Clinical Study Protocol

NCT Number: NCT03324880

Title: A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]

Study Number: SHP634-401

Document Version and Date: Protocol Amendment 3: 11 Nov 2020

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL: SHP634-401

TITLE:	A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]
SHORT TITLE:	BALANCE
DRUG:	rhPTH(1-84)
IND:	076514
EUDRACT NO.:	2017-000284-32
BLA:	125511
SPONSOR:	Shire Human Genetic Therapies, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Protocol Amendment 3: 11 Nov 2020 Protocol Amendment 2: 03 May 2018 Protocol Amendment 1: 15 Jun 2017 Original Protocol: 04 Aug 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** 11-Nov-2020 | 09:58:27 EST
[redacted] MD	

Investigator's Acknowledgem[redacted]

I have read this protocol for Shire Study SHP634-401.

Title: A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]

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 Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

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

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

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

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

The table and the summary below provide an overview of the changes from the previous version (dated 03 May 2018) to the current version of the protocol (Amendment 3).

Grammatical, typographical errors, minor edits for clarity, and general formatting revisions are not identified.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date** 11 Nov 2020	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
The short title of the study "BALANCE" has been added.		Cover Page
Added that Shire is now a wholly owned subsidiary of Takeda Pharmaceutical Company Limited		Cover Page
Updated name for Global Drug Safety to Global Patient Safety Evaluation		Emergency Contact Information; Section 6.2.4; Section 8.1.6; Section 8.2.2; Section 8.2.4
Updated Emergency Contact Information to provide accurate details: "In the event of a serious adverse event (SAE), the investigator must enter SAE directly into the Electronic Data Capture (EDC) system by completing a SAE electronic Case Report Form (eCRF) or report via the paper SAE report form (only as back-up method, when EDC is down) within 24 hours to Shire Global Patient Safety Evaluation. In both cases Investigator signature should be present when submitting the forms. Applicable fax numbers and e-mail address (back-up method) can be found on the form (If SAE is submitted via fax, the SAE fax cover sheet including the site e-mail address details must be attached)."		Emergency Contact Information; Section 8.2.2
The information on product quality complaints has been clarified and updated to follow the sponsor's current language.		Product Quality Complaints
End-of-study (EOS), end-of-treatment (EOT), and early termination (ET) have been added to the abbreviations list and the abbreviations used in the text across sections.		Abbreviations; throughout protocol
Revised text to indicate that active vitamin D and calcium supplements will be provided by the sponsor, designee, or study sites.		Synopsis; Section 3.1.1; Section 5.2.3; Appendix 2
Sample size and power estimates have been revised as follows: • Change interim analysis sample size from 60 to **approximately 68** subjects. • Change total sample size from 118 subjects (59 subjects per arm) to **92** subjects (**46** subjects per arm). • Change 50% information at interim analysis to approximately **74%** information at interim analysis. • Change study power from 89% to **82.5%**. • Change power for PCS derived from the SF-36v2 from >80% to **>70%**		Synopsis; Section 3.1.1; Figure 1 footnote; Section 9.5; Section 9.6

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date** 11 Nov 2020	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
Eligibility criteria have been revised as follows: • Inclusion 10: A typo in the unit of 25-hydroxyvitamin D levels required for eligibility has been corrected (inclusion criterion #10) and it now reads ≥50 **n**mol/L (20 ng/mL). Per administrative Change Memo #4 (dated 05 Jul 2018)		Synopsis; Section 4.1; Section 5.2.1
Updated text on the sensitivity analysis, "If data collection modalities change during the trial, sensitivity analyses may be performed to evaluate the impact of the alternate mode of data collection on the primary endpoint."		Synopsis; Section 9.8.1
Addition of COVID-19-related Changes to Study Conduct Per Administrative Change Memo (dated 30 March 2020): Due to the COVID-19 pandemic and in order to ensure the safety of subjects, the ability of subjects to continue to make on-site visits may be impacted. If visit occurs on the site, proceed with all assessments. If visit is done by phone, labs should be done locally, and urine tests and vital signs are not necessary.		Table 1, Schedule of Assessments, footnote *
The timing for the call from sites to remind subjects to complete their patient-reported outcome instruments has been changed to 2 days prior to the applicable visits.		Table 1; Section 7.1.2.1; Section 7.1.3.3; Section 7.1.3.5; Section 7.1.3.8
It has been clarified that the day of the following visit should be calculated based on the day of the visit and not based on the day of the baseline. Each window should be applied to the calculated day.		Table 1; Section 7.1
All subjects will complete an EOS contact (Week 30 visit) that is a safety follow-up site visit for subjects who discontinued treatment with rhPTH(1-84) or is a telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments for subjects treated with commercial rhPTH(1-84).		Section 3.1.1
The following restriction text was deleted, "Subjects should strive to the greatest extent possible to maintain consistent daily dietary (non-supplement) intake of calcium, phosphate, and sodium prior to study blood draws, and during 24-hour urine collections. To assist with planning food intake on these days, a nutritionist or other qualified individual will evaluate the subject's usual calcium, phosphate, and sodium intake during the screening period. At this evaluation, the subject should be provided with recommended meal plans to match their usual baseline intake when performing study blood draws and urine collections. Dietary adherence will be assessed at follow up dietary evaluations as specified in Table 1 and Sections 7.1.1.2, 7.1.3.4, and 7.1.3.5. See Appendix 5 for the United States Department of Agriculture nutrient database for standard reference release for calcium, phosphorus, and sodium (mg) measured by household and by 100 grams."		Section 4.3

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Amendment Number 3	**Amendment Date** 11 Nov 2020	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
Pregnancy text was updated for clarification, "Females of childbearing potential, who are sexually (heterosexual) active 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 the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product."		Section 4.4.1
Per Administrative Change Memo (dated 11 Jan 2019) Clarifications have been made on data collection related to pregnancies that occurred during the study. It is not necessary to collect information regarding the pregnancy in the partner of a study participant. The sponsor added information to be collected during the pregnancy and after birth.		Section 8.1.6
Added that "In the case of an unplanned event that disallows/prevents the administration of the PRO on a device for reasons including but not limited to, device outage or other technical limitation, subjects may record on a paper version of the assessments that is provided by the CRO or PRO vendor."		Appendix 3
Minor edits for clarity of language, and corrections of spelling		Throughout protocol (see text throughout Section 7.1 for examples of minor changes)

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must enter SAE directly into the Electronic Data Capture (EDC) system by completing a SAE electronic Case Report Form (eCRF) or report via the paper SAE report form (only as back-up method, when EDC is down) within 24 hours to Shire Global Patient Safety Evaluation. In both cases Investigator signature should be present when submitting the forms. Applicable fax numbers and e-mail address (back-up method) can be found on the form (If SAE is submitted via fax, the SAE fax cover sheet including the site e-mail address details must be attached).

Interactive Response Technology (IRT) Country-specific Help Desk Numbers:

In case an emergency unblinding of a subject's treatment assignment is required AND the IRT is out of order, the site will be able to contact the IRT by phone using the country-specific help desk numbers shown below (numbers are also available in the IRT User Manual provided under a separate cover):

Country	Help Desk (Primary Phone Number)	Country	Help Desk (Primary Phone Number)
Belgium	0800-792-89	Norway	800-15-800
Denmark	8070-5304	Portugal	800-180-125
France	0805-080038	Spain	900-809-759
Germany	0800-182-5990	Sweden	020-791-782
Italy	800-872-748	United Kingdom	0800-014-8130
Netherlands	0-800-023-2186	United States	877-810-4786

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that a product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	Capsule fill empty or overage Bottle/vial fill shortage or overage Capsule/tablet damaged/broken Syringe/vial cracked/broken	Syringe leakage Missing components Product discoloration Device malfunction
Labeling	Label missing Leaflet or Instructions For Use (IFU) missing Label illegible	Incomplete, inaccurate, or misleading labeling Lot number or serial number missing
Packaging	Damaged packaging (eg, secondary, primary, bag/pouch) Tampered seals Inadequate or faulty closure	Missing components within package
Foreign material	Contaminated product Particulate in bottle/vial Particulate in packaging	

Please report the product quality complaint using the "Product Complaint Data Collection Form" via the email address:

PQC@shire.com

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ABBREVIATIONS

ACSC	Albumin-corrected serum calcium
AE	adverse event
β-HCG	beta-human chorionic gonadotropin
CI	confidence interval
CRF	case report form
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOS	end-of-study
EOT	end-of-treatment
EQ-5D	EuroQol five dimensions questionnaire
EQ-5D-5L	EuroQol five dimensions questionnaire 5-level version
ET	early termination
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-Cog	Functional Assessment of Cancer Therapy-Cognitive Function
FGF	fibroblast growth factor
GCP	Good Clinical Practice
HPT-SD	Hypoparathyroidism Symptom Diary
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intention-to-treat
MCS	mental component summary
MMRM	mixed-effect model for repeated measures
PCS	physical component summary
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PPS	Per-protocol Set
PRO	patient-reported outcome
PTH	parathyroid hormone
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36v2	36-Item Short Form Health Survey version 2
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US(A)	United States of America
VAS	visual analog scale
WPAI:Hypoparathyroidism	Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism

STUDY SYNOPSIS

Protocol number: SHP634-401	**Drug:** rhPTH(1-84)

Title of the study: A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]

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

It is intended to enroll a minimum of 92 and no more than 150 subjects in a 1:1 ratio to either active treatment or placebo. When approximately 68 subjects complete 26 weeks of treatment, an unblinded interim analysis will be performed to reassess the assumptions used for the sample size and assess for futility. Based on the results of this interim analysis, the number of subjects to be enrolled may be increased from 92 to up to 150 subjects or the trial may be stopped due to futility.

