone; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone
a See Table 1, Table 2, and Table 3.
b Females only.
c Parathyroid hormone at screening and Day -1 is for baseline eligibility use only and not for PK analysis.

Urinalysis pH, glucose, protein, blood, ketones, bilirubin, nitrites, leukocyte esterase, specific gravity.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 4. The number and percentage of subjects with post-baseline PCI values will be tabulated by ethnic group and dose. The percentages will be calculated relative to the number of subjects with available assessments at that dose level. The numerator is the total number of subjects with at least 1 post-baseline PCI value at that dose level. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, ethnic group, dose, baseline, and post-baseline values.

Listings for serum and urinary clinical laboratory results will be produced for all patients in the Safety Analysis Set. Clinically potential important test results will be listed as well.

Table 4 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Classification (on CDRs)	Criteria
Biochemistry		
Sodium	HIGH	> 5 mmol/L (5 mEq/L) above ULN
	LOW	> 5 mmol/L (5 mEq/L) below LLN
Potassium	HIGH + INCREASE	Above ULN and increase of > 0.5 mmol/L (0.5 mEq/L) from baseline value
	LOW + DECREASE	Below LLN and decrease of > 0.5 mmol/L (0.5 mEq/L) from baseline value
Creatinine	HIGH + INCREASE	> 150µmol/L and increase > 30% from baseline value
BUN	HIGH	> 1.5 x ULN
Glucose (fasting)	HIGH	≥ 6.7 mmol/L
	LOW	≤ 4.2 mmol/L
Calcium	HIGH and INCREASE	Above ULN and Increase of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
Magnesium	HIGH and INCREASE	Above ULN and Increase of ≥ 0.21 mmol/L (0.5 mg/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 0.21 mmol/L (0.5 mg/dL) from baseline value
Phosphorus	HIGH	> 0.162 mmol/L (0.5 mg/dL) above ULN
	LOW	> 0.162 mmol/L (0.5 mg/dL) below LLN
Total protein	HIGH and INCREASE	Above ULN and Increase of ≥ 20 g/L (2.0 g/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 20 g/L (2.0 g/dL) from baseline value
Albumin	HIGH and INCREASE	Above ULN and Increase of ≥ 10 g/L (1.0 g/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 10 g/L (1.0 g/dL) from baseline value
Uric acid (with normal diet)	HIGH and INCREASE	Above ULN and Increase of > 0.119 mmol/L (2.0 mg/dL) from baseline value
	LOW and DECREASE	Above LLN and Decrease of > 0.119 mmol/L (2.0 mg/dL) from baseline value
ALT	HIGH	> 2 x ULN
AST	HIGH	> 2 x ULN
ALP	HIGH	> 1.5 x ULN
GGT	HIGH	> 1.5 x ULN
Total bilirubin	HIGH	> 1.5 x ULN
T4	HIGH	> 140.28 nmol/L
	LOW	< 57.92 nmol/L
T3	LOW	< 0.922 nmol/L

