PROTOCOL:	SHP634-102
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)
IND:	076514
EUDRACT NO.:	2015-004757-40
SPONSOR:	Shire 300 Shire Way Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	PPD MD PAREXEL Glendale Adventist Medical Center 1560 E. Chevy Chase Drive Suite 140 Glendale, CA, 91206 Telephone: PPD Fax: PPD Email: PPD
PROTOCOL HISTORY:	Original Protocol: 29 Jan 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: PPD PPD PPD DDS, Ph.D. PPD	**Date:** PPD

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP634-102.

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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by email using the details below.

E-mail: PPD

For protocol- or safety-related issues, the investigator must contact the Shire Medical Monitor:

PPD DDS, Ph.D.

Telephone: PPD (business hours)

PPD (24-hour coverage)

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including non-safety related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire Study Manager:

PPD

Study Manager

Telephone: PPD (business hours)

PPD (24-hour coverage)

Email: PPD

If unavailable, please contact:

PPD

Clinical Pharmacology Group Lead

Telephone: PPD (business hours)

PPD (24-hour coverage)

Email: PPD

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Origin of Product Quality Complaint	E-mail Address
North and South America	PPD
European Union and Rest of World	PPD

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
PPD

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ABBREVIATIONS

λ_z	first order rate constant associated with the terminal (log linear) portion of the curve
%CV	percent coefficient of geometric mean
AE	adverse event
AUC_{last}	area under the curve from the time of dosing to the last measurable concentration
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CaSR	calcium-sensing receptor
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum concentration occurring at t_{max}
CO_2	carbon dioxide
CRC	clinical research center
CRF	case report form
CRO	contract research organization
CV%	coefficient of variation
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
EMA	European Medicines Agency
E_{max}	maximum effect
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board

MHLW	Ministry of Health, Labor and Welfare
PD	pharmacodynamic
pH	potentia hydrogenii (measure of acidity/alkalinity)
PK	pharmacokinetic
PMDA	Pharmaceuticals Medical Devices Agency
PR	time elapsed from P wave to R wave in an electrocardiogram
PTH	parathyroid hormone
QTcB	measure of time between the start of the Q wave and the end of the T wave using Bazett's formula in an electrocardiogram
QD	quaque die (once a day)
QRS	measure of time for the 3 main deflections in an electrocardiogram
QT	measure of time between the start of the Q wave and the end of the T wave in an electrocardiogram
QTcF	measure of time between the start of the Q wave and the end of the T wave using Fridericia's formula in an electrocardiogram
rhPTH	recombinant human parathyroid hormone
RR	the time between heart beats in an electrocardiogram
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SC	subcutaneous
SD	standard deviation
$t^{1}/_{2}$	terminal half-life
T_3	triiodothyronine
T_4	thyroxine
TEAE	treatment emergent adverse event
TE_{max}	time to maximum effect
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid stimulating hormone
UK	United Kingdom
US	United States
Vd_z/F	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP634-102	**Drug:** Recombinant Human Parathyroid Hormone (rhPTH[1-84])

Title of the study:

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

Number of subjects (total and for each treatment arm):

A total of 24 healthy, adult, male and/or female subjects will be enrolled into the study, comprising 12 subjects of Japanese descent and 12 matched, non-Hispanic, Caucasian subjects. Study subjects who withdraw or discontinue early may be replaced at the discretion of the sponsor. Non-Hispanic, Caucasian subjects will be matched to subjects of Japanese descent based on sex (1:1 male: female), age (±5 years), weight (±10%), and body mass index (±15%)

- The subjects of Japanese descent will be exposed to 3, randomized, cross-over single doses of rhPTH(1-84) at 25µg, 50µg and 100µg.
- Matched, non-Hispanic, Caucasian subjects will be exposed to a single dose of rhPTH(1-84) at 100µg.

Investigator(s):

PPD, MD

Site(s) and Region(s):

PAREXEL
Glendale Adventist Medical Center
1560 E. Chevy Chase Drive
Suite 140
Glendale, CA, 91206, USA

Study period (planned): May 2017-June 2017	**Clinical phase:** 1

Objectives:

Primary:

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

Secondary:

- To assess the dose proportionality of the PKs 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 pharmacodynamic (PD) profile (including measurement of serum calcium and phosphate levels) 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 (including measurement of serum calcium and phosphate levels) 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 single 100µg SC injection of rhPTH(1-84) in matched, non-Hispanic, healthy, adult volunteer Caucasian subjects.

Rationale:

This study is being conducted to evaluate the PK, PD, safety and tolerability of rhPTH(1-84) after single-dose SC administration in adult healthy volunteers of Japanese descent in comparison with adult, healthy, non-Hispanic, Caucasian volunteers. In addition, this study will assess the PK dose-proportionality and similarity of rhPTH(1-84) in healthy volunteers of Japanese descent as compared with historical data obtained in non-Japanese healthy volunteers.

The Japanese regulatory agencies, Pharmaceuticals Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare (MHLW) require evidence that current data in non-Japanese subjects can be extrapolated to the Japanese population.

This study can be conducted in a facility that is located outside of the country of Japan as long as steps are taken to ensure that the subjects will be viewed as Japanese (or of direct Japanese descent).

The results from this study will be utilized to guide dose selection for a future Phase 3 study in Japanese patients with hypoparathyroidism.

Investigational product, dose, and mode of administration: The investigational product (rhPTH[1-84]) is a lyophilized powder form of recombinant human parathyroid hormone produced from genetically modified *Escherichia coli* and contained within a glass cartridge that includes sterile diluent as well. The investigational product is reconstituted within the glass cartridge and administered from an injector pen (Haselmeier) as a SC injection at doses of 25µg, 50µg and 100µg into the mid-thigh (100µg only in non-Hispanic, Caucasian subjects). The volume of reconstituted drug administered at 1 dose is 71.4µL.This study is open-label and does not require the use of a placebo.

Methodology:

This 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 (±5 years), weight (±10%), 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 from single dose to single dose 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 each subject. 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 for a non-Hispanic, Caucasian subject is 62 days 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 Periods:

- 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 (original and baseline-adjusted) 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) 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.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Age 18-65, inclusive, at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Subjects must be either:
    a) A subject of Japanese descent born in Japan, who has resided outside of Japan for no longer than 5 years and is of Japanese parentage, defined as having 2 Japanese parents, and 4 Japanese grandparents, all born in Japan.
    b) A non-Hispanic, Caucasian subject who has 2 non-Hispanic, Caucasian parents and 4 non-Hispanic, Caucasian grandparents.
5. Male or nonpregnant, nonlactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of nonchildbearing potential.
6. Considered "healthy" by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
7. Body mass index between 18.5 and 25 kg/m², inclusive, with a body weight ≥45 kg (99lbs). This inclusion

criterion will only be assessed at the first screening visit.

8. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume the identical meals on study days when serial PK and PD blood samples are collected.
9. A clinical safety laboratory parameter of hemoglobin greater than 11.7g/dl (females) or 13.1g/dl (males) and less than 16g/dl (females) or 17.4g/dl (males).
10. Total serum calcium within laboratory normal limits.
11. Serum parathyroid hormone (PTH) levels within laboratory normal limits.

Exclusion Criteria:

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely-related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of investigational product.
5. Known history of alcohol or other substance abuse within the last year.
6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
7. Use of the following prior to administration of investigational product within:
    - 30 days – loop diuretics, lithium, antacids, systemic corticosteroids (medical judgment is required by the investigator. Primarily high doses of systemic corticosteroids [eg, prednisone] should be excluded. Stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable).
    - 3 months – calcitonin, cinacalcet hydrochloride, treatment with rhPTH(1-84) or N-terminal PTH or PTH-related peptide fragments or analogs
    - For females: changes in hormone replacement therapy within 3 months are excluded. Stable (≥ 3 months) hormone replacement therapy is acceptable.
    - 6 months – fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators (SERMs)
    - 12 months – intravenous bisphosphonates, drug or alcohol abuse, as determined by the investigator
8. Confirmed systolic blood pressure (BP) >139mmHg or <89mmHg, and diastolic BP >89mmHg or <49mmHg.
9. Twelve-lead ECG demonstrating measure of time between the start of the Q wave and the end of the T wave using Fridericia's formula in an electrocardiogram (QTcF) >450msec at screening. If QTcF exceeds 450msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
10. Positive screen for drugs of abuse at screening or drugs of abuse or alcohol on Day -1.
11. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5oz/150 mL) or 1 liquor (1.5oz/40 mL) or 0.75 oz alcohol).
12. Positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody screen.

13. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of investigational product.
14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. (1 caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
15. Prior screen failure, randomization, participation, or enrollment in this study or prior exposure to any exogenous PTH, PTH fragments or analogs.
16. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of hormonal replacement therapy or hormonal contraceptives and occasional use of ibuprofen and acetaminophen). Current use is defined as use within 14 days of the first dose of investigational product.
17. History of abnormalities of calcium homeostasis including hyperparathyroidism, hypoparathyroidism, hyperthyroidism, osteoporosis, Cushing's syndrome, hypercalcemia, hypocalcemia, or any other calcium disorder.