Investigator(s): Multicenter study

Site(s) and region(s):

It is planned to enroll subjects at approximately 30 sites, primarily in the European Union and the United States of America. It is anticipated that approximately 3 to 4 subjects will be enrolled at each site.

Study period (planned): 2017–2021	**Clinical phase:** 3b-4

Objectives:

Primary: The primary objective is to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in the symptoms of hypoparathyroidism as assessed by the Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale compared with standard therapy.

Key Secondary:

The key secondary objectives are to test the hypotheses that rhPTH(1-84) treatment can result in superior improvements in:

- Fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) compared with standard therapy.
- The physical component summary (PCS) derived from the 36-Item Short Form Health Survey version 2 (SF-36v2) acute version compared with standard therapy.

Secondary:

The secondary objectives are as follows:

- To evaluate the efficacy of rhPTH(1-84) as assessed by the following patient-reported outcomes:
  - HPT-SD impact subscale, total and individual items
  - HPT-SD symptom item anxiety and symptom item sadness or depression individual items
  - Individual symptom items of the HPT-SD symptom subscale
  - Evaluate response to the HPT-SD symptom subscale (as measured by a ≥30% reduction in symptom subscale score)
  - The most bothersome symptom of hypoparathyroidism
  - Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)
  - Individual domains and mental component summary of the SF-36v2
  - Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism)
  - Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism
  - Patient Global Impression of Change (PGI-C) for Hypoparathyroidism.
- To evaluate the effect of rhPTH(1-84) on neurocognitive performance as assessed by the following neurocognitive assessments (CogState Brief Battery; CogState Groton Maze Learning Test, CogState International Shopping List Task, CogState International Shopping List Task-Delayed Recall).

- To evaluate the effect of rhPTH(1-84) on metabolic control as assessed by serum albumin-corrected calcium, serum phosphate, and 24-hour urine calcium excretion, as well as active vitamin D and calcium supplement doses.
- To evaluate the effect of rhPTH(1-84) on bone turnover.
- To assess safety and tolerability of rhPTH(1-84).

Rationale:

The study is designed to test the hypothesis that treatment with rhPTH(1-84), a recombinant human parathyroid hormone (PTH), can result in superior improvements in the symptoms of hypoparathyroidism compared with standard therapy.

Investigational product, dose, and mode of administration:

- rhPTH(1-84) by subcutaneous (SC) injection, titrated within the dose range of 25-100 µg once daily (QD) based on metabolic response
- Placebo QD by SC injection which will be mock dose titrated.

Methodology:

This is a randomized, double-blind, placebo-controlled, 2-arm, adaptive study in a minimum of 92 to no more than 150 adult subjects with symptomatic chronic hypoparathyroidism on standard therapy. The study periods will be as follows: a 3-week screening period; a 16-week dose-titration period; a 10-week maintenance-dosing period with minimal change in investigational product dose; and a 4-week safety follow-up period that includes an end-of study contact for all subjects 30 days following the last dose of investigational product. The safety follow-up period includes weekly visits for subjects discontinuing rhPTH(1-84) treatment after the end-of-treatment (EOT) visit (Week 26) or early termination (ET) visit. Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 day after the EOT (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed.

Immediately before dosing at the baseline visit (Week 0), eligible subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- rhPTH(1-84) as adjunctive treatment with active vitamin D and/or calcium supplements
- Placebo with active vitamin D and/or calcium supplements.

Investigational product [rhPTH(1-84) or placebo] will be administered each day in the morning by SC injection into the thigh, alternating the left and right thighs each day, via a multidose injection pen device. Subjects and site personnel will remain blinded to the treatment assignments for the duration of the study. Active vitamin D and calcium supplements will be provided by the sponsor, designee, or study sites.

Changes in investigational product dose can occur approximately every 4 weeks up to and including Week 16 in 25 µg increments up to a maximum dose of 100 µg QD. Following Week 16 (maintenance dosing period [Weeks 17-26]), investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor. At any time during the study as needed for safety reasons, investigational product doses may be decreased in 25 µg decrements to a minimum of 25 µg QD. Dosing of active vitamin D and calcium supplements (calcium supplement refers to prescribed nondietary oral calcium supplement) will also be adjusted for each subject to achieve specified biochemical target levels. Active vitamin D and/or calcium may be increased, decreased and/or stopped during titration. The dosing guidelines, including biochemical target levels, are presented in Appendix 2. Native vitamin D and magnesium should be prescribed as needed throughout the study to achieve a serum 25 hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the upper limit of normal (ULN) and a serum magnesium level within the central laboratory normal range, respectively. Native vitamin D and magnesium will not be provided by the sponsor.

Subjects will be asked to complete patient-reported outcome (PRO) instruments on an electronic device daily from screening to the end-of-treatment or early termination visit. Serum calcium, albumin, phosphate, magnesium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D will be measured at specified time points to assess efficacy and/or to provide information for adjustment of investigational product and supplement doses. Urine chemistry and markers of bone turnover will be measured at specified time points to assess efficacy. Subjects will also be asked to complete neurocognitive assessments and healthcare resource utilization measures.

Safety measures will include adverse event (AE) monitoring, serum chemistry, hematology, urinalysis, vital signs, electrocardiograms (ECGs), physical examinations, and measurement of anti-PTH antibodies. Subjects who discontinue treatment with rhPTH(1-84) following completion of the end-of-treatment (EOT) (or ET) visit or are not immediately continuing treatment with commercial rhPTH(1-84) (gap >7 days) will enter a weekly safety follow up period with serum calcium measurements until the subject is able to begin outpatient rhPTH(1-84) treatment or until a maximum of 30 days has elapsed. All subjects will complete an end-of-study (EOS) contact (Week 30 visit) that is a safety follow-up site visit for subjects who discontinued treatment with rhPTH(1-84) or is a telephone call initiated by the site staff to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments for subjects treated with commercial rhPTH(1-84).

Inclusion and exclusion criteria:

Inclusion criteria:

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

1. Has an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Is able to voluntarily provide a signed and dated informed consent form before any study-related procedures are performed.
3. Is an adult male or female 18 to 85 years of age, inclusive.
4. In subjects 18- 25 years of age, has radiological evidence of epiphyseal closure based on bone age X-ray (single posteroanterior X-ray of left wrist and hand) before randomization
5. Has chronic hypoparathyroidism with onset 12 months or more before screening. The diagnosis of hypoparathyroidism is established based on hypocalcemia in the setting of inappropriately low serum PTH levels.
6. During the Week -3 screening visit, the subject reports by history at least 2 of the following symptoms related to hypoparathyroidism occurring within the 2 weeks before Week -3 visit: muscle cramps, muscle spasms or twitching, tingling, numbness, heaviness in arms or legs, physical fatigue, or slowed or confused thinking (brain fog).
7. The subject must have a Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale Sum Score of ≥10 during the 14-day period immediately prior to the baseline (Week 0) visit (Day -14 to Day -1). In addition, the subject must have at least 4 HPT-SD diaries completed in the first 7 day period and at least 4 HPT-SD diaries completed in second 7 day period. See Appendix 3 for the calculation of the sum score.
8. Must be treated with active vitamin D (calcitriol or alfacalcidol) alone or in conjunction with calcium supplements for at least 4 months prior to the screening visit.
   - The subject must be taking ≥0.5 µg/day of calcitriol or ≥1.0 µg/day of alfacalcidol.
   - If the subject is treated with a lower dose of active vitamin D the subject must also be taking calcium supplements of at least 800 mg/day of elemental calcium
9. Has serum thyroid-stimulating hormone (TSH) results within normal laboratory limits at screening for all subjects not receiving thyroid hormone replacement therapy. For subjects on thyroid hormone replacement therapy, the thyroid hormone dose must have been stable for at least 4 weeks before screening, and serum TSH level must be within the central laboratory normal range. A serum TSH level below the lower limit of the normal range but not undetectable in subjects treated with thyroid hormone may be allowed if there is no anticipated need for a change in thyroid hormone dose during the trial.

10. Has serum 25-hydroxyvitamin D levels ≥50 nmol/L (20 ng/mL) and <1.5 times the upper limit of normal (ULN) for the central laboratory normal range.
11. Has estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2.
12. Prior to randomization, is able to perform daily SC self-injections of study medication (or have a designee perform injection) via a multidose injection pen into the thigh.
13. Willing to use oral active vitamin D and calcium supplements provided for the study unless directed to remain on the supplements used prior to enrollment in the current study by the investigator after consultation with the medical monitor.
14. With regard to female subjects: women who are postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years) and women who are surgically sterilized can be enrolled. Women of childbearing potential must have a negative pregnancy test at randomization and be willing to comply with any applicable contraceptive requirements of the protocol and pregnancy testing for the duration of the study.

Exclusion criteria:

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

1. History of hypoparathyroidism resulting from a known activating mutation in the *CaSR* gene or impaired responsiveness to PTH (pseudohypoparathyroidism).
2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as poorly controlled hyperthyroidism; Paget disease; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver (Child-Pugh score >9) (US FDA, 2003), or renal disease; Cushing syndrome; rheumatoid arthritis; myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer); primary or secondary hyperparathyroidism; or documented parathyroid carcinoma within the previous 5 years, acromegaly, or multiple endocrine neoplasia types 1 and 2.
3. Very low or very high blood calcium level (eg, ACSC <1.87 mmol/L [<7.5 mg/dL] or ≥2.97 mmol/L [≥11.9 mg/dL]) at the Week -3 screening visit. Results from the central laboratory must be used for this assessment
4. Blood calcium level above the ULN at the baseline (Week 0) visit. Results from a local laboratory may be used for this assessment.
5. Use of prohibited medications, such as loop and thiazide diuretics, phosphate binders (other than calcium carbonate), digoxin, lithium, methotrexate, or systemic corticosteroids, within respective prohibited periods. See Section 5 (Prior and Concomitant Treatment) for a list of prohibited and restricted medications.
6. Participation in any other investigational study in which receipt of investigational drug or device occurred within 6 months before screening for this study. Prior treatment with PTH-like drugs (whether commercially available or through participation in an investigational study), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 3 months before screening.
7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride, within the prohibited period.
8. Use of oral bisphosphonates within the previous 6 months or intravenous bisphosphonate preparations within the previous 24 months before screening.
9. Nonhypocalcemic seizure disorder with a history of a seizure within the previous 6 months before screening. Subjects with a history of seizures that occur in the setting of hypocalcemia are allowed.
10. The subject is at increased baseline risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of external beam or implant radiation therapy involving the skeleton.