Table 4 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Classification (on CDRs)	Criteria
Biochemistry		
	HIGH	> 2.765 nmol/L
TSH	HIGH	>5.0 μU/L
	LOW	0.5 μU/L
Hematology		
RBC count	HIGH	>7.5 $x10^{12}$/L
	LOW	<3 $x10^{12}$/L
Hematocrit	LOW and DECREASE	≤0.6 x LLN and Decrease of ≥ 0.06 L/L (6.0%) from baseline value
	HIGH	>1.3 x ULN
Hemoglobin	LOW and DECREASE	< 100g/L (10g/dL) and Decrease of ≥ 20g/L (2.0 g/dL) from baseline value
	HIGH	>200 g/L (20g/dL)
WBC count	HIGH	>2xULN OR >16.0 x 10^9/L (16 x 10^3/μL)
	LOW	< 0.5xLLN OR < 3.0 x 10^9/L (3 x 10^3/μL)
Neutrophils	LOW	< 1.5 x 10^9/L (1.5 x 10^3 μL) OR < 40%
	HIGH	> 6.2 x 10^9/L (6.2 x 10^3 μL) OR > 70 %
Lymphocytes	HIGH	> 4.0 x 10^9/L (1.5 x 10^3 μL) OR > 44 %
	LOW	< 0.8 x 10^9/L (0.8 x 10^3 μL) OR < 22 %
Monocytes	HIGH	>11 %
Eosinophils	HIGH	> 0.5 x 10^9/L (> 500/μL) and > 10.0%
	LOW	NA
Basophils	HIGH	2%
	LOW	NA
Platelet count (thrombocytes)	HIGH	>1.5 x ULN OR > 500 x 10^9/L (100 x 10^3/μL)
	LOW	0.6 x LLN OR < 100 x 10^9/L (100 x 10^3/μL)
Urinalysis		
Glucose	HIGH	≥ 1+
Blood	HIGH	≥ 2+
Bilirubin		Normally not found
Protein	HIGH	≥ 2+
Nitrite		Normally not found
Ketones	HIGH	≥ 2+
Leukocyte Esterase		Negative

11.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature) and their changes from baseline at each post-baseline assessment and at the end of study will be presented by ethnic group and dose. All vital signs will be listed for each subject in the Safety Analysis Set.

Vital sign values will be considered PCI if they meet either the low or high PCI criteria listed in Table 5. The number and percentage of subjects with PCI values at each time point will be tabulated by ethnic group and dose. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment at that dose level and time point. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value at that dose level and time point. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, ethnic group, dose, baseline, and post-baseline PCI values.

Table 5 Criteria for Potentially Clinically Significant Vital Signs

Parameter	Classification (on CDRs)	Criteria
Systolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 140 and increase of ≥ 20 from baseline value
	LOW and DECREASE	≤ 90 and decrease of ≥ 20 from baseline value
Diastolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 90 and increase of ≥ 15 from baseline value
	LOW and DECREASE	≤ 50 and decrease of ≥ 15 from baseline value
Pulse rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	≤ 45 and decrease of > 15 from baseline value
Temperature	HIGH	> 38.3°C or > 100.9°F
	LOW	< 35°C or < 95°F

11.4 Electrocardiogram (ECG)

At each timepoint, ECGs are collected in triplicate (any readings after the first three valid readings at a particular timepoint will be considered unscheduled). For numeric ECG variables, the mean of the valid values at each timepoint will be taken. For qualitative ECG results, the worst case will be used. The averages of the ECG triplicate collected predose on Day 1 and predose on Days 4 and 7 (for subjects of Japanese descent) will serve as the subject's baseline ECG for the dose received on that day.

Descriptive statistics for ECG variables (heart rate, PR interval, RR, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by ethnic group and dose. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula. ECG interpretation will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will be presented.

Electrocardiogram variables will be considered PCI if the average value for that subject at that time point meets or exceeds the upper limit values listed in Table 6. The number and percentage of subjects with PCI values at each time point will be tabulated by ethnic group and dose. The percentages will be calculated relative to the number of subjects with available baseline and at least 1 post-baseline assessment at that dose level and visit. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value at that dose level and visit. A listing of all subjects with post-baseline PCI values will be provided including the subject number, ethnic group, dose, baseline, and post-baseline PCI values.

Table 6 Criteria for Potentially Clinically Important ECG Values

Parameter	Classification (on CDRs)	Criteria
Overall Evaluation	ABNORMAL	Overall Evaluation is ABNORMAL
Heart rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	≤ 45 and decrease of > 15 from baseline value
PR interval (msec)	HIGH and INCREASE	≥ 200 and increase of ≥ 20 from baseline value
QRS interval (msec)	HIGH	≥ 120
QTC interval (men) (msec)	HIGH	> 430 and increase from baseline value > 30
QTC interval (women) (msec)	HIGH	> 450 and increase from baseline value > 30

11.5 Other Safety Variables

Anti-PTH antibodies will be assessed at Day 1 (pre-dose) and at Follow-up. The results at each timepoint will be summarized by ethnic group, and these data will be listed.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population and Pharmacodynamic Population

The Pharmacokinetic Set consists of all subjects who have received at least 1 dose of investigational product and have at least 1 evaluable post dose PK concentration value.