Maximum duration of subject involvement in the study:

Subjects will be screened within 28 days prior to the dose of the investigational product.

- There will be 1 treatment period for the non-Hispanic, Caucasian group consisting of one SC injection of rhPTH(1-84) and 1 treatment period for the subjects of Japanese descent consisting of 3, randomized (only two of the doses will be randomized), SC injections of rhPTH(1-84); each subject will check in to the unit on Day -1 and remain in the unit until discharge (Day 2 for the non-Hispanic, Caucasian subjects and Day 8 for the subjects of Japanese descent). Non-Hispanic, Caucasian subjects will be dosed on Day 1 only and will spend 3 days and 2 nights in the unit. Volunteers of Japanese descent will be dosed on Days 1, 4 and 7 and will spend 9 days and 8 nights in the unit.
- There will be a follow-up clinic visit 30 ± 2 days after the last dose of the investigational product for each subject.
- The total number of nights non-Hispanic, Caucasian subjects will be expected to stay at the clinical research center (CRC) is 2. The total number of nights subjects of Japanese descent will be expected to stay at the clinical research center (CRC) is 8. The maximal total duration of study participation for any subject is 68 days, if the maximum screening, treatment and follow-up visit durations are used.

Endpoints and statistical analysis:

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.

Subject Populations:

- The safety population includes subjects who have received at least 1 dose of rhPTH(1-84).
- The PK population consists of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post dose PK concentration value.
- The PD population consists of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post dose PD concentration value.

Pharmacokinetic Endpoint(s):

A PK evaluation of PTH concentrations and baseline-adjusted PTH concentrations will be performed following the administration of rhPTH(1-84) on Day 1 for non-Hispanic, Caucasian subjects and Days 1, 4 and 7 for subjects of Japanese descent.

Pharmacokinetic parameters will be calculated from original and baseline-adjusted plasma concentration-time data using non-compartmental methods and all calculations will be based on actual sampling times. Baseline is defined as the average Day 1 pre-dose concentration for all subjects (and the Day 4 and Day 7 average pre-dose concentration for the subjects of Japanese descent for those respective dosing intervals). PK parameters will be estimated based on non-compartmental analysis and will include, but not be limited to, the following:

- C_{max}: Maximum concentration occurring at t_{max}
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration
- λ_z: First order rate constant associated with the terminal (log linear) portion of the curve
- $t_{½}$: Terminal half-life
- CL/F: Apparent clearance
- $Vd_{z/F}$: Apparent volume of distribution

Non-body weight adjusted and body weight-adjusted AUC_{last}, C_{max}, CL/F, and Vd_z/F will be estimated. In addition, dose-normalized baseline-adjusted AUClast and Cmax will be calculated.

Statistical Methodology for Pharmacokinetic Endpoint(s):

Individual concentrations (original and baseline-adjusted) and 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, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean. The 95% confidence intervals of the geometric means of PK parameters will be presented as well. Figures of individual and mean (±SD) concentration-time profiles of the original and baseline-adjusted plasma rhPTH(1-84) will be generated on linear and semi-log scales. The mean plots will be generated by overlaying the Japanese cohort and Non-Japanese cohort. Figures of baseline-adjusted PK parameters and dose-normalized baseline-adjusted PK parameters vs dose in Japanese subjects will be generated. Box-Whisker plots for selected PK parameter will be generated with Japanese cohort and Non-Japanese side by side. Forest plots of geometric mean ratios for selected PK parameters between Japanese cohort vs Non-Japanese cohort will be generated.

Dose proportionality of PK parameters will also be examined for the Japanese subjects. Dose proportionality will be assessed for Cmax and AUC (AUC0-last) using the power model. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose.

$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{Random error}$

Where α is the intercept, β is the slope, and Random error is a random residual error. Dose proportionality implies that slope = 1 and will be assessed by estimating mean slope with the corresponding two sided 90% confidence interval (CI) from the power model.

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 100ug dose will be examined between groups using an analysis of variance model. The geometric mean ratio and its 90% confidence interval (CI) will be provided from the model. Baseline-adjusted PK parameters will be the primary PK endpoints, and other PK parameters will be the secondary PK endpoints. In addition, the difference of log-transformed dose-normalized baseline-adjusted AUClast and Cmax will be examined between the Japanese cohort estimated at the 50ug dose and the Non-Japanese cohort estimated at 100ug dose, as well as between the Japanese cohort estimated at the 25ug dose and the Non-Japanese cohort estimated at 100ug dose using an analysis of variance model. The geometric mean ratio and its 90% CI will be provided from the model.

Pharmacodynamic Endpoint(s):

Pharmacodynamic parameters will be computed from individual post dose values of serum calcium (uncorrected and

corrected for serum albumin levels and both unadjusted and baseline-adjusted) and phosphate using non-compartmental methods. Pharmacodynamic parameters will be estimated based on both original and baseline-adjusted values of serum calcium and phosphate. The calcium-phosphate product will be computed. Baseline is defined as the pre-dose value on Day 1 for all subjects and, additionally, also on Day 4 and Day 7 for the subjects of Japanese descent. All calculations will be based on actual sampling times. Pharmacodynamic parameters will be estimated based on non-compartmental analyses and will include, but not be limited to, the following:

- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- $E_{max:}$ Maximum effect
- TE_{max}: Time to maximum effect

Statistical Methodology for Pharmacodynamic Endpoint(s):

Individual values (original and baseline-adjusted) and PD parameters (original and baseline-adjusted) of serum total calcium, albumin-corrected calcium, phosphate and the calcium-phosphate (albumin-corrected calcium) product will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). Figures of individual and mean (±SD) concentration-time profiles of the original and baseline-adjusted PD markers, serum calcium (total and corrected for serum albumin) and phosphate, will be generated. Mean plots will be overlaid for the Japanese cohort and the Non-Japanese cohort. Box-Whisker plots for selected PD parameters will be prepared with the Japanese cohort and Non-Japanese cohort side by side.

Safety Endpoint(s):

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit as indicated below:

- Number, severity, seriousness and causality of treatment-emergent adverse events
- Anti-PTH antibodies
- Changes in vital signs, ECGs, and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post baseline time points

Statistical Methodology for Safety Endpoint(s)

Safety data, including TEAEs, laboratory tests, anti-PTH antibodies, and vital signs, will be summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data. Direct safety comparisons between the two ethnic groups will be presented from the rhPTH(1-84) 100µg dosing data. All other safety data from the 25µg and 50µg in the subjects of Japanese descent will be summarized and listed. Treatment-emergent AEs (TEAEs) are defined as AEs with start dates between the time of the first exposure to study drug and the last dose of the study drug.

STUDY SCHEDULE(S)

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									
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[j]			X[j]	X[j]	X
HIV, HBsAg, and HCV antibodies	X										
Pregnancy test (females	X	X		X						X[j]	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**	
only)[a, d]											
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.

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	

[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 (see Section 7.1.3)

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
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.

[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
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.
[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.

1. BACKGROUND INFORMATION

Hypoparathyroidism is a rare disorder characterized by hypocalcemia in the presence of inappropriately low or undetectable levels of circulating parathyroid hormone (PTH) (Avioli 1974; Haussler and Cordy 1982; Shoback 2008). The most frequent cause of hypoparathyroidism is resection of, or damage to, parathyroid glands during neck surgery (eg, thyroidectomy), although multiple other genetic, metabolic and congenital etiologies exist. Hypoparathyroidism occurs in about 0.9% to 6.6% of thyroidectomies, with higher rates associated with more complicated interventions (Shoback 2008; Thomusch et al. 2003; Zarnegar et al. 2003; Page and Strunski 2007). In 1 year spanning 2007-2008 (Powers et al. 2013) the incidence of chronic hypoparathyroidism (≥6 months) was said to be approximately 60,000 subjects in the United States, which rises to approximately 117,000 if the transient hypoparathyroid population is included (≤6 months). The same authors suggest that, of those 117,000 transient hypoparathyroid subjects, about 5% will become chronic.

Parathyroid hormone is an 84-amino acid protein that is secreted by the parathyroid glands. PTH has a variety of important physiological functions that are outlined below to explain the effects of absent or deficient PTH levels. Parathyroid hormone functions to help regulate bone metabolism and serum levels of calcium and phosphate. In general, if serum calcium concentrations decrease, the parathyroid glands consequently increase PTH secretion, and, if serum calcium concentrations increase, the parathyroid glands consequently reduce PTH secretion. The parathyroid glands sense the level of extracellular calcium at the surface of the parathyroid cell and adjust the synthesis and secretion of PTH accordingly. The relationship between ionized extracellular calcium and PTH secretion is a steep sigmoidal curve where small variations in calcium level lead to significant changes in PTH secretion. Calcium sensing is initiated by the binding of calcium to a calcium sensing receptor (CaSR) that is present at high levels on the plasma membrane of the parathyroid cells. The CaSR, a member of the G-protein coupled receptor superfamily, is activated by calcium binding to it that, in turn, induces intracellular signals and, through largely unknown mechanisms, regulates the synthesis and secretion of PTH. The net physiological effects are an increase in circulating PTH levels when the extracellular calcium decreases and a decrease in PTH levels when the extracellular calcium increases (Bilezikian et al. 2011).