11. Any disease or condition that, in the opinion of the investigator, may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures. For example, illness that is anticipated to be chronic and not transient.
12. Pregnant or lactating women.
13. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients. Refer to the investigator's brochure for the list of excipients.
14. History of diagnosed drug or alcohol dependence within the previous 3 years.
15. Poorly controlled short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn disease.
16. Chronic or severe cardiac disease including but not limited to heart failure (according to the New York Heart Association classification Class II to Class IV) (Dolgin and NYHA, 1994), arrhythmias, bradycardia (resting heart rate <50 beats/minute).
17. History of cerebrovascular accident.

Maximum duration of subject involvement in the study:

The maximum duration of subject participation in the study is expected to be approximately 33 weeks with

- Planned duration of screening period: 3 weeks
- Planned duration of treatment period: 26 weeks
- Planned duration of follow-up: 4 weeks [all subjects will have contact at the EOS (Week 30 contact) 30 days following the last dose of investigational product; subjects interrupting (>7 days) or discontinuing rhPTH(1-84) treatment after the EOT visit (Week 26) or an ET visit will complete weekly follow-up visits.

Endpoints and statistical analysis:

Analysis sets:

The Intention-to-treat (ITT) Set will consist of all randomized subjects. Subjects in the ITT Set will be analyzed in the treatment group assigned at randomization, regardless of the actual treatment received (analyzed as randomized). All efficacy analyses will be based on the ITT Set unless otherwise specified.

The Safety Set will consist of all subjects who have taken at least 1 dose of investigational product. Subjects in the Safety Set will be analyzed in the treatment group corresponding to actual treatment received (analyzed as treated). All safety analyses will be based on the Safety Set.

The Per-protocol Set (PPS) will consist of all subjects in the ITT Set who complete the study and who do not have predefined protocol deviations that impact the primary efficacy assessment. Subjects in the PPS will be analyzed as treated. Detailed specification of protocol deviations will be documented in the statistical analysis plan (SAP).

Primary efficacy endpoint:

- Change in the HPT-SD symptom subscale score from baseline to Week 26

The null hypothesis for the primary efficacy endpoint is that there is no difference in symptom improvement at Week 26 from baseline between the rhPTH(1-84) and placebo treatment groups. The alternative hypothesis is that the rhPTH(1-84) treatment group shows superior symptom improvement compared with the placebo treatment group.

The primary efficacy analysis will be performed on subjects from the ITT Set using a mixed-effect model for repeated measures (MMRM) analysis at post-baseline visits (Weeks 2, 4, 8, 12, 16, 20, 24, 26) with change from baseline in the HPT-SD symptom subscale score as the outcome variable; treatment group, visit, and their interaction as fixed effect factors and subjects as a random effect, with adjustment for baseline HPT-SD symptom subscale score. The null hypothesis will be rejected if the statistical analysis results in a 1-sided p-value for treatment at Week 26 less than or equal to 0.025.

In the model, visit will be treated as a class variable, assuming an unstructured covariance matrix to model the within-subject variability. If there is a convergence problem due to the use of unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. With a mixed effects model based on restricted maximum likelihood estimation used for the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed in the primary analysis. The primary result obtained from the model will be the estimated main treatment effect at Week 26. The estimated main treatment effect of mean difference between rhPTH(1-84) and placebo, and a 95% confidence interval (CI) will be provided. In addition, least squares means estimated from the model for each treatment group at each post baseline visit, and the estimated treatment effect along with 2-sided 95% CI at each post baseline visit, will also be provided. Descriptive statistics for HPT-SD symptom subscale score at each assessment including baseline, Weeks 6, 10, and 14, and change from baseline at each post-baseline assessment will be reported.

Sensitivity analyses to explore the impact of missing data on the primary endpoint will be conducted. If data collection modalities change during the trial, sensitivity analyses may be performed to evaluate the impact of the alternate mode of data collection on the primary endpoint. Additional sensitivity analyses will also be conducted to explore the impact of adjustments to calcium and active vitamin D supplements on the primary endpoints. All sensitivity analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, baseline calcium supplement dose, baseline active vitamin D dose, history of thyroid hormone replacement, and other important subgroups if feasible. A full list of subgroup analyses will be described in the SAP.

Key secondary efficacy endpoints:

- Change in FACIT-Fatigue score at Week 26
- Change in the PCS derived from SF-36v2 scores at Week 26.

The key secondary efficacy analyses will be conducted over the ITT Set. All tests will be performed as 1-sided tests at the 0.025 level of significance. Each key secondary endpoint will be analyzed similarly as the primary endpoint using MMRM model to compare treatment effect between the rhPTH(1-84) and placebo groups, with change in score from baseline at post-baseline visits as dependent variable; treatment group, visit, and their interaction as fixed effect factors and subjects as a random effect, with adjustment for corresponding baseline score. Additionally, the statistical inference of interest is based on the p-value for treatment at Week 26.

Adjustment for Multiplicity

In order to maintain study-wide Type I error control, a hierarchical testing procedure will be used in the comparisons between rhPTH(1-84) and placebo on the primary and key secondary efficacy endpoints. Specifically, the testing will be conducted in the following order: primary endpoint, FACIT-Fatigue, and then PCS from the SF-36v2. A later test can only be reported as significant if all earlier tests are also found significant.

Multiplicity is not adjusted for other efficacy endpoints in this study.

Secondary efficacy endpoints (assessed at Week 26)**:**

- Change in the HPT-SD impact subscale score
- Change in score of individual HPT-SD impact items
- Change in the HPT-SD symptom item anxiety and symptom item sadness or depression individual item score
- Change in score of individual HPT-SD symptom items
- Response as defined as a 30% reduction in HPT symptom subscale score from Baseline to Week 26
- Change in the most bothersome symptom score
- Change in FACT-Cog score (Perceived Cognitive Impairment, Impact on Quality of Life domains)

- Change in score of individual domains of SF-36v2
- Change in score of mental component summary (MCS) of SF-36v2
- Change in Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism) score
- Change in scores of patient's assessment of overall health status using:
  - Patient Global Impression of Severity (PGI-S for Hypoparathyroidism)
  - Patient Global Impression of Change (PGI-C for Hypoparathyroidism)
- Change in in-clinic neurocognitive assessment scores (assessed through Week 24) (CogState Brief Battery; CogState Groton Maze Learning Test, CogState International Shopping List Task, CogState International Shopping List Task-Delayed Recall)
- Change in at-home neurocognitive assessment scores (CogState Brief Battery)
- Change in 24-hour urine calcium excretion
- Change in serum phosphate level
- Changes in doses of active vitamin D and calcium supplements
- Albumin-corrected serum calcium control, defined as a concentration between 1.87 mmol/L (7.5 mg/dL) and ULN for the central laboratory normal range
- Composite endpoint, as defined as achieving all of the following:
  - Albumin-corrected serum calcium between 1.87 mmol/L (7.5 mg/dL) and the ULN for the central laboratory normal range
  - Dose of active vitamin D decreased by 50%
  - At least a 50% reduction from the baseline oral calcium supplement dose (this criterion will be considered met if the subject's baseline calcium dose is <1000 mg and it does not increase during the study).
- Changes in bone turnover markers.

Secondary efficacy analyses will be performed on the ITT Set. Secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint using an MMRM model. Secondary efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by mean, standard deviation, minimum, maximum, and 95% confidence intervals (CIs). For categorical variables, statistical summaries will include number of subjects and percentages and 95% CIs for binary endpoints.

No multiplicity adjustment will be done on the secondary efficacy endpoints. Summary statistics including nominal p-values will be reported.

Safety endpoints:

- AEs
- Hypocalcemic AEs
- Vital signs
- Laboratory safety data (serum chemistry, hematology, urinalysis)
- ECGs
- Anti-PTH antibodies.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent AEs 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. Hypocalcemic AEs, AEs related to investigational product, AEs leading to withdrawal, serious AEs, and deaths will be similarly summarized and/or listed. Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed. Descriptive statistics will be presented by treatment group at each assessment visit for quantitative safety data as well as for the change from baseline, if applicable. Frequency counts and percentage will be calculated for the classification of qualitative safety data.

Interim analyses:

An unblinded, interim analysis for the primary endpoint will be performed after approximately 74% of all randomized subjects (N = approximately 68) subjects have either completed 26 weeks of treatment (completed the study) or prematurely withdrawn from the study, whichever comes first. The purpose of this unblinded interim analysis is to reassess the appropriateness of assumptions used for the sample size calculation of the primary efficacy endpoint when the study was designed and to assess for futility. The reassessment of the sample size will utilize the conditional power approach under certain conditions that do not inflate the type I error. The planned interim analysis will be conducted by an external independent statistical group; the individuals involved in the day-to-day conduct of the trial will not be involved in the interim analysis or have access to the results of the interim analysis. The sponsor will only be notified by the external independent statistical group of their recommendations to (1) stop the trial early for futility, (2) maintain the sample size as outlined in the current study design, or (3) update the sample size from the conditional power calculation; this will be detailed in the pre-specified interim SAP.

