PROTOCOL: SHP634-101

TITLE: An Open-Label, Randomized, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Profiles of Once-Daily and Twice-Daily Dose Regimens of recombinant human Parathyroid Hormone (rhPTH[1-84]) Administered Subcutaneously to Subjects with Hypoparathyroidism

DRUG: rhPTH(1-84)

IND: 076514

BLA: 125511

EUDRACT NO.: 2015-004757-40

SPONSOR:

Shire
300 Shire Way, Lexington, MA 02421 USA

PRINCIPAL/ COORDINATING INVESTIGATOR: [redacted]

PROTOCOL HISTORY:

Protocol Amendment 5: 18 Jun 2018
Protocol Amendment 4: 12 Jun 2017
Protocol Amendment 3: 29 Jul 2016
Protocol Amendment 2: 03 Jun 2016
Protocol Amendment 1: 26 Feb 2016
Original Protocol: 23 Nov 2015

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP634-101.

Title: An Open-Label, Randomized, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Profiles of Once Daily and Twice Daily Dose Regimens of recombinant human Parathyroid Hormone (rhPTH[1-84]) Administered Subcutaneously to Subjects with Hypoparathyroidism

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 Harmonization 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: _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **18 Jun 2018**	**Global**

Item #	**Description of Change**	**Section(s) Affected by Change**
1	The email address to report product quality complaints for the European Union and Rest of World has been revised from [redacted] to [redacted] Reason for change: Clarification	Product Quality Complaints
2	Language has been added to the protocol to: • Indicate that cohorts must have at least 8 subjects who must provide sufficient data to meet study objectives. Therefore, the number of subjects per cohort has been revised from 8 subjects to at least 8 subjects and the number of subjects expected to complete the study has been revised from 32 subjects to approximately 32 subjects. • Indicate that the planned safety review will take place after 8 subjects have completed Cohorts 1, 2, or 3 before a subject can be entered into the next cohort rather than after completion of the respective cohorts. • Allow previous cohorts to be expanded to include additional subjects to ensure that sufficient data for analysis are collected to complete study objectives. Reason for change: The protocol is being amended to allow additional enrollment, if needed, to ensure that 8 evaluable subjects per cohort complete the trial.	Study Synopsis, Section 3.1 (including Table 5), Section 4.5, Section 9.6
3	Study period (planned): The concluding date of the planned study period has been revised from Nov 2017 to May 2019. The planned study period was revised from approximately 18 months to approximately 36 months. Reason for change: Study recruitment has gone more slowly than originally anticipated. The anticipated end of the study has been revised to May 2019 to reflect the expected pace of subject recruitment.	Study Synopsis and Section 3.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **18 Jun 2018**	**Global**

Item #	Description of Change	Section(s) Affected by Change
4	The following analysis population definitions have been revised: The all-enrolled population was revised from consisting of all subjects who meet the inclusion/exclusion criteria and sign the informed consent form to consisting of all subjects who sign the informed consent form and are randomized in the study. The pharmacokinetic population was revised from consisting of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacokinetic concentration value available for 1 dose regimen to consisting of all-enrolled subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacokinetic concentration value available for 1 dose regimen. The pharmacodynamic population was revised from consisting of subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacodynamic value available for 1 dose regimen to consisting of all-enrolled subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacodynamic value available for 1 dose regimen. Reason for the change: Clarification.	Study Synopsis and Section 9.7
5	Sites and regions: The word "approximately" has been added to indicate that more than 1-2 subjects might be enrolled at any investigational site. Reason for change: Clarification needed.	Section 3.3
6	Rescreening of subjects: Wording has been clarified regarding when a subject may be rescreened. Previously, rescreening was allowed one additional time only for subjects whose failure to meet inclusion/ exclusion criteria was transient and temporary. The language has been revised to remove the restriction on the number of times that these subjects can be rescreened.	Section 7.2.1.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **18 Jun 2018**	**Global**

Item #	Description of Change	Section(s) Affected by Change
	These subjects can now be rescreened based on investigator discretion and sponsor approval. Previously rescreening, based on investigator discretion and sponsor approval, was also allowed for subjects who continued to meet all inclusion/exclusion criteria, but were unable participate in the study due to scheduling conflicts/timing. This language has been revised to specify that subjects who continued to meet all inclusion/exclusion criteria can also be rescreened if they were unable to participate in the study due to appropriate slot availability at an investigational site. Reason for change: Clarification was needed for investigational sites that subjects could be rescreened if needed based on investigator judgment because of (1) screen failure due to conditions that were transient and temporary; or (2) scheduling issues.	

See Appendices for protocol history, including all amendments

EMERGENCY CONTACT INFORMATION

In the event of an 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 Pharmacovigilance and Risk Management 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) by fax or e-mail using the details below. PPD is the CRO for this study.

PPD e-mail: (for US sites only): [redacted]

PPD e-mail (for EU sites only): [redacted] PPD Fax (for US sites only): [redacted]

PPD Fax (for EU sites only): [redacted]

For protocol- or safety-related issues, the investigator must contact the PPD Safety Hotline:

By telephone at:

PPD 24-hour safety Hotline (for US sites only): [redacted]

PPD 24-hour safety Hotline (for EU sites only): [redacted]

The PPD Medical Monitors for this study are:

[redacted], MD: Medical Monitor- North America

[redacted], MD: Medical Monitor- Europe

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 CRO (PPD):

[redacted] **or**

[redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire (and local or regional Regulatory authorities if required) within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational; including Shire provided devices used in the process of drug delivery) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

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

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

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ABBREVIATIONS

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3, 1,25-dihydroxycholecalciferol, calcitriol
25(OH)D	25-hydroxyvitamin D
$1(OH)D_3$	α-calcidol
AE	adverse event
β-HCG	beta-human chorionic gonadotropin
AUC	area under the curve
AUC_{0-24}	area under the curve between two time points (0-24 hours)
AUC_{0-t}	area under the curve between two time points (0-defined time)
AUC_{0-inf}	area under the curve between two time points (0-infinity)
BID	twice-daily
cAMP	cyclic adenosine monophosphate
CaSR	calcium sensing receptor
CL/F	clearance of drug from plasma
C_{max}	maximum concentration
CRA	clinical research associate
CRC	clinical research center
CRF	case report form
CRO	contract research organization
CV%	coefficient variation percent
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
FGF23	fibroblast growth factor 23
FSH	follicle stimulating hormone
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	health Insurance portability and accountability act
ICH	international conference on harmonization
IRB	institutional review board
IRT	interactive response technology

IV	intravenous
K_{el}	elimination constant
PD	pharmacodynamic
PK	pharmacokinetic
PR	a time interval on an ECG trace starting from the beginning of the P-wave to the beginning of the Q-wave
PTH	parathyroid hormone
QD	once-daily
QRS	a time interval on an ECG trace that represents the depolarization of the ventricles
QSPM	quantitative system pharmacology model
QT	a time interval on an ECG trace starting at the beginning of the QRS complex and finishing at the end of the T-wave (represents the time taken for the ventricles to depolarize & then repolarize)
QTc	the QT interval on an ECG trace that has been corrected
QTcB	the QT interval on an ECG trace that has been corrected using Bazett's formula
QTcF	the QT interval on an ECG trace that has been corrected using Fridericia's formula
RACE	PAR C10 008 protocol
rhPTH(1-84)	recombinant human parathyroid hormone (1-84 amino acids)
REPLACE	CL1-11-040 protocol
RR	a time interval on an ECG trace starting at the peak of one R wave to the peak of the next R wave
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SERMs	selective estrogen receptor modulators
$t_{½}$	time to elimination of half of the drug
T_{max}	time to maximum concentration
TE_{max}	time to maximum effect
UK	United Kingdom
US	United States
V_Z/F	volume of distribution during terminal phase

STUDY SYNOPSIS

Protocol number: SHP634-101	**Drug:** rhPTH(1-84)

Title of the study:

An Open-Label, Randomized, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Profiles of Once-Daily and Twice-Daily Dose Regimens of recombinant human Parathyroid Hormone (rhPTH[1-84]) Administered Subcutaneously to Subjects with Hypoparathyroidism

Number of subjects (total and for each treatment arm):
Approximately thirty-two (32) subjects are expected to complete the study. A sufficient number of subjects will be screened and enrolled to ensure that at least 8 subjects complete each treatment in their assigned cohort and provide sufficient data to meet study objectives. Enrollment in the study will be staggered as 4 sequential cohorts (of at least 8 subjects/cohort) and, within each cohort, subjects will be randomly assigned to 1 of 2 treatment sequences in that cohort. Each cohort must have 8 subjects completed before subjects can be enrolled into the next cohort. A safety review will be conducted after 8 subjects have completed in each of Cohorts 1, 2, and 3 at which time a decision will be made whether to proceed to the next cohort. Additionally, expansion of previous cohorts can occur, if needed to meet study objectives. Subjects may not participate in more than 1 cohort.
Replacement subjects may be enrolled in the event that any subject does not complete each treatment (which would include the crossover dose). Replacement subjects may be enrolled on a case-by-case basis (as a subject is discontinued), and, if a subject is replaced, that subject will follow the same 2-period treatment sequence as the subject who discontinued (regardless of when the subject discontinued). Cohorts may be expanded to include additional subjects to ensure that sufficient data for analysis are collected to complete the study objectives.

Investigator(s):

Coordinating Investigator:
[redacted]

Site(s) and Region(s):

This is a global study, with sites planned in North America and countries within Europe. Approximately 20-30 study sites are planned to participate in the study.

Study period (planned): May 2016-May 2019	**Clinical phase:** 1

Objectives:

Primary:

- To assess the pharmacokinetic profile and pharmacodynamic effects (control of serum calcium and urinary calcium excretion) of rhPTH(1-84) administered as SC doses of 25µg administered twice-daily, 50µg administered twice-daily, and 100µg administered once-daily, as well as the effect of supplemental oral calcium intake, in subjects with hypoparathyroidism.

Secondary:

- To assess the safety and tolerability of rhPTH(1-84) administration in subjects with hypoparathyroidism.

Rationale:

This study is being conducted to characterize the effect of twice-daily administration of rhPTH(1-84) on pharmacokinetics, pharmacodynamics, safety and tolerability over the course of 24-36 hours as compared with the currently approved once-daily dosing regimen, with and without oral calcium and without active vitamin D.

Investigational product, dose, and mode of administration:

- The investigational product (rhPTH[1-84]) is provided as a lyophilized powder for reconstitution and is administered as a subcutaneous (SC) injection in alternating thighs. The lyophilized powder and sterile water are provided in a dual chamber glass cartridge that requires mixing with a provided mixing apparatus and delivered with a provided injector pen. Doses of rhPTH(1-84) to be used in this study are 25µg, 50µg and 100µg as SC injections dependent upon cohort assignment and the order of treatment according to the randomization schedule.
- Dosing of rhPTH(1-84) will be administered in the presence or absence of supplemental oral calcium (dependent upon randomized treatment allocation) which will be provided by the subject or the study site. No rescue treatment will be provided by the sponsor.

Methodology:

For each cohort, this study will consist of the Administrative Screening Period (up to 120 days prior to first dose , if needed), the Clinical Screening Period (within 28 days prior to first dose), 2 treatment periods, the respective doses of which are to be separated by a washout (≥5 days but ≤30 days) between the administration of rhPTH(1-84) or the first administration for once daily or twice daily dosing, respectively, in each period, and a follow-up visit (30±2 days after the last dose of rhPTH[1-84]) is administered). The maximal total duration of study participation for a subject is 90 days (~3 months), if the maximum clinical screening, washout and follow- up visit durations are used. If the Administrative Screening Period is required, the maximum duration of study participation is 182 days.

The Administrative Screening Period (within 120 days of the first dose) is permitted (if needed) to allow for the time required to obtain medical records for subjects interested in participating at a site outside of their immediate care network. In this case, the subject must sign an informed consent in order to have their medical records released to a participating site. Clinical screening will occur within 28 days of the first dose. Subjects who meet the inclusion/exclusion criteria as specified in the protocol will report to the Clinical Research Center (CRC) for admission on Day -2 of Treatment Period 1 in order to confirm entry criteria assessed at that time and collect 24-hour serum calcium and urinary calcium profiles prior to treatment on Day 1. Subjects will be randomly assigned to 1 of 2 treatment sequences prior to administration of rhPTH(1-84) on Day 1 of Treatment Period 1, only after all entry criteria have been confirmed. The treatment sequence assignments within each cohort are as follows:

Treatment Scheme

Cohort		Treatment Period 1 (Day 1)		Treatment Period 2 (Day 1)
1 (n=8*)	n=4	**A** (25 µg BID, no calcium)	→	**B** (100 µg QD, no calcium)
	n=4	**B** (100 µg QD, no calcium)	→	**A** (25 µg BID, no calcium)
2 (n=8*)	n=4	**C** (50 µg BID, no calcium)	→	**B** (100 µg QD, no calcium)
	n=4	**B** (100 µg QD, no calcium)	→	**C** (50 µg BID, no calcium)
3 (n=8*)	n=4	**D** (25 µg BID, with calcium)	→	**E** (100 µg QD, with calcium)
	n=4	**E** (100 µg QD, with calcium)	→	**D** (25 µg BID, with calcium)
4 (n=8*)	n=4	**F** (50 µg BID with calcium)	→	**E** (100 µg QD with calcium)
	n=4	**E** (100 µg QD with calcium)	→	**F** (50 µg BID with calcium)

BID=twice-daily; QD=once-daily
Where:
Treatment A= 25 µg BID, no supplemental oral calcium
Treatment B= 100 µg QD, no supplemental oral calcium
Treatment C= 50 µg BID, no supplemental oral calcium
Treatment D= 25 µg BID, with supplemental oral calcium
Treatment E= 100 µg QD, with supplemental oral calcium
Treatment F= 50 µg BID, with supplemental oral calcium
With/without calcium refers to adjunctive therapy with dose; no active vitamin D
* at least 8 subjects per cohort

On Day 1 of Treatment Period 1:

- Subjects in Cohort 1 will receive rhPTH(1-84) as either a twice-daily regimen (12 hours apart) of two 25µg doses (without calcium; Treatment A) or a once-daily regimen of one 100µg dose (without calcium) in the morning (Treatment B).

- Subjects in Cohort 2 will receive rhPTH(1-84) as either as a twice-daily regimen (12 hours apart) of two 50µg doses (without calcium; Treatment C) or a once-daily regimen of one 100µg dose (without calcium; Treatment B).

- Subjects in Cohort 3 will receive rhPTH(1-84) either as a twice-daily regimen (12 hours apart) of two 25µg doses (with calcium; Treatment D) or a once-daily regimen of one 100µg dose (with calcium; Treatment E).

- Subjects in Cohort 4 will receive rhPTH(1-84) either as a twice-daily regimen (12 hours apart) of two 50µg doses (with calcium; Treatment F) or a once-daily regimen of one 100µg dose (with calcium; Treatment E).

On Day 1 of Treatment Period 2, subjects will receive the alternative treatment (according to the randomization schedule). For example, if a subject was randomized to cohort 1 and they received Treatment A in the first treatment period, they would receive Treatment B in the second treatment period. All rhPTH(1-84) will be administered via SC injection into alternating thighs at each administration.

Subjects enrolled in the study must require daily doses of calcium supplements of ≥1000mg prior to baseline (Day 1). Subjects enrolled in the study must also require minimum daily doses of active vitamin D ($1,25[OH]_2D_3$ [1,25-dihydroxycholecalciferol, (eg, calcitriol, α-calcidol [$1(OH)D_3$])]) of ≥0.25µg calcitriol or equivalent. Subjects will be expected to adhere to standard meals provided during their confinement in the CRC during each period (from check-in on Day -2 until discharge on Day 2). All subjects (in all treatment arms) will take their usual doses at the usual regimen of supplemental oral calcium and active vitamin D on Day -2 and Day-1. For all subjects in all cohorts, active vitamin D supplements must be withheld on Day 1 through the completion of all study procedures on Day 2. Subjects may then resume active vitamin D following final study procedures on Day 2 at the discretion or direction of the investigator.

During Treatments A, B, and C (Cohorts 1 and 2), supplemental oral calcium and active vitamin D will be withheld starting on Day 1 (predose), through the completion of all study procedures on Day 2 for both the once-daily and twice-daily dosing regimens. Upon completion of all study procedures on Day 2, subjects will then resume their usual supplemental oral calcium and active vitamin D at their next usual daily schedule.

During Treatments D, E, and F (Cohorts 3 and 4), subjects will withhold active vitamin D on Day 1 but take their usual dose(s) of supplemental oral calcium according to their usual regimen, regardless of the schedule/timing of IP administration(s). Critically, oral calcium supplementation should be identical on Day-1, Day 1 and Day 2 in Treatment Period 1 and Treatment Period 2. On Day 2, subjects will continue with their usual supplemental calcium regimen (ie, identical on Day -1 and Day 1) and, following the completion of all study procedures, subjects will then re-start their active vitamin D at their next usual daily schedule.

During the crossover washout period, subjects will be instructed to take their usual doses of supplemental oral calcium and active vitamin D.

For all dosing regimens, rhPTH(1-84) will be administered in the morning of Day 1 of each treatment period following an overnight fast of at least 8 hours. Subjects will continue to fast until approximately 2 hours after rhPTH(1-84) administration, at which time a standardized meal will be served. For subjects assigned to the twice-daily dose regimen, the evening dose of rhPTH(1-84) will be administered 12 hours after the morning dose, and 2 hours prior to the evening meal. A snack or light meal may be provided to the subjects prior to the evening dose, provided it is consumed ≥2 hours prior to rhPTH(1-84) dose administration.

Serial blood samples for pharmacokinetic analyses will be collected on Day 1 of each treatment period for the determination of PTH concentrations at predose and up to 24 hour postdose (for those randomized to the twice- daily regimen, serial PK samples will be collected up to 24 hours post the second dose). These blood samples will be collected according to the schedule of assessment tables. Serial blood and urine samples for pharmacodynamic analysis will be collected on Day-1 and on Day 1 predose and following the administration of rhPTH(1-84) according to the schedule of assessment tables.

Additional blood samples for safety purposes will be collected as specified on the schedule of assessment tables for assessment of anti-PTH antibodies.

Safety and tolerability will be closely monitored during the time the subject is confined to the CRC during the study. Adverse events will be recorded from the time the informed consent is signed, through completion of the study at follow-up.

A safety review will be conducted at the completion of 8 subjects in each of Cohorts 1, 2, and 3 (with or without the inclusion of the follow-up visit data), before any subject can be enrolled in the next cohort. The review will include all available safety data and will include, at a minimum, the Coordinating Investigator and the PPD and Shire Medical Monitors. Minutes of the review will be disseminated to all participating investigators.

One or more interim analyses may be performed in this study. If an analysis is deemed to be necessary, then a prospective statistical analysis plan will be developed prior to the analysis. The plan will include, at a minimum:

- rationale to perform the interim analysis; (2) parameters to be analyzed; and (3) the distribution list for the interim analysis results. Interim data may be used for (but not limited to) PK/PD modeling and/or regulatory submissions. The trial will not stop due to the results of any interim analysis.