Acute symptoms of hypoparathyroidism, linked mainly to the hypocalcemia, are generally reversible. The key symptoms associated with hypocalcemia involve mainly the neuromuscular system: numbness, paresthesias, twitching, and tetany. More serious and potentially life threatening effects of hypocalcemia such as seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm are also recognized in hypoparathyroidism (Behaghel and Donal 2011). Other symptomatology includes difficulty in concentrating described by many subjects as “brain fog” (Bilezikian et al. 2011). Hypoparathyroidism has also been linked to effects on mood and ideation (Arlt et al. 2002; Velasco et al. 1999).

The kidneys are especially vulnerable in subjects with hypoparathyroidism. Circulating PTH promotes renal calcium reabsorption, especially at the level of the distal convoluted tubule (Blaine et al. 2015). This additional fraction of calcium is instead excreted through the kidneys (Shoback 2008), leading to hypercalciuria which, together with a high-calcium-phosphate

product, can potentially can lead to nephrocalcinosis and kidney stones and, ultimately, to renal impairment (Blaine et al. 2015).

For further details see the current rhPTH(1-84) investigator brochure.

1.1 Indication and Current Treatment Options

Prior to 2015, in the absence of an approved PTH replacement therapy, management of hypoparathyroidism consisted of supplemental oral calcium and active vitamin D in pharmacological doses sufficient to maintain the serum calcium level without the disabling symptoms of hypocalcemia. In order to improve the absorption of calcium from the gastrointestinal tract, pharmacological supplementation with active forms of vitamin D (eg, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], calcitriol, 1,25-dihydroxycholecalciferol or α-calcidol [$1(OH)D_3$]) is also required. Since PTH also functions in the kidney to stimulate the conversion of $25(OH)D_3$, the major circulating form of vitamin D, to the active vitamin D hormone ($1,25[OH]_2D_3$), the relative lack of circulating PTH results in a reduction of the production of active vitamin D. Thus, exogenous active vitamin D overcomes the synthetic block in endogenous production of the active vitamin D hormone in hypoparathyroidism. Together, supplemental oral calcium and active vitamin D have formed the mainstay of current treatment of subjects with hypoparathyroidism. As noted above, the additional calcium load that results from supplementation with exogenous calcium and active vitamin D contributes to the hypercalciuria and renal risks often noted in patients with hypoparathyroidism.

In an effort to limit the extent and effect of hypercalciuria, thiazide diuretics can be helpful since they promote renal calcium reabsorption. However, thiazides are associated with their own adverse events including hypokalemia and, more importantly, have no proven long-term effect to reduce hypercalciuria or kidney damage or improve the safety profile in this patient population (Shoback 2008). Although an accepted adjunct to the use of calcium and active vitamin D in hypoparathyroidism, thiazides are prescribed to only a minority of hypoparathyroid patients.

The investigational product (rhPTH[1-84]) is a recombinant human PTH that is identical in structure to endogenous human PTH, a single-chain polypeptide consisting of 84 amino acid residues and is manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. rhPTH(1-84) was approved for marketing in the United States on 23 January 2015 under the brand name NATPARA® as a once-daily injectable dose as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

1.2 Product Background

1.2.1 Preclinical Information

A total of 46 in vivo studies in mouse, rat, rabbit, dog, and rhesus and cynomolgus monkeys have evaluated the PKs, PDs and toxicology of rhPTH(1-84) at doses ranging from 0.1 to 10,000 µg/kg given as single doses or as daily doses for up to 2 years. In the vast majority of studies, rhPTH(1-84) was administered by subcutaneous (SC) injection, the intended route of administration of rhPTH(1-84) in humans. A total of 7 in vitro pharmacology and toxicology studies have been performed.

In male and female rats, the administration of PTH was associated with an increase in the incidence of osteosarcoma. These data were interpreted as an increased risk for osteosarcoma in the clinic. Therefore, administration of rhPTH(1-84) should be avoided in subjects who are considered to be at increased risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a history of prior external beam or implant radiation therapy involving the skeleton). Currently available results from animal reproductive toxicology studies suggest that rhPTH(1-84) is not associated with significant fetal or neonatal toxicity; however the safety of rhPTH(1-84) in pregnant or nursing women is not established.

For full details see the rhPTH(1-84) investigator brochure.

1.2.2 Clinical Information

Few studies of PTH use have been performed in the setting of hypoparathyroidism. Study CL1-11-040 (REPLACE) was a double-blind, placebo controlled study of once daily (QD) administration of 50µg to 100µg of rhPTH(1-84) which resulted in 54.8% of the rhPTH(1-84) subjects meeting a 3-tiered primary endpoint vs 2.5% of the placebo subjects ($p<0.001$). Long-term, open-label studies have supported these findings with subjects maintaining the physiologic benefit derived from rhPTH(1-84) treatment. One study, PAR-C10-008 (RACE), is ongoing with subjects receiving treatment for more than 5 years.

In clinical trials, rhPTH(1-84) significantly reduced the calcium-phosphate product. In these studies hypercalciuria was defined as an excretion of calcium in the urine greater than 300mg per 24 hours. Data from the REPLACE Study and the long-term open label study, RACE, show that rhPTH(1-84) has a calcium-sparing effect, consistent with the reduction of calcium excretion seen in a previous PK/PD study (C09-002) of single dose administration of rhPTH(1-84) in patients with hypoparathyroidism in comparison with calcitriol administration.

The Phase 3 clinical study, REPLACE, was the largest, randomized, placebo controlled clinical study conducted in hypoparathyroidism population and was the pivotal study demonstrating that rhPTH(1-84) is effective in maintaining serum calcium levels and enabling significant decreases in active vitamin D and oral calcium doses. REPLACE also established the rhPTH(1-84) dose and dose titration and evaluated the physiologic effects of PTH replacement on serum calcium, serum phosphate, urinary calcium excretion and bone turnover markers. Eighty-four subjects were evaluated in the active treatment group and 40 subjects received placebo. Subjects received at a flexible dose range of 50 to 100µg SC in the thigh once daily for 6 months. The study met the primary efficacy triple endpoint, with a statistically higher responder rate (54.8%) versus placebo (2.5%). To meet the primary endpoint a subject had to fulfill all 3 conditions as follows: a 50% or greater reduction in oral calcium requirement, a 50% or greater reduction in active vitamin D therapy and an albumin corrected serum calcium (ACSC) concentration that was maintained within a range of 7.5 to 10.6 mg/dL.

A review of safety data across the hypoparathryodism program indicated that rhPTH(1-84) administered in the dose range of 25 to 100µg SC QD is safe for use for the treatment of hypoparathyroidism. Very common adverse reactions (ie, reported in at least 1 in every 10 subjects) included hypocalcemia, hypercalcemia, headaches, diarrhea, vomiting, and

hypercalciuria. Common adverse reactions (ie, reported in at least 1 in every 100 subjects, but less than 1 in every 10 subjects) included hypomagnesemia, anxiety symptoms, palpitations, flushing, coughing and associated symptoms, neck pain, pollakiuria, chest pain, thirst, blood 25-hydroxycholecalciferol decreased, and blood alkaline phosphatase increased.

There was no suggestion that rhPTH(1-84) causes drug-induced liver injury in humans. There were no renal-related adverse events (AEs) or abnormalities in renal function tests or urinalysis tests in clinical studies apart from changes expected from the mechanism of action of rhPTH(1-84). Despite significant increases in total serum calcium levels and improved calcium homeostasis, treatment with rhPTH(1-84) did not result in worsening of hypercalciuria.

Potential risks include those effects which are extensions of the pharmacologic actions of PTH including hypercalcemia. Post-treatment hypocalcemia following the abrupt withdrawal of rhPTH(1-84) can be particularly problematic. Following sustained withdrawal of rhPTH(1-84), serum calcium levels must be carefully monitored with reinstatement of appropriate dosages of oral calcium and active vitamin D. No on-treatment events of hypocalcemia occurred following incidental missed doses of rhPTH(1-84) during any of the clinical studies; patients should be advised, however, to take their rhPTH(1-84) dose as soon possible following a missed dose and to take oral calcium.

The investigational product (rhPTH[1-84]) has been developed for the treatment of hypoparathyroidism. In the United States the drug is currently marketed under the brand name NATPARA as a once a day injectable treatment, indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. However, because of the potential risk of osteosarcoma, NATPARA is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone.