STUDY SCHEDULE

Table 1 Schedule of Assessments

	Screening		Baseline	Dose-titration Period (Weeks 1-16)[b]									Maintenance-dosing Period (Weeks 17-26)[c]			Follow-up[d]			
Visit[a]															End of Treatment/ET				EOS/
Study Week	-3	-2	0	1	2	4	6	8	10	12	14	16	20	24	26	27	28	29	30
Study Procedures*		±2-day window											±3-day window			±2-day window			
Visit Type (S=site/P=phone)	S	S	S	S/P	S/P	S	P	S	P	S	P	S	S	S	S	S	S	S	S/P
Informed consent	X																		
Inclusion/exclusion	X	X	X																
Medical history and demography	X																		
Prior/concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X														X				
Vital signs[e]	X	X	X	X*	X*	X		X		X		X	X	X	X	X	X	X	X
ECG (12-lead)	X									X					X				
Dietary evaluation and recommendations		X					X			X									
X-ray to ensure epiphyseal closure[f]	X																		
Hematology	X									X					X				
Serum chemistry[g]	X		X							X					X				
Serum TSH	X														X				
Serum pregnancy test[h]	X																		
Urine pregnancy test[h]	X		X	X*	X*	X		X		X		X	X	X	X				X
FSH levels[i]	X																		
Serum PTH	X		X																
In-clinic predose nadir level: serum calcium, albumin, phosphate, magnesium[j]	X		X	X*	X*	X		X		X		X	X		X	X	X	X	X
Between visit predose nadir levels (serum calcium, albumin, phosphate, magnesium)[j,k]			As needed following adjustment of investigational product, active vitamin D and/or calcium supplements																
Between visit post-dose peak levels (serum calcium, albumin, phosphate, magnesium)[j,k]			As needed following adjustment of investigational product, active vitamin D and/or calcium supplements																
Serum 25-hydroxyvitamin D	X		X		X	X		X		X		X	X		X				

Table 1 Schedule of Assessments

	Screening		Baseline	Dose-titration Period (Weeks 1-16)[b]									Maintenance-dosing Period (Weeks 17-26)[c]			Follow-up[d]			
Visit[a]															End of Treatment/ET				EOS/
Study Week	-3	-2	0	1	2	4	6	8	10	12	14	16	20	24	26	27	28	29	30
Study Procedures*		±2-day window											±3-day window			±2-day window			
Visit Type (S=site/P=phone)	S	S	S	S/P	S/P	S	P	S	P	S	P	S	S	S	S	S	S	S	S/P
Serum 1,25-dihydroxyvitamin D			X							X					X				
Plasma FGF-23			X												X				
Bone turnover markers			X							X					X				
Anti-PTH antibodies[l]			X							X					X				X
Urinalysis	X														X				
24-hour urine collection[m]		X			X			X		X			X		X				
Randomization			X																
Review Hypoparathyroidism Symptom Diary[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Review Most Bothersome Hypoparathyroidism-related Symptom		X[o]																	
Review compliance with IP, active vitamin D, and calcium supplement dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurocognitive assessment training		X																	
Neurocognitive assessments – in clinic		X												X					
Remind subject of at-home neurocognitive assessments completion[p]		X							X					X					
Phone call to remind subjects to complete PROs prior to visit			X[s] (Day -2)			X[s]				X[s]				X[s]	X[s] (Day prior to the visit)				
Review at-home neurocognitive assessments[q]			X												X				
Review focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)[s]			X			X				X				X	X				
Review health-related quality of life (SF-36v2, EQ-5D-5L)[s]			X			X				X					X				

Table 1 Schedule of Assessments

	Screening		Baseline	Dose-titration Period (Weeks 1-16)[b]									Maintenance-dosing Period (Weeks 17-26)[c]			Follow-up[d]			
Visit[a]															End of Treatment/ET				EOS/
Study Week	-3	-2	0	1	2	4	6	8	10	12	14	16	20	24	26	27	28	29	30
Study Procedures*		±2-day window											±3-day window			±2-day window			
Visit Type (S=site/P=phone)	S	S	S	S/P	S/P	S	P	S	P	S	P	S	S	S	S	S	S	S	S/P
Review work productivity (WPAI:Hypoparathyroidism)[s]			X			X				X				X	X				
Review Patient Global Impression of Severity for Hypoparathyroidism[s]	X	X	X			X				X				X	X				
Review Patient Global Impression of Change for Hypoparathyroidism[s]		X	X							X					X				
Healthcare resource utilization[t]			X		X	X		X		X		X	X	X	X				X
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP self-administration training and review			X[v]	X	X	X	X	X	X	X	X	X	X	X	X[v]				
Dispense/account for IP and supplements[u]			X		X	X		X		X		X	X	X	X				
Collection of unused IP, supplements, injection pen, mixing apparatus, and PRO and neurocognitive devices															X				

Note: See Section 7.2 for guidance about standardized meals and timing of active vitamin D, calcium supplements, and or investigational product doses on study visit days.

* COVID-19-related Changes: Due to the COVID-19 pandemic and in order to ensure the safety of subjects, the ability of subjects to continue to make on-site visits may be impacted. If visit occurs on the site, proceed with all assessments. If visit is done by phone, labs should be done locally and urine tests and vital signs are not necessary.

AE=adverse event; ECG=electrocardiogram; EOS=end of study; EQ-5D-5L= EuroQol five dimensions questionnaire 5-level version; ET=early termination; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-Cog=Functional Assessment of Cancer Therapy-Cognitive Function; FGF-23=fibroblast growth factor-23; FSH=follicle-stimulating hormone; HPT=hypoparathyroidism; IP=investigational product; PTH=parathyroid hormone; SAE=serious adverse event; SF-36v2=36-Item Short Form Health Survey version 2; TSH=thyroid-stimulating hormone; WPAI: Hypoparathyroidism=Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism

[a] The day of the following visit should be calculated based on the day of the current visit, **not** on the day of the baseline visit. The visit window (eg, ±2 days) applies to the calculated day.

[b] Changes in investigational product dose can occur approximately every 4 weeks up to and including Week 16. Active vitamin D and calcium supplements should be taken as determined by the investigator in order to achieve albumin-corrected serum calcium levels in the target range (see Appendix 2). Native vitamin D should be taken as determined by the investigator to target a serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the upper limit of normal (ULN). Magnesium supplements should be given, as appropriate, to achieve a serum magnesium concentration within the laboratory normal range

[c] Following Week 16, investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor (see Appendix 2). At any time during the study as needed for safety reasons, investigational product doses may be decreased in 25 µg decrements to a minimum of 25 µg QD.

Table 1 Schedule of Assessments

Visit[a]	Screening		Baseline	Dose-titration Period (Weeks 1-16)[b]									Maintenance-dosing Period (Weeks 17-26)[c]			Follow-up[d]			
															End of Treatment/ET				EOS/
Study Week	-3	-2	0	1	2	4	6	8	10	12	14	16	20	24	26	27	28	29	30
Study Procedures*		±2-day window											±3-day window			±2-day windo			
Visit Type (S=site/P=phone)	S	S	S	S/P	S/P	S	P	S	P	S	P	S	S	S	S	S	S	S	S/P

[d] All subjects will have an EOS (Week 30) contact 30 days following the last dose of investigational product. Weekly follow-up visits will be performed for subjects discontinuing treatment with rhPTH(1-84) after Week 26 (EOT or ET) visit. These subjects will be prescribed appropriate oral calcium and/or active vitamin D supplements to compensate for the cessation of the rhPTH(1-84). Subjects transferring immediately to commercial rhPTH(1-84) after Week 26 visit (EOT visit) will continue to be monitored under the care of a physician according to rhPTH(1-84) labeling instructions. Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 days after the EOT (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed (see Section 7.1.4 for additional details). If a subject transfers to commercial rhPTH(1-84) treatment before the EOS (Week 30) visit, assessments scheduled at the EOS (Week 30) visit should be performed at their last follow-up visit before transferring to commercial rhPTH(1-84); these subjects will have an EOS contact 30 days following their last dose of investigational product.. The EOS contact (Week 30 visit) is a safety follow-up telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments. Subjects who will be returning to the site for their last weekly follow-up visit can complete the EOS contact (Week 30 visit) at the site.

[e] Vital signs include blood pressure, pulse, body temperature, and respiratory rate.

[f] For subjects 18-25 years of age, bone age X-ray (single posteroanterior X-ray of the left wrist and hand).

[g] Serum chemistry panel excludes albumin, calcium, phosphate, and magnesium, which are noted separately.

[h] Pregnancy tests for female subjects of childbearing potential. The urine pregnancy test results obtained at screening will be confirmed by a serum pregnancy test.

[i] FSH levels required for newly menopausal women.

[j] In addition to protocol specified laboratory testing processed in the central laboratory, blood for the evaluation of serum calcium, albumin, phosphate, and magnesium levels obtained on scheduled visit days can be analyzed locally at the sites or other local laboratories that are authorized by the investigator. These values may be used for titration of investigational product and supplements. When these samples are drawn locally, these samples can be analyzed per local laboratory standards (eg, ionized or total serum or plasma calcium) and should be interpreted using the local laboratory normal values. If a local laboratory is used on scheduled study site visit days (ie, Weeks -3, -2, 0, 1, 2, 4, 8, 12, 16, 20, 24, 26), 27, 28, 29, and 30) a duplicate sample must be collected and provided to the central laboratory. See Appendix 2 for testing between scheduled visits.