Subjects who complete this study may have the opportunity to enroll into an open-label extension trial if an open-label extension study is available and approved by the site's IRB/EC

Inclusion and exclusion criteria:

Inclusion Criteria:

The subject must meet all of the criteria below in order to be eligible for the study:

- An understanding, ability and willingness to fully comply with study procedures and restrictions.
- Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
- Adult men or women aged ≥18 years, at the time of consent. The date of subject signature of the informed consent is defined as the beginning of the Screening Period. The Screening Period for this study may encompass both the Administrative Screening Period (if needed) and the Clinical Screening Period. For purposes of this inclusion criterion, age will only be assessed at the time the informed consent is first signed by the study subject.

- History of hypoparathyroidism for ≥12 months, post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia with concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range.
- Requirement for supplemental oral calcium treatment ≥1000 mg elemental calcium per day.
- Requirement for therapy with active forms of vitamin D at a minimum dose of ≥0.25µg per day (ie, ≥0.25µg calcitriol or equivalent per day).
- Serum calcium level within the laboratory normal reference range based on clinical chemistry lab results at the Clinical Screening Visit (based on central and/or local lab results) and Treatment Period 1, Day -2 (based on central and/or local lab results), or, if outside of normal range, considered not clinically significant by the investigator.
- Urinary calcium excretion ≥200mg (5mmol)/24h, based on a 24-hour collection, collected anytime during the Clinical Screening Period, but prior to check-in to the CRC at Treatment Period 1, Day -2 (based on central and/or local lab results).
- Serum magnesium level within the laboratory normal range at the Clinical Screening Visit or, if outside of normal range, considered not clinically significant by the investigator.
- Serum thyroid function tests within normal laboratory limits at the Clinical Screening Visit, or, if outside of normal range, considered as not clinically significant by the investigator.
- Serum 25(OH)D level between the lower limit of normal and 1.5-fold the laboratory upper limit of normal, or if outside of this range, considered not clinically significant by the investigator, at the Clinical Screening Visit.
- Serum creatinine <1.5mg/dL (<133µmol/L) AND estimated creatinine clearance >60mL/minute (>1.002mL/s) at the Clinical Screening Visit, and serum creatinine <1.5mg/dL (<133µmol/L) at Treatment Period 1, Day -2.
- Male or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.

Exclusion Criteria:

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

- Participation in any other investigational drug study in which the last dose of investigational drug occurred within 3 months prior to Day 1 of Treatment Period 1 (or within 5 half-lives, if the elimination half-life is greater than 18 days).
- Presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine (with exception of the condition under study), or neurologic system(s) or psychiatric disease as determined by the investigator.
- Known history of hypoparathyroidism resulting from an activation mutation in the calcium sensing receptor (CaSR) gene or impaired responsiveness to PTH (Pseudohypoparathyroidism).
- Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, including but not limited to, active hyperthyroidism; poorly controlled insulin-dependent diabetes mellitus or type 2 diabetes mellitus; severe and chronic cardiac, liver or renal disease; Cushing's syndrome; neuromuscular disease such as rheumatoid arthritis; myeloma; pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy, bone metastases or a history of skeletal malignancies; primary or secondary hyperparathyroidism; a history of parathyroid carcinoma; hypopituitarism, acromegaly; or multiple endocrine neoplasia types 1 and 2, as determined by the investigator.

- 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). Therefore, 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 are excluded.
- Subjects who have a known history of hypercalcemia during initiation of treatment with PTH, PTH analogues or fragments of PTH.
- Subjects who have a known history of hypocalcemia following abrupt withdrawal of treatment with PTH, PTH analogues or fragments of PTH.
- Subjects dependent on regular parenteral calcium infusions (eg, calcium gluconate) to maintain calcium homeostasis within 3 months prior to enrollment, as determined by the investigator.
- Use of the following medications prior to administration of investigational product within:
  - 14 days – thiazide diuretics
  - 30 days – loop diuretics, lithium, 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.
- Presence of any clinically significant results from laboratory tests, vital signs assessments, or ECGs, as judged by the investigator.
- Twelve-lead ECG values (average of triplicate readings) demonstrating QTc >450msec (males) or >470msec (females) at the Clinical Screening Visit and/or any time points up to and including predose of Day 1 (Period 1).
- Any medical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for this study.
- Positive test result for any of the following viral infections at the Clinical Screening Visit:
  - Hepatitis B surface antigen
  - Hepatitis C
- Known significant bleeding diathesis that could preclude multiple venipunctures as determined by the investigator.
- Subjects who have donated a total of 100 mL to 499 mL of whole blood within 30 days prior to dosing, or subjects who have donated a total of more than 499 mL of whole blood within 56 days prior to dosing.
- A positive screen for drugs of abuse at the Clinical Screening Visit, and/or a positive screen for drugs of abuse and alcohol at check-in to the CRC at Treatment Period 1. Subjects taking prescription medications that might be detected during the urine screen for drugs of abuse (listed in Section 7.3.2.7) may be enrolled per the investigator's medical judgment.

- History of a clinically significant illness during the 4 weeks prior to dosing (as determined by the investigator).
- History of any clinically significant surgery or procedure within 8 weeks of first dose, as determined by the investigator.
- History of an allergic response(s) to PTH or PTH analogs, or other clinically significant allergies, as determined by the investigator.

Maximum duration of subject involvement in the study:

The maximal total duration of study participation for a subject is 90 days (~3 months), if the maximum clinical screening, washout and follow-up visit durations are used. If the Administrative Screening Period is required, the maximum duration of study participation is 182 days.

- The Administrative Screening Period (if needed) may be permitted (up to 120 days prior to first dose) to allow for the time required to authorize release and obtain medical records for subjects outside of their immediate care network. The subject must sign an informed consent at the onset of the Administrative Screening Period in order to authorize and have their medical records released to a participating site.
- The Clinical Screening Period is a maximum of 28 days between the first clinical visit to the CRC and Day 1 of the first treatment period. Note that this period includes the initial overnight period for the first treatment period (Day -2 to Day -1 inclusive).
- There are 2 treatment periods; investigational product is administered on Day 1 of each period. The 2 treatment periods are separated by a minimum of a 120 hour (5 day) washout period and a maximum of a 30 day washout period between the administration of the dose (QD), or first dose (BID) in each period.
- The total maximum duration of active study participation is approximately 90 days which would include the full 28 day Clinical Screening Period, Treatment Period 1, a maximum washout of 30 days between treatments, Treatment Period 2 and follow up of 30±2 days following the last dose of investigational product.
- The total overnight stays for the study (independent of the amount of time used for screening or washout periods) comprises 3 nights per treatment period. Therefore, a total of 6 overnight stays are required during treatment.
- The follow up for the study is defined as 30±2 days after the last dose of investigational product.

Endpoints and Statistical Analysis:

Analysis populations

Four analysis populations are defined for this study: the all-enrolled, safety, pharmacokinetic, and pharmacodynamic populations:

- The all-enrolled population consists of all subjects who sign the informed consent form and are randomized in the study.
- The safety population includes enrolled subjects who have received at least 1 dose of rhPTH(1-84). All analyses of safety data will be based on this population.
- The pharmacokinetic population consists of all-enrolled subjects who, receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable postdose pharmacokinetic concentration value available for 1 dose regimen.
- The pharmacodynamic population consists of all-enrolled subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable postdose pharmacodynamic value available for 1 dose regimen.

Pharmacokinetic Endpoints:

PTH concentrations will be used to calculate the following pharmacokinetic parameters using a non- compartmental approach: maximum observed concentration maximum (C_{max}), time of maximum concentration (T_{max}), area under the concentration curve (from time zero to the last measurable concentration and from time zero to infinity (AUC_{0-t} and AUC_{0-inf}), area under the concentration curve from time zero to 24 hours post the first dose ([AUC_{0-24h}] for those on the QD regimen, and up to 24 hours post the second dose for those on the BID regimen), elimination rate constant (K_{el}), apparent clearance (CL/F), apparent volume of distribution (V_Z/F) and elimination half-life ($t_{1/2}$).

All assessment dates will be related to the first day of rhPTH(1-84) administration. This first day of investigational product administration is referred to as Day 1. Day-1 is the day that is preceding Day 1, and a Day 0 will not be defined.

Pharmacokinetic analyses based on raw and baseline-adjusted PTH concentrations will be performed. The baseline is defined as the predose endogenous PTH level on Day 1, and baseline-adjusted PTH concentrations are to be calculated by subtracting baseline PTH from the raw PTH concentrations.

Pharmacodynamic Endpoints:

Pharmacodynamic parameters will be computed from the individual concentrations of serum calcium (uncorrected and corrected for serum albumin levels), phosphate, albumin, creatinine, magnesium, $1,25(OH)_2D_3$, and FGF23 using a non-compartmental approach. The calcium-phosphate product will be computed. Pharmacodynamic parameters will be estimated based with and without baseline adjustments.

The following parameters will be calculated using the serum concentration data:

- AUC_{0-24h}: the area under the concentration versus time curve, from time 0 to 24 hours
- TE_{max}: time to maximum effect
- E_{max}: maximum effect

The parameters representing urinary excretion of each analysis will be calculated, if data allow:

- Total amount of sodium, calcium, magnesium, citrate, phosphate, cyclic AMP (cAMP), and creatinine in each sample
- Total amount of sodium, calcium, magnesium, citrate, cAMP, and phosphate excreted in each sample relative to the total amount of creatinine excreted
- Renal clearance of sodium, calcium, magnesium, citrate, creatinine, and phosphate (mL/min)
- Fractional excretion of sodium, calcium, citrate, magnesium, and phosphate

Safety Endpoints:

Safety will be assessed by the following evaluations:

- AEs including episodes of hypocalcemia, hypercalcemia, and hypercalciuria
- Laboratory test results (hematology, serum chemistries, creatinine clearance, urinary chemistries (24-hr urinary calcium, sodium, citrate, phosphate, cAMP, magnesium, and creatinine excretion), immunology (anti-PTH antibody), and urinalysis

- ECG
- Physical examinations (including vital signs).

Sample Size Justification:
At least 8 subjects with sufficient data to meet the study objectives will be required to complete each treatment in each cohort. The sample size was determined based on a similar, prior pharmacokinetic/pharmacodynamic study. The number of subjects in this study is not based on statistical power considerations because the statistical analyses are primarily descriptive, and no hypothesis testing is specified in the study.

Statistical Methodology for Safety Endpoint(s):
Safety data including clinical laboratory tests, anti-PTH antibodies, concomitant medications, AEs, ECG, and vital signs will be summarized by treatment and time of collection. Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) 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.

Statistical Methodology for Pharmacokinetic Endpoint(s):
Individual concentrations and pharmacokinetic parameters of PTH will be listed and summarized with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by treatment. Figures of individual and mean (+/-SD) concentration-time profiles of raw and baseline-adjustment plasma PTH will be generated on both linear and log scales.

Statistical Methodology for Pharmacodynamic Endpoint(s):
Individual concentrations and pharmacodynamic parameters of serum total calcium and albumin-corrected calcium, phosphate, albumin, creatinine, magnesium $1,25(OH)_2D_3$, and FGF23 will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%).

The urinary excretion of calcium, sodium, citrate, magnesium, cAMP, and phosphate will also be expressed relative to that of creatinine and will be summarized with descriptive statistics.

Pharmacokinetic-pharmacodynamic correlation between PTH concentrations and the above indicators of PTH bioactivity will be assessed using exploratory figures. If required, pharmacokinetic/ pharmacodynamic models may be developed to describe the effect of PTH concentrations and biochemical indicators of PTH activity.

STUDY SCHEDULE(S)

Table 1 Schedule of Assessments

	Screening		Predose Assessment		Treatment Period 1		Washout	Predose Assessment		Treatment Period 2		Follow-up
Study Visit	**Admin.**	**Clinical**	**TP1, D-2**	**TP1, D-1**	**TP1, D1**	**TP1, D2**	**W [a,b]**	**TP2, D-2**	**TP2, D-1**	**TP2, D1**	**TP2, D2**	**FU**
Study Relative Day/ Study Procedures	**-120 to -03**	**–28 to -03**	**-2**	**-1**	**1**	**2**		**-2**	**-1**	**1**	**2**	**Follow-up [c]**
Informed consent	X [d]	X										
Medical record release	X [d]	X [d]										
Inclusion/exclusion criteria		X	X [e]	X [e]								
Demography and medical/medication history		X	X [e]									
Physical exam [f]		X		X [e]							X [g]	
Randomization					X [h]							
Vital signs (blood pressure, pulse) [f,i,j]		X		X	X	X			X	X	X	X
Height and weight [f]		X	X [k]								X [k,g]	
Electrocardiogram (12-lead) [f,j,l]		X		X	X	X			X	X	X	X
Biochemistry, hematology, and urinalysis [f]		X [m]	X			X [g]		X			X [g]	X
Serum 25(OH)D		X										
Anti-PTH antibody sampling [f]					X							X
HIV, HBsAg, and HCV screen		X										
Pregnancy test [f,n]		X	X					X			X [g]	X
FSH levels [o]		X										
Urine drug screening		X	X					X				

Table 1 Schedule of Assessments

	Screening		Predose Assessment		Treatment Period 1		Washout	Predose Assessment		Treatment Period 2		Follow-up
Study Visit	**Admin.**	**Clinical**	**TP1, D-2**	**TP1, D-1**	**TP1, D1**	**TP1, D2**	**W [a,b]**	**TP2, D-2**	**TP2, D-1**	**TP2, D1**	**TP2, D2**	**FU**
Study Relative Day/ Study Procedures	**-120 to -03**	**–28 to -03**	**-2**	**-1**	**1**	**2**		**-2**	**-1**	**1**	**2**	**Follow-up [c]**
Alcohol breath test screening			X					X				
Urine collection container provided to subject		X [p]										
IP administration					X					X		
PK blood sampling [j]					X	X				X	X	
PD blood sampling [j]				X	X	X			X	X	X	
PD urine (continuous collection) [j]				X	X	X			X	X	X	
Check-in to CRC			X					X				
24-hour urine collection obtained		X [q]										
In-house confinement				X	X	X			X	X	X	
Discharge from CRC (after last assessment)						X					X	
Adverse events/serious adverse events [f]	X [r]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication [f]		X	X	X	X	X	X	X	X	X	X	X
Administration of usual supplemental oral calcium and active vitamin D		X	X	X			X	X	X			X

Table 1 Schedule of Assessments

	Screening		Predose Assessment		Treatment Period 1		Washout	Predose Assessment		Treatment Period 2		Follow-up
Study Visit	**Admin.**	**Clinical**	**TP1, D-2**	**TP1, D-1**	**TP1, D1**	**TP1, D2**	**W [a,b]**	**TP2, D-2**	**TP2, D-1**	**TP2, D1**	**TP2, D2**	**FU**
Study Relative Day/ Study Procedures	**-120 to -03**	**–28 to -03**	**-2**	**-1**	**1**	**2**		**-2**	**-1**	**1**	**2**	**Follow-up [c]**
Withhold supplemental oral calcium and active vitamin D [s]					X [t]					X [t]		
Administration of supplemental oral calcium only (no active vitamin D) [u]					X [v]					X [v]		

HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] Washout period should be ≥5 days (ie, 120 hours) and ≤30 days between first dose of each treatment period (whether dosing regimen is BID or QD).

[b] The investigator may elect to keep the subject in-clinic for the duration of the study, if the washout period is short (eg, 120-172 hours) and/or there are any safety concerns, and provided that there is a minimum washout of ≥120 hours between administration of IP in each treatment period.

[c] A follow-up visit must be completed 30±2 days after the last dose of IP.

[d] If applicable.

[e] Review and update medical history and re-confirm eligibility.

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

[g] The safety blood and urine assessments (Period 1 and Period 2), pregnancy test (for all females, Period 2), physical exam (Period 2), and weight (Period 2) should be collected after the scheduled serial PK and PD assessments have been completed on this study day, and prior to discharging the subject from the Clinical Research Center.

[h] Randomization will occur prior to administration of IP at Treatment Period 1, Day 1 only after all eligibility criteria have been confirmed/re-confirmed.

[i] Vital sign measurements should be collected in the supine position at each time point.

[j] See Table 2, Table 3, and Table 4 for detailed collection time points.

[k] Weight measurement only.

[l] ECGs will be performed in triplicate measurement at each time point.

[m] Includes thyroid function tests, and estimated creatinine clearance (Cockcroft–Gault formula) at Clinical screening visit only.

[n] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points.

[o] Females only, to confirm menopausal status.

[p] At the end of the Clinical Screening Visit, subjects will be provided with a urine collection container to take home. Subjects will be given instructions to provide a 24-hour urine collection starting anytime during the Clinical Screening Period, but prior to their next admission to the CRC (eg, Day -3 and ending 24 hours later on Day -2). The sample must be kept in cold conditions (~4°C) and returned to the CRC upon collection, as per the instructions provided by the site.

[q] A 24-hour urine sample should be collected and provided to the site anytime during the Clinical Screening Period, but provision of the sample should be no later than check-in to the CRC at Period 1, Day -2.

[r] Adverse events to be collected from time of informed consent. This includes the period of an administrative screen, if utilized.

[s] Applies to subjects assigned to Treatment A, Treatment B and Treatment C only.

Table 1 Schedule of Assessments

	Screening		Predose Assessment		Treatment Period 1		Washout	Predose Assessment		Treatment Period 2		Follow-up
Study Visit	**Admin.**	**Clinical**	**TP1, D-2**	**TP1, D-1**	**TP1, D1**	**TP1, D2**	**W [a,b]**	**TP2, D-2**	**TP2, D-1**	**TP2, D1**	**TP2, D2**	**FU**
Study Relative Day/ Study Procedures	**-120 to -03**	**–28 to -03**	**-2**	**-1**	**1**	**2**		**-2**	**-1**	**1**	**2**	**Follow-up [c]**

[t] Supplemental oral calcium and active vitamin D will be withheld starting on day of dosing, and through the end of Day 1. Subjects will then resume their usual supplemental oral calcium and active vitamin D at their next usual daily schedule on Day 2.
[u] Applies to subjects assigned to Treatment D, Treatment E and Treatment F only.
[v] Supplemental oral calcium should be taken according to the subject's usual daily regimen (but active vitamin D must be withheld).

Table 2: Detailed Schedule of Assessments: Day -1 (Prior to Treatment Periods 1 and 2)

Study Day	**-1**																	**1**
Time point (relative to scheduled dosing time on Day 1 [QD, 1st dose BID]) (hour)	**Predose**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**13**	**13.5**	**14**	**15**	**16**	**18**	**20**	**22**	**24**
Vital signs (blood pressure, pulse) [a, b]	X [c]	X		X		X	X	X	X	X	X		X		X	X	X	X	X [d]
ECG (12-lead) [a, e]	X [c]	X		X		X	X	X	X	X	X		X		X	X	X	X	X [d]
IP administration																			X [d]
PK blood sampling																			X [d]
PD blood sampling [f]	X [c]		X			X	X	X	X	X		X			X				X [d]
PD urine sampling [g, h]	X [i]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X [d]

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.