The Pharmacodynamic Set consists of all subjects who have received at least 1 dose of investigational product and have at least 1 evaluable post dose PD concentration value.

12.2 Handling BLQ, Zero Values, Missing Values

The following procedures will be used for original plasma PTH concentrations and serum PD data below the lower limit of quantification (LLOQ) and baseline-adjusted PTH and PD concentration data:

- Samples that are BLQ are reported as <LLOQ on the data listings, where LLOQ is replaced by the actual value for LLOQ for specific PK or PD assay.

- Samples that are BLQ are treated as zero in the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma concentrations at individual time points.

- Mean concentrations are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.

- For calculation of area under the plasma concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokinetic analysis. WinNonlin uses the zero values that occur before the first time point with a concentration greater than LLOQ. Values that are BQL after the first measurable concentration are set to “missing” in the dataset loaded into WinNonlin.

- Missing values will not be imputed.

12.3 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set. After database lock, a visual inspection of concentration-time profiles and pharmacokinetic parameters will be performed by PRA to determine dataset integrity and potential outliers. Descriptive statistics of pharmacokinetic parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by Shire for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

12.3.1 Original PTH Concentration Data

For non-Hispanic, Caucasian subjects on Day 1 and for subjects of Japanese descent on Day1, 4 and 7, samples for pharmacokinetic analysis are taken at Predose 1 (within 90 ± 30 min prior to dose administration), Predose 2 (within 30 min prior to dose administration), and 10, 20, 30 and 45 minutes, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 hours after administration of the investigational product. Plasma concentrations of PTH will be measured using a validated analytical method.

Individual original PTH concentrations will be listed and summarized with descriptive statistics by ethnic group, dose and time point, including number, arithmetic mean, standard deviation, coefficient of variation [CV%], median, minimum, and maximum. Figures of individual original concentration-time profiles and mean (± SD) by ethnic group and dose will be generated on linear and semi-log scale. The mean plot will be created by overlaying each ethnic group and dose on the same figure.

12.3.2 Baseline-adjusted PTH Concentration Data

Baseline-adjusted PTH concentrations are to be calculated by subtracting baseline endogenous PTH from the original PTH concentrations. Such baseline adjustment is subject- and dose-specific. For each subject, baseline is defined for each dosing period as follows: the baseline for Day 1 dosing is defined as the average predose concentration on Day 1 (average of predose 1 and predose 2 PTH concentrations); for subjects of Japanese descent the baseline for Day 4 dosing is defined as the average predose concentration on Day 4 (average of predose 1 and predose 2 PTH concentrations); the baseline for Day 7 dosing is defined as the average predose concentration on Day 7 (average of predose 1 and predose 2 PTH concentrations). If the baseline-adjusted PTH concentration gives a negative value, then the baseline-adjusted PTH concentration should be set to zero. In the terminal log-linear phase, if two consecutive baseline-adjusted PTH concentrations give negative values, then all the subsequent values will be set to zero.

Individual baseline-adjusted PTH concentrations will be listed and summarized by ethnic group and dose as in section 12.3.1. Individual plots and mean plots will be generated in the same way as described in section 12.3.1 but using the baseline-adjusted PTH concentrations. If the baseline-adjusted PTH concentration is zero, it will be presented as missing on the semi-log scale.