[k] It is recommended that between visit predose nadir and post-dose peak levels should be assessed following adjustment of the dose of investigational product, active vitamin D, and/or calcium supplements to aid in titration. If between visit predose nadir and post-dose peak levels are not assessed, the reason for not completing the measurements should be documented. Blood for the assessment of these levels should be collected approximately 2-5 days following any adjustment(s). The post-dose peak level blood draw for the evaluation of serum calcium, albumin, phosphate, and magnesium should be drawn approximately 8-12 hours following administration of the investigational product dose. The predose nadir level blood draw for the evaluation of serum calcium, phosphate, albumin, and magnesium should be drawn in the morning prior to the administration of the dose of investigational product that day, within 24 hours of the last dose of investigational product. Blood for predose nadir and post-dose peak levels can be drawn on the same day or different days as long as the blood draws are completed within the 2-5 day window and within the window specified for each level. Local laboratories can be used for these assessments; duplicate samples do not need to be sent to the central laboratory. Additional between visit blood draws can be completed at any time at the discretion of the investigator.

[l] Blood samples for the detection of anti-PTH antibodies must be collected prior to dosing with the investigational product (at least 14 hours after the prior dose of investigational product).

[m] Subjects should strive to the greatest extent possible to maintain consistent daily dietary (non-supplement) intake of calcium, phosphate, and sodium during 24-hour urine

Table 1 Schedule of Assessments

	Screening		Baseline	Dose-titration Period (Weeks 1-16)[b]									Maintenance-dosing Period (Weeks 17-26)[c]			Follow-up[d]			
Visit[a]															End of Treatment/ET				EOS/
Study Week	-3	-2	0	1	2	4	6	8	10	12	14	16	20	24	26	27	28	29	30
Study Procedures*		±2-day window											±3-day window			±2-day windov			
Visit Type (S=site/P=phone)	S	S	S	S/P	S/P	S	P	S	P	S	P	S	S	S	S	S	S	S	S/P

collections. The 24-hour urine collection is to be completed the morning of the specified visits. Subjects taking vitamin C or a multivitamin containing vitamin C must stop this medication for the 5 days prior to and during each 24-hour urine collection period. Subjects should take their usual calcium, vitamin D (both native and active), and investigational product doses. On urine collection days, subjects should drink enough water to ensure that at least 1 liter of urine is collected over 24 hours.

[n] Subjects will be asked to complete a Hypoparathyroidism Symptom Diary at a consistent time every day from the day of screening (Week -3) until the end-of-treatment/ET visits. During treatment with investigational product, it will be expected that subjects record responses approximately 5-12 hours after morning investigational product doses. Data collected during Week -2 to baseline (Week 0) will be used to confirm eligibility to proceed in the study.

[o] Subjects will be asked to complete the question once at home within the 2 days before the Week -2 visit; if the question was not completed at home prior to the Week-2 visit, it can be completed once at home within the 2 days after the scheduled visit. The question cannot be completed during the Week -2 visit.

[p] Subjects will be asked to record their doses of active vitamin D and calcium supplements each day from screening (Week -3) until the safety follow-up visit at the EOS visit (Week 30) or EOT/ET visit, as applicable. Subjects will also be asked to record their doses of investigational product each day from the baseline visit (Week 0) until the EOT/ET visit.

[q] Subjects will be reminded to complete the neurocognitive assessments (CogState Brief Battery) at home twice daily on each of the 14 days before the visit, ending 1 day before the visit. For the baseline visit, the assessments are to be completed twice daily on each of the days between the Week -2 visit and baseline visit (Week 0). Subjects will complete the testing once each morning after their morning routine (eg, dressing, eating, and taking medication) and once in the evening before dinner.

[r] Review subject's compliance with completion of at-home neurocognitive assessment.

[s] At the Week -3 visit, subjects should complete the PGI-S for hypoparathyroidism at the clinic after the subject has received and has been trained on the PRO device. PRO instruments (including PGI-S for hypoparathyroidism and PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to baseline (Week 0) and EOT (Week 26) visits. Two days before the baseline (Week 0) and the EOT (Week 26) visits, subjects should receive a phone call to remind them to complete their PRO instruments. Subjects who do not complete their PRO instruments prior to the baseline (Week 0) visit will not be able to be randomized and can be rescreened starting at the Week -3 visit per the discretion of the investigator. Subjects should complete the PRO instruments for the Week -2 visit (including the most bothersome hypoparathyroidism-related symptom, PGI-S for hypoparathyroidism, and PGI-C for hypoparathyroidism) and for applicable visits between Week 1 and Week 24 (including PGI-S for hypoparathyroidism, PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) once at home within the 2 days prior to the scheduled visit. If the PRO instruments are not completed prior to the scheduled visit, they can be completed once at home within the 2 days after the scheduled visit. PRO instruments cannot be completed during scheduled visits. During treatment with investigational product, the instruments should be completed approximately 5-12 hours after investigational product dosing. Review subject's compliance with completion of indicated instruments at specified visits.

[t] Baseline Visit version to be used at the baseline visit (Week 0) only. Follow-up version to be used at all subsequent visits.

[u] Subjects will use their pre-existing active vitamin D and calcium supplements during the screening period. Investigational product, active vitamin D, and calcium supplements to be taken after randomization will be dispensed at the baseline (Week 0) visit. Subjects can also use a local source of active vitamin D and calcium supplements during the study in the regimen prescribed by the site PI.

[v] The IP administration starts at Baseline (Week 0) and the last dose of IP is administered at the Week 26 visit.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Chronic hypoparathyroidism is a rare disease characterized by hypocalcemia and insufficient levels of parathyroid hormone (PTH).

Until recently, standard therapy for hypoparathyroidism consisted of calcium and vitamin D supplementation, which only addresses the hypocalcemia characteristic of this disorder. Other metabolic disorders associated with hypoparathyroidism are not addressed by standard therapy. Because PTH deficiency results in inadequate renal resorption of calcium, standard therapy often results in hypercalciuria, potentially leading to long-term renal complications such as nephrocalcinosis, nephrolithiasis, and renal insufficiency commonly seen in these patients. Other long-term complications associated with hypoparathyroidism treated conventionally include basal ganglia calcification, and other intracerebral calcifications. Symptoms suggestive of cognitive impairment, as well as muscle cramps, muscle spasms or twitching, tingling, numbness, heaviness in arms or legs, physical fatigue, depression and anxiety have also been reported by patients.

1.2 Product Background and Clinical Information

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. rhPTH(1-84) was approved by the United States Food and Drug Administration in January 2015 and the European Commission in April 2017.

The pivotal Phase 3 clinical study in the rhPTH(1-84) program, Study CL1-11-040 (REPLACE), demonstrated that rhPTH(1-84) is effective in maintaining serum calcium levels and enabling significant decreases in active vitamin D and oral calcium doses, when administered at subcutaneous (SC) doses of 50 to 100 μg in the thigh once daily (QD) for 6 months. Long-term, open-label studies have supported these findings with subjects maintaining the physiologic benefit derived from rhPTH(1-84) treatment at doses of 25 to 100 μg.

A review of safety data across the hypoparathyroidism program indicated that rhPTH(1-84) 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, nausea, vomiting, arthralgia, muscle spasms, hypoesthesia, and parathesia. Common adverse reactions (ie, reported in at least 1 in every 100 subjects, but fewer than 1 in every 10 subjects) included hypomagnesemia, tetany, anxiety, insomnia, palpitations, abdominal pain upper, cough, muscle twitching, musculoskeletal pain, myalgia, neck pain, pain in extremity, somnolence, hypercalciuria, pollakiuria, asthenia, chest pain, fatigue, injection site reactions, thirst, anti-PTH antibody positive, blood 25-hydroxycholecalciferol decreased, vitamin D decreased, and hypertension.

No evidence for drug related objective laboratory or ECG abnormalities were seen in clinical trials other than serum calcium changes associated with the known pharmacology of the drug. There was no evidence for clinically significant immunologic responses.

Nonclinical data suggest that rhPTH(1-84) may increase the risk of osteosarcoma. 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 disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult subjects with open epiphyses, subjects with hereditary disorders predisposing to osteosarcoma, and subjects with a history of prior external beam or implant radiation therapy involving the skeleton).

Additional risks include extensions of the pharmacologic effects 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 known on-treatment events of hypocalcemia occurred following incidental missed doses of rhPTH(1-84) during clinical studies; however, subjects should be advised to take their rhPTH(1-84) dose as soon possible following a missed dose and to take additional oral calcium if symptomatic.

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.

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

1.3 Benefit/Risk Assessment

See Appendix 4 for the benefit/risk assessment.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The study is designed to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in the symptoms of hypoparathyroidism compared with standard therapy.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective is to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in the symptoms of hypoparathyroidism as assessed by the Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale compared with standard therapy.

2.2.2 Key Secondary Objectives

The key secondary objectives are to test the hypotheses that rhPTH(1-84) treatment can result in superior improvements in:

- Fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) compared with standard therapy.
- The physical component summary (PCS) derived from the 36-Item Short Form Health Survey version 2 (SF-36v2) acute version compared with standard therapy.

2.2.3 Secondary Objectives

The secondary objectives are as follows:

- To evaluate the efficacy of rhPTH(1-84) as assessed by the following patient-reported outcomes
  - HPT-SD impact subscale, total and individual items
  - HPT-SD symptom item anxiety and symptom item sadness or depression individual items
  - Individual symptom items of the HPT-SD symptom subscale
  - Evaluate response to the HPT-SD symptom subscale (as measured by a ≥30% reduction in symptom subscale score)
  - The most bothersome symptom of hypoparathyroidism
  - Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)
  - Individual domains and mental component summary of the SF-36v2
  - Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism)
  - Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism

- Patient Global Impression of Change (PGI-C) for Hypoparathyroidism.