[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.

[c] These assessments should be performed within 30 minutes prior to the relative time of scheduled administration of IP on Day 1.

[d] Refer to Detailed Schedule of Assessments (Table 3 and Table 4) for collection time points (note: this time point is the same as the predose collection time point on Day 1.

[e] ECGs will be performed in triplicate measurement at each time point.

[f] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.

[g] 24- hour urine collection for PD analysis will be collected according to the following collection intervals (relative to the Day 1 morning dose): 0-3 hours, 3-6 hours, 6-9 hours, 9-12 hours, 12-15 hours, 15-18 hours, 18-24 hours. 'X' denotes the start and stop of the entire urine collection period and '→' denotes continuous collection.

[h] PD urine collection assessments will include: calcium, sodium, citrate, phosphate, magnesium, cAMP and creatinine.

[i] The predose time point for PD urine sampling is used to signify the action that the subject needs to empty his/her bladder immediately before the start of the 0-3 urine collection based on the predicted dosing time of Day 1. It is not a separate predose urine collection.

Table 3: Detailed Schedule of Assessments: Treatment Periods 1 and 2, Day 1/Day 2 (QD Regimen)

Study Day	**1**																				**2**
Time point (relative to dosing time on Day 1) (h=hour/m=minute)	**Pre-dose**	**0**	**10m**	**20m**	**30m**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**13.5**	**14**	**16**	**18**	**20**	**22**	**24**
Vital signs (blood pressure, pulse) [a,b]	X [c]					X		X	X	X	X	X	X	X		X	X	X	X	X	X [j]
ECG (12-lead) [a, d]	X [c]					X		X	X	X	X	X	X	X		X	X	X	X	X	X [j]
Randomization	X [e]																				
IP administration		X																			
PK blood sampling	X [c]		X	X	X	X	X	X	X		X		X				X				X
PD blood sampling [f]	X [c]						X		X	X	X	X	X		X		X		X		X
Anti-PTH antibody sampling [g]	X [c]																				
PD urine sampling [h, i]	X [k]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.

[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.

[c] These assessments should be performed within 30 minutes prior to the scheduled time for IP dose administration on Day 1.

[d] ECGs will be performed in triplicate measurement at each time point.

[e] Randomization will occur prior to administration of IP of Treatment Period 1, Day 1 only (and only after all eligibility criteria have been confirmed/re-confirmed).

[f] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.

[g] The anti-PTH antibody sample should only be collected at Treatment Period 1, predose (regardless of BID or QD regimen), and the sample collected within 30 minutes prior to dosing.

[h] 24- hour urine collection for PD analysis will be collected according to the following collection intervals: 0-3 hours, 3-6 hours, 6-9 hours, 9-12 hours, 12-15 hours, 15- 18 hours, 18-24 hours. 'X' denotes the start and stop of the entire urine collection period and '→' denotes continuous collection.

[i] PD urine collection assessments will include: calcium, sodium, citrate, phosphate, magnesium, cAMP, and creatinine.

[j] The last scheduled serial time point (ie, 24 hours) will also serve as the discharge procedure for these assessments on Day 2.

[k] The urine sampling under predose in this table is to signify the stop of Day -1, 18-24 hour PD urine collection period, and the start of the Day 1, 0-3 hour PD urine collection period. It is not a separate predose collection.

Table 4: Detailed Schedule of Assessments: Treatment Periods 1 and 2, Day 1/Day 2 (BID Regimen)

Study Day	**1**																							**2**			
Time point (relative to first dosing time on Day 1) (h=hour/m=minute)	**Predose**	**0**	**10m**	**20m**	**30m**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**Pre-dose (12hr)**	**12**	**12h 10m**	**12h 20m**	**12.5**	**13**	**13.5**	**14**	**16**	**18**	**20**	**22**	**24**	**28**	**32**	**36**
Vital signs (blood pressure, pulse) [a, b]	X [c]					X		X	X	X	X	X	X [c]					X		X	X	X	X	X	X	X	X	X [k]
ECG (12-lead) [a,d]	X [c]					X		X	X	X	X	X	X [c]					X		X	X	X	X	X	X	X	X	X [k]
Randomization	X [e]																											
IP administration		X												X														
PK blood sampling	X [c]		X	X	X	X	X	X	X		X		X [f]		X	X	X	X	X	X	X		X		X	X		X
PD blood sampling [g]	X [c]						X		X	X	X	X	X [f]						X		X	X	X	X	X	X		X
Anti-PTH antibody sampling [h]	X [c]																											
PD urine sampling [i, j]	X [l]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Table 4: Detailed Schedule of Assessments: Treatment Periods 1 and 2, Day 1/Day 2 (BID Regimen)

Study Day	**1**																							**2**			
Time point (relative to first dosing time on Day 1) (h=hour/m=minute)	**Predose**	**0**	**10m**	**20m**	**30m**	**1**	**1.5**	**2**	**4**	**6**	**8**	**10**	**Pre-dose (12hr)**	**12**	**12h 10m**	**12h 20m**	**12.5**	**13**	**13.5**	**14**	**16**	**18**	**20**	**22**	**24**	**28**	**32**	**36**

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.

[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.

[c] These assessments should be performed within 30 minutes prior to the scheduled time for IP dose administration on Day 1.

[d] ECGs will be performed in triplicate measurement at each timepoint.

[e] Randomization will occur prior to administration of IP of Treatment Period 1, Day 1 only (and only after all eligibility criteria have been confirmed/re-confirmed).

[f] Predose PK/PD collection for the second dose of the BID regimen should be completed within 15 minutes prior to the dose.

[g] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.

[h] The anti-PTH antibody sample should only be collected at Treatment Period 1, predose (regardless of BID or QD regimen), and the sample collected within 30 minutes prior to dosing.

[i] 36- hour urine collection for PD analysis will be collected according to the following collection intervals: 0-3 hours, 3-6 hours, 6-9 hours, 9-12 hours, 12-15 hours, 15-18 hours, 18-24 hours, 24-30 hours, 30-36 hours. 'X' denotes the start and stop of the entire urine collection period and '→' denotes continuous collection.

[j] PD urine collection assessments will include: calcium, sodium, citrate, phosphate, magnesium, cAMP, and creatinine.

[k] The last scheduled serial time point (ie, 36 hour time point) will also serve as the discharge procedure for these assessments on Day 2.

[l] The urine sampling under predose in this table is to signify the stop of Day -1, 18-24 hour PD urine collection period, and the start of the Day 1, 0-3 hour PD urine collection period. It is not a separate predose collection.

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 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 pharmacokinetics, pharmacodynamics 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 50 μg to 100 μg 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 some subjects receiving treatment for more than 3 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 pharmacokinetic/pharmacodynamic 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 100 μg 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 total 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 hypoparathryoidism program indicated that rhPTH(1-84) administered in the dose range of 25 to 100 μg 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 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; however, patients should be advised 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, pharmacokinetics, 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, use rhPTH(1-84) only in subjects 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. Avoid use of rhPTH(1-84) 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 again on admission to Treatment Period 2, 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 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.

The present study is being conducted to characterize the effects of twice-daily administration of rhPTH(1-84) on pharmacokinetics, pharmacodynamics, safety and tolerability over the course of 24 hours as compared with the current once-daily dosing regimen.

2.2 Study Objectives

2.2.1 Primary Objectives

To assess the pharmacokinetic profile and pharmacodynamic effects (control of serum calcium and urinary calcium excretion) of rhPTH(1-84) administered as SC doses of 25µg administered twice-daily, 50µg administered twice-daily, and 100µg administered once-daily, as well as the effect of supplemental oral calcium intake, in subjects with hypoparathyroidism.

2.3 Secondary Objectives

To assess the safety and tolerability of rhPTH(1-84) administration in subjects with hypoparathyroidism.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

The present study is an open-label, randomized, multi-center, 4 cohort, 2-period crossover study comparing QD and BID dosing regimens of rhPTH(1-84) and the effect of adjunctive calcium (with no active vitamin D) in male and female adult subjects with a history of hypoparathyroidism.

A sufficient number of subjects will be screened and enrolled to ensure that at least 8 subjects complete each treatment and provide sufficient data to meet the study objectives in their assigned cohort. Enrollment in the study will be staggered as 4 sequential cohorts (of at least 8 subjects per cohort, including 1 treatment crossover within each cohort), such that at least 8 subjects in 1 cohort must complete the study before subjects can be enrolled in the next cohort. A safety review will be conducted after 8 subjects have completed in each of Cohorts 1, 2 and 3 at which time a decision will be made whether to proceed to the next cohort. Cohorts may be expanded to include additional subjects to ensure that sufficient data for analysis are collected to complete the study objectives. Subjects may not participate in more than 1 cohort. Within each cohort, subjects will be randomly assigned to 1 of 2 treatment sequences prior to first dosing on Day 1 of Treatment Period 1. The treatment sequence assignments within each cohort are as follows:

Table 5: Treatment Scheme

Cohort		Treatment Period 1 (Day 1)		Treatment Period 2 (Day 1)
1 (n=8*)	n=4	**A** (25 µg BID, no calcium)	→	**B** (100 µg QD, no calcium)
	n=4	**B** (100 µg QD, no calcium)	→	**A** (25 µg BID, no calcium)
2 (n=8*)	n=4	**C** (50 µg BID, no calcium)	→	**B** (100 µg QD, no calcium)
	n=4	**B** (100 µg QD, no calcium)	→	**C** (50 µg BID, no calcium)
3 (n=8*)	n=4	**D** (25 µg BID, with calcium)	→	**E** (100 µg QD, with calcium)
	n=4	**E** (100 µg QD, with calcium)	→	**D** (25 µg BID, with calcium)
4 (n=8*)	n=4	**F** (50 µg BID with calcium)	→	**E** (100 µg QD with calcium)
	n=4	**E** (100 µg QD with calcium)	→	**F** (50 µg BID with calcium)

BID=twice-daily; QD=once-daily
Where:
Treatment A= 25 µg BID, no supplemental oral calcium Treatment B= 100 µg QD, no supplemental oral calcium Treatment C= 50 µg BID, no supplemental oral calcium Treatment D= 25 µg BID, with supplemental oral calcium Treatment E= 100 µg QD, with supplemental oral calcium Treatment F= 50 µg BID, with supplemental oral calcium
With/without calcium refers to adjunctive therapy with dose; no active vitamin D
*at least 8 subjects per cohort

Replacement subjects may be enrolled in the event that any subjects do not complete each treatment (which would include the crossover dose). Replacement subjects may be enrolled on a case-by-case basis (as a subject is discontinued), and, if a subject is replaced, that subject will follow the same 2-period treatment sequence as the subject who discontinued (regardless of when the subject discontinued).

This study will consist of the Administrative Screening Period (within 120 days of Day 1 of Period 1) that includes the time required to authorize release and obtain medical records for subjects participating at sites outside their immediate care network (if applicable); the Clinical Screening Period; 2 treatment periods which are to be separated by a washout (≥5 days but ≤30 days) between the dose or first dose of investigational product in each period (for QD or BID dosing, respectively); and a follow-up visit (30±2 days after the last dose of investigational product is administered). The maximal total duration of study participation for a subject is 90 days (~3 months), if the maximum clinical screening, washout and follow-up visit durations are used. If the Administrative Screening Period is required, the maximum duration of study participation is 182 days.

Clinical screening will occur within 28 days of the first dose. Subjects who meet the inclusion/exclusion criteria as specified in the protocol will report to the Clinical Research Center (CRC) for admission on Day -2 of Treatment Period 1, in order to confirm entry criteria assessed at that time, and collect 24-hour serum calcium and urinary calcium profiles prior to treatment, starting on Day 1. Subjects will be randomized prior to administration of investigational product on Day 1 of Treatment Period 1, only after all entry criteria have been confirmed.

On Day 1 of Treatment Period 1:

- Subjects in Cohort 1 will receive rhPTH(1-84) as either a twice-daily regimen (12 hours apart) of two 25µg doses (without calcium) or a once-daily regimen of one 100µg dose (without calcium) in the morning
- Subjects in Cohort 2 will receive rhPTH(1-84) as either as a twice-daily regimen (12 hours apart) of two 50µg doses (without calcium) or a once-daily regimen of one 100µg dose (without calcium)
- Subjects in Cohort 3 will receive rhPTH(1-84) either as a twice-daily regimen (12 hours apart) of two 25µg doses (with calcium) or a once-daily regimen of one 100µg dose (with calcium).
- Subjects in Cohort 4 will receive rhPTH(1-84) either as a twice-daily regimen (12 hours apart) of two 50µg doses (with calcium) or a once-daily regimen of one 100µg dose (with calcium).

On Day 1 of Treatment Period 2, subjects will receive the alternative treatment (according to the randomization schedule), following a washout period (≥5 days [ie, 120 hours] and ≤30 days) between administration of the dose or first dose ([for once-daily or twice-daily dosing, respectively] of each treatment period). All investigational product will be administered via SC injection into alternating thighs at each administration.

At each treatment period, subjects will report to the CRC on Day-2, remain in the CRC through Day 2, and be discharged following the last scheduled assessment on Day 2 (investigators may elect, at their discretion, to keep the subject in-clinic after Treatment Period 1 for the duration of the washout period, eg, if the washout period is short [eg, 120-172 hours] or there are any safety concerns).

For once-daily treatments (Treatments B and E), subjects will receive a single subcutaneous dose of rhPTH(1-84) in the morning on Day 1. For twice-daily treatments (Treatments A, C, D, and F), subjects will receive a subcutaneous dose of rhPTH(1-84) in the morning followed by the second dose 12 hours later on Day 1 (in the opposite thigh). If randomized to rhPTH(1-84) with calcium, subjects will take their usual supplemental oral calcium on Day 1 per their usual schedule. Prior to discharge from the CRC at each treatment period, subjects will be given specific instructions for when to take their supplemental oral calcium and active vitamin D supplements during the day(s) when subjects are not in the CRC.

Subjects enrolled in the study must require daily doses of calcium supplements of ≥ 1000 mg prior to baseline (Day 1). Subjects enrolled in the study must also require minimum daily doses of active vitamin D of ≥0.25µg (ie, 0.25µg calcitriol or equivalent). Subjects will be expected to adhere to standard meals provided during their confinement in the CRC during each period (from check-in on Day -2 until discharge on Day 2). All subjects (in all treatments) will take their usual doses at the usual regimen of supplemental oral calcium and active vitamin D on Day -2 and Day -1. For all subjects in all cohorts, active vitamin D supplements must be withheld on Day 1 through completion of all study procedures on Day 2. Subjects may resume active vitamin D following final procedures on Day 2 at the discretion or direction of the investigator.

During Treatments A, B, and C (Cohorts 1 and 2), supplemental oral calcium and active vitamin D will be withheld starting on Day 1 (predose), through the completion of all study procedures on Day 2 for both the once-daily and twice-daily dosing regimens. Upon completion of all study procedures on Day 2, subjects will then resume their usual supplemental oral calcium and active vitamin D at their next usual daily schedule.

During Treatments D, E, and F (Cohorts 3 and 4), subjects will withhold active vitamin D on Day 1 but take their usual dose(s) of supplemental oral calcium according to their usual regimen, regardless of the schedule/timing of investigational product administration(s).

Critically, oral calcium supplementation should be identical on Day -1, Day 1 and Day 2 in Treatment Period 1 and Treatment Period 2. On Day 2, subjects will continue with their usual supplemental calcium regimen (ie, identical on Day -1 and Day 1), and, following the completion of all study procedures, subjects will then re-start their active vitamin D at their next usual daily schedule.

During the washout period, subjects will be instructed to take their usual doses of supplemental oral calcium and active vitamin D.

Any subject who experiences symptoms of hypocalcemia or hypercalcemia may be treated at the investigator's discretion, as per local standards. This may include, but is not limited to, intravenous (IV) calcium and/or fluids.

For all dosing regimens, rhPTH(1-84) will be administered in the morning of Day 1 of each treatment period following an overnight fast of at least 8 hours. Subjects will continue to fast until approximately 2 hours after rhPTH(1-84) administration, at which time a standardized meal will be served (see Section 4.3 item 5). For subjects assigned to the twice-daily dose regimen, the evening dose of investigational product will be administered 12 hours after the morning dose, and 2 hours prior to the evening meal. A snack or light meal may be provided to the subjects prior to the evening dose, provided it is consumed ≥2 hours prior to investigational product dose administration. It is suggested that lunch be divided into 2 portions, the first portion consumed at lunch, and the second portion consumed as the snack or light meal.

Serial blood samples for pharmacokinetic analysis will be collected on Day 1 of each treatment period for the determination of PTH concentrations at predose and up to 24 hours post morning dose (up to 24 hours post second dose for the twice-daily regimen). These blood samples will be collected according to the Schedule of Assessments (Table 3 and Table 4). Serial blood and urine samples for pharmacodynamic analysis will be collected on Day -1, predose and on Day 1 following the administration of rhPTH(1-84) for the determination of concentrations of serum total calcium (uncorrected and corrected for serum albumin levels), phosphate, magnesium, creatinine, albumin, $1,25(OH)_2D_3$, and fibroblast growth factor 23 (FGF23), and urinary excretion of calcium, sodium, citrate, phosphate, cAMP, magnesium, and creatinine and the calcium-phosphate product will be determined. In addition, serum samples will be collected and analyzed for anti-PTH antibodies (for safety purposes) at the time points specified in Table 1, Table 3, and Table 4. Samples will be analyzed using a validated methodology.

Safety and tolerability will be monitored closely during the time the subject is in-clinic during the study. AEs will be recorded from the time the informed consent is signed, through completion of the study at follow-up.

A safety review will be conducted at the completion of 8 subjects in each of Cohorts 1, 2 and 3 (with or without the inclusion of the follow-up visit data), before any subject can be enrolled in the next cohort. The review will include all available safety data and will include, at a minimum, the Coordinating Investigator and the PPD and Shire Medical Monitors. Minutes of the review will be disseminated to all participating investigators. Expansion of previous cohorts can occur concurrently if further information is required. Cohorts may be expanded to include additional subjects to ensure that sufficient data for analysis are collected to complete the study objectives.

One or more interim analyses may be performed in this study. If the analysis is deemed to be necessary, then a prospective statistical analysis plan will be developed prior to the analysis. The plan will include, at a minimum: (1) rationale to perform the interim analysis; (2) parameters to be analyzed; and (3) the distribution list for the interim analysis results. Interim data may be used for (but not limited to) PK/PD modeling and/or regulatory submissions. The trial will not stop due to the results of any interim analysis.

Subjects who complete this study may have the opportunity to enroll into an open-label extension trial if an open-label extension study is available and approved by the site's IRB/EC.