Always refer to the latest version of the rhPTH(1-84) investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, PKs, efficacy, and safety of rhPTH(1-84).

1.3 Risk/Benefit and Ethical Assessment

There is no anticipated benefit from taking part in this study.

Risks for subject exposure to rhPTH(1-84) are listed in the current investigator brochure and include, but are not limited to, the following:

- Osteosarcoma: In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor). The occurrence of osteosarcoma was dependent on parathyroid hormone dose and treatment duration. This effect was observed at parathyroid hormone exposure levels ranging from 3 to 71 times the exposure levels in humans receiving a 100μg dose of rhPTH(1-84). These data could not exclude a risk to humans. Because of a potential risk of osteosarcoma, it is recommended to use rhPTH(1-84) only in subjects with hypoparathyroidism who cannot be well-controlled on calcium and active forms of vitamin D alone and for whom the potential benefits are considered to

outweigh this potential risk. Use of rhPTH(1-84) is to be avoided in subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult subjects with open epiphyses, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton.

- Hypercalcemia during initiation of rhPTH(1-84) administration: In previous efficacy and safety studies in hypoparathyroidism, 29 of 121 (24.0%) rhPTH(1-84)-treated subjects experienced an on-treatment event of hypercalcemia. Monitoring of serum calcium during the treatment process can mitigate the risk, along with appropriate medical treatment.
- Hypocalcemia with abrupt withdrawal of rhPTH(1-84) therapy: In previous efficacy and safety studies in hypoparathyroidism, 24 of 121 (19.8%) subjects experienced a post-treatment event of hypocalcemia. Monitoring of serum calcium during the treatment process and after withdrawal can mitigate the risk, along with appropriate medical treatment.
- The safety of rhPTH(1-84) in pregnant or nursing women has not been established. Pregnancy tests will be performed on all females on 2 occasions prior to entering the treatment phase of the study, and at discharge after treatment and at follow-up. Both men and women must agree to adequate contraception methods (see Section 4.4) before taking part in the study.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Recombinant human PTH (rhPTH[1-84]) is approved for use in the United States (US) as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. As a once-daily SC injection for hypoparathyroidism, it has been shown to provide a 24-hour sustained increase in serum calcium. Administration of rhPTH(1-84) resulted in dose-related increases in total serum calcium levels, with maximum mean increases (approximately 0.125 to 0.175 mmol/L) observed 12 hours after dosing. Serum calcium levels did not return to baseline levels by 24 hours. This sustained increase may explain the reduction in the observed daily amounts of calcium and active vitamin D that were taken in the placebo-controlled trial.

Other clinical studies have reported experience with twice-daily use of a fragment of PTH (PTH[1-34]) injected SC in the setting of adult and pediatric subjects with hypoparathyroidism (Winer et al. 1998; Winer et al. 2003; Winer et al. 2008). In this setting, PTH(1-34) maintained eucalcemia and reduced urinary calcium excretion. In these studies, a comparison with calcitriol showed that either twice-daily PTH(1-34) or twice-daily calcitriol each maintained similar serum calcium levels, although urinary calcium excretion was lower in the PTH(1-34)-treated subjects.

Shire intends to develop rhPTH(1-84) for use in Japan. The Japanese regulatory agencies, Pharmaceuticals Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare (MHLW), require evidence that current data in non-Japanese subjects can be extrapolated to the Japanese population, since Japanese patients may require different doses of medication of some drug classes.

To satisfy the PMDA and MHLW requirements, sponsors will provide data to support doses for a later study in Japanese subjects. The present study to compare PK and PD profiles and safety and tolerability in Japanese and (non-Hispanic) Non-Hispanic, Caucasian healthy volunteer subjects is designed for this reason. In addition, this study will also assess the PK dose-proportionality of rhPTH(1-84) using three, randomized, single, SC doses of 25µg, 50µg and 100µg in healthy volunteers of Japanese descent.

2.2 Study Objectives

2.2.1 Primary Objective

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

2.2.2 Secondary Objectives

- To assess the dose proportionality of the PKs 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 (including measurement of serum calcium and phosphate levels) 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 (including measurement of serum calcium and phosphate levels) 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, 50 µg 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. STUDY DESIGN

3.1 Study Design and Flow Chart

This 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 (±5 years), weight (±10%), 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 from single dose to single dose 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 each subject. 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 for a non-Hispanic, Caucasian subject is 62 days 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

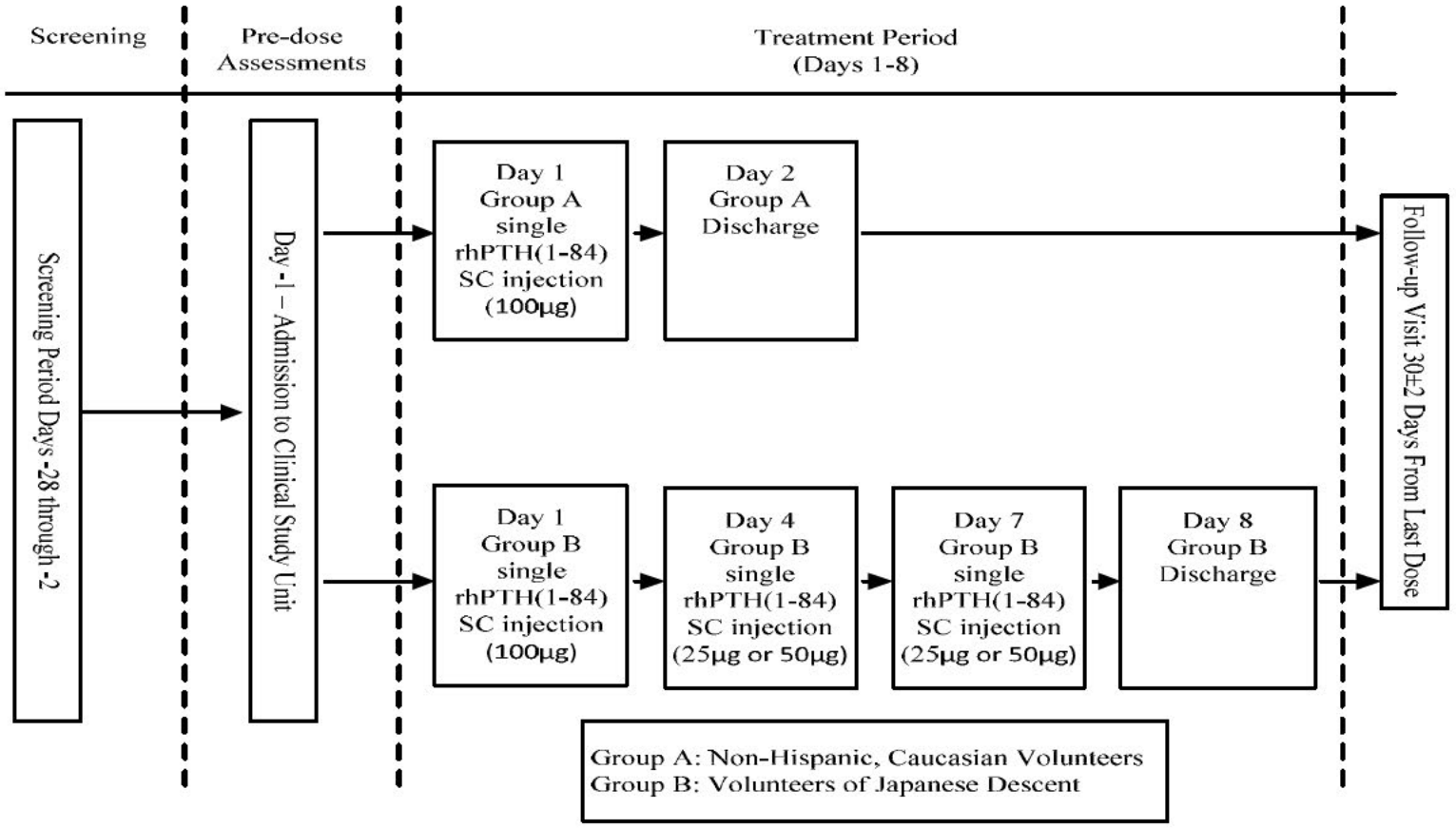
- Serial blood samples for PK analysis will be collected on Day 1 (and Day 4 and Day 7 for the subjects of Japanese descent) for the determination of parathyroid hormone (PTH) concentrations (original and baseline-adjusted) at pre-dose and up to 24 hours post dose. These blood samples will be collected 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) 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 is an open-label study to evaluate the PKs, PDs, safety, and tolerability of single doses of rhPTH(1-84) in healthy adult subjects of Japanese descent and matched, non-Hispanic, healthy, adult Non-Hispanic, Caucasian subjects.