- To evaluate the effect of rhPTH(1-84) on neurocognitive performance as assessed by the following neurocognitive assessments (CogState Brief Battery; CogState Groton Maze Learning Test, CogState International Shopping List Task, CogState International Shopping List Task-Delayed Recall).
- To evaluate the effect of rhPTH(1-84) on metabolic control as assessed by serum albumin-corrected calcium, serum phosphate, and 24-hour urine calcium excretion, as well as active vitamin D and calcium supplement doses.
- To evaluate the effect of rhPTH(1-84) on bone turnover.
- To assess safety and tolerability of rhPTH(1-84).

3 STUDY DESIGN

3.1 Study Design and Flow Chart

3.1.1 Overall Study Design

This is a randomized, double-blind, placebo-controlled, 2-arm, adaptive study in a minimum of 92 and no more than 150 adult subjects with symptomatic chronic hypoparathyroidism. The study periods will be as follows: a 3-week screening period; a 16-week dose-titration period; a 10-week maintenance-dosing period with minimal change in the investigational product dose; and a 4-week safety follow-up period that includes an end-of-study (EOS)(Week 30 visit) contact for all subjects 30 days following the last dose of investigational product. The safety follow-up period includes weekly visits for subjects discontinuing rhPTH(1-84) treatment after the end-of-treatment (EOT) visit (Week 26) or early termination visit. Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 days after the EOT (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. See Section 7.1.4 for additional details related to the follow-up period.

Immediately before dosing at the baseline visit (Week 0), eligible subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- rhPTH(1-84) as adjunctive treatment with active vitamin D and/or calcium supplements
- Placebo with active vitamin D and/or calcium supplements.

Investigational product [rhPTH(1-84) or placebo] will be administered each day in the morning by SC injection into the thigh, alternating the left and right thighs each day, via a multidose injection pen device. Subjects and site personnel will remain blinded to the treatment assignments for the duration of the study. Active vitamin D and calcium supplements will be provided by the sponsor, designee, or study sites.

Changes in investigational product dose can occur approximately every 4 weeks up to and including Week 16 in 25 µg increments up to a maximum dose of 100 µg QD. Following Week 16 (maintenance dosing period [Weeks 17-26]), investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor. At any time during the study as needed for safety reasons, investigational product doses may be decreased in 25 µg decrements to a minimum of 25 µg QD. Dosing of active vitamin D and calcium supplements will also be adjusted for each subject to achieve specified biochemical target levels. Active vitamin D and/or calcium may be increased, decreased and/or stopped during titration. The dosing guidelines, including biochemical target levels, are presented in Appendix 2. Native vitamin D and magnesium should be prescribed as needed throughout the study to achieve a serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the upper limit of normal (ULN) and a serum magnesium level within the central laboratory normal range, respectively. Native vitamin D and magnesium will not be provided by the sponsor.

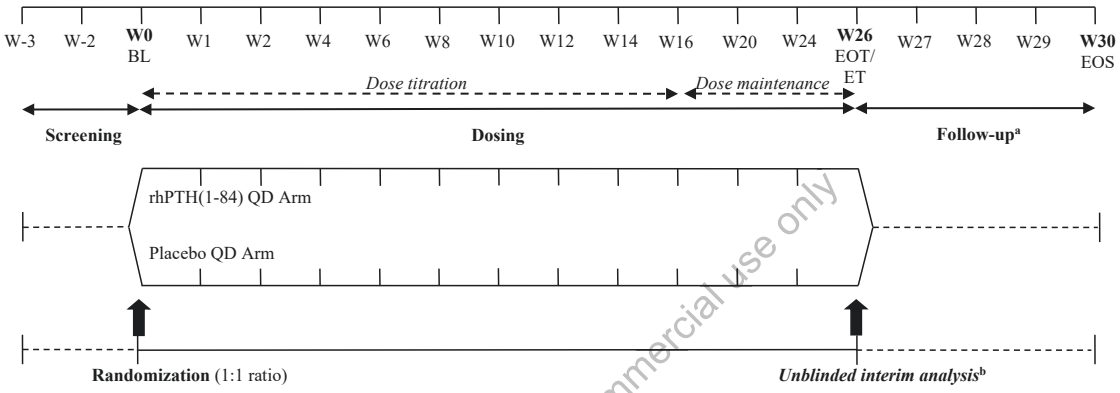
Subjects will be asked to complete the indicated patient-reported outcome (PRO) instruments on an electronic device daily from screening to the EOT/ET visit. Serum calcium, albumin, phosphate, magnesium, 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D will be measured at specified time points to assess efficacy and to provide information for adjustment of investigational product and supplement doses. Urine chemistry and markers of bone turnover will be measured at specified time points to assess efficacy and safety. Subjects will be asked to complete neurocognitive assessments and healthcare resource utilization measures.

Safety measures will include adverse event (AE) monitoring, serum chemistry, hematology, urinalysis, vital signs, electrocardiograms (ECGs), physical examinations, and measurement of anti-PTH antibodies. Subjects who discontinue treatment with rhPTH(1-84) following completion of the EOT (or early termination [ET]) visit or are not immediately continuing treatment with commercial rhPTH(1-84) (gap >7 days) will enter a weekly safety follow up period with serum calcium measurements until the subjects are able to begin commercial rhPTH(1-84) treatment or until a maximum of 30 days has elapsed. All subjects will complete an EOS contact (Week 30 visit) that is a safety follow-up site visit for subjects who discontinued treatment with rhPTH(1-84) or is a telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments for subjects treated with commercial rhPTH(1-84).

An unblinded interim analysis for the primary endpoint will be performed when approximately 68 subjects have completed 26 weeks of treatment (completed the study) or prematurely withdrawn from the study, whichever comes first. The purpose of this unblinded interim analysis is to reassess the appropriateness of assumptions used for the sample size calculation of the primary efficacy endpoint when the study was designed and to assess for futility (see Section 9.5).

A schematic representation of the study design and titration period is displayed in Figure 1.

Figure 1 Study Design Flow Chart



Dosing consists of a 16-week dose-titration period (Weeks 1-16) and a 10-week maintenance-dosing period (Weeks 17-26) with minimal change in investigational product dose.

BL=baseline; EOT=end of treatment; ET=early termination; FU=follow-up; QD=once daily; rhPTH(1-84)=recombinant human parathyroid hormone; W=week

[a] All subjects will complete an EOS (Week 30) contact 30 days following the last dose of investigational product. Weekly follow-up visits (Weeks 27-30) applies to subjects discontinuing treatment with rhPTH(1-84) after Week 26 (EOT/ET) visit. Subjects transferring immediately to commercial rhPTH(1-84) after the EOT (Week 26) visit will continue to be monitored under the care of a physician according to rhPTH(1-84) labeling instructions. Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 day after the EOT (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. See Section 7.1.4 for additional details related to the follow-up period. The EOS contact (Week 30 visit) is a safety follow-up telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments. Subjects who will be returning to the site for their last weekly follow-up visit can complete the EOS contact (Week 30 visit) at the site.

[b] The interim analysis will be performed when approximately 68 subjects are enrolled and complete 26 weeks of treatment or prematurely withdrawn from the study, whichever comes first. This unblinded interim analysis will be performed by a third party to reassess the assumptions used for the sample size and assess for futility. The total number of subjects enrolled in the study may be maintained at 92, increased from 92 up to 150 subjects or the study may be stopped due to futility.

3.1.2 Discussion of Study Design

The doses of rhPTH(1-84) are based upon the range of doses marketed in the USA and the European Union (EU); doses will be individualized depending on metabolic needs. The route of dosing is the same as is used for the marketed product.

A double-blind design was chosen to reduce the risk of bias when assessing the performance of HPT-SD and other patient reported outcome instruments. Subjects in both arms of the study will use oral calcium and active vitamin D supplements as needed to achieve biochemical targets as specified in Appendix 2.

Use of placebo in the comparator arm will allow rhPTH(1-84) with active vitamin D and calcium supplements to be compared with active vitamin D and calcium supplements only.

The HPT-SD is an instrument that has been tested for content and construct validity, and internal consistency reliability. Additional psychometric properties of this instrument will be evaluated in the present study. Other patient-reported outcome and neurocognitive instruments used in this study have been previously validated.

The efficacy and safety measures in this study are generally accepted measures for evaluating the efficacy and safety of treatments for hypoparathyroidism.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 33 weeks (8 months). All subjects will have an EOS contact (Week 30) 30 days following the last dose of investigational product. Subjects discontinuing treatment with rhPTH(1-84) will perform the weekly follow-up visits (Weeks 27-30). Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 day after the EOT visit (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. See Section 7.1.4 for additional details related to the follow-up period. The study will be completed in approximately 3 years.

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 planned to enroll subjects at approximately 30 sites, primarily the EU and the USA. It is anticipated that approximately 3 to 4 subjects will be enrolled at each site.

3.4 Early termination of the Study

After performance of the interim analysis an external independent statistical group may recommend that the sponsor stop the trial early for futility.

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 following criteria.