Figure 1: Study Design Flow Chart

Figure 1a: Cohort 1

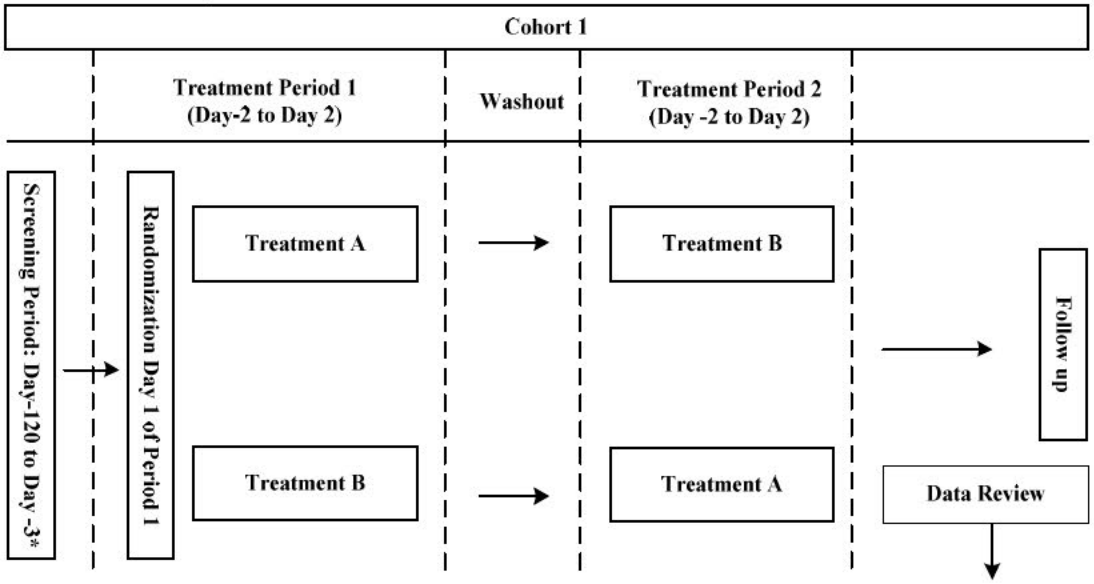
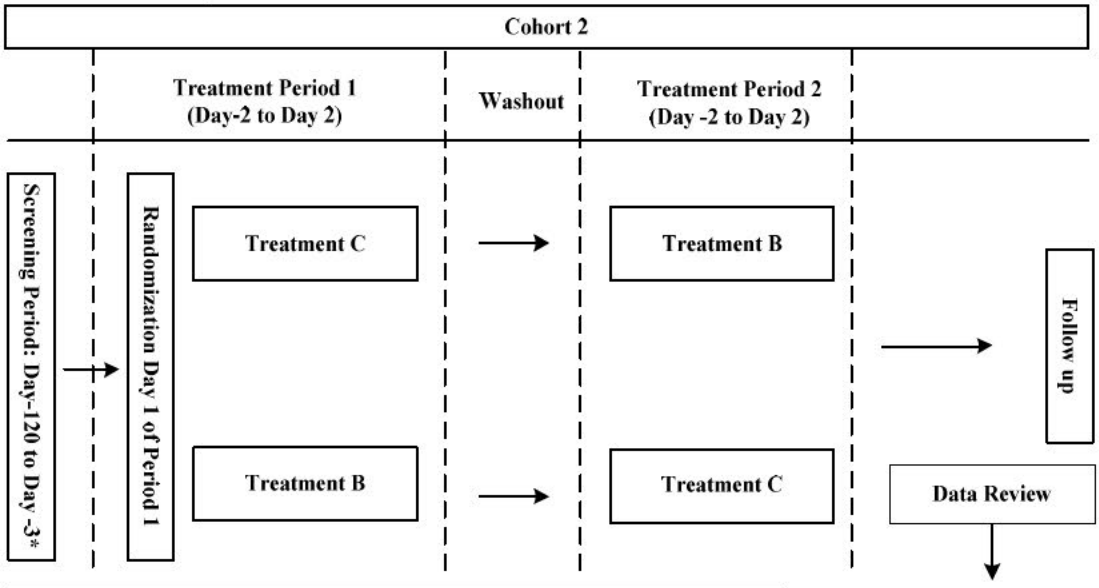


Figure 1b: Cohort 2



Treatment A: rhPTH (1-84): 25µg BID, no oral calcium/no active vitamin D
Treatment B: rhPTH (1-84): 100µg QD, no oral calcium/no active vitamin D
Treatment C: rhPTH (1-84): 50µg BID, no oral calcium/no active vitamin D
Washout period: ≥ 5 days ≤30 days between first dose of each period (regardless of BID or QD regimen)
Follow-up: 30±2 days after last administration of IP
*Screening period includes an administrative screen (if needed) as well a clinical screen (clinical screen days -28 to -3 only)

Figure 1c: Cohort 3

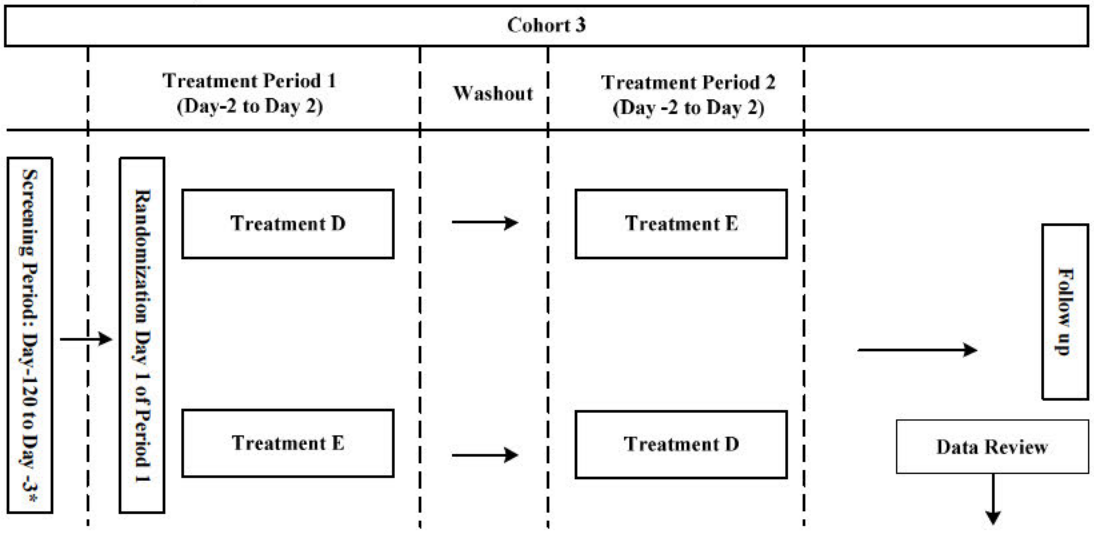
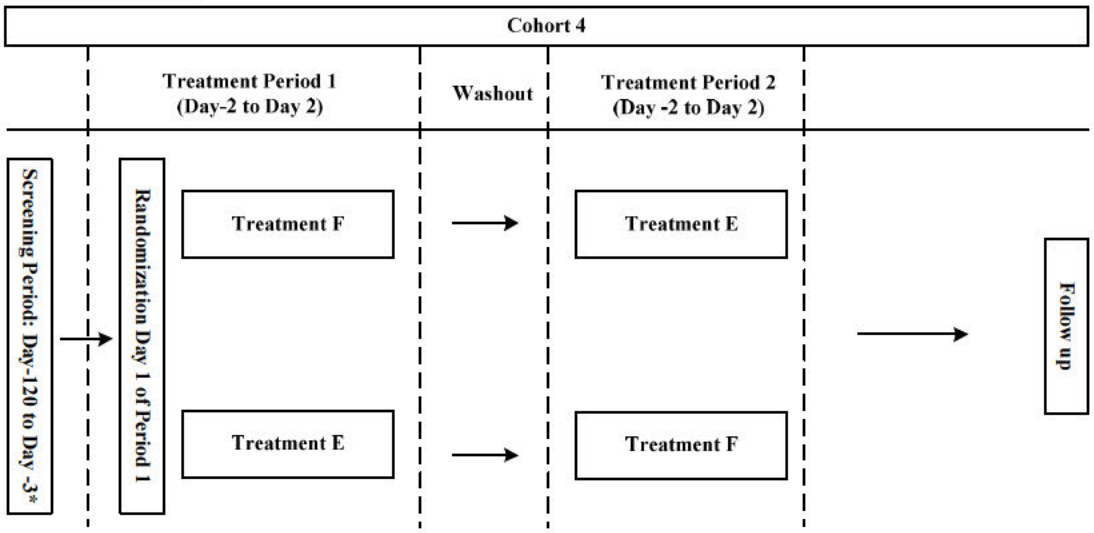


Figure 1d: Cohort 4



Treatment D: rhPTH (1-84): 25µg BID, with oral calcium/no active vitamin D
Treatment E: rhPTH (1-84): 100µg QD, with oral calcium/no active vitamin D
Treatment F: rhPTH (1-84): 50µg BID, with oral calcium/no active vitamin D
Washout period: ≥ 5 days ≤30 days between first dose of each period (regardless of BID or QD regimen)
Follow-up: 30±2 days after last administration of IP
*Screening period includes an administrative screen (if needed) as well a clinical screen (clinical screen days -28 to -3 only)

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 90 days or 3 months (if the maximum Clinical Screening Period, washout and follow-up periods are utilized). If the Administrative Screening Period is required, the maximum duration of study participation is 182 days. The study will be completed in approximately 36 months.

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.

3.3 Sites and Regions

It is anticipated that this study will be a multi-site, multi-country study. The regions to be targeted include North America and countries within Europe. It is expected that approximately 20-30 sites in those regions will enroll approximately 1-2 subjects per site.

4. STUDY POPULATION

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

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Adult men or women aged ≥18 years at the time of consent. The date of subject signature of the informed consent is defined as the beginning of the Screening Period. The Screening Period for this study may encompass both the Administrative Screening Period (if needed) and the Clinical Screening Period. For purposes of this inclusion criterion, age will only be assessed at the time the informed consent is first signed by the study subject.
4. History of hypoparathyroidism for ≥12 months, post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia with concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range.
5. Requirement for supplemental oral calcium treatment ≥1000 mg elemental calcium per day.
6. Requirement for therapy with active forms of vitamin D at a minimum dose of ≥0.25µg per day (ie, ≥0.25µg calcitriol or equivalent per day).
7. Serum calcium level within the laboratory normal reference range based on clinical chemistry lab results at the Clinical Screening Visit (based on central and/or local lab results) and Treatment Period 1, Day -2 (based on central and/or local lab results), or if outside of normal range, considered not clinically significant by the investigator.
8. Urinary calcium excretion ≥200mg (5mmol)/24h, based on a 24-hour collection, collected anytime during the Clinical Screening Period, but prior to check-in to the CRC at Treatment Period 1, Day -2 (based on central and/or local lab results).
9. Serum magnesium level within the laboratory normal range at the Clinical Screening Visit or, if outside of normal range, considered not clinically significant by the investigator.
10. Serum thyroid function tests within normal laboratory limits at the Clinical Screening Visit, or, if outside of normal range, considered as not clinically significant by the investigator.

11. Serum 25(OH)D level between the lower limit of normal and 1.5-fold the laboratory upper limit of normal, or, if outside of this range, considered not clinically significant by the investigator, at the Clinical Screening Visit.
12. Serum creatinine <1.5 mg/dL (<133µmol/L) AND estimated creatinine clearance >60 mL/minute (>1.002mL/s) at the Clinical Screening Visit, and serum creatinine <1.5 mg/dL (<133µmol/L) at Treatment Period 1, Day -2.
13. Male or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.

4.2 Exclusion Criteria

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

1. Participation in any other investigational drug study in which the last dose of investigational drug occurred within 3 months prior to Day 1 of Treatment Period 1 (or within 5 half-lives, if elimination half-life is greater than 18 days).
2. Presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine (with exception of the condition under study), or neurologic system(s) or psychiatric disease as determined by the investigator.
3. Known history of hypoparathyroidism resulting from an activation mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism).
4. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, including but not limited to, active hyperthyroidism; poorly controlled insulin-dependent diabetes mellitus or type 2 diabetes mellitus; severe and chronic cardiac, liver or renal disease; Cushing's syndrome; neuromuscular disease such as rheumatoid arthritis; myeloma; pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy, bone metastases or a history of skeletal malignancies; primary or secondary hyperparathyroidism; a history of parathyroid carcinoma; hypopituitarism, acromegaly; or multiple endocrine neoplasia types 1 and 2, as determined by the investigator.
5. 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). Therefore, 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 are excluded.
6. Subjects who have a known history of hypercalcemia during initiation of treatment with PTH, PTH analogues or fragments of PTH.

7. Subjects who have a known history of hypocalcemia following abrupt withdrawal of treatment with PTH, PTH analogues or fragments of PTH.

8. Subjects dependent on regular parenteral calcium infusions (eg, calcium gluconate) to maintain calcium homeostasis within 3 months prior to enrollment, as determined by the investigator.

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

    - 14 days– thiazide diuretics
    - 30 days – loop diuretics, lithium, 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.

10. Presence of any clinically significant results from laboratory tests, vital signs assessments, or electrocardiograms (ECGs), as judged by the investigator.

11. Twelve-lead ECG values (average of triplicate readings) demonstrating QTc >450msec (males) or >470 msec (females) at the Clinical Screening Visit and/or any time points up to and including predose of Day 1 (Period 1).

12. Any medical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for this study.

13. Positive test result for any of the following viral infections at the Clinical Screening Visit:

    - Hepatitis B surface antigen
    - Hepatitis C
    - HIV

14. Known significant bleeding diathesis that could preclude multiple venipunctures as determined by the investigator.

15. Subjects who have donated a total of 100 mL to 499 mL of whole blood within 30 days prior to dosing, or subjects who have donated a total of more than 499 mL of whole blood within 56 days prior to dosing.

16. A positive screen for drugs of abuse at the Clinical Screening Visit, and/or a positive screen for drugs of abuse and alcohol at check-in to the CRC at Treatment Period 1. Subjects taking prescription medications that might be detected during the urine screen for drugs of abuse (listed in Section 7.3.2.7) may be enrolled per the investigator's medical judgment.
17. History of a clinically significant illness during the 4 weeks prior to dosing (as determined by the investigator).
18. History of any clinically significant surgery or procedure within the past 8 weeks, as determined by the investigator.
19. History of an allergic response(s) to PTH or PTH analogs, or other clinically significant allergies, as determined by the investigator.

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 alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
3. Subjects should refrain from use of tobacco or any products containing nicotine within 60 minutes prior to the collection of any vital signs, ECG or blood draw while confined in the CRC during each treatment period.
4. On Day 1 when the investigational product is to be administered in the morning (for all dosing regimens), subjects will be required to fast for at least 8 hours prior to dose of administration and continuing through 2 hours after administration of the investigational product. For subjects assigned to the BID dose regimen, the evening dose of investigational product will be administered 12 hours after the morning dose, and 2 hours prior to the evening meal. A snack or light meal may be provided to the subjects prior to the evening dose, provided it is consumed ≥2 hours prior to investigational product dose administration.
5. 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 (meaning that the food options/choices offered to each subject within the site are the same, not the specifics of each food choice at each meal). The meal choices for each subject in Period 2 should be identical with the meal choices in Period 1. This does not mean that the same meal choices need to be the same within a treatment period, but must be identical per day across both Period 1 and Period 2. Copies of the menus will be provided to the sponsor/sponsor's designee for approval prior to the start of the study for each subject (ie, prior to the first in- patient visit per subject at each site). 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 child-bearing potential should be using an acceptable form of contraception. Females of child-bearing 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 child-bearing 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 30 days following the last dose of investigational product.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea).Post-menopausal status will be confirmed at Screening with a follicle-stimulating hormone (FSH) 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 child-bearing potential with a negative urine and/or serum β-HCG pregnancy test at the screening visit, upon check-in for each treatment period, at discharge from clinic after the second treatment period and at follow up. Females 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 one 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 last dose of investigational product. Male subjects must be advised not to donate sperm during the course of the study and within 3 months of the 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 CRF and source documents.

Randomized subjects who discontinue from the study may be replaced at the sponsor's discretion to ensure that at least 32 subjects complete the study and provide sufficient data to meet the study objectives.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. 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 entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Other (If "Other" is selected, the investigator must specify on the CRF)

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 [except where required by the study] and non-pharmacological treatment such as psychotherapy, as appropriate) received within 30 days (or as defined elsewhere in this protocol) or pharmacokinetic equivalent of 5 half-lives, (whichever is longer) of the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate CRF page.

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 CRF page. Calcium and vitamin D used prior to, and during, the study must be included as concomitant medication.

For this study it is imperative that the administration times and dose strengths of all calcium and active vitamin D be documented accurately and completely in the source document and recorded in the CRF for Days -1, 1, and 2 of both treatment periods.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications and supplements during the course of the study except for those prescribed by their physician (including calcium and vitamin D as mandated by protocol) and not excluded in the exclusion criteria. Any medication which is considered necessary for the subject's safety and wellbeing may be given at the discretion of the investigator. The administration of all medications and supplements (including investigational products) must be listed on the appropriate CRF page.

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 test product in the cartridge must be mixed using the provided mixing apparatus, and only administered via the injector pen which is also provided. 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.

No additional investigational product will be supplied. It is expected that subjects will continue to take their own supplemental oral calcium and vitamin D (except when instructed to hold at the times indicated in the current protocol) and that any products required for emergency treatment, eg, fluid or calcium replacement, be provided by the study physician.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomize a subject into the study (for any of the proposed treatment groups). Randomization will occur through an interactive response system. Randomization of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

This is an open label, randomized, 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 screen failures, the screening number will be the identifying number used throughout the CRF.

The actual treatment given to individual subjects is determined by a randomization schedule.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, and will be allocated prior to dosing after eligibility has been determined.

A randomization number is allocated immediately prior to dosing once eligibility has been determined. Once a randomization number has been assigned, that number must not be used again (if for example, a subject is withdrawn from the study). If a randomization number is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

Individual subject treatment is automatically assigned by via interactive response technology (IRT).

6.2.3 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 randomly assigned to 1 of 2 treatment sequences (according to the randomization schedule) prior to dosing on Day 1 of Treatment Period 1, and administered investigational product (see Table 5):

- On Day 1 of Treatment Period 1, subjects in Cohort 1 will receive rhPTH(1-84) as either a twice-daily regimen (12 hours apart) of two 25µg doses (without calcium; Treatment A) or a once-daily regimen of one 100µg dose (without calcium) in the morning (Treatment B). On Day 1 of Treatment Period 2, subjects in Cohort 1 will receive the alternative treatment.

- On Day 1 of Treatment Period 1, subjects in Cohort 2 will receive rhPTH(1-84) as either as a twice-daily regimen (12 hours apart) of two 50µg doses (without calcium; Treatment C) or a once-daily regimen of one 100µg dose (without calcium; Treatment B). On Day 1 of Treatment Period 2, subjects in Cohort 2 will receive the alternative treatment.