3.2 Rationale for Dose Selection and Study Design Elements

The primary objective of this study is to compare the PK profile of plasma rhPTH(1-84) between subjects of Japanese descent and non-Hispanic, Caucasian volunteers. Although endogenous PTH levels are different between healthy subjects and patients with hypoparathyroidism, historically, evaluations of different formulations, injection devices and dose proportionality, with PK as the primary objective, have been conducted in healthy subjects due to the distinct PK profile of plasma rhPTH(1-84) following subcutaneous administration compared to endogenous PTH. The PK profile of rhPTH(1-84) following subcutaneous administration had been shown to be similar between healthy subjects and patients with hypoparathyroidism in previous studies. Therefore, this study is to be conducted in healthy subjects. Due to the presence of endogenous PTH in healthy subjects and that the current PTH assay measures the total PTH concentration (combination of both endogenous PTH and rhPTH [the assay cannot distinguish between endogenous PTH and administered rhPTH(1-84)]), the PK analysis will be performed based on both the original and baseline-adjusted PTH concentrations. Due to the potential differences in body weight between enrolled subjects of Japanese descent and non-Hispanic, Caucasian subjects, in addition to the non-body weight adjusted PK parameters we will also use body weight-adjusted PK parameters for comparison.

rhPTH(1-84) (Natpara), is currently approved in the US at doses of 25, 50, 75 and 100µg administered once daily. rhPTH(1-84) has demonstrated dose-proportional PKs over this dose range in studies performed in the western countries. No significant differences in either the PKs or PDs of rhPTH(1-84) are anticipated between Japanese and non-Japanese; therefore, the 100µg dose, the highest marketed dose, will be used in this study for direct comparative purposes. Further doses of 25µg and 50µg will be used in the subjects of Japanese descent to examine the dose proportionality of PKs in Japanese subjects

Group comparison of the PK, PD, and safety of rhPTH(1-84) will be evaluated after a single dose administration in this study. Following subcutaneous administration of rhPTH(1-84) at 100µg, plasma PTH levels quickly increase and reach the first peak concentration (approximately 150pg/mL) at around 0.5 hour post dose, which is then followed by a second peak of a similar magnitude at 2-3 hours post dose. After the second peak, PTH levels decline quickly, with an estimated terminal half-life of about 1-2 hours. PTH levels return to baseline at about 12 hours post dose. Therefore there is no accumulation of plasma rhPTH after repeat dosing, and single dose treatment is considered sufficient to characterize the comparative PKs of rhPTH in this study at that dose.

To examine the PK dose-proportionality of rhPTH(1-84) in the subjects of Japanese descent, Japanese subjects will receive single, SC doses of 25µg, 50µg, and 100µg rhPTH(1-84) and PK parameters will be evaluated for dose proportionality.

3.3 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 62 days for the non-Hispanic, Caucasian volunteers and 68 days for the subjects of Japanese descent. The study will be completed in approximately 9 weeks.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.4 Sites and Regions

It is anticipated that this study will be performed at 1 study site within the United States.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

1. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Age 18-65 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Subjects must be either:
    a. A subject of Japanese descent born in Japan, who has resided outside of Japan for no longer than 5 years and is of Japanese parentage, defined as having 2 Japanese parents, and 4 Japanese grandparents, all born in Japan.
    b. A non-Hispanic, Caucasian subject who has 2 non-Hispanic, Caucasian parents and 4 non-Hispanic, Caucasian grandparents.
5. Male or nonpregnant, nonlactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of nonchildbearing potential.
6. Considered “healthy” by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
7. Body mass index between 18.5 and 25 kg/m², inclusive, with a body weight ≥45 kg (99lbs). This inclusion criterion will only be assessed at the first screening visit.
8. Willing and able to consume standardized meals during the confinement period of the study. All participants will be required to consume the identical meals on study days when serial PK and PD blood samples are collected.
9. A clinical safety laboratory parameter of hemoglobin greater than 11.7g/dl (females) or 13.1g/dl (males) and less than 16g/dl (females) or 17.4g/dl (males).
10. Total serum calcium within laboratory normal limits.
11. Serum parathyroid hormone (PTH) levels within laboratory normal limits.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.

2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.

3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely-related compounds, or any of the stated ingredients.

4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of investigational product.

5. Known history of alcohol or other substance abuse within the last year.

6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.

7. Use of the following prior to administration of investigational product within:

   - 30 days – loop diuretics, lithium, antacids, systemic corticosteroids (medical judgment is required by the investigator. Primarily high doses of systemic corticosteroids [eg, prednisone] should be excluded. Stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable).
   - 3 months – calcitonin, cinacalcet hydrochloride, treatment with rhPTH(1-84) or N-terminal PTH or PTH-related peptide fragments or analogs
   - For females: changes in hormone replacement therapy within 3 months are excluded. Stable (≥3 months) hormone replacement therapy is acceptable.
   - 6 months – fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators (SERMs)
   - 12 months – intravenous bisphosphonates, drug or alcohol abuse, as determined by the investigator

8. Confirmed systolic blood pressure (BP) >139mmHg or <89mmHg, and diastolic BP >89mmHg or <49mmHg.

9. Twelve-lead ECG demonstrating measure of time between the start of the Q wave and the end of the T wave using Fridericia's formula in an electrocardiogram (QTcF) >450msec at screening. If QTcF exceeds 450msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.

10. Positive screen for drugs of abuse at screening or drugs of abuse or alcohol on Day -1.

11. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5oz/150 mL) or 1 liquor (1.5oz/40 mL) or 0.75 oz alcohol).

12. Positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or HCV antibody screen.

13. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of investigational product.

14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. (1 caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine).

15. Prior screen failure, randomization, participation, or enrollment in this study or prior exposure to any exogenous PTH, PTH fragments or analogs.

16. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of hormonal replacement therapy or hormonal contraceptives and occasional use of ibuprofen and acetaminophen). Current use is defined as use within 14 days of the first dose of investigational product.

17. History of abnormalities of calcium homeostasis including hyperparathyroidism, hypoparathyroidism, hyperthyroidism, osteoporosis, Cushing's syndrome, hypercalcemia, hypocalcemia, or any other calcium disorder.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRC and during the in-house stays at the CRC.
2. Subjects should refrain from consuming grapefruit, Seville oranges, and products containing these items from 7 days prior to Day 1 of the first treatment period through the completion of the last treatment period.
3. Subjects should refrain from alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
4. Subjects should refrain from use of tobacco or any products containing nicotine within 30 days of Day 1 of the first treatment period through the completion of the last treatment period.
5. Subjects should refrain from taking or regularly using any medication (including over-the-counter multivitamin, herbal, or homeopathic preparations) with the exception of those listed in Section 5.2 from 14 days prior to receiving the first dose of the investigational

product through the completion of the discharge assessments and procedures at Treatment Period 2.

6. Subjects should refrain from foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
7. On Day -1, Day 1, Day 4, and Day 7 when the investigational product is to be administered, subjects will be required to fast for approximately 8 hours prior to dose of administration and continuing through 2 hours after administration of the investigational product. Water will be allowed ad libitum.
8. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRC. No outside food or beverages (including gum, mints, etc.) will be permitted. Menus will be identical for all subjects at the CRC. Copies of the menus will be provided to the sponsor for approval prior to the start of the study. While confined, the total daily nutritional composition should be approximately 50% carbohydrate, 35% fat, and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and for 30 days following the last dose of investigational product.

Female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea with follicle-stimulating hormone [FSH] concentrations in the laboratory post menopausal range).
- Surgically sterile (having undergone one of the following surgical procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post sterilization, or
- Females of childbearing potential with a negative serum β-hCG pregnancy test at the screening visit and at Day -1. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)

- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of investigational product, plus condoms. Note: If subject becomes sexually active during the study, they should use 1 of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

Male subjects must be advised to use acceptable contraceptives throughout the study period and for 3 months following the dose of investigational product. Male subjects must be advised not to donate sperm during the course of the study and within 3 months of last dose of investigational product. Acceptable methods of contraception for male subjects are:

- Double-barrier methods (eg, condoms with spermicidal gel or foam)

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 1 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and date of stopping investigational product must be recorded in the source documents.

Enrolled subjects who discontinue from the study may be replaced at the sponsor's discretion.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be noted.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Physician decision
- Other {If "Other" is selected, the investigator must specify the reason}

4.5.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, nonpharmacological treatments such as psychotherapy as appropriate) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of dose of investigational product. Prior treatment information must be recorded on the source documentation.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate source document.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study. Any medication which is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be listed on the appropriate source document.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of childbearing potential administered according to the package insert (see Section 4.4.1)
- Hormone replacement therapy that has been in use for at least 30 days prior to date of first dose of rhPTH(1-84)
- Occasional use of a nonsteroidal anti-inflammatory drug as prescribed by the principal investigator (or delegate)

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is rhPTH(1-84), which will be provided as a multiple dose, dual chamber, glass cartridge containing a sterile lyophilized powder and a sterile diluent for reconstitution at doses of 25µg, 50µg and 100µg.