12.3.3 Pharmacokinetic Parameters

The pharmacokinetic analysis will be conducted by using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic parameters will be determined from the plasma PTH concentration-time data by non-compartmental analysis. Both original and baseline-adjusted PTH concentrations will be used to compute all the PK parameters respectively.

The pharmacokinetic parameters will include, but may not be limited to:

- C_{max} : Maximum observed concentration, to be reported in the unit of pg/mL (both original and baseline-adjusted PTH)
- t_{max} : Time of maximum observed concentration sampled during a dosing interval, to be reported in the unit of hour (both original and baseline-adjusted PTH)
- AUC_{last} : Area under the curve from the time of dosing to the last measurable concentration. Calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (both original and baseline-adjusted PTH)
- $AUC_{0\text{-}inf}$: Area under the curve extrapolated to infinity calculated as $AUC_{last} + C_{last}/\lambda_z$. Calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (for baseline-adjusted PTH only)
- %AUC extrapolated: % of AUC extrapolated from the last measurable concentration to infinity over AUC(0-inf) (for baseline-adjusted PTH only)
- λ_z: Elimination rate constant associated with the terminal (log-linear) portion of the curve. The log-linear portion of the curve must contain at least three points after Tmax and have an r^2 value $\geq$ 0.8 (for baseline-adjusted PTH only)
- $t_{½}$: Terminal half-life, calculated as 0.693/ λ_z (for baseline-adjusted PTH only)
- CL/F: Apparent total body clearance, calculated as Dose/$AUC_{0\text{-}inf}$ (for baseline-adjusted PTH only)
- $Vd_{z/F}$: Apparent volume of distribution, calculated as Dose/$AUC_{0\text{-}inf}$ * λ_z (for baseline-adjusted PTH only)

All PK parameter calculations will be performed using actual sampling times calculated relative to the day of rhPTH(1-84) administration. The PK parameters λ_z, $t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, and Vdz/F will not be calculated for subjects with PTH concentration-time profiles (baseline-adjusted) that do not exhibit a terminal log-linear phase, or if %AUC extrapolated > 20%.

In addition, body-weight adjusted AUC_{last} (calculated as AUC_{last}/body-weight), $AUC_{0\text{-}inf}$ (calculated as $AUC_{0\text{-}inf}$/body-weight), C_{max} (calculated as C_{max}/body-weight), CL/F (calculated as CL/F/body-weight), and $Vd_{z/F}$ (calculated as $Vd_{z/F}$/body-weight) will be calculated based on baseline-adjusted PTH concentrations.

In addition, dose-normalized AUC_{last} (calculated as AUC_{last}/Dose), $AUC_{0\text{-}inf}$ (calculated as $AUC_{0\text{-}inf}$/Dose), and dose-normalized C_{max} (calculated as C_{max}/Dose) will be calculated based on baseline-adjusted PTH PK parameters.

Baseline-adjusted PK parameters will be the primary PK endpoints, and other PK parameters will be the secondary PK endpoints.

12.3.4 Statistical Analysis of Pharmacokinetic Parameters

12.3.4.1 Descriptive Statistic Analysis of PK Parameters

All PK parameters (original, baseline-adjusted, body weight-adjusted, and dose-normalized-baseline-adjusted) of rhPTH(1-84) will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, %CV of geometric mean, and 95% confidence interval of the geometric means) by ethnic group and dose..

The geometric mean and individual values of dose-normalized baseline-adjusted PK parameters vs dose in Japanese subjects will also be presented in plots.

Box-Whisker plots for selected PK parameters for 100µg dose level will be generated with both ethnic groups side by side. These PK parameters are C_{max} and AUC_{last} based on original concentrations, and baseline-adjusted C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$, and body weight adjusted baseline-adjusted C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$.