- On Day 1 of Treatment Period 1, subjects in Cohort 3 will receive rhPTH(1-84) as either a twice-daily regimen (12 hours apart) of two 25µg doses (with calcium; Treatment D) or a once-daily regimen of one 100µg dose (with calcium; Treatment E). On Day 1 of Treatment Period 2, subjects in Cohort 3 will receive the alternative treatment.

- On Day 1 of Treatment Period 1, subjects in Cohort 4 will receive rhPTH(1-84) as either a twice-daily regimen (12 hours apart) of two 50µg doses (with calcium, Treatment F) or a once-daily regimen of one 100µg dose (with calcium, Treatment E). On Day 1 of Treatment Period 2, subjects in Cohort 4 will receive the alternative treatment.

A full description of the preparation of the investigational product and guidelines for administration can be found in documents that will be provided.

6.2.4 Unblinding the Treatment Assignment

Not Applicable.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling and Packaging

Study sites 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.

A caution statement limiting the investigational product to the clinical trial will be appended as regionally required. For example, in the US the following statement will be appended ‘For clinical trial use only’, and/or ‘CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use’ and the statement ‘Keep out of the reach of children’.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, and 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.

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

6.3.2 Storage

The investigator has overall responsibility for ensuring that the 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 study team. The pharmacist/nominated team member will enter the unique subject identifier (if allowed by local law/regulations) on the investigational product labels 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

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 medication will be documented on the CRFs 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 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 (or designated contract research organization [CRO]). 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 must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor or sponsor representative for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Only in exceptional circumstances, and when agreed by the sponsor in advance, a site may be required to destroy the used/unused supplies locally (based on their institution's SOPs, guidelines, hospital/pharmacy regulations, etc.). In this case, and only with the written agreement of the sponsor, all unused stock, and empty/used investigational product may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance 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

Compliance must be assessed by observation of dosing by the investigator or designee. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured in the appropriate CRF.

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not Applicable.

7. STUDY PROCEDURES

7.1 Dosing and Procedure Observations

7.2 Study Schedule

See Table 2, Table 3, and Table 4 schedules of 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 AE reporting
- ECG
- Vital signs
- Pharmacodynamic blood sampling*
- Pharmacokinetic blood sampling*
- Clinical laboratory tests*
- Physical examination

* In order to avoid potential for cross-contamination of tube additives when collecting blood samples at one time point for different assays, all tubes requiring serum (eg. pharmacodynamic samples, anti-PTH antibody, chemistry panel, T3, T4, TSH, serum β-HCG, FSH, HBsAG, HIV, and 25[OH]D samples) should be drawn prior to any tubes requiring plasma (eg, pharmacokinetic and hematology samples). This sequence is important because serum samples require collection without anticoagulant (red top tube) which should be collected prior to samples requiring an anticoagulant (ie, purple top tube: being either a K3EDTA tube or a K2EDTA tube).

NOTE: Blood sampling for pharmacodynamic and pharmacokinetic evaluations must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate CRF.

7.2.1 Screening Period

The Screening Period may consist of the Administrative Screening Period (if needed) prior to the Clinical Screening Period.

7.2.1.1 Administrative Screening and Remote Consent Process

The Administrative Screening Period is the time needed to assist those subjects and study sites who may need to obtain historical medical records of a potential subject to confirm partial eligibility and who may, or may not, be remote from the study site. An informed consent document must be signed by the subject at the start of the administrative screen process and be provided to the study site. A copy of the signed informed consent must be given to the subject for their records.

The consent process may be performed remotely only if it is in compliance with the site's local and/or regional regulations, and approved by the site's IRB/EC. Details of the remote consent process are provided in Appendix 2. From the time the subject provides a signed consent form, the subject will be registered as a study participant. The Administrative Screening Period is only for information gathering purposes (medical records), and NOT for any active screening procedures performed on the study subject. As such, it is not part of the active screening process.

The Administrative Screening Period to collect appropriate medical records may be performed up to 120 days prior to Day 1 of Treatment Period 1. Adverse events will be captured from the date the subject signs the informed consent document. If the subject appears to be eligible for the study from a review of the medical records, the subject must then complete a clinical screen (described below).

7.2.1.2 Clinical Screening

The Clinical Screening Period differs from the Administrative Screening Period in that the subject is physically present at the CRC during the Clinical Screening Visit and/or completes a required assessment in the study (outlined in Table 1). Following a subject's informed consent, the study specific screening procedures can be conducted.

- For any subject who does not require an administrative screen, the subject must sign an informed consent at the Clinical Screening Visit, prior to any study-specific procedures being performed.

- For any subject who completes an administrative screen, the subject must sign a (new) informed consent (and be given a new subject number) at the Clinical Screening Visit, prior to any study-specific procedures being performed (the subject will be considered as an administrative screen failure under the prior assigned subject number).

Clinical screening visit procedures must be completed within 28 days prior to receiving the first dose of Investigational Product. All clinical screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See Table 1 for a complete list of clinical screening procedures to be performed.

The Clinical Screening Period is comprised of 2 parts, Day -28 to Day -3 and Day -2 to Day -1 of Treatment Period 1. In the first part (Day -28 to Day -3) eligibility for study participation will be checked on an out-patient basis. In the second part of the Clinical Screening Period, the remaining procedures for eligibility will be confirmed as an in-patient. This is outlined in Table 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.

7.2.1.3 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 randomized or administered investigational product(s).

For purposes of data collection, all subjects who give consent to the study, but are not enrolled and/or randomized, will be reported as screen failures, even if they were otherwise fully eligible for the study, for example alternates/reserve subjects.

7.2.1.4 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will be permitted to be rescreened based on investigator discretion and sponsor approval if the investigator assesses the reason for screen failure is transient and temporary.

Potentially eligible subjects who continue to meet all inclusion/exclusion criteria, but are unable to participate in the study due either to scheduling conflicts/timing (including the time required to obtain medical records release, if applicable) or appropriate slot availability at an investigational site, 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.

7.2.2 Treatment Period

7.2.2.1 Day 1 to Day 2 (Treatment Periods 1 and 2)

Study assessments for Day 1 to Day 2 of each treatment period are outlined in Table 3 and Table 4. Subjects will be randomized to treatment assignment prior to dosing on Day 1 of Treatment Period 1. Administration of investigational product will occur on Day 1 of each treatment period.

The time points for pharmacokinetic/pharmacodynamic assessments will be performed according to the BID or QD dose regimen assigned to the subject in the treatment period. Subjects will be discharged from the CRC following completion of the last study assessment on Day 2 of Treatment Period 1. Following a washout of (at least 120 hours [5 days] to 30 days between the dose or the first dose of each treatment period [QD or BID dosing, respectively]) subjects will be admitted to the CRC for Treatment Period 2 procedures at Day -2.

7.2.3 Final Visit

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

7.2.4 Follow-up Period

The follow-up period for this protocol is 30±2 days after the last 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, a blood sample for anti-PTH antibodies, 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).

7.2.5 Additional Care of Subjects after the Study

There is no planned aftercare in this study.

Subjects who complete this study may have the opportunity to enroll in an open-label extension trial if an open-label extension study is available and approved by the site's IRB/EC.

7.3 Study Evaluations and Procedures

7.3.1 Demographic and Other Baseline Characteristics

7.3.1.1 Demographics

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

- Date of birth
- Sex
- Race and ethnicity

7.3.2 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. Unless otherwise noted, 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.

AEs (defined as AEs occurring from the time of informed consent signature to first dose of investigational product), TEAEs (all AEs occurring after the first 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 blood pressure 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.

7.3.2.1 Medical and Medication History

A complete medical and medication history will be performed at the Clinical 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 use of medication (30 days prior to the first dose of study treatment)

- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

7.3.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the time points described in Table 1 by a qualified licensed physician, physician's assistant, or a 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 Clinical Screening Visit will be documented in the subject's source documents and on the medical history CRF. Changes after the Clinical Screening Visit will be captured as AEs on the AE CRF, as deemed by the investigator.

7.3.2.3 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.)

7.3.2.4 Vital Signs, Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Table 1, Table 2, Table 3, and Table 4 of this protocol. With exception of the predose assessment on Day 1 (which must be within 30 minutes prior to administration of IP), any subsequently scheduled vital signs assessment collected during Periods 1 and 2 that deviates from the scheduled assessment time in Table 2, Table 3, and Table 4 by more than ±15 minutes will be considered a protocol deviation.

Additional blood pressure 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 blood pressure 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 mm Hg/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 (as specified in the study restrictions; Section 4.3) or within 30 minutes of collection. The subject should be instructed to lie down, remain supine and 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).One reading (supine systolic blood pressure/diastolic blood pressure-pulse) 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, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.3.2.5 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. Samples for all clinical laboratory evaluations will be sent to a central laboratory. If an immediate (stat) result is required, a local laboratory may be used but a duplicate sample must be sent to the central laboratory. A manual fully describing the schedule and method of sample handling will be provided.

In order to qualify the subject for randomization at Treatment Period 1, the site can base eligibility on the local lab results if the central lab results are not available, but, if results are available from both labs, eligibility should be based on the central lab results.

However, local lab results will not be entered in the eCRF/clinical database, and copies of local lab reports must be maintained in the subject source documents. The central lab results (once received) will be entered in the eCRF/clinical database.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (8.5 mL) for serum biochemistry will be collected into a gel separator tube at the timepoints described in Table 1. The following parameters will be assessed:

Sodium	Phosphorus	β-HCG [b]
Potassium	Total protein	FSH [b]
Glucose	Total CO_2 (Bicarbonate)	Magnesium
Blood urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
Thyroxine (T4 total) [a]	Total bilirubin	
Triiodothyronine (T3) [a]	Uric acid	
25(OH)D	Creatinine clearance (estimated) [a]	

β-HCG=beta-human chorionic gonadotropin; FSH=follicle stimulating hormone; T3=triiodothyronine; TSH=thyroid stimulating hormone

[a] See Table 1.

[b] Females only.

Hematology

Blood samples (4 mL) for hematology will be collected into ethylenediaminetetraacetic acid tubes at the time points described in Table 1. 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. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity
Calcium		

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.

7.3.2.6 Pregnancy Test

A serum β-HCG pregnancy test is to be performed on all females at the Clinical Screening Visit. A urine pregnancy test is performed on all female subjects at all subsequent visits as outlined in Table 1.

7.3.2.7 Drug and Alcohol Screen

A urine screen for drugs of abuse and 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 breath test 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 clinical screening or drugs of abuse or alcohol on Day-1 (both treatment periods) will exclude the subject from further participation in the study (except as noted in Exclusion Criterion #16).

7.3.2.8 Serology Screen

At the Clinical Screening Visit, a blood sample of approximately 8.5 mL will be drawn into a gel separator tube to test for the presence of HIV, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody as outlined in Table 1.

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.

7.3.2.9 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1, Table 2, Table 3, and Table 4. All ECGs will be performed in triplicate (with a minimum 2 minute gap between traces) using the equipment supplied by the CRC. Two identical trace ECG recordings for each time point will be collected and one original provided to the study sponsor or ECG vendor. With exception of the predose assessment on Day 1 (which must be within 30 minutes prior to administration of IP) any subsequently scheduled ECG assessment collected during Periods 1and 2 that deviates from the scheduled assessment time in Table 2, Table 3, and Table 4 by more than ±15 minutes will be considered a protocol deviation.

The following parameters will be provided to the sponsor or the sponsor representative by the central ECG reader: heart rate, PR, RR, QRS, and QT intervals along with information on T and U-wave morphology; U-waves should be captured as absent/normal or abnormal. The QTcB and QTcF will be derived from the data provided by the central ECG reader. 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 recorded in the CRF.

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, alcohol, or nicotine within 60 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 approximately the same positions each time in order to achieve precise ECG recordings. Only valid ECG tracings will be submitted to the ECG vendor for analysis.

Triplicate recording, including a 10 second rhythm strip, will be obtained approximately 2-4 minutes apart for all assessments. The time and date of each valid ECG tracing obtained with the 3 assessments will be recorded in the CRF. The ECG parameters as described above will be evaluated by a central reader and the interpretation provided to the sponsor or the sponsor representative. The average of the triplicate valid ECG measurements collected at each nominal time point will be used for analysis. The 3 recordings should be immediately assessed as valid recordings and, if not valid, they should be repeated in order to obtain a total of 3 valid recordings. Invalid recordings will not be entered in the CRF.

When (triplicate) ECGs are obtained, the average of the triplicate ECG measurements collected predose on Day 1 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 QTcF interval (calculated on site) is increased by >45msec 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 (>45msec increase 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 >45msec increase 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/QTcB value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF/QTcB values are in the acceptable range.

In cases where a central ECG reader is used, the eligibility of the subject is based on the assessment of the ECG by the investigator. If abnormal results are observed following assessment by the central reader, the investigator, in consultation with the appointed sponsor's medical monitor, reconfirms the subject's eligibility to continue to participate in the study.

7.3.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at the/each site and in the Trial Master File at the sponsor. A manual fully describing the schedule and method of sample handling will be provided.

Actual pharmacokinetic 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 pharmacokinetic blood samples at the precise protocol scheduled time. Pharmacokinetic 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 4 hours post-dose and beyond. Samples drawn outside these parameters will be considered a protocol deviation.

7.3.3.1 Pharmacokinetic Blood Sample Collection and Handling Procedures

Pharmacokinetic blood samples will be collected at the time specified in Table 1, Table 2, Table 3, and Table 4 to measure plasma concentrations of PTH.

A full description of the pharmacokinetic 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: SHP634-101
- Subject identifier

- Treatment Period
- Nominal day
- Nominal time
- Matrix identifier (plasma)
- Split (primary or back-up).

7.3.3.2 Shipment of Plasma Pharmacokinetic Samples

All pharmacokinetic plasma 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. 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 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.

All pharmacokinetic samples, along with the corresponding documentation will be shipped according to the instructions in the provided laboratory manual.

Pharmacokinetic samples will be stored nominally at -70°C prior to and after analysis at the assay laboratory until their disposal is authorized by Shire.

7.3.3.3 Pharmacokinetic Plasma Assay Methodology

Plasma concentrations of PTH will be measured using the most current validated bioanalytical method according to the relevant Standard Operating Procedure in place at the designated bioanalytical contract laboratory. In addition, selected plasma 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.

7.3.4 Pharmacodynamic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at the/each site and in the Trial Master File at the sponsor. A manual fully describing the schedule and method of sample handling will be provided.

Actual pharmacodynamic blood sample and urine 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 pharmacodynamic blood and urine 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 4 hours post-dose and beyond. Samples drawn outside these parameters will be considered a protocol deviation.

7.3.4.1 Pharmacodynamic Blood Sample Collection and Handling Procedures

Pharmacodynamic blood samples will be collected at the time specified in Table 1, Table 2, Table 3, and Table 4 to measure serum calcium (total and albumin corrected), magnesium, phosphate, albumin, creatinine, fibroblast growth factor 23 (FGF23) and 1,25- dihydroxycholecalciferol ($1,25(OH)_2D_3$).

A full description of the pharmacodynamic 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: SHP634-101
- Subject identifier
- Treatment Period
- Nominal day
- Nominal time
- Matrix identifier (serum)
- Analyte (if there is more than 1)
- Split (primary or back-up).

7.3.4.2 Shipment of Serum Pharmacodynamic Samples

All pharmacodynamic serum 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. 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 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.

All pharmacodynamic serum samples, along with the corresponding documentation, will be shipped to the address provided in the laboratory manual.

Pharmacodynamic serum samples will be stored nominally at -70 C prior to and after analysis at the assay laboratory until their disposal is authorized by Shire.

7.3.4.3 Pharmacodynamic Serum Assay Methodology

Pharmacodynamic serum parameter concentrations will be measured using the most current validated bioanalytical methods according to the relevant Standard Operating Procedure(s) in place at the designated bioanalytical contract laboratory. In addition, selected plasma 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. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.3.4.4 Pharmacodynamic Urine Sample Collection and Handling Procedures

Pharmacodynamic urine samples will be collected at the time specified in Table 1, Table 2, Table 3, and Table 4 to measure calcium, sodium, citrate, phosphate, magnesium, cAMP and creatinine.

Urine samples for pharmacodynamic analysis will collected over 24 hours (or 36 hours from the first dose of the BID regimen) in discrete time periods according the schedules in Table 1, Table 2, Table 3, and Table 4. A full description of the pharmacodynamic urine collection, handling (including additives), storage and shipping can be found in the provided laboratory manual.

Urine 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: SHP634-101
- Subject identifier
- Treatment Period
- Nominal day
- Nominal time
- Matrix identifier (urine)
- Analyte (if there is more than 1)
- Split (primary or back-up).

7.3.4.5 Shipment of Urine Pharmacodynamic Samples

All pharmacodynamic urine 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. 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 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.

All pharmacodynamic urine samples, along with the corresponding documentation, will be shipped to the assay laboratory outlined in the provided laboratory manual.

Pharmacodynamic urine samples will be stored nominally at -70°C prior to and after analysis at the assay laboratory until their disposal is authorized by Shire.

7.3.4.6 Pharmacodynamic Urine Assay Methodology

Pharmacodynamic urine parameter concentrations will be measured using the most current validated bioanalytical methods according to the standard operating procedures at the contract bioanalytical laboratory. In addition, selected urine 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.

7.3.5 Volume of Blood to be Drawn from Each Subject

Table 6: Volume of Blood to be Drawn from Each Subject

Assessment		**Sample Volume (mL)**	**# Samples at Clinical Screening/Day -2**	**# Baseline Samples (Day -1 and/or Day-2)**	**# Samples each QD regimen (Days 1-2)**	**# Samples each BID regimen**	**Follow Up**	**Total # Samples**	**Total Volume (mL)**
PK samples (plasma PTH) [a,d]		4* *(unless otherwise specified)	0	0	12 *(7 samples of 3mL + 5 samples of 4mL)	21 *(11 samples of 3mL + 10 samples of 4mL)	0	33 *(18 samples of 3mL + 15 samples of 4mL)	114 *(54mL+ 60 mL)
HBsAg, HIV, HCV		6	1	0	0	0	0	1	6
Safety	Biochemistry and β-HCG [b]	6	1 (Clinical Screening)	2 (TP1 D-2 + TP2 D-2)	1	1	1	6	36
	Hematology	2	1	2	1	1	1	6	12
	Serum 25(OH)D	2	1	0	0	0	0	1	2
PD samples Baseline (D-1)	total serum calcium, magnesium, phosphate, creatinine, $1,25(OH)_2D_3$ [c]	4 (3mL+1mL discard)	0	18 (9TP1+9TP2)	0	0	0	18	72
	FGF23, Albumin	2	0	18 (9TP1+9TP2)	0	0	0	18	36

Table 6: Volume of Blood to be Drawn from Each Subject

Assessment		**Sample Volume (mL)**	**# Samples at Clinical Screening/Day -2**	**# Baseline Samples (Day -1 and/or Day-2)**	**# Samples each QD regimen (Days 1-2)**	**# Samples each BID regimen**	**Follow Up**	**Total # Samples**	**Total Volume (mL)**
PD samples (Days 1-2)	total serum calcium, magnesium, phosphate, creatinine, $1,25(OH)_2D_3$ [c,d]	4 (3mL+1mL discard)	0	0	11	15	0	26	104
	FGF23, Albumin	2	0	0	11	15	0	26	52
anti-PTH antibody		3	0	1 (TP1, predose	0	0	1	2	6
Total mL									**440** [e]

BID=twice-daily; β-HCG=beta-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; QD=once=daily.