1. Has an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Is able to voluntarily provide a signed and dated informed consent form before any study-related procedures are performed.
3. Is an adult male or female 18 to 85 years of age, inclusive.
4. In subjects 18- 25 years of age, has radiological evidence of epiphyseal closure based on bone age X-ray (single posteroanterior X-ray of left wrist and hand) before randomization
5. Has chronic hypoparathyroidism with onset 12 months or more before screening. The diagnosis of hypoparathyroidism is established based on hypocalcemia in the setting of inappropriately low serum PTH levels.
6. During the Week -3 screening visit, the subject reports by history at least 2 of the following symptoms related to hypoparathyroidism occurring within the 2 weeks before Week -3 visit: muscle cramps, muscle spasms or twitching, tingling, numbness, heaviness in arms or legs, physical fatigue, or slowed or confused thinking (brain fog).
7. The subject must have a Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale Sum Score of ≥10 during the 14-day period immediately prior to the baseline (Week 0) visit (Day -14 to Day -1). In addition, the subject must have at least 4 HPT-SD diaries completed in the first 7 day period and at least 4 HPT-SD diaries completed in second 7 day period. See Appendix 3 for the calculation of the sum score.
8. Must be treated with active vitamin D (calcitriol or alfacalcidol) alone or in conjunction with calcium supplements for at least 4 months prior to the screening visit.
   - The subject must be taking ≥0.5 µg/day of calcitriol or ≥1.0 µg/day of alfacalcidol.
   - If the subject is treated with a lower dose of active vitamin D the subject must also be taking calcium supplements of at least 800 mg/day of elemental calcium.
9. Has serum thyroid-stimulating hormone (TSH) results within normal laboratory limits at screening for all subjects not receiving thyroid hormone replacement therapy. For subjects on thyroid hormone replacement therapy, the thyroid hormone dose must have been stable for at least 4 weeks before screening, and serum TSH level must be within the central laboratory normal range. A serum TSH level below the lower limit of the normal range but not undetectable in subjects treated with thyroid hormone may be allowed if there is no anticipated need for a change in thyroid hormone dose during the trial.

10. Has serum 25-hydroxyvitamin D levels ≥50 nmol/L (20 ng/mL) and <1.5 times the upper limit of normal (ULN) for the central laboratory normal range.
11. Has estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2.
12. Prior to randomization, is able to perform daily SC self-injections of study medication (or have a designee perform injection) via a multidose injection pen into the thigh.
13. Willing to use oral active vitamin D and calcium supplements provided for the study unless directed to remain on the supplements used prior to enrollment in the current study by the investigator after consultation with the medical monitor.
14. With regard to female subjects: women who are postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years) and women who are surgically sterilized can be enrolled. Women of childbearing potential must have a negative pregnancy test at randomization and be willing to comply with any applicable contraceptive requirements of the protocol and pregnancy testing for the duration of the study.

4.2 Exclusion Criteria

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

1. History of hypoparathyroidism resulting from a known activating mutation in the *CaSR* gene or impaired responsiveness to PTH (pseudohypoparathyroidism).
2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as poorly controlled hyperthyroidism; Paget disease; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver (Child-Pugh score >9) (US FDA, 2003), or renal disease; Cushing syndrome; rheumatoid arthritis; myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer); primary or secondary hyperparathyroidism; or documented parathyroid carcinoma within the previous 5 years, acromegaly, or multiple endocrine neoplasia types 1 and 2.
3. Very low or very high blood calcium level (eg, ACSC <1.87 mmol/L [<7.5 mg/dL] or ≥2.97 mmol/L [≥11.9 mg/dL]) at the Week -3 screening visit. Results from the central laboratory must be used for this assessment.
4. Blood calcium level above the ULN at the baseline (Week 0) visit. Results from a local laboratory may be used for this assessment.
5. Use of prohibited medications, such as loop and thiazide diuretics, phosphate binders (other than calcium carbonate), digoxin, lithium, methotrexate, or systemic corticosteroids, within respective prohibited periods. See Section 5 (Prior and Concomitant Treatment) for a list of prohibited and restricted medications.
6. Participation in any other investigational study in which receipt of investigational drug or device occurred within 6 months before screening for this study. Prior treatment with PTH-like drugs (whether commercially available or through participation in an investigational study), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 3 months before screening.

7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride, within the prohibited period.
8. Use of oral bisphosphonates within the previous 6 months or intravenous bisphosphonate preparations within the previous 24 months before screening.
9. Nonhypocalcemic seizure disorder with a history of a seizure within the previous 6 months before screening. Subjects with a history of seizures that occur in the setting of hypocalcemia are allowed.
10. The subject is at increased baseline risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of external beam or implant radiation therapy involving the skeleton.
11. Any disease or condition that, in the opinion of the investigator, may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures. For example, illness that is anticipated to be chronic and not transient.
12. Pregnant or lactating women.
13. Known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients. Refer to the investigator's brochure for the list of excipients.
14. History of diagnosed drug or alcohol dependence within the previous 3 years.
15. Poorly controlled short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn disease.
16. Chronic or severe cardiac disease including but not limited to heart failure (according to the New York Heart Association classification Class II to Class IV) (Dolgin and NYHA, 1994), arrhythmias, bradycardia (resting heart rate <50 beats/minute).
17. History of cerebrovascular accident.

4.3 Restrictions

Not applicable.

4.4 Reproductive Potential

4.4.1 Female Contraception

Female subjects should fulfill one of the following criteria:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks poststerilization, or

- Females of childbearing potential with a negative urine and/or serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the screening visit (Week -3) and before randomization (Week 0). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Females of childbearing potential, who are sexually (heterosexual) active 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 the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days before the screening visit (Week -3), plus condoms. Note: If a subject becomes sexually active during the study, she 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

Not applicable.

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).

If investigational product is discontinued, regardless of the reason, the evaluations listed for the EOT/ET visit are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up (see Section 7.1.4). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the source documents.

Subjects who discontinue will not be replaced.

4.5.1 Reasons for Discontinuation

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

Reasons for discontinuation include but are not limited to:

- Adverse event
  - For example, the subject must be discontinued from the study if they experienced any of the following symptoms of the disease under study:
    - Persistent severe hypocalcemia not responsive to supplement or investigational product dose adjustment.
    - Persistent severe hypercalcemia not responsive to supplement or investigational product dose adjustment.

    See Section 8.1.4 for definition of severe hypocalcemia. Severe hypercalcemia is defined as a serum calcium concentration increase that is associated with changes in sensorium or a level that is above 14 mg/dL (3.5 mmol/L).
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Other (eg, death, physician decision, pregnancy, site terminated by sponsor, study terminated by sponsor).

If "other" is selected as the reason, then the investigator must specify the reason.

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

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before 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

All nonstudy treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, nonpharmacological treatment, such as psychotherapy, as appropriate) received within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) before the date of first dose of investigational product and through the final study contact (including protocol-defined follow-up period) must be recorded in the source document.

5.1 Prior Treatment

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

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 (or EOT, as specified in the protocol), inclusive. Concomitant treatment information must be recorded in the source document.

5.2.1 Permitted Treatment

Thyroid hormone replacement therapy is permitted providing that the dose has been stable for at least 4 weeks before screening, and that the subject's serum TSH level is within the central laboratory normal range at screening. A serum TSH level below the lower limit of the normal range is allowed if necessary for medical reasons (eg, prior thyroid carcinoma). Other medications are also permitted, with the exception of those listed in Section 5.2.2.

See Section 5.2.3 for information on vitamin D, calcium, and magnesium supplementation.

5.2.2 Prohibited Treatment

Prior treatment with PTH-like drugs (whether commercially available or through participation in an investigational trial), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, is prohibited within 3 months before screening. The use of any other investigational drug or device is prohibited within 6 months before screening.

The washout periods for common prior treatments that are excluded medications for this study are shown in Table 2. Treatments not listed in Table 2 are considered allowable (see also Section 5.2.1).

Table 2 Common Excluded Treatments and Associated Washout Period

		Time Before First Dose				
Treatment	**1 month**	**3 months**	**4.25 months**	**6 months**	**1 year**	**2 years**
Loop diuretics	X					
Thiazide diuretics	X					
Phosphate binders (other than calcium carbonate)	X					
Digoxin				X		
Lithium		X				
Methotrexate				X		
Systemic corticosteroids				X		
Calcitonin	X					
Fluoride supplements					X	
Cinacalcet hydrochloride	X					
Denosumab			X			
Oral bisphosphonates				X		
Intravenous bisphosphonates						X

Subjects taking vitamin C or a multivitamin containing vitamin C must stop this medication for the 5 days prior to and during each 24-hour of urine collection period.

5.2.3 Active Vitamin D, Calcium, Native Vitamin D, and Magnesium Supplementation

During the screening period, subjects will use their pre-existing active vitamin D and calcium supplements. Supplement doses during the screening period should not be changed other than for safety reasons. Investigational product, active vitamin D, and calcium supplements to be taken after randomization will be dispensed at the baseline (Week 0) visit.

Active vitamin D and calcium supplements should be taken as determined by the investigator in order to achieve albumin-corrected serum calcium levels in the target range (see Appendix 2).

Active vitamin D and calcium supplements will be provided by the sponsor, designee, or study sites.

Native vitamin D should be prescribed throughout the study as needed to target a serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the ULN. Native vitamin D supplements will not be provided by the sponsor.

Throughout the study, normal serum magnesium levels should be targeted. Subjects with low serum magnesium should receive oral magnesium supplementation, as appropriate, to achieve serum magnesium concentrations within the laboratory normal range. Magnesium supplements will not be provided by the sponsor.

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 dose strengths of 25 µg, 50 µg, 75 µg, and 100 µg. The contents of the cartridge must be mixed using the provided mixing apparatus and administered via the provided injector pen. Additional information is provided in the current rhPTH(1-84) investigator's brochure.

The reference/comparator product is placebo, which will be provided in a multiple-dose, dual-chamber, glass cartridge containing a sterile lyophilized powder and a sterile diluent for reconstitution. The contents of the cartridge must be mixed using the provided mixing apparatus and administered via the provided injector pen.

6.1.1 Blinding the Treatment Assignment

This is a double-blind study. Subjects and investigational personnel will remain blinded to their treatment assignment for the duration of the study. The placebo will be identical in appearance to the test product.

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 randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

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.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

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

6.2.3 Dosing

Investigational product will be administered each day in the morning by a single SC injection into the thigh, alternating the left and right thighs each day, using the provided multidose injection pen. Subjects will either perform the injections themselves or will have a designee perform the injections. Training for investigational product administration will take place at the baseline (Week 0) visit.