12.3.4.2 Inferential Analysis of PK Parameters

Comparison of PK between Ethnic Groups

In order to compare the PK of rhPTH(1-84) between subjects of Japanese descent and matched non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters from the rhPTH(1-84) 100µg dose will be examined between the two ethnic groups using Welch's t-test with Satterthwaite's approximation to the degrees of freedom. The difference between the two means will be back transformed to provide an estimate for the geometric mean ratio and its 90% confidence interval (CI). The following PK parameters will be evaluated using this test: C_{max} and AUC_{last} based on original concentration, baseline-adjusted C_{max}, AUC_{last}, $AUC_{0\text{-}inf}$.

For C_{max}, AUC_{last} (original and baseline-adjusted) and $AUC_{0\text{-}inf}$ (baseline-adjusted), Forest plots of geometric mean ratios (two-sided 90% CI) between Japanese cohort at 100 µg vs Non-Japanese cohort at 100µg will be generated.

In addition, same Welch's t-test will be applied to compare the PK parameters between different doses and ethnic groups. The log-transformed dose-normalized AUC_{last} and C_{max} will be examined between the Japanese cohort at 50µg dose and the Non-Japanese cohort at 100µg as well as between the Japanese cohort at 25µg and the Non-Japanese cohort at 100µg. The geometric mean ratio estimates and their 90% CI will be provided from the model for each comparison.

Evaluation of Dose Proportionality (Exploratory)

Dose proportionality of baseline-adjusted PK parameters, will be examined for the Japanese subjects. Dose proportionality will be assessed for baseline-adjusted C_{max}, AUC_{last}, and

$AUC_{0\text{-}inf}$, using the power model. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose.

$\ln(\text{Parameter}_{ijk}) = \alpha + \beta \times \ln(\text{Dose in } \mu g) + \pi_j + \gamma_i + \xi_{k(i)} + \varepsilon_{ijk}$ (Patterson and Jones, 2006)

Where α is the intercept, β is the slope, π_j and γ_i identify the period j of sequence i, $\xi_{k(i)}$ is the random-intercept accounting for each subject within sequence as their own control, and ε_{ijk} denotes within-subject error. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% confidence interval (CI) from the power model. The estimate and 90% confidence interval for the slope will be presented.

The example SAS code for the above model could be:

```
proc mixed method = reml data=ADPP ;
      class subject sequence period ;
      model  lnauc = sequence period lndose / s ddfm = kenwardroger cl alpha = .1 ;
      random intercept/ subject = subject (sequence) ;
run ;
```

In addition, a simple regression model will be used to plot the relationship between these three above baseline-adjusted PK paramters and dose for Japanese subjects.

$\ln(\text{Parameter}) = \text{intercept} + \text{slope} \times \ln(\text{Dose in } \mu g) + \text{residual}$

Plots of observed geometric mean and observed individual values of baseline-adjusted PK parameters C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ vs dose in Japanese subjects will be generated. The regression line along with the formula and r^2 will be presented in the same plot with both axes on log scale.

12.4 Pharmacodynamic Methods

All summaries and analyses of the PD data will be based on the Pharmacodynamic Set. After database lock, a visual inspection of concentration-time profiles and PD parameters will be performed by PRA to determine dataset integrity and potential outliers. Descriptive statistics of PD parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by Shire for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

12.4.1 Original Pharmacodynamic Data

Blood samples for PD analysis will be collected at Predose 2 (within 30 min prior to dose administration), 4, 8, 12 and 24 hours after dose administration of rhPTH(1-84) for the determination of concentrations of serum calcium (uncorrected [total] and corrected for serum albumin levels), phosphate. Serum calcium will be corrected for serum albumin levels using the following equation:

Corrected calcium (mmol/L) = serum calcium (mmol/L) + 0.02 (40 - serum albumin (g/L)) (Parent X, 2009)

The serum calcium-phosphate product (using albumin-corrected calcium) will also be determined. This is calculated as serum calcium concentration (albumin-corrected) x serum phosphate concentration.

Individual original concentrations of serum total calcium, albumin-corrected calcium, phosphate and calcium-phosphate product will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum) by ethnic group, dose and time point.