[a] If a catheter is used, the first 1mL is to be discarded when the PK sample is collected alone at a time point (ie without collection of a PD sample); then take 3mL into appropriate tube for PK sample. A total of 4mL of blood drawn has been used in determination of this sample volume.

[b] β-HCG testing for females only.

[c] If a catheter is used, the first 1mL is to be discarded; then take 3mL into appropriate tube(s) for PD assessments for total serum calcium, magnesium, phosphate, creatinine, 1,25(OH)2D3. A total of 4mL of blood drawn has been used in determination of sample volume. An additional sample of 2mL will be collected for FGF23 and albumin in a separate tube.

[d] When a PD and PK sample are collected at the same time point, the PD sample is to be drawn prior to the PK sample (to avoid any potential for cross-contamination of tube additives), and if a catheter is used for this collection, the first 1mL of blood should be discarded prior to the PD blood sample collection. When either a PK or a PD sample is drawn alone at a scheduled time point, 1mL of blood should be discarded prior to the scheduled blood sample collection.

[e] This is an **approximate** calculation of total blood volume required for the study for each subject

During this study, it is expected that approximately 440 mL of blood will be drawn from all subjects, 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 440 mL. 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 (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 7.2.4. 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 AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

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 pre-treatment 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 on the appropriate CRF).

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 CRF. Outcomes are as follows:

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

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 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.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.2.4.

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 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.

8.1.7 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 non-medical 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.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors. Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment is/are always reportable as a medication error. The administration and/or use of an expired investigational product should be considered as a reportable medication error.

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) investigator brochure which the sponsor has provided under separate cover.

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 CRO/Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24 hours reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) 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 CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An 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 in-subject hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which 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 in-subject 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 7.2.4, and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the CRO/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 in the US and EU of related, unexpected SAEs.

In addition, the CRO (PPD) is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhPTH(1-84) program.

The investigator is responsible for notifying the local institutional review board (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 on 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 approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO 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, as such, there are no special handling considerations for blinded data.

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 pharmacokinetic, pharmacodynamic, 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.

One or more interim analyses may be performed in this study. If an analysis is deemed to be necessary, then a prospective statistical analysis plan will be developed prior to the analysis. The plan will include, at a minimum: (1) rationale to perform the interim analysis; (2) parameters to be analyzed; (3) the distribution list for the interim analysis results. Interim data may be used for (but not limited to) PK/PD modeling and/or regulatory submissions. The trial will not stop due to the results of any interim analysis.

9.6 Sample Size Calculation and Power Considerations

At least 8 subjects will be required to complete treatment in each cohort. The sample size was determined based on a similar, prior pharmacokinetic/pharmacodynamic study. The number of subjects in this study is not based on statistical power considerations because the statistical analyses are primarily descriptive, and no hypothesis testing is specified in the study.

9.7 Study Population

Four analysis populations are defined for this study: the all-enrolled, safety, pharmacokinetic, and pharmacodynamic populations:

- The all-enrolled population consists of all subjects who sign the informed consent form and are randomized in the study.
- The safety population includes enrolled subjects who have received at least 1 dose of rhPTH(1-84). All analyses of safety data will be based on this population.
- The pharmacokinetic population consists of all-enrolled subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacokinetic concentration value available for 1 dose regimen.
- The pharmacodynamic population consists of all-enrolled subjects who receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacodynamic value available for 1 dose regimen.

9.8 Pharmacokinetic and Pharmacodynamic Analyses

9.8.1 Pharmacokinetic Analysis

All pharmacokinetic analyses will be performed using the pharmacokinetic population.

Pharmacokinetic parameters will be determined from the plasma concentration-time data for PTH and by non-compartmental analysis. Pharmacokinetic analyses based on raw and baseline-adjusted PTH concentrations will be performed. The baseline is defined as the predose endogenous PTH level on Day 1, and baseline-adjusted PTH concentrations are to be calculated by subtracting baseline PTH from the raw PTH concentrations. All assessment dates will be related to the first day of rhPTH(1-84) administration.

This first day of investigational product administration is referred to as Day 1. Day 1 is the day that is preceding Day 1, and a Day 0 will not be defined.

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

- maximum observed concentration maximum (C_{max})
- time of maximum concentration (T_{max})
- area under the concentration curve (from time zero to the last measurable concentration and from time zero to infinity (AUC_{0-t} and AUC_{0-inf})
- area under the concentration curve from time zero to 24 hours post the first dose (AUC_{0-24h})
- elimination rate constant (K_{el})
- apparent clearance (CL/F)
- apparent volume of distribution (V_z/F)
- elimination half-life ($t_{½}$)

9.8.1.1 Statistical Analysis of Pharmacokinetic Parameters

Individual concentrations and Pharmacokinetic parameters of PTH will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by treatment. Figures of individual and mean (+/-SD) concentration-time profiles of raw and baseline-adjustment plasma PTH will be generated.

9.8.2 Pharmacodynamic Analysis

All pharmacodynamic analyses will be performed using the pharmacodynamic population.

Pharmacodynamic parameters will be computed from the individual concentrations of serum calcium (uncorrected and corrected for serum albumin levels), phosphate, albumin, creatinine, magnesium, $1,25(OH)_2D_3$ and FGF23 using a non-compartmental approach. The calcium- phosphate product will be computed. Pharmacodynamic parameters will be estimated based with and without baseline adjustments.

Individual concentrations and pharmacodynamic parameters of serum total calcium and albumin- corrected calcium, phosphate, creatinine, albumin, magnesium, $1,25(OH)_2D_3$ and FGF23 will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%).

The urinary excretion of calcium, sodium, citrate, magnesium, cAMP, and phosphate will also be expressed relative to that of creatinine and will be summarized with descriptive statistics.

9.8.2.1 Statistical Analysis of Pharmacodynamic Parameters

The following parameters will be calculated using the serum concentration data:

- $AUC_{0\text{-}24h}$: the area under the concentration versus time curve, from time 0 to 24 hours
- TE_{max}: time to maximum effect
- E_{max}: maximum effect

The parameters representing urinary excretion of each analysis will be calculated, if data allow:

- Total amount of sodium, calcium, magnesium, citrate, phosphate, cAMP, and creatinine in each sample
- Total amount of sodium, calcium, magnesium, citrate, cAMP, and phosphate excreted in each sample relative to the total amount of creatinine excreted
- Renal clearance of sodium, calcium, magnesium, citrate, creatinine, and phosphate (mL/min)
- Fractional excretion of sodium, calcium, citrate, magnesium, and phosphate

9.8.3 Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic-pharmacodynamic correlations between PTH concentrations and the above indicators of PTH bioactivity will be assessed using exploratory figures. If required, pharmacokinetic/pharmacodynamic models may be developed to describe the effect of PTH concentrations and biochemical indicators of PTH activity.

9.8.4 Population Pharmacokinetic and Quantitative System Pharmacology Modeling and Simulation

Additional modeling and simulation will be performed to evaluate the PK of PTH and the effect on serum calcium concentration and urine calcium excretion from alternative dosing regimens other than the once daily and twice daily doses used in the study. A population PK model and a quantitative system pharmacology model (QSPM) will be developed by fitting PK and PD data obtained from historical studies in hypoparathyroid patients as well as data from this study.

Inter-subject variability on model parameters will be fully evaluated. Once the population PK model and the QSPM are satisfactorily validated, simulations using the final validated models will be performed to explore the effects of alternative dosing other than once-daily and twice- daily dosing, eg, 3 times daily (TID), pump infusion dosing, and possibly new formulations of PTH, on the control of serum calcium concentration and urinary excretion of calcium in hypoparathyroid patients. A separate data analysis plan and report will be prepared for this additional modeling and simulation work. These data will not be used in conjunction with any study patient identifiers.

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 AEs 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.

Safety data including clinical laboratory tests, anti-PTH antibodies, concomitant medications, adverse events, ECG monitoring and vital signs assessments will be summarized by treatment and time of collection. Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) 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.

Safety will be assessed by the following evaluations:

- AEs and TEAEs (including episodes of hypocalcemia and/or hypercalcemia [including paresthesia, numbness, tetany] and hypercalciuria)
- Laboratory test results (hematology, serum chemistries, creatinine clearance, urinary chemistries (24-hr urinary calcium, sodium, citrate, phosphate, cAMP, magnesium and creatinine excretion), immunology (anti-PTH antibody), and urinalysis
- ECG
- Physical examinations (including vital signs)

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study will be conducted in accordance with current applicable regulations, ICH, 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

Unless legally prohibited, study sites taking part in this clinical study must agree that the sponsor or sponsor representative may be on-site at the CRC to observe appropriate investigational product preparation and administration as well as observation of study procedures to ensure that the protocol mandated procedures are followed correctly. Study subject privacy will be maintained during all procedures including intimate procedures such as ECG lead placement.

In addition to the Sponsor's responsibilities as outlined in this section and in Section 8 it may be incumbent upon the individual investigator to report AEs (including SAEs) and any failures of devices (Injector Pen and/or Mixing Apparatus) to their local, regional, or country specific regulatory authorities.

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 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 of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

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 non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

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.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

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.

A coordinating principal investigator (has been/will be) appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report will be documented by the signed and dated signature of the coordinating 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 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.

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 clinical research associate (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: subject's medical file, original clinical laboratory reports, and histology and pathology 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 the 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 FDA, EMA, 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 which was reviewed by the IRB/EC and which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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, the investigator or for multicenter studies 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 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' may review 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 IRBs/ECs 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 will be 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 non-commercial 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 current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	23 Nov 2015	Global
Amendment 1	26 Feb 2016	Global
Amendment 2	03 Jun 2016	Global
Amendment 3	29 Jul 2016	Global
Amendment 4	12 Jun 2017	Global
Amendment 5	18 Jun 2018	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 26 Feb 2016**	**Global**
Item #	**Description of Change**	**Section(s) Affected by Change**
1.	100µg QD with oral calcium treatment arms have been added; treatment arms have been rearranged so that 25µg BID and 50µg BID (in the absence or presence of oral calcium) are each cross-compared with 100µg QD (in the absence or presence of oral calcium). Corresponding tables, figure(s), and text modified accordingly to incorporate this design change. Reason for change: To provide direct comparisons within the same study of the alternative dosing regimens (BID with and without oral calcium) to the 100µg QD dose with and without oral calcium, in order to more fully characterize and understand the effects of both the PTH dosing regimen and oral calcium on serum calcium concentrations and urinary calcium excretion in various conditions.	Synopsis; Section 3.1 (including Figure 1); Section 6.2.3
2.	An additional cohort (of 8 subjects) has been added, increasing the total number of subjects required to complete the study from 24 to 32. Reason for change: To accommodate the additional comparisons of all BID doses with and without oral calcium with the 100µg QD dose with and without oral calcium in the study design.	Synopsis; Section 3.1 (including Table 5 and Figure 1); Section 4.5; Section 6.2.3
3.	Number of sites has been increased from “approximately	Synopsis; Section 3.3

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	20" to "approximately 20-30". Reason for change: The number of sites has been increased to accommodate for the increase in the number of patients required to complete this study.	
4.	The planned study period has been extended to Nov 2017 (approx. 18 months duration). Reason for change: To accommodate the increase in the number of subjects required to enroll and complete the study.	Synopsis; Section 3.2
5.	Access to participate in, and reference to the RACE (PAR-C10-008) open-label extension study has been removed from the protocol. Reason for Change: The RACE (PAR-C10-008) open label extension study is no longer available for subjects completing this study.	Synopsis; Section 1.3; Section 7.2.5
6.	Canada has been removed as a participating country.	Synopsis; Section 3.3
7.	Treatment scheme in tabular format added to methodology section of synopsis. Reason for change: Reflects Table 4 of Section 3.1, and has been added to the synopsis for ease of reference.	Synopsis
8.	Inclusion criterion # 6 has been modified to clarify active forms of vitamin D and minimum daily dose required for study entry. Reason for change: Clarification.	Synopsis; Section 4.1
9.	Inclusion criterion # 8 has been modified to allow for an expanded timeframe (from 6 mos. to 12 mos.) for historical 24-hour urine calcium excretion. Additionally, "calcium concentration" was corrected to "calcium excretion".	Synopsis; Section 4.1

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	Reason for change: To accommodate common clinical practice, since qualifying 24-hour urine collection may have been performed greater than 6 months prior to baseline. Correction to term for calcium excretion.	
10.	Inclusion criterion # 9: "calcium concentration" was corrected to "calcium excretion". Reason for change: Correction to term for calcium excretion.	Synopsis; Section 4.1
11.	Inclusion criterion # 11 has been modified to clarify how criterion should be interpreted if outside of the normal range. Reason for change: Clarification.	Synopsis; Section 4.1
12.	Exclusion criterion # 9 has been modified to incorporate wording re: raloxifine or similar selective estrogen receptor modulators (SERMs), and to exclude subjects on these medications, due to their potential impact on calcium kinetics. Reason for change: Raloxifine and SERMs as a drug class are known potentially to impact bone cell function and skeletal metabolism. Since SERMs theoretically could impact study pharmacodynamic outcomes with respect to calcium (as could eg, bisphosphonates), an exclusion for SERMs has been added.	Synopsis; Section 4.2
13.	Exclusion criterion # 11 has been revised to specify >450msec (males) or >470msec (females), based on the difference in normal QT/QTc observed in males versus females. Reason for change: The gender-independent QTc exclusion of >450msec which is a typical norm for healthy volunteer studies has been revised to raise the exclusion to >470msec for females. The sex difference in the normal QT/QTc between men and women is well accepted, and the QTc upper limit of normal is	Synopsis; Section 4.2

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	commonly accepted as 450msec for men and 470msec for women.	
14.	The minimum washout period between 1st dose in Treatment Period 1 and 1st dose in Treatment Period 2 has been changed from "≥4 days (ie, 96 hours)" to "≥5 day (ie, 120 hours)". Reason for Change: A 120-hour minimum duration between first dosing in each treatment period ensures that at least 4 days (96) hours duration has elapsed between the last dose of BID treatment in Treatment Period 1, and first dose of QD treatment in Treatment Period 2.	Synopsis; Section 3.1 (including Figure 1); Section 7.2.2
15.	cAMP (Cyclic AMP) has been added as a urinary analyte for pharmacodynamic assay. Reason for change: Cyclic AMP (cAMP) has been added as a pharmacodynamic analyte to help confirm true hypoparathyroidism.	Abbreviations; Synopsis; Table 2; Table 3; Section 7.3.4.4; Section 9.8.2; Section 9.8.2.1; Section 9.9
16.	Albumin-corrected calcium has been removed from descriptions of PD sample collections in the Table footnotes (Tables 2 and 3), and in the assessment column for the blood volume table (Table 6). Reason for change: Correction.	Table 2; Table 3; Table 6
17	Statistical Methodology for Safety Endpoints (Synopsis), and Safety Analysis (Section 9.9): physical exams were removed from this section, anti-PTH antibodies were added to this section. Reason for change: Physical examinations are deleted since they are not summarized by treatment and time of collection. Anti-PTH antibodies have been added as a safety parameter.	Synopsis; Section 9.9
18.	Footnote "r" of Table 1 is revised to indicate that supplemental oral calcium should be taken within 15 minutes prior to IP administration (for subjects assigned to treatment D, E and F on Day 1/dosing).	Table 1

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	Reason for change: The time window between oral calcium administrations prior to IP dosing was reduced from 1 hour prior, to 15 minutes prior to dosing, to align oral calcium intake as closely as possible to dosing, in order to get a true characterizing of calcium kinetics.	
19.	For the BID regimen, the PK/PD sample collection period has been extended to 24 hours post the second dose for BID treatment. In addition, PK and PD sample collection time points were added at 16 and 24 hours after the second dose in the BID treatment regimen (corresponding to 28 hours and 36 hours post first dose, respectively). In addition, vital signs and ECG assessments were added at the 28, 32 and 36 hour time points for this regimen. Reason for change: Sample collection period extended to 24 hours post-second (BID) dose (including a 16 and 24 hour time point) to better characterize the PK/PD profile at trough and to collect corresponding safety assessments (vitals, ECGs) at these same time points.	Table 4; Section 7.3.4.4
20.	For the QD regimen, a PK sample collection time point at 16 hrs postdose was added. Reason for change: Added to better characterize the PK of rhPTH.	Table 3
21.	These changes (item 19 and 20 above) necessitated the reorganization of Table 3 (from the original protocol v 1.0) to be split into 2 separate tables in the amended protocol: Table 3 now summarizes assessments for the QD treatment period, and Table 4 (now added) summarizes assessments for BID treatment period. Subsequent tables in this protocol were renumbered accordingly (ie, Table 4 becomes Table 5, Table 5 becomes Table 6). Reason for change: Clarification to tables.	Table 3; Table 4 (newly added)

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22.	Table 2: Day -1 (Prior to Treatments 1 and 2): Table revised to remove reference relative to BID post evening dose collection time points in the header; streamlined to remove time point/columns where no PD sampling is required. Reason for change: Clarification to table.	Table 2
23.	Table 2: Day -1 (Prior to Treatments 1 and 2): PD blood collections were removed at 18, 20, and 22 hours post-dose time points. Reason for change: To correspond to the revised pharmacodynamic sampling time points on Day 1 for QD and BID treatment schedules, and to serve as a baseline (Day -1) comparison for each respective time point on Day 1 of each treatment period. This should enable the assessment and comparisons of the treatment effects on serum calcium and urinary calcium profiles for each of the 6 treatments to their corresponding respective baseline time points.	Table 2
24.	Blood volumes required for pharmacodynamic and anti-PTH antibody assays were revised/corrected. Total blood volume required for the study is revised to 468.5mL. Additionally, table rows and columns were modified, and pharmacodynamic collections separated according to those samples collected at Baseline (D-1), and during treatment (Days 1-2), and further specifying which pharmacodynamic sample (analytes) can be grouped together (eg, FGF23, albumin). Reason for change: Corrections/revisions required to blood sample volumes, based on current information from the bioanalytical lab(s) performing the assay work. Rearrangement to columns based on revised treatment comparisons (ie, all subjects now receive 1 BID regimen and 1 QD regimen, which is reflected in re-ordered columns).	Table 6 (previously Table 5, per protocol version 1.0)