The study drug cartridge (together with the study drug cartridge holder) is initially placed onto a mixing device to break the internal seal and allow the lyophilized powder and diluent to fully mix. Once mixed, the study drug and cartridge are placed into the Haselmeier injector pen in preparation for dosing.

Please note that in each administration of the drug by the pen injector (Haselmeier), a sterile, disposable pen needle is used and is specified as a Becton-Dickinson (BD™) 0.25 mm x 8 mm (31G x 5/16").

Additional information related to the investigational product, including preparation and administration, is provided in the current rhPTH(1-84) investigator brochure, and in an investigational product preparation and administration manual that will be provided.

6.1.1 Blinding the Treatment Assignment

Not Applicable.

6.2 Administration of Investigational Product(s)

6.2.1 Allocation of Subjects to Treatment

This is an open-label study.

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.

Once a subject number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a subject number is allocated incorrectly, the clinical research associate/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers, separate from subject numbers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

Each eligible subject will be assigned to 1 study drug cartridge (with a unique identifier). Each study drug cartridge should only be used for the subject to which it is assigned. Although each study drug cartridge holds multiple doses, only 1 dose from the cartridge must be used for the subject it is assigned to. Study drug cartridges and injector pens must be regarded as single use only and never used on more than 1 subject.

A study drug allocation scheme will be provided. The study drug allocation scheme must be maintained securely in the pharmacy.

6.2.2 Dosing

After each subject has completed the screening process and found to be eligible to proceed to dosing (inclusive of all clinical laboratory values), the subject will be assigned a study cartridge, mixing device and injector pen and, following preparation of the study drug, will be administered a single dose of investigational product in the mid-thigh on the morning of Day 1 (for all study subjects) and Days 4 and 7 (for subjects of Japanese descent only). A detailed pharmacy manual will be provided that describes the materials to be used, the preparation of materials and administration of study drug.

6.2.3 Unblinding the Treatment Assignment

Not Applicable.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

The study site will receive open label supplies of investigational product, injection pens and mixing devices required for dosing.

All clinical supplies will be manufactured, tested, labeled and released according to current legal and local country specific regulatory requirements and will comply with Good Manufacturing Practices.

Space is allocated on the label so that the site representative can record a unique subject identifier and initials.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor’s prior full agreement.

In addition to labeling requirements for the investigative study drug, rhPTH(1-84), mixing devices and injector pens must also be labeled with the unique subject identifier. One mixing

device and 1 injector pen will be supplied for each subject taking part in the study for each dose. Mixing devices and injector pens must **never** be used between study subjects.

6.3.2 Packaging

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the site study team. The pharmacist/nominated study team member will enter the unique subject identifier on the injector pen (containing the study drug cartridge) as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered investigational product will be documented on the source documents and/or other investigational product record.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor. For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational products, if possible, must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

The investigator/nominated person will record details on the drug accountability log(s) and/or source documents of study drug administration (including which thigh was used) and dosing details (time, date, dose level).

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not Applicable.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1, Table 2 and Table 3 for study procedures.

The following "priority order" will be in effect when more than 1 procedure or assessment is required at a particular time point.

- Spontaneous or solicited adverse event (AE) reporting
- Electrocardiogram (ECG)
- Vital signs
- Pharmacodynamic blood sampling
- Anti-PTH blood sampling
- Clinical laboratory tests
- PK blood sampling
- Physical examination

NOTE: Blood sampling for PD and PK evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document.

7.1.1 Screening Period

Screening procedures must be completed within 28 days prior to receiving the dose of investigational product. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See Table 1 for a complete list of screening procedures to be performed. Immediately before dosing on Day 1 (but still within the screening period), subjects will check into the CRC (Day -1) for an overnight stay prior to dosing on Day 1. Eligibility procedures performed on Day -1 must be confirmed as meeting inclusion/exclusion criteria before dosing on Day 1.

Written, signed, and dated informed consent from the subject prior to the performance of any study-related procedures must be obtained by the principal investigator or a designee. A copy of the signed informed consent form must be given to the subject for their records.

7.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been enrolled or administered investigational product(s).

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on investigator discretion and sponsor approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is rescreened and a new informed consent form must be signed.

7.1.2 Treatment Period

7.1.2.1 Days 1 to 8

Study assessments for Day 1 to Day 8 of the treatment period are outlined in Table 1,Table 2, and Table 3. Administration of investigational product will occur on Day 1 (all study subjects) of the treatment period and Days 4 and 7 (subjects of Japanese descent) of the treatment period.

Subjects will be discharged from the CRC following completion of the last study assessment on Day 2 (all non-Hispanic, Caucasian subjects) and Day 8 (all subjects of Japanese descent) of the treatment period.

7.1.2.2 Final Visit

For this study, the final visit will be the follow-up visit, which is intended to be an out-patient clinic visit.

7.1.3 Follow-up Period

The follow-up period for this protocol is 30±2 days after the dose of investigational product. At the end of this period there will be a follow-up visit to obtain a blood sample for clinical safety labs, to obtain a blood sample for anti-PTH antibodies, and to query for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1.)

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

7.2.1.1 Demographics

Demographic information will be collected at the initial screening visit. Information to be collected will include:

- Date of birth
- Sex
- Race and ethnicity

7.2.2 Safety

The name and address of each third party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes will be considered a protocol deviation (unless otherwise noted in the protocol).

Adverse events (defined as AEs occurring from the time of informed consent signature to the dose of investigational product), TEAEs (all AEs occurring after the treatment), prior medication and concomitant medication use will be assessed and monitored from the time the subject signs the informed consent form to completion of study (including to time of screen failure or drop out/discontinuation). While confined in the CRC, subject safety will also be closely monitored through BP measurements, ECG measurement, clinical safety labs and physician oversight.

In the event anti-PTH antibodies are detected following analysis for a subject, the investigator will be notified by the sponsor. It will be the investigator's responsibility to notify the subject.

7.2.2.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be performed at the screening visit/time points described in Table 1 by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

7.2.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the time points described in Table 1, Table 2, and Table 3 by a qualified licensed physician, physician's assistant, or nurse practitioner.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory

- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys)

Clinically significant abnormalities identified at the screening visit will be documented in the subject's source documents. Changes after the screening visit will be captured as AEs on the AE source documentation, as deemed by the investigator.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.2.4 Vital Signs

BLOOD PRESSURE AND PULSE RATE

Blood pressure and pulse rate will be measured at times specified in Table 1, Table 2 and Table 3 of this protocol. Additional BP and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining BP measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in the assumed position.

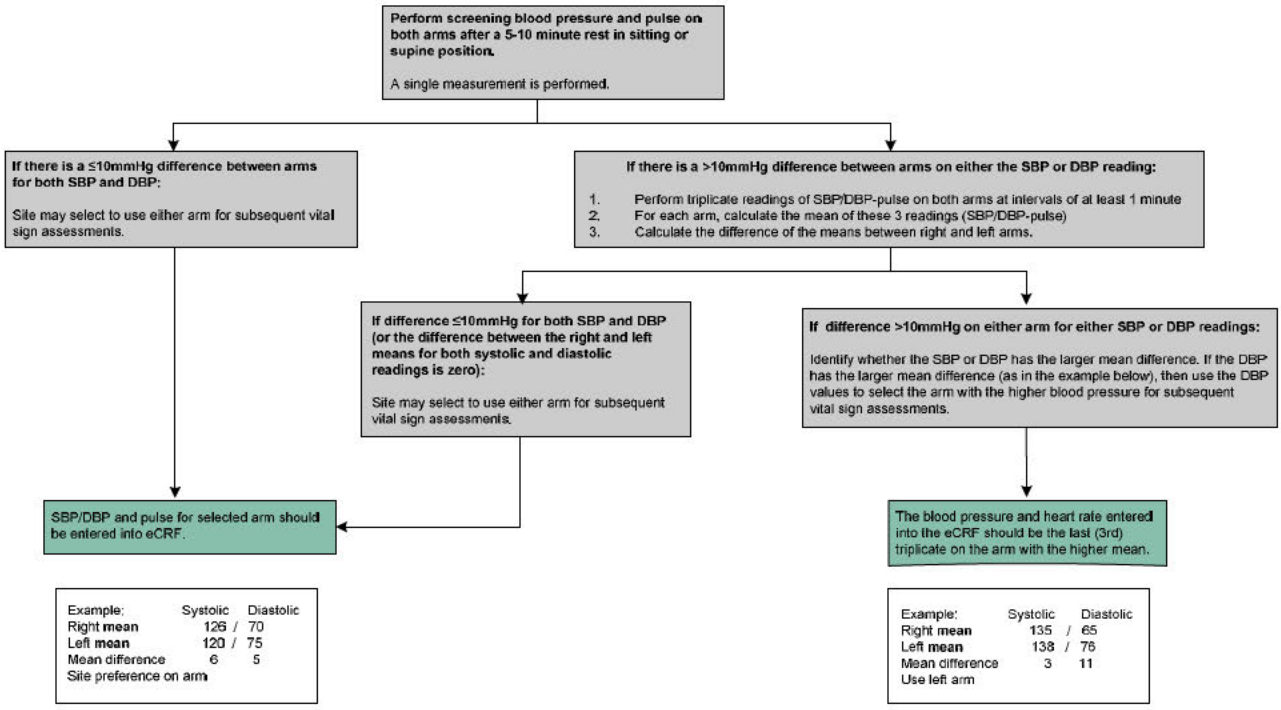
The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be lying comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

At the screening visit, blood pressure should be compared between both arms. If, after a single measurement is taken, there is a difference between arms in either systolic or diastolic blood pressure of ≥10mmHg, the site will perform triplicate BP measurements in each arm to determine the arm with the higher BP. The arm with the higher BP (based on the average of the 3 BP measurements for each arm) should be used for inclusion at screening, and the last of the 3 measurements recorded in the source documentation as the screening BP. The same (right or left) arm with the higher blood pressure will be used throughout the study, see Figure 2.