Figures of individual original concentration-time profiles and mean (± SD) will be generated on linear scale for serum total calcium, albumin-corrected calcium, phosphate and calcium-phosphate product by ethnic group and dose. The mean plots will be created for the original concentrations of the above four PD markers by overlaying the mean values for each ethnic group and dose on the same figure.

12.4.2 Baseline-adjusted Pharmacodynamic Data

Individual serum concentrations of PD markers, calcium (uncorrected and corrected for albumin), phosphate and calcium-phosphate product will be baseline-adjusted at each time point. Albumin-corrected calcium will be used to calculate the calcium-phosphate product. Baseline adjustment is subject- and dose-specific. For each subject, baseline is defined for each dosing period as follows: the baseline for Day 1 dosing is defined as the predose concentration on Day 1; the baseline for Day 4 dosing is defined as the predose concentration on Day 4; the baseline for Day 7 dosing is defined as the predose concentration on Day 7. Baseline-adjusted concentrations of PD markers are to be calculated by subtracting the appropriate baseline values from the original concentrations at each time point. If the baseline-adjusted concentration gives a negative value then the baseline-adjusted concentration should be set to zero.

Individual baseline-adjusted concentrations of serum total calcium, albumin-corrected calcium, phosphate and calcium-phosphate product will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum,) by ethnic group, dose and time point.

Figures of individual baseline-adjusted concentration-time profiles and mean (± SD) will be generated on linear scale for serum total calcium, albumin-corrected calcium, phosphate and calcium-phosphate product by ethnic group and dose. The mean plots will be created for the baseline-adjusted concentrations of the above four PD markers by overlaying all ethnic groups and doses on the same figure.

12.4.3 Serum Pharmacodynamic Parameters

Pharmacodynamic parameters will be computed from the individual original and baseline-adjusted concentrations of serum calcium (uncorrected and corrected for serum albumin

levels), phosphate and calcium-phosphate product using a non-compartmental approach and actual sampling times. Pharmacodynamic parameters will be estimated for each dose.

The following parameters will be calculated using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA):

- AUC_{last}: the area under the concentration versus time curve, from time of dosing to last measurable concentration
- TE_{max}: time to maximum effect
- E_{max}: maximum effect

12.4.4 Statistical Analysis of Pharmacodynamic Parameters

Pharmacodynamic parameters of serum total calcium, albumin-corrected calcium and phosphate and calcium-phosphate product will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by ethnic group, dose and time point. This will be done for both original and baseline-adjusted values.

Box-Whisker plots for AUC_{last} and E_{max} based on both original and baseline-adjusted concentrations will be prepared for the 100µg dose with the Japanese cohort and Non-Japanese cohort side by side.

13. OTHER ANALYSES

13.1 Quality of Life Analyses

Not applicable.

13.2 Health Economics and Outcomes Research Analyses

Not applicable.

14. INTERIM ANALYSIS

No formal interim analysis is planned for this study.

15. DATA MONITORING/REVIEW COMMITTEE

Not applicable, as no data monitoring review is planned for this study.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA) will be used for calculating PK and PD parameters.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Section 9.8.1.1 (Statistical Analysis of Pharmacokinetic Parameters) of the protocol states that:

Dose proportionality of PK parameters will also be examined for the Japanese subjects. Dose proportionality will be assessed for C_{max} and AUC (AUC_{last}) using the power model. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose.
ln (Parameter) = $\alpha + \beta \times$ ln (Dose) + Random error

In order to compare the PKs of rhPTH(1-84) between subjects of Japanese descent and matched non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters from the rhPTH(1-84) 100μg dose will be examined between groups using an analysis of variance model.