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	Clarification to pharmacodynamic samples being collected.	
25.	The following PK/PD sample collection time points were removed from the study schedule: PK sample collection time points removed: ▫ QD: 5 min, 3 hr, 6 hr postdose. ▫ BID: 5 min, 3 hr, 6 hr post first dose, and 5 min, 3 hr, 6 hr post second dose. PD sample collection time points removed: ▫ QD: 18, 22 hrs postdose. Reason for change: Due to the overall increase in total volume of blood samples required for pharmacodynamic assessments, it was necessary to revise the blood collection schedule in order to maintain total blood volume within safe and acceptable ranges for a clinical study. The specific collection time points removed do not compromise the intent or integrity of the planned PK/PD analysis for this study.	Table 3; Table 4; Table 6
26.	Table 1 (Schedule of Assessments): Anti-PTH antibody collection time point moved from Treatment Period 1 Day -2, to Treatment Period 1, Day 1 (predose). This collection time point has been removed from Table 1, and newly added as a line item to Table 3 and Table 4, with a corresponding footnote that the anti-PTH antibody sample should be collected at Treatment Period 1, predose (regardless of QD or BID regimen). Reason for change: The assessment/collection time point was moved to predose on Day 1, Period 1, in order to avoid the potential (and unnecessary) collection of a blood sample on subjects who may screen fail between Day -2 and Day 1 at predose.	Table 1; Table 3; Table 4
27.	Schedule of Assessments: Urine pregnancy test added to the Follow-up visit.	Table 1

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	Reason for change: To confirm pregnancy status at the final in-house study visit.	
28.	Schedule of Assessments: Collection time point for serum 25(OH)D sample was removed from Period 1, Day -2. Reason for change: Since serum 25(OH)D results collected at Period 1, Day -2 are not being used to determine eligibility, this sample collection was removed. The 25(OH)D sample collected at Screening will be used to determine eligibility.	Table 1
29.	An additional safety review has been added after completion of Cohort 3 (and prior to start of Cohort 4), as a result of the additional cohort (4) now added. Reason for change: Added to be consistent with safety reviews required after each completed cohort.	Synopsis; Section 3.1 (including Figure 1)
30.	Reproductive Potential (Female and male contraception): Abstinence has been deleted as an acceptable form of contraception for females and males participating in the study. Reason for change: Abstinence is not an acceptable form of contraception.	Section 4.4.1; Section 4.4.2
31.	Clarification made that calcium and vitamin D used prior to and during the study be included as a concomitant medication. Reason for change: Clarification.	Section 5.2
32.	Specific labeling requirements have been removed. Reason for change: To allow for flexibility in labeling. Labeling will include all required elements based on regional differences, local regulations, and requirements.	Section 6.3.1

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33.	Pharmacokinetic Plasma Assay Methodology section has been revised to reflect the SOPs being followed for pharmacokinetic sample assays for this study. Reason for change: Correction/update warranted.	Section 7.3.3.3
34.	Reference to pharmacodynamic "plasma" samples have been changed to pharmacodynamic "serum" samples. Reason for change: Correction.	Section7.3.4.1; Section 7.3.4.2; Section 7.3.4.3
35.	Pharmacodynamic (Serum) Assay Methodology section has been revised to reflect the SOPs being followed for pharmacodynamic sample assays for this study. Reason for change: Correction/update warranted.	Section 7.3.4.3
36.	Pharmacodynamic urine assay methodology has been revised to reflect the SOPs being followed for pharmacodynamic sample assays for this study. Reason for change: Correction/update warranted.	Section 7.3.4.6
37.	Reference to Natpara® package insert has been removed from the protocol. The reference for safety information for this study is the rhPTH (1-84) investigator brochure. Reason for change: This study will be recruiting sites and patients internationally. Therefore, the investigator brochure is appropriate for referencing safety information regarding rhPTH (1-84).	Section 1.1; Section 1.3; Section 8.2.1
38.	Pharmacodynamic Analysis: creatinine has been added to this section. Reason for change: Creatinine was added to help clarify pharmacodynamic data.	Section 9.8.2
39.	The following acronyms/abbreviations have been added: $1(OH)D_3$ (α-calcidol), cAMP (cyclic adenosine monophosphate), SERMs (selective estrogen receptor modulators).	Abbreviations

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	Reason for change: Acronyms added to coincide with the amended text that has been added to the protocol.	
40	A sentence has been added under safety to allow for notification of a positive anti-PTH result to the Investigator. Clarification of procedure for safety that wasn't addressed in the original protocol.	Section 7.3.2
41.	Email addresses added to sponsor contact information.	Additional Contact Information
42.	Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made throughout the document as appropriate. Reason for change: Clarification and/or typographical corrections.	All sections (as warranted)

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Amendment Number **2**	**Amendment Date** **03 Jun 2016**	**Global**

Item #	Description of Change	Section(s) Affected by Change
1.	Emergency contact information page has been updated with CRO (PPD) contact information.	Emergency Contact Information
2.	Additional Contact Information page has been updated with CRO (PPD) contact information.	Additional Contact Information
3.	Safety reviews at the end of Cohorts 1, 2 and 3 will be performed with or without the follow-up visit data for the corresponding cohort. Reason for change: Clarification made for when these safety review meetings will occur. There is no anticipated impact to patient safety, given the short half-life of PTH. The primary purpose of the follow-up visit is to collect an anti-PTH antibody sample.	Synopsis; Section 3.1
4.	Exclusion criterion 4: Text in parentheticals "(HbA1C >8%; >64 mmol)" has been deleted for type 2 diabetes mellitus. Reason for change: To allow for Investigator discretion in determining if subject meets this criterion.	Synopsis; Section 4.2
5.	Analysis Populations: PK and PD population definitions are bulleted separately for the analysis population. Reason for Change: Clarification made, since these 2 populations are needed to define PK and PD assessments separately. This change has no impact on subject treatment.	Synopsis; Section 9.7
6.	Table 1: Footnote "e" moved to far left column (study procedure column) rather than the Period 2, Day 2 column (for procedures where indicated). Footnote "k" clarification added to specify that creatinine clearance will be calculated using the Cockroft-Gault formula. Reason for change: Clarification warranted.	Table 1
7.	Table 3: columns (5 min, 3 hr post-dose) which have no assessments to be collected are now deleted. Reason for change: Clarification warranted.	Table 3
8.	Table 4: columns (5 min, 12 hr 5 min, 15 hr post-dose) which have no assessments to be collected are now deleted. The PK and PD sampling predose footnote "f" should be	Table 4

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Amendment Number 2	Amendment Date 03 Jun 2016	Global
Item #	**Description of Change**	**Section(s) Affected by Change**
	corrected to state footnote "c". The last row "1,25 (OH)2D" should be deleted (as this is already included in the PD blood sample assessment in the same table above, and is already specified in footnote "g"). Footnote "f" clarified to remove reference to "1,25(OH)2D. Footnote "i" 24 hour urine collection corrected to "36" hour urine collection (ie, 24 hours after the 2nd BID dose). Reason for change: Minor clarification and/or corrections warranted to the table.	
9.	Figure 1: Revised to illustrate that safety data review will occur after Treatment Period 2, but not necessarily after the follow-up visit) for Cohorts 1, 2 and 3. Reason for change: Clarification warranted.	Figure 1
10.	Biochemistry: Magnesium and creatinine clearance have been added to the safety lab biochemistry panel. Reason for change: to confirm and evaluate Inclusion Criterion # 10, and Inclusion Criterion # 13, respectively.	Section 7.3.2.5
11.	Urinalysis: an asterisk was added to the calcium parameter being collected (with note provided to clarify that eligibility of the subject's urinary calcium excretion result, based on a 24-hour collection prior to check-in to the CRC at Treatment Period 1, Day -2, will be based on the assessment of these results by the Investigator (using local labs, if necessary). Reason for change: Clarification warranted.	Section 7.3.2.5
12.	Table 6: Safety blood volumes reduced for serology, biochemistry and hematology panel, and increased (by 1 mL) for serum 25(OH)D sample. Reason for change: The sample volumes were updated, based on the central lab's confirmation of required sample volumes. This resulted in an overall reduction of total blood volume required for each subject (ie, from 468.5 mL to 440 mL).	Section 7.3.5, Table 6
13.	Two sentences were revised to clarify respective roles of the sponsor and the CRO in reporting responsibilities to regulatory authorities and active study sites.	Section 8.2.7

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	Reason for Change: Clarification warranted.	
14.	Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made throughout the document as appropriate. Reason for change: Clarification and/or typographical corrections.	All sections (as warranted)

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Amendment Number **3**	**Amendment Date** **29 Jul 2016**	**Global**

Item #	Description of Change	Section(s) Affected by Change
1.	Schedule of Assessments: a) Table 1: The assessments for clinical safety blood and urine tests (Treatment Period 1 and Treatment Period 2), pregnancy test (for all females, Treatment Period 2), physical exam (Treatment Period 2), and weight (Treatment Period 2) should be collected after the scheduled serial assessments (for pharmacokinetic [PK] and pharmacodynamic [PD]) have been completed for this study day, and prior to discharging the subject from the Clinical Research Center. Footnote "s" has been added to Table 1 to clarify/specify this. An "X" has also been placed in Table 1 in the washout period column for AEs and Concomitant Medications. b) Tables 3 and 4: The last scheduled serial time point for vital signs and ECG will also serve as the discharge procedure for that assessment on Day 2 for the QD regimen (see Table 3) and for the BID regimen (see Table 4). Footnote "j" has been added to Table 3, and footnote "k" has been added to Table 4, to clarify/specify this. <u>Reason for change</u>: Clarification made that AEs and concomitant medications should be reported during the washout period (Table 1), and clarification made to the order of procedures to be collected prior to discharge in Tables 1, 3 and 4.	Table 1, Table 3, and Table 4
2.	Schedule of Assessments a) Table 2: Detailed Schedule of Assessments: Day -1 (Prior to Treatment Periods 1 and 2), PD urine sampling: For PD urine sampling, the X under the "pre-dose" column in this table is used to signify the action that the subject needs to empty his/her bladder immediately before the start of the 0-3-hour urine collection based on the predicted dosing time on Day 1 (eg, if a dose is	Table 2, Table 3, and Table 4

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	planned to be given at 08.00 on Day 1, the start of the 0-3 hour PD urine collection on Day -1 should be 08.00). It is not a separate pre-dose collection. Footnote "i" in Table 2 has been added to clarify this. Also, reference to "pre-dose" in footnote "g" of Table 2 has been deleted. b) Table 3: Detailed Schedule of Assessments: Treatment Periods 1 and 2, Day 1/Day 2 (QD Regimen), PD urine sampling: For PD urine sampling, the X under the "pre-dose" column on Day 1 in this table is to signify the stop of the Day -1, 18-24 hour PD urine collection period, and the start of the Day 1, 0-3 hour PD urine collection period. It is not a separate pre-dose collection (this is also explained in Table 2, footnote d which indicates that the last assessment time point from Day -1 (ie 18-24 hour PD urine collection) is the same as the pre-dose collection time point on Day 1, in Table 3). Footnote "k" in Table 3 has been added to clarify this. Also, reference to "pre-dose" in footnote "h" of Table 3 has been deleted. c) Table 4: Detailed Schedule of Assessments: Treatment Periods 1 and 2, Day 1/2 (BID Regimen), PD urine sampling: For PD urine sampling, the X under the "pre-dose" column on Day 1 in this table is to signify the stop of the Day -1, 18-24 hour PD urine collection period, and the start of the Day 1, 0-3 hour PD urine collection period. It is not a separate pre-dose collection. This is also explained in Table 2, footnote d which indicates that the last assessment time point from Day -1 (ie 18-24 hour PD urine collection) is the same as the pre-dose collection time point on Day 1, in Table 4. Footnote "l" in Table 4 has been added to clarify this. Also, reference to "pre-dose" in footnote "i" of Table 4 has	

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	been deleted. Reason for change: Clarification made to the Schedule of Assessments tables to clarify that a separate pre-dose pharmacodynamic urine sample is NOT required to be collected for Day -1 and Day 1 of Treatment Periods 1 or 2. Footnotes added to respective tables for clarity.	
3.	Study Schedule 4th and 5th bullets have been reversed: where it currently reads: • "Pharmacokinetic blood sampling • Pharmacodynamic blood sampling" Has been revised to: • "Pharmaco**dynamic** blood sampling • Pharmaco**kinetic** blood sampling" Reason for change: The order of PK and PD sampling was reversed (when samples are collected at the same time point) in order to avoid the potential for EDTA contamination (from PK samples requiring an EDTA tube) being collected before PD serum samples are collected, which could impact assay integrity and/or assay results.	Section 7.2
4.	Rescreening of Subjects: The last sentence of this section which reads: "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." has been moved as a separate paragraph at the end of this section. Reason for change: Making this sentence as a separate (stand-alone) paragraph indicates that this sentence will apply to all subjects who are rescreened (per scenarios described in the 1st and 2nd	Section 7.2.1.4

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	paragraphs in this section).	
5.	Pharmacokinetic Procedures: 2nd paragraph, 3rd sentence which read: "Pharmacokinetic 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 beyond 4 hours post-dose." Has been changed to read: "Pharmacokinetic 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 4 hours post-dose and beyond." Reason for change: Clarification made that the ±15 minute window will apply to samples drawn at the 4 hour post-dose time point.	Section 7.3.3
6.	Pharmacokinetic Blood Sample Collection and Handling Procedures, 3rd bullet: "Cohort" has been deleted from the list of bulleted information that will appear on the PK sample labels. Reason for change: Correction to tube label information required, following confirmation from the bioanalytical lab.	Section 7.3.3.1
7.	Pharmacokinetic Procedures Section header has been revised from "Pharmacokinetic Procedures" to "Pharmaco**dynamic** Procedures" Reason for change: Section header corrected to be consistent with the sub-section headers (and content) below it (ie, Sections 7.3.4.1, 7.3.4.2, 7.3.4.3, 7.3.4.4, 7.3.4.5,	Section 7.3.4

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	7.3.4.6).	
8.	Pharmacokinetics (now corrected to Pharmaco**dynamics**) Procedures: 2nd paragraph, 3rd sentence which read: "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 beyond 4 hours post-dose." Has been changed to read: "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 4 hours post-dose and beyond." Reason for change: Clarification made that the ±15 minute window will apply to samples drawn at the 4 hour post-dose time point.	Section 7.3.4
9.	Pharmacodynamic Blood Sample Collection and Handling Procedures: a) "Cohort" should be deleted from the list of bulleted information that will appear on the PD sample labels. b) "Analyte name (if there is more than 1)" should be added to the bulleted list of information that will appear on the PD sample labels. Reason for change: Correction to tube label information required, following confirmation from the bioanalytical lab.	Section 7.3.4.1
10.	Pharmacodynamic Urine Sample Collection and Handling Procedures: a) "Cohort" should be deleted from the list of bulleted	Section 7.3.4.4

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	information that will appear on the PD sample labels. b) "Analyte name (if there is more than 1)" should be added to the bulleted list of information that will appear on the PD sample labels. Reason for change: Correction to tube label information required, following confirmation from the bioanalytical lab.	
11.	Table 6: Volume of Blood to be Drawn from Each Subject a) PK Samples (first line item of table): "PK samples (serum PTH)[a]" has been revised to: PK samples (**plasma** PTH)[a]". b) Footnote "a" revised and footnote "d" added to clarify that when a PD and PK sample are collected at the same time point, the PD sample is to be drawn prior to the PK sample (to avoid any potential for cross-contamination of tube additives), and if an indwelling catheter is used for this collection, the first 1mL of blood should be discarded prior to the PD blood sample collection. When either a PK or a PD sample is drawn alone at a scheduled time point (using a catheter), 1mL of blood should be discarded prior to the scheduled blood sample collection. c) An 18mL adjustment in the blood volumes was made: the PK volume decreased 18mL, and the PD volume (Day 1-2) increased 18mL. However, the overall blood volume required for the study remains unchanged. d) Footnote "c" added to 8th row description (PD samples [Day 1-2] for total serum calcium, magnesium, phosphate, creatinine, $1,25[OH]_2D_3$). Reason for change:	Section 7.3.5

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	a) The sample matrix was corrected to plasma, to be consistent with the protocol, Section 7.3.3. b) Clarification made (footnote a and d), regarding the order of the 1mL discharge, and the PD and PK sample when collected at the same scheduled time point. c) The 18mL volume "shift" (from the PK total volume to the PD [Day 1-2] total volume) was due to the 1mL discard being required prior to the PD sample (instead of the PK sample), when these samples are collected together using an indwelling catheter. This "shift" does <u>not</u> change the overall blood volume required for the study. d) Footnote "c" was missing for this line item description in the prior version of the protocol, and has been added to this version.	
12.	Pharmacokinetic Analysis 1st paragraph which states: "All the pharmacokinetic analyses will be performed using the pharmacokinetic/pharmacodynamic population." Has been changed to read: "All the pharmacokinetic analyses will be performed using the pharmacokinetic population." <u>Reason for change</u>: Reference to pharmacodynamic population in this section is incorrect, and has been deleted.	Section 9.8.1
13.	Pharmacodynamic Analysis New sentence added at the beginning of this section which reads:	Section 9.8.2

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Amendment Number **3**	**Amendment Date** **29 Jul 2016**	**Global**

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	"All the pharmacodynamic analyses will be performed using the pharmacodynamics population." Reason for change: Sentence added to clarify the population being used for the analysis.	
14.	Population Pharmacokinetic and Quantitative System Pharmacology Modeling and Simulation (**new section and text added**): "Additional modeling and simulation will be performed to evaluate the PK of PTH and the effect on serum calcium concentration and urine calcium excretion from alternative dosing regimens other than the once daily and twice daily doses used in the study. A population PK model and a quantitative system pharmacology model (QSPM) will be developed by fitting PK and PD data obtained from historical studies in hypoparathyroid patients as well as data from this study. Inter-subject variability on model parameters will be fully evaluated. Once the population PK model and the QSPM are satisfactorily validated, simulations using the final validated models will be performed to explore the effects of alternative dosing other than once-daily and twice-daily dosing, eg, 3 times daily (TID), pump infusion dosing, and possibly new formulations of PTH, on the control of serum calcium concentrations and urinary excretion of calcium in hypoparathyroid patients. A separate data analysis plan and report will be prepared for this additional modeling and simulation work. These data will not be used in conjunction with any study patient identifiers." "QSPM" was also added to the list of abbreviations as a result of the term added to protocol text. Reason for change: The addition of text regarding PK/PD modeling was provided to recognize that future work (ie, modeling and simulation), outside of this protocol, could potentially examine alternative dosing regimens. This	Abbreviations; Section 9.8.4 (new section added)

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	added text will not affect the study conduct or patient safety in any way. A separate data analysis plan and report will be prepared for this work.	
15.	Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made throughout the document as appropriate. Reason for change: Clarification and/or typographical corrections.	All sections (as warranted)