Figure 2 Procedures for Screening Vital Signs (Blood Pressure – Pulse)



DBP=diastolic blood pressure; eCRF=electronic case report form; SBP=systolic blood pressure

One reading (supine systolic BP/diastolic BP-heart rate) should be taken.

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

BODY TEMPERATURE

Oral temperature should be taken by placing a digital thermometer under the tongue as per study site documented procedures and the temperature reported in degrees Celsius.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

BIOCHEMISTRY

Blood samples (8.5 mL) for serum biochemistry will be collected into a red top gel separator tube at the time points described in Table 1, Table 2 and Table 3. The following parameters will be assessed:

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	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
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.

HEMATOLOGY

Blood samples (4mL) for hematology will be collected into a K_2-EDTA (ethylenediaminetetraacetic acid) tube at the time points described in Table 1, Table 2 and Table 3. The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute)
Hematocrit	Eosinophils (absolute)
Red blood cells	Monocytes (absolute)
Platelet count	Basophils (absolute)
White blood cell count; total and differential	Lymphocytes (absolute)

URINALYSIS

A urine sample for urinalysis will be collected at the time points described in Table 1, Table 2 and Table 3. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.6 Pregnancy Test

A serum β-hCG pregnancy test is required for all females at screening, on admission to the CRC on Day -1 and upon discharge from the CRC on Day 2 (for non-Hispanic, Caucasian subjects) or Day 8 (for subjects of Japanese descent) and at the final follow-up visit for all females. In addition, a pregnancy test is required if pregnancy is suspected or on early withdrawal/termination from the study.

7.2.2.7 Drug and Alcohol Screen

A urine screen for drugs of abuse and an alcohol breath test will be performed at the time points described in Table 1. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of urine drug and alcohol screens will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Any positive result for drugs of abuse at screening or drugs of abuse and alcohol on Day -1 will exclude the subject from further participation in the study.

7.2.2.8 Serology Screen

At the screening visit, a blood sample of approximately 8.5mL will be drawn into a serum separator tube to test for the presence of HIV, HBsAg, and HCV antibody.

The test results must be confirmed negative prior to enrollment in the study. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Positive serology results may be reported to the relevant health authorities by study site personnel if required by law.

7.2.2.9 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1, Table 2 and Table 3. All ECGs will be performed using the equipment supplied by the CRC.

The following parameters will be recorded in the source documentation: heart rate, time elapsed from P wave to R wave in an electrocardiogram (PR), the time between heart beats in an electrocardiogram (RR), measure of time for the 3 main deflections in an electrocardiogram (QRS), and QT intervals along with information on T and U wave morphology (T waves should be captured as normal/abnormal; U waves should be captured as absent/normal or abnormal). The measure of time between the start of the Q wave and the end of the T wave using Bazett's formula in an electrocardiogram (QTcB) and QTcF will be derived from the data in the database. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and the source documentation (if different).

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Triplicate ECG recordings, including a 10-second rhythm strip, should be taken at each time point. They should be immediately assessed as valid recordings and if not valid, they should be repeated. Invalid recordings will not be entered included in the CRF database.

A triplicate ECG recording is to be performed at each time point approximately 2-4 minutes apart. The averages of the ECG triplicate collected predose on Day 1 (all subjects) and predose on Days 4 and 7 (subjects of Japanese descent) will serve as the subject's baseline ECG.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the triplicate average QTcF interval (calculated online on site) is increased by >45 msec from the baseline or an absolute QTcF value is >500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from the baseline; or is >500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. When triplicate ECGs are collected, the mean of the triplicate measurements should be used to trigger the decision to collect follow-up ECGs.

If QTcF values remain above 500 msec (or >45 msec from the baseline) for >4 hours (or sooner at the discretion of the investigator) or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory (Celerion) for this study will be maintained in the investigator's files at the site and in the Trial Master File at the sponsor.

Actual PK blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. PK blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours postdose or by more than ±15 minutes for samples drawn at 4 hours post dose and beyond. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.3.1 Pharmacokinetic Sample Collection and Handling Procedures

Pharmacokinetic blood samples will be collected at the time specified in Table 1, Table 2 and Table 3 to measure plasma concentrations of PTH. A full description of the PK blood collection, handling, storage and shipping can be found in the provided laboratory manual. Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number: SHP634-102
- Subject identifier
- Nominal day
- Nominal time

- Matrix identifier (plasma)
- Split (primary or back-up)

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

All PK samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday-Wednesday only (do not ship on a local, regional or national holiday). Samples should be transported to ensure that they arrive at the bioanalytical laboratory between the hours of 9:00 AM and 4:00 PM. The recipient (Celerion) and primary Shire contact must be notified by telephone or e-mail when the samples are shipped and they must be provided with the shipment tracking number.

Full directions for shipment of all PK samples, (along with the corresponding documentation) can be found in the laboratory manual provided under separate cover.

Pharmacokinetic samples will be stored nominally at -70º C (-94ºF) prior to and after analysis at the bioanalytical labs until their disposal is authorized by Shire.

7.2.3.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to the relevant Standard Operating Procedures at the contract bioanalytical lab (Celerion).

Plasma concentrations will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan).

7.2.4 Pharmacodynamic Assessments

The name and address of the bioanalytical laboratory (InVentiv Health) for this study will be maintained in the investigator's files at the site and in the Trial Master File at the sponsor.

Actual PD blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PD blood samples at the precise protocol scheduled time. Pharmacodynamic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours post dose or by more than ±15 minutes for samples drawn at 4 hours post dose and beyond. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.4.1 Pharmacodynamic Sample Collection and Handling Procedures

Pharmacodynamic blood samples will be collected at the time specified in Table 1, Table 2 and Table 3 to measure serum concentrations of calcium, phosphate and albumin. A full description of the PD blood collection, handling, storage and shipping can be found in the provided

laboratory manual. Serum sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number: SHP634-102
- Subject identifier
- Nominal day
- Nominal time
- Matrix identifier (serum)
- Analyte (calcium/phosphate or albumin)
- Split (primary or back-up)

7.2.4.2 Shipment of Serum Pharmacodynamic Samples

All PD samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday-Wednesday only (do not ship on a local, regional or national holiday). Samples should be transported to ensure that they arrive at the bioanalytical laboratory between the hours of 9:00 AM and 4:00 PM. The recipient (inVentiv) and primary Shire contact must be notified by telephone or e-mail when the samples are shipped and they must be provided with the shipment tracking number.

Full directions for shipment of all PD samples, (along with the corresponding documentation) can be found in the laboratory manual provided under separate cover.

Pharmacodynamic samples will be stored nominally at -70º C (-94ºF) prior to and after analysis at the bioanalytical labs until their disposal is authorized by Shire.

7.2.4.3 Serum Pharmacodynamic Assay Methodology

Serum sample analysis will be performed according to relevant Standard Operating Procedures at the contract bioanalytical lab (inVentiv Health).

Serum PD concentrations will be measured using the most current validated bioanalytical methods. In addition, selected serum samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate.

7.2.5 Immunogenicity Testing for Anti-Parathyroid Hormone Antibodies

The name and address of the bioanalytical laboratory (Covance) conducting anti-PTH immunogenicity testing for this study will be maintained in the investigator's files at the each site and in the Trial Master File at the sponsor.

Actual anti-PTH blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all

anti-PTH blood samples at the precise protocol scheduled time. Anti-PTH blood collection will be collected on Day 1 prior to dose (within 30 minutes of dose) and at the follow-up visit.

In the event anti-PTH antibodies are detected following analysis for a subject, the investigator will be notified by the sponsor. It will be the investigator's responsibility to notify the subject.