However, to take account of the different sequences, the dose proportionality of PK parameters will be assessed by the power model with more factors:

ln (Parameter $_{ijk}$) = $\alpha + \beta \times$ ln (Dose in μg) + $\pi_j + \gamma_k + \xi_{k(i)} + \varepsilon_{ijk}$ (Patterson and Jones, 2006)

Where α is the intercept, β is the slope, π_j and γ_i identify the period j of sequence i, $\xi_{k(i)}$ is the random-intercept accounting for each subject within sequence as their own control, and ε_{ijk} denotes within-subject error. Dose proportionality will be assessed by estimating mean slope with the corresponding two-sided 90% confidence interval (CI) from the power model.

For the comparison of PKs between subjects of Japanese descent and matched non-Hispanic, Caucasian subjects, the differences of log-transformed PK parameters from the rhPTH(1-84) 100μg dose will be examined between the two ethnic groups using Welch's t-test with Satterthwaite's approximation to the degrees of freedom, rather than by ANOVA as stated in the protocol. The reason for this method of comparison is that the variance in the two ethnic groups is not expected to be the same.

Table 1 Schedule of Assessments from protocol states that randomization takes place on Day 4 for subjects of Japanese descent. It is changed to be on Day 1 in Table 1 in SAP.

Table 3 Detailed Schedule of Assessments (Subjects of Japanese Descent) from protocol states that anti-PTH antibody sampling occurs at Predose 2 on Day 1, 4 and 7. However, it is not consistent with Table 1 in protocol. Therefore, "Anti-PTH antibody sampling on Day 1 only, not on Day 4 and 7" is added to the footnote e of Table 3 in SAP.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics if not otherwise specified: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented to 1 decimal place.

The rules for the number of decimal places to present data and p-values are listed below:

1. For measures of median and mean, use 1 decimal place beyond those used for the measurement.
2. For measures of standard deviation and standard error, use 2 decimal places beyond those used for the measurement.
3. For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
4. >=5 is rounded up away from zero, whereas <5 is rounded down toward zero to account for rounding of negative numbers.
5. For p-values use 3 decimal places.
6. Presentation of p-values, display p-values that would round to 0.000 as <0.001.
7. BMI should be rounded to 1 decimal place for reporting.

18.2 Derived Efficacy Endpoints

Not applicable.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If post-baseline assessments are repeated, these will be captured as unscheduled visits, and the value recorded at the scheduled visit will be used for generating descriptive statistics. However, all post-baseline assessments will be used for PCI value determination and all assessments will be presented in the data listings.

18.4 Missing Date of Investigational Product

Since the investigational products will be administered during in-patient confinement at a CRC, there should not be any missing dates of investigational product.

18.5 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.5.1 Incomplete Start Date and Time

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

Missing/Incomplete Time

- If the time is missing and the date is complete and is the same as the date of the first dose of investigational product, or the date is imputed to be this date, then the time will be set to the time of the first dose of investigational product. Otherwise, missing times will be imputed as 00:00.
- If the minutes are given but the hour is not, then the time will be regarded as completely missing and handled as above. If the hour is given but the minutes are not, then if the hour is the same as the hour of the first dose of investigational product, then the minutes of that

dose of investigational product will be assigned to the missing fields. Otherwise 00 will be assigned to the missing minutes.

18.5.2 Incomplete Stop Date and Time

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

Missing Time

- If the time is missing it will be imputed as 23:59.

18.6 Missing Date and Time Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates will be imputed. Incomplete stop dates will not be imputed.

18.6.1 Incomplete Start Date and Time

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date and Time

Not applicable.

18.7 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable (e.g. <5), then the appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

19. REFERENCES

Patterson Scott, Jones Byron 2006. Bioequivalence and statistics in clinical pharmacology. Chapman and Hall, New York.

Parent X, Spielmann C, Hanser AM. 2009. ["Corrected" calcium: calcium status underestimation in non-hypoalbuminemic patients and in hypercalcemic patients]. Ann Biol Clin (Paris). [Online]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19654080

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Note: There are no shells provided for statistical appendices, since they are raw output from SAS.