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1.	Site(s) and Region(s): "United States" has been changed to "North America" as one of the regions participating. Reason for change: United States has been corrected to the region it is located in (North America). This will also permit additional countries within this region that may decide to participate in the future (without warranting a subsequent amendment for this change).	Synopsis, Section 3.3
2.	An administrative screening (within 120 days of the first dose) has been added prior to the normal screening period for the study. The administrative screen is only for purpose of requesting, authorizing and releasing medical records for a potential subject (if needed). As such, it is not part of the active screening process. The subject must sign an informed consent and a medical records release authorization as the first step of the administrative screening process. This wording and addition to Table 1 clarify the current process to obtain any necessary medical records. Reason for change: To allow for the necessary time required to obtain medical records for subjects interested in participating at a site that is outside of their immediate care network (if needed).	Synopsis; Table 1; Section 3.1; Figure 1; Section 3.2; Section 7.2.1
3.	Details of a remote informed consent process have been added to the protocol. Reason for change: To support remote informed consenting as it relates to subjects who are located at a distance from the site and/or who would require consent and medical record release for conducting an administrative screen (see above, item # 2). To incorporate the wording from the Shire Note to File, (dated 06 Dec 2016) entitled "Remote Informed Consent	Section 7.2.1.1; Appendix 2

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	Process" into the protocol.		
4.	"Screening" has been re-stated as "Clinical Screening", "Clinical Screening Period", or "Clinical Screening Visit" (as applicable) throughout the document. Reason for change: To distinguish the study-specific screening procedures (now called "Clinical Screening") from the newly added "Administrative Screening" process.		Synopsis; Table 1; Section 3.1; Figure 1; Section 7.2.1, Table 6
5.	Table 1: Schedule of Assessments a) Screening Column has been separated into 2 columns: 1 column for Administrative Screening and 1 column for Clinical Screening. b) New line item for medical records release has been added (for admin screen) and informed consent has been added to the administrative screening. New footnote (d) regarding medical records release added. c) Subsequent footnotes thereafter on this table have been re-ordered alphabetically. d) Footnote r (regarding Adverse Events to be collected at the Administrative Screening Period) and Footnote q (regarding 24-hr urine sample collected during the Clinical Screening Period) have been added. e) "Evening check-in to CRC" (22nd row) is corrected to read "Check-in to CRC" Reason for changes (a-d): To distinguish the study-specific screening procedures (now called "Clinical Screening") from the "Administrative Screening" process. Footnotes have been added for clarity. Reason for change (e):		Table 1

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	"Evening" should be deleted from description of time to check-in to the CRC. This change will allow sites and subjects more flexibility in arrival time to CRC on Day -2 for each period, and based on the schedule and timing of required study assessments that need to be completed and/or results received on this study day. Per Administrative Clarification Memo # 1 (dated 21 Oct 2016).	
6.	For Cohorts 3 and 4 (Treatment D, E, and F), subjects should take their supplemental calcium at their usual dose(s)/regimen, and the dose/regimen and timing of their calcium administration should be identical at Day -1, Day 1 and Day 2 in each treatment period. Furthermore, subjects in Cohorts 3 and 4 (Treatment D, E and F) will take their usual supplemental calcium at their usual dose(s)/regimen in Day 1, regardless of the rhPTH (1-84) dosing regimen. The 30 minute window in which calcium supplement was to be taken prior to IP administration was removed. Reason for changes: The intent of the protocol was to allow for subjects to continue their usual regimen of supplemental calcium. Since many subjects may take multiple calcium supplements throughout the day, the present protocol's instructions to take the calcium supplement 30 minutes prior to dose are inconsistent with the usual supplement regimen. The revised wording clarifies that the supplements taken on study will be as intended by the subject's usual regimen. The revised wording clarifies that subjects are to continue their usual regimen of supplemental calcium as intended on study Day 1, regardless of whether subjects are to receive one or two doses of rhPTH(1-84) on that day.	Synopsis; Section 3.1
7.	One or more interim analyses may be performed in this study. If an analysis is deemed to be necessary, then a prospective statistical analysis plan will be developed prior	Synopsis; Section 3.1; Section 9.5

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	to the analysis. The plan will include, at a minimum: (1) rationale to perform the interim analysis; (2) parameters to be analyzed; (3) the distribution list for the interim analysis results. Interim data may be used for (but not limited to) PK/PD modeling and/or regulatory submissions. The trial will not stop due to the results of any interim analysis. Reason for change: To indicate that one or more interim analyses may be performed, as described above.	
8.	Statement added that subjects who complete this study may have the opportunity to enroll in an open-label extension trial. Reason for change: Wording has been added to indicate that subjects may have an opportunity to enroll in an open-label trial, if an open-label extension study is available and approved by the site's IRB/EC.	Synopsis; Section 3.1, Section 7.2.5
9.	Sentence has been added regarding subjects assigned to the BID regimen, suggesting that lunch be divided into 2 portions; the first portion consumed at lunch, and the second portion consumed as the snack or light meal. Reason for change: Statement added to protocol, per Clarification Memo (21 Dec 2016) regarding Site Meal Menus.	Section 3.1
10.	Inclusion criterion #3: the upper age limit has been removed. The Screening Period has been defined to encompass both the Administrative and Clinical Screening Periods, and age assessed at the time the consent is first signed by the subject. Reason for changes: An upper age limit is unnecessary; deletion of this upper limit does not compromise subject safety. Per the US	Synopsis; Section 4.1

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	Package Insert, "Clinical studies of NATPARA did not include sufficient numbers of subjects aged 65 and over to determine whether response in these subjects is different from younger subjects." NATPARA is therefore indicated for adults; there is no age limitation. No dose adjustment is recommended for patients ≥65 years of age. The US Package Insert also notes that physicians should be cautious regarding dose and treatment of geriatric patients. Exclusions #2 and #12 ensure that medical conditions that often tend to occur in geriatric patients are already excluded based on investigator judgment. Clarification regarding when age will be assessed for the study.	
11.	Inclusion criterion #5: elemental calcium specified. Reason for change: Clarification warranted that the strength of supplemental calcium required per day is based on the calcium within the formulation, irrespective of the counter ion.	Synopsis; Section 4.1
12.	Inclusion criterion #7: serum calcium level range revised to state within lab normal reference range, and based on central and/or local lab results at the Clinical Screening Visit and Period 1, Day -2, and if not within normal range, considered as not clinically significant by the investigator. Reason for change: Prior range (≥7.0 to ≤9.5 mg/dL) was restrictive and not consistent with lab normal range for this assessment. Changed to be consistent with lab normal range but also to allow some investigator flexibility in this regard based on medical judgment. Subjects will be confined to the CRC during treatment periods and will be closely monitored by the investigator for clinical signs of hypocalcemia or hypercalcemia. Subject safety is not compromised because of this change.	Synopsis; Section 4.1
13.	Inclusion criterion #8 (historical 24h urinary calcium	Synopsis; Section 4.1

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	excretion) has been deleted. All subsequent criteria in this section have been re-numbered as a result. Reason for change: An historical 24-hr urinary calcium may be variable and not predictive of findings during screening; thus it is not needed to help identify the patient population for this study. The change does not impact subject safety.	
14.	Inclusion criterion #9 (re-numbered as #8): The time window for the 24-hour urine collection is expanded; the sample is to be collected anytime during the Clinical Screening Period, but prior to check-in to the CRC at Treatment Period 1, Day -2. Eligibility to be based on central or local lab urine calcium excretion results. Reason for changes: To allow for more flexibility in the time interval in which the urine collection is obtained during screening. Clarification made regarding which lab results can be used to determine eligibility.	Synopsis; Section 4.1
15.	Inclusion criterion #12 (re-numbered as #11): The inclusion criterion for serum 25(OH)D has been revised to within lower limit of normal and 1.5 fold the laboratory upper limit of normal, or, if outside of this range, considered not clinically significant by the investigator, at the Clinical Screening Visit. Reason for change: Changed to allow for some investigator flexibility in this regard based on medical judgment.	Synopsis; Section 4.1
16.	Inclusion criterion #13 (re-numbered as #12): Study visits at which the serum creatinine value and creatinine clearance values must be met have been added to the text. Creatinine clearance is now corrected to read as	Synopsis; Section 4.1

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	estimated creatinine clearance. Reason for changes: Clarification warranted.	
17.	Exclusion criterion #9 (first bullet) Thiazide diuretics (within 14 days prior to first administration of investigational product) has been added as an exclusion criterion, as new (first) bullet. Reason for change: This exclusion criterion added to restrict the use of a concomitant medication which could have an effect on urinary calcium in this study.	Synopsis; Section 4.2
18.	Exclusion criterion #9 (first bullet, now re-positioned as 2nd bullet): Antacids have been removed from the list of exclusionary medications. Reason for change: Subjects may be taking antacid tablets (Tums® for example) as a source of supplemental calcium. This restriction was removed to allow for inclusion of these subjects. This change does not compromise subject safety.	Synopsis; Section 4.2
19.	Exclusion criterion #10: "…(not related to hypoparathyroidism)"… has been deleted from the text of this criterion. Reason for change: Clarification warranted.	Synopsis; Section 4.2
20.	Exclusion criterion #11: ECG "values (average of triplicate readings)" has been added and last sentence has been deleted. Reason for change:	Synopsis; Section 4.2

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	Since triplicate ECG tracings are already being performed at each time point, clarification was warranted in this criterion, and last sentence was unnecessary (therefore deleted).	
21.	Exclusion criterion #16: Criterion regarding herbal supplements has now been deleted. All subsequent criteria in this section have been re-numbered as a result. Reason for change: The need for the exclusion of herbal supplements is not relevant to this study in this patient population and is not needed; deletion of this exclusion does not compromise patient safety.	Synopsis; Section 4.2
22.	Exclusion criterion #17 (now re-numbered as #16): Criterion regarding screen for drugs of abuse has been modified to allow for investigator discretion to enroll subjects who take prescription medications. Reason for change: Exclusion criterion has been modified to allow subjects on prescription medications that might be detected during the urine screen for drugs of abuse (listed in section 7.3.2.7) to be enrolled per the investigator medical judgment.	Synopsis; Section 4.2
23.	Restrictions: the following item #s have been deleted: • #2 (grapefruit/Seville oranges products) • #5 (regular use of any medications, including OTC, multi-vitamin, herbal, homeopathics) • #6 (foods or beverages containing caffeine/xanthine) All subsequently numbered restrictions in this section have been re-numbered as a result. Reason for change:	Section 4.3

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	The restriction of these food or beverage items and/or medications is unnecessary for this patient-population study; deletion of these restrictions does not compromise subject safety.	
24.	Restrictions #4 (re-numbered as #3): Tobacco (or nicotine products) use has been revised to specify that this restriction only applies to its use within 60 minutes prior to the collection of any vital signs, ECG or blood draws while confined to the CRC. Reason for change: Prior restriction was too limiting and unnecessary for this patient population. This change does not compromise subject safety.	Section 4.3
25.	Restriction #8 (re-numbered as #5): Clarifications added to the text surrounding meal menus, food options/choices and the need for meal choices to be identical for each subject within a site between Period 1 and Period 2. Reason for change: To incorporate wording from the Sponsor's Memo to File (dated 21 Dec 2016) entitled "Site Meal Menus" which was previously forwarded to all participating study sites.	Section 4.3
26.	Concomitant Treatment Statement added that administration times and dose strengths of all calcium and active vitamin D must be recorded accurately and completely in subject's source documents. Reason for change: Statement added to emphasize this point.	Section 5.2
27.	Text added to allow for local destruction of used/unused investigational product/supplies, and only in exceptional circumstances (with prior written agreement by the sponsor).	Section 6.4

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	Reason for change: To permit local destruction of used/unused supplies for sites who are not permitted to return them to the vendor (due to institution's SOPs, hospital/pharmacy regulations, etc.)	
28.	Study Schedule (priority order) Statement added regarding the order/sequence of blood sampling, in order to avoid the potential for cross-contamination of tube additives when collecting blood samples at the same time point for different assays (based on tubes requiring serum versus tubes requiring plasma, which require an anticoagulant). Reason for change: Statement added to protocol, per Administrative Clarification Memo #1 (dated 21 Oct 2016).	Section 7.2
29.	Rescreening of Subjects Clarification and statement added that a total of 2 re-screenings are permitted in this study: one re-screening due to failure to meet inclusion/exclusion criteria that is considered as transient/temporary, and one re-screening due to scheduling/timing issues related to the study schedule (including the time to release medical records, if applicable). Reason for change: Statement added to protocol, per Administrative Clarification Memo # 1 (dated 21 Oct 2016).	Section 7.2.1.4
30.	Vital Signs: Sentence added regarding scheduled assessment time and allowable window in which vital signs must be obtained. A measurement made outside of this window would be considered a protocol deviation.	Section 7.3.2.4

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	Reason for change: Clarification warranted.	
31.	Clinical Lab Evaluations: a) Two statements added: In order to qualify the subject for randomization at Treatment Period 1, the site can base eligibility on the local lab results if the central lab results are not available, but, if results are available from both labs, eligibility should be based on the central lab results. However, local lab results will not be entered in the eCRF/clinical database, and copies of local lab reports must be maintained in the subject source documents. The central lab results (once received) will be entered in the eCRF/clinical database. b) Asterisked Note at end of this section (regarding urinary calcium eligibility) was deleted as this is now redundant with (and encompassed by) the newly added text. c) Creatinine clearance is now corrected to read as estimated creatinine clearance. Reason for changes: Clarification warranted regarding the use of local lab results for eligibility purposes. Clarification made to how creatinine clearance was being assessed.	Section 7.3.2.5
32.	4th paragraph: Sentence modified to include qualifier statement "(except as noted in Exclusion Criterion # 16)" at end of the sentence, so it reads: "Any positive result for drugs of abuse at clinical screening or drugs of abuse or alcohol on Day -1 (both treatment	Section 7.3.2.7

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	periods) will exclude the subject from further participation in the study (except as noted in Exclusion Criterion #16)" Reason for change: Clarification warranted.	
33.	ECGs: a) Sentence added regarding scheduled assessment time and allowable window in which ECGs must be obtained. A measurement made outside of this window would be considered a protocol deviation. b) "sponsor representative" has been revised as "ECG vendor" c) Added "Only valid ECG tracings will be submitted to the ECG vendor for analysis". d) "Valid" added in 2 places within the 5th paragraph to clarify the ECG measurements. e) Third paragraph: sentence which reads: "The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection" is changed to: "The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 60 minutes prior to collection". Reason for changes (a-d): Clarifications warranted. Reason for change (e): The time (30 minutes) was revised (to 60 minutes) to be consistent with the time required for withhold nicotine use	Section 7.3.2.9

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	prior to blood collections in the revised restriction # 4 (re-numbered as # 3).	
34.	PD Blood Sample Collection and Handling Procedures 3rd paragraph, 6th bullet: "Matrix identifier (plasma)" is corrected to read "Matrix identifier (serum)" Reason for change: Matrix corrected to be consistent with other sections of the protocol (sections 7.3.4.2, 7.3.4.3, 7.3.5). Per Administrative Clarification Memo # 1 (dated 21 Oct 2016).	Section 7.3.4.1
35.	Safety Analysis, 3rd paragraph: 1st and 2nd bullets which read: • AEs and TEAEs • Clinical episodes of hypocalcemia and/or hypercalcemia (including, paresthesia, numbness, tetany) and hypercalcemia These 2 bullets have been combined into 1 bullet which reads: • AEs and TEAEs (including episodes of hypocalcemia and/or hypercalcemia [including, paresthesia, numbness, tetany] and hypercalciuria) Reason for changes: The term "hypercalcemia" was inadvertently stated twice in the 2nd bullet. The 2nd appearance of this term in this 2nd bullet was a typographical error and is now corrected to "hypercalciuria". The 1st bullet was combined with the 2nd to be consistent with the safety endpoints section of the synopsis.	Section 9.9

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36.	Synopsis, Safety Endpoints, 1st bullet The update made in Section 9.9 (see item #35 above), is also reflected in the synopsis (Safety Endpoints, 1st bullet). "AEs including episodes of hypo- and hypercalcemia" This sentence is now clarified to read: "AEs including episodes of hypocalcemia, hypercalcemia, and hypercalciuria" Reason for change: To be consistent with the typographical correction made in Section 9.9. Per Administrative Clarification Memo # 1 (dated 21 Oct 2016).	Synopsis
37.	Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made throughout the document as appropriate. Reason for change: Clarification and/or typographical corrections.	All sections (as warranted)

Appendix 2 Remote Informed Consent Process

The remote informed consent process is primarily intended for any potential patient who is distant from a participating study site and also needs to have medical records released to assess preliminary suitability for participation. The remote consent process may be performed only if it is in compliance with the site's local and/or regional regulations and approved by the site's IRB/EC prior to institution.

The study staff of the site selected will contact the potential study subject (patient) and arrange for two copies of their informed consent document to be sent out to the study subject (patient) along with two copies of a medical records release form by courier. The initial package will also contain a pre-paid self-addressed courier envelope and form for return of signed documents.

Within a reasonable time after the initial package has been mailed, the study site will contact the potential study subject (patient) and arrange to go over the informed consent form by telephone. This step should include the opportunity for the potential study subject (patient) to ask medical questions of a site physician listed on the clinical study Statement of Investigator (FDA 1572) form.

Following the telephone call with the study site, if the potential study subject (patient) remains interested in the study, the subject would sign and date one copy of the informed consent form and one copy of the medical record release form and return both documents to the study site in the courier envelope provided. One copy of the informed consent form and one copy of the medical release form would be retained by the potential study subject (patient) for reference.

The study site personnel must document this remote consenting process in their source documents and include the date and time of when they reviewed this process with the prospective subject (patient).

Upon receipt of the signed informed consent and medical release forms, the study site staff will register (enroll) the potential study subject (patient) in the study (IRT) and then request historical medical records from the potential study subject's (patient's) current care provider.

Upon receipt of the signed informed consent document, the study site personnel who discussed the informed consent over the telephone should sign and date the last page (with the date of signature) of the subject's signed consent form and indicate that the consent process was carried out by telephone. The study site personnel must not sign the consent in the witness block, if one exists.

Once the historical medical records are received, the study site physician will review the record to determine if the subject (patient) remains potentially eligible for the study (pending completion of full screening). The potential study subject (patient) will then be contacted. If the potential study subject (patient) does not meet eligibility criteria, they will be informed and regarded as a screen failure in the study.

If the potential study subject (patient) appears to be eligible, they will be informed, and the study site personnel will arrange travel (if applicable) to the study site for further eligibility screening.

Based on site policy, the study site may confirm the identity of the potential study subject (patient [once at the study site]) to verify the signature on the informed consent document that was signed remotely.

Should the potential subject (patient) not be able to complete screening within the designated screening window per protocol (eg, due to a delay in the receipt of medical records or because of travel), the potential subject (patient) would be considered a screen failure. In this case, if the potential subject (patient) remains interested in study participation, they would sign a new informed consent form, either on site or remotely, and restart the screening process (with a new screen number).