7.2.5.1 Sample Collection and Handling Procedures for Immunogenicity Testing for Anti-Parathyroid Hormone Antibodies

Blood samples will be collected at the time specified in Table 1, to detect anti-PTH antibodies in serum. A full description of the anti-PTH blood collection, handling, storage and shipping can be found in the provided laboratory manual. Serum sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number: SHP634-102
- Subject identifier
- Nominal day
- Nominal time
- Matrix identifier (serum)
- Split (primary or back-up)

7.2.5.2 Anti-Parathyroid Hormone Antibody Assay Methodology

Serum sample analysis will be performed according to relevant Standard Operating Procedures at the contract bioanalytical lab (Covance).

Detection of anti-PTH antibodies from serum blood samples will use the most currently validated bioanalytical method.

7.2.6 Volume of Blood to Be Drawn from Each Subject

Table 4 Volume of Blood to Be Drawn from Each Subject

			Caucasian		Japanese	
Assessment		**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Pharmacokinetic samples[a]		4	18	72	54	216
Serum PTH sample[a]		2	2	4	2	4
Pharmacodynamic samples[a]		6	5	30	15	90
HBsAg, HIV, HCV[a]		8.5	1	8.5	1	8.5
Safety	Biochemistry, FSH and β-hCG[a, b]	8.5	4	34	7	59.5
	Hematology[a]	4	4	16	7	28
Anti-PTH Antibody Samples[a]		3	2	6	2	6
Total mL				170.5		412

β-hCG=beta-human chorionic gonadotropin; FSH=follicle stimulating hormone, HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] If a catheter is in use for any blood draw or series of blood draws then the first 1mL is to be discarded. The 1mL discard has been taken into account in the table above and the total blood volume required for study.

[b] β-hCG and FSH testing for females only.

During this study, it is expected that approximately 412mL of blood will be drawn from all subjects of Japanese descent, regardless of sex. For the non-Hispanic, Caucasian volunteers it is expected that 170.5mL of blood will be drawn, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 170.5mL (non-Hispanic, Caucasian subjects) or 412mL (subjects of Japanese descent). When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE source documentation.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded in the source documentation).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the source documentation. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment

or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the contract research organization (CRO)/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

The administration of rhPTH(1-84) to an eligible volunteer following an excursion in temperature requirements (outlined in the pharmacy manual), without assessment of the excursion and permission of the sponsor to proceed, is deemed a medication error.

It is not expected that overdose would occur in this protocol. The investigative product used in this study is supplied in 1 strength only, and is administered once only per volunteer, by a trained and responsible staff member at the study site with sponsor oversight.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the rhPTH(1-84) investigators brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports)

must also be sent to the Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A ***serious adverse event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the

event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities and the US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP634 clinical program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol from the source documentation to the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within a reasonable window of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

This is an open label study and therefore there are no particular data handling concerns.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the PK, PD, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or data monitoring committee (DMC) in this study.

9.6 Sample Size Calculation and Power Considerations

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.

9.7 Study Population

The following study subject populations are defined for this study:

- The safety population includes subjects who have received at least 1 dose of rhPTH(1-84).
- The PK population consists of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post dose PK concentration value.
- The PD population consists of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post dose PD concentration value.

9.8 Pharmacokinetic and Pharmacodynamic Analyses

9.8.1 Pharmacokinetic Analysis

All the PK analyses will be performed using the PK set.

A PK evaluation of PTH concentrations and baseline-adjusted PTH concentrations will be performed following the administration of rhPTH(1-84) administered on Day 1 for non-Hispanic, Caucasian subjects and Days 1, 4 and 7 for subjects of Japanese descent.

Pharmacokinetic parameters will be calculated from original and baseline-adjusted plasma concentration-time data using noncompartmental methods and all calculations will be based on actual sampling times. Baseline is defined as the average Day 1 predose concentration for all subjects (and the Day 4 and Day 7 average predose concentration for the subjects of Japanese descent for those respective dosing intervals). Pharmacokinetic parameters will be estimated based on noncompartmental analysis and will include, but not be limited to, the following:

- C_{max}: Maximum concentration occurring at t_{max}
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration
- λ_z: First order rate constant associated with the terminal (log linear) portion of the curve
- $t_{½}$: Terminal half-life
- CL/F: Apparent clearance
- $Vd_{z/F}$: Apparent volume of distribution

Non-body weight adjusted and body weight-adjusted AUC_{last}, C_{max}, CL/F, and Vd_z/F will be estimated. In addition, dose-normalized baseline adjusted AUClast and Cmax will be calculated.

9.8.1.1 Statistical Analysis of Pharmacokinetic Parameters

Individual concentrations (original and baseline-adjusted) and 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, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and %CV of geometric mean. The 95% confidence intervals of the geometric means of PK parameters will be presented as well. Figures of individual and mean (±SD) concentration-time profiles of the original and baseline-adjusted plasma rhPTH(1-84) will be generated on linear and semi-log scales. The mean plots will be generated by overlaying the Japanese cohort and Non-Japanese cohort. Figures of baseline-adjusted PK parameters and dose-normalized baseline-adjusted PK parameters vs dose in Japanese subjects will be generated. Box-Whisker plots for selected PK parameter will be generated with Japanese cohort and Non-Japanese side by side. Forest plots of geometric mean ratios for selected PK parameters between Japanese cohort vs Non-Japanese cohort will be generated.

Dose proportionality of PK parameters will also be examined for the Japanese subjects. Dose proportionality will be assessed for Cmax and AUC (AUC0-last) using the power model. The power model assumes a linear relationship between the natural log transformed parameter and the natural log transformed dose.

$\ln(\text{Parameter}) = \alpha + \beta \times \ln(\text{Dose}) + \text{Random error}$

Where α is the intercept, β is the slope, and Random error is a random residual error. Dose proportionality implies that slope = 1 and will be assessed by estimating mean slope with the corresponding two sided 90% confidence interval (CI) from the power model.

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 100ug dose will be examined between groups using an analysis of variance model. The geometric mean ratio and its 90% confidence interval (CI) will be provided from the model. Baseline-adjusted PK parameters will be the primary PK endpoints, and other PK parameters will be the secondary PK endpoints. In addition, the difference of log-transformed dose-normalized baseline-adjusted AUClast and Cmax will be examined between the Japanese cohort estimated at the 50ug dose and the Non-Japanese cohort estimated at 100ug dose, as well as between the Japanese cohort estimated at the 25ug dose and the Non-Japanese cohort estimated at 100ug dose using an analysis of variance model. The geometric mean ratio and its 90% CI will be provided from the model.

9.8.2 Pharmacodynamic Analysis

All the PD analyses will be performed using the PD set.

Pharmacodynamic parameters will be computed from individual post dose values of serum calcium (uncorrected and corrected for serum albumin levels and both unadjusted and baseline-adjusted) and phosphate using non-compartmental methods. Pharmacodynamic parameters will be estimated based on both original and baseline-adjusted values of serum calcium and phosphate. The calcium-phosphate product will be computed. Baseline is defined as the pre-dose

value on Day 1 for all subjects and, additionally, also on Day 4 and Day 7 for the subjects of Japanese descent. All calculations will be based on actual sampling times. Pharmacodynamic parameters will be estimated based on non-compartmental analyses and will include, but not be limited to, the following:

- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- $E_{max:}$ Maximum effect
- TE_{max}: Time to maximum effect

9.8.3 Statistical Analysis of Pharmacodynamic Values

Individual values (original and baseline-adjusted) and PD parameters (original and baseline-adjusted) of serum total calcium, albumin-corrected calcium, phosphate and the calcium-phosphate (albumin-corrected calcium) product will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). Figures of individual and mean (±SD) concentration-time profiles of the original and baseline-adjusted PD markers, serum calcium (total and corrected for serum albumin) and phosphate, will be generated. Mean plots will be overlaid for the Japanese cohort and the Non-Japanese cohort. Box-Whisker plots for selected PD parameters will be prepared with the Japanese cohort and Non-Japanese cohort side by side.

9.9 Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent adverse events will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

9.9.1 Safety Endpoint(s)

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit as indicated below:

- Number, severity, seriousness and causality of treatment-emergent adverse events
- Anti-PTH antibodies
- Changes in vital signs, ECGs, and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post baseline time points

9.9.2 Statistical Methodology for Safety Endpoint(s)

Safety data, including TEAEs, laboratory tests, anti-PTH antibodies, and vital signs, will be summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of

qualitative safety data. Direct safety comparisons between the two ethnic groups will be presented from the rhPTH(1-84) 100µg dosing data. All other safety data from the 25µg and 50µg in the subjects of Japanese descent will be summarized and listed. Treatment-emergent AEs (TEAEs) are defined as AEs with start dates between the time of the first exposure to study drug and the last dose of the study drug.

9.10 Other Analyses

No other analyses are planned in this study.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the investigator as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for nonpediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for

multicenter studies, the coordinating principal investigator, according to national provisions, and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the sponsor or sponsor representative and should be handled in accordance with instructions from the sponsor or sponsor representative.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to the subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), United Kingdom (UK) Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting

information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or investigator, or, for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market rhPTH(1-84); national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter

study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	29 Jan 2017	Global