The investigator may titrate the daily dose of rhPTH(1-84) in 25 µg increments up to a maximum of 100 µg QD or down to a minimum of 25 µg QD. The investigational product dose titration should follow the dosing guidelines presented in Appendix 2; dose titration other than that in the proposed dosing guidelines should be discussed with the medical monitor when possible. Following Week 16 (maintenance dosing period [Weeks 17-26]), investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor. At any time during the study as needed for safety reasons, investigational product doses may be decreased in 25 µg decrements to a minimum of 25 µg QD. See Appendix 2 for additional details on the dosing guidelines. The EOT/ET visit will take place at the end of the 26-week dosing period.

All subjects will also receive active vitamin D and calcium supplements (see Section 5.2.3) as appropriate. Active vitamin D and calcium supplements will be provided by the sponsor, designee, or study sites. Calcium supplement refers to prescribed nondietary oral calcium supplement.

6.2.4 Unblinding the Treatment Assignment

This is a double-blind study. The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The option to unblind a subject's treatment assignment will be available through the IRT for the investigator, medical monitor, and Shire Global Patient Safety Evaluation.

A confirmation e-mail will be sent through the IRT to the sponsor or designee after the unblinding process is completed in the system. Upon breaking the blind, the subject is automatically withdrawn from the study, but should be followed up for safety purposes.

In case an emergency unblinding of a subject's treatment assignment is required AND the IRT system is out of order, the site will be able to contact the IRT by phone using the country-specific help desk numbers shown in the emergency contact information section of the protocol and the IRT User Manual (provided under a separate cover). The date, the signature of the person who broke the code, and the reason for breaking the code will be recorded on the source documents.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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.

Labels containing study information will be applied to the investigational product containers.

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, but must not:

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

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

6.3.2 Packaging

The study site will receive blinded supplies of investigational product, injection pens, and mixing devices required for dosing. Each subject will receive the injection pen for use during the study period and sufficient cartridges to provide daily doses for the duration of the study. Drug cartridges will be packaged in kits. Each cartridge will contain investigational product for 14 doses. Drug cartridges will be provided at each clinic visit in sufficient quantity and at appropriate dose levels to ensure uninterrupted administration until the next study visit. Ancillary supplies, including single-use injection pen needles (31-gauge) and alcohol wipes, will be provided by the CRO to the site. A direct- to-subject service may be required to exchange the expiring study supplies between the site visits.

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

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton 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 minimum and maximum thermometer) would require manual resetting upon each recording. Shire must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. Shire 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.

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

6.4 Drug Accountability

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

The investigator has overall responsibility for 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 dispense 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 dispensed medication will be documented. The investigator is responsible for assuring the retrieval of all study supplies from subjects. The investigator must request that subjects keep the empty investigational product packaging after use and return it to the site for drug accountability purposes.

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.

Shire 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, subject-returned investigational product, and empty or used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational product being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated 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 before shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Whenever possible, returned investigational product must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product before shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

In the event that unused stock, subject-returned investigational product, and empty or used investigational packaging cannot be returned to the distribution depot for destruction, the material may be destroyed at the site or a local facility with the written agreement of the sponsor. In this case, destruction records identifying what was destroyed, when, and how must be obtained with copies provided to the sponsor. Destruction of investigational product 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

Investigational product, active vitamin D, and calcium supplements will be dispensed at specified visits. Subjects must be instructed to bring their unused investigational product and their empty or used investigational product packaging to every visit. A direct- to-subject service may be required to exchange the expiring study supplies between the site visits. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

Active vitamin D and calcium supplements provided by the sponsor, designee or study sites will also be accounted for. Native vitamin D and magnesium supplements will not be accounted for.

7 STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for study procedures and assessments. The day of the following visit should be calculated based on the day of the current visit, not on the day of the baseline visit. The visit window (eg, ±2 days) applies to the calculated day.

At site visit, procedures and assessments should be performed in the following order (as applicable at each visit):

- PGI-S for hypoparathyroidism (following training on the use of the PRO device ([Week -3 only])
- Vital sign measurements (blood pressure, pulse, body temperature, and respiratory rate)
- Blood sample collection
- Administration of active vitamin D and calcium supplements (as appropriate) and investigational product, except at Week -2 and Week 24 visits in preparation for the in-clinic neurocognitive assessments:
  - At Week -2 visit, subjects should take their usual active vitamin D and calcium supplement doses prior to the visit
  - At Week 24, subjects should take their usual active vitamin D, calcium supplement, and investigational product doses prior to the visit
- In-clinic neurocognitive assessment and healthcare resource utilization assessment
- Review the following for completion: Hypoparathyroidism Symptom Diary (HPT-SD) and at home neurocognitive assessment
- Other procedures and assessments.

The following set of core procedures and assessments will be performed at every visit from Week -3 through the EOS visit (Week 30) or at EOT/ET visit, as specified in the protocol:

- Vital signs (except at phone visits)
- Prior and concomitant medication review
- Review subject's compliance with investigational product (during treatment period), calcium, and active vitamin D supplements dosing
- Adverse event and serious adverse event (SAE) monitoring.

Additional procedures are described in subsequent sections.

At home, subjects will complete:

- At-home neurocognitive assessment (CogState Brief Battery) twice daily on each of the days between the Week -2 visit and the baseline (Week 0) visit, and twice daily on each of the 14 days before the Week 12 and Week 26 visits, ending 1 day before the visit. Subjects will complete the testing once each morning after their morning routine (eg, dressing, eating, and taking medication) and once in the evening before dinner.
- Patient-reported outcomes instruments (as applicable at each visit) in the following order:
  - Hypoparathyroidism Symptom Diary (HPT-SD) at a consistent time every day from the Week -3 to Week 26 (EOT/ET) visits.
  - Most Bothersome Hypoparathyroidism-related Symptom to be completed at home once within the 2 days before the Week -2 visit.
  - Other patient-reported outcomes (PRO) instruments once at home within the 2 days before the visit*:
    - Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism
    - Patient Global Impression of change (PGI-C) for Hypoparathyroidism
    - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
    - Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)
    - 36-Item Short Form Health Survey version 2 (SF-36v2)
    - EuroQol five dimensions questionnaire 5-level version (EQ-5D-5L)
    - Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism).

  *Note: For the baseline (Week 0) visit, if the PRO instruments are not completed as required prior to the baseline (Week 0) visit, the subject cannot be randomized and can be rescreened starting at Week -3 per the discretion of the investigator.

  For the Week -2 visit and ~~for~~ applicable visits between Week 1 and Week 24, if the PRO instruments are not completed as required prior to the scheduled visit, they can be completed once at home within the 2 days after the scheduled visit.

  PRO instruments cannot be completed during scheduled visits.

During treatment with investigational product, the PRO instruments should be completed approximately 5-12 hours after investigational product dosing.

At visits specified in Table 1, the site personnel will review the subject's compliance with completion of at-home neurocognitive assessment and PRO instruments. Responses to neurocognitive assessment and PRO instruments will not be monitored for AEs. Each subject will be given 2 electronic devices: 1 containing the PRO assessments (received at Week -3) and 1 containing the neurocognitive assessments (received at Week -2).

See Appendix 2"Dosing guidelines for active vitamin D and calcium supplements and investigational product" for details on additional laboratory testing.

It is recommended that between visit predose nadir and post-dose peak levels should be assessed following adjustment of investigational product, active vitamin D, and/or calcium supplements to aid in titration. If between visit predose nadir and post-dose peak levels are not assessed, the reason for not completing the measurements should be documented. Blood for the assessment of these levels should be collected approximately 2-5 days following any adjustment(s). The post-dose peak level blood draw for the evaluation of serum calcium, albumin, phosphate, and magnesium should be drawn approximately 8-12 hours following administration of the investigational product dose. The predose nadir level blood draw for the evaluation of serum calcium, phosphate, albumin, and magnesium should be drawn in the morning prior to the administration of the dose of investigational product that day, within 24 hours of the last dose of investigational product. Blood for predose nadir and post-dose peak levels can be drawn on the same day or different days as long as the blood draws are completed within the 2 to 5 day window and within the window specified for each level. Local laboratories can be used for these assessments; duplicate samples do not need to be sent to the central laboratory. Additional between visit blood draws can be completed at any time at the discretion of the investigator.

7.1.1 Screening Period

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).

Subjects who fail to meet all inclusion/exclusion criteria will be permitted to be rescreened only if the investigator assesses the reason for screen failure is transient and temporary. Subjects who did not complete all required PROs prior to the baseline (Week 0) visit are allowed to be rescreened based on investigator discretion.

Eligible subjects who meet all inclusion/exclusion criteria, but are unable to participate in the study due to scheduling conflicts/timing, may be rescreened based on investigator discretion.

7.1.1.1 Week -3

Informed consent will be collected and the inclusion and exclusion criteria checked.

During the screening period, subjects will use their pre-existing active vitamin D and calcium supplements. Supplement doses should only be changed during the screening period for safety reasons.

An electronic device to be used at home and in the clinic containing PRO instruments (see Section 7.2.4.2), will be handed out and the subject will be taught how to use it. At the clinic, following training on the use of the PRO instruments, subjects should complete the PGI-S for hypoparathyroidism prior to completing any core or additional procedures and assessments.

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Medical history
- Demography
- Physical examination
- ECG (12-lead)
- Bone age X-ray (single posteroanterior X-ray of the left wrist and hand) to ensure epiphyseal closure in subjects 18-25 years of age
- Clinical laboratory evaluations: hematology, serum chemistry (including serum calcium, albumin, phosphate, and magnesium), serum TSH, serum pregnancy test, urine pregnancy test, FSH levels, serum PTH, urinalysis
- Serum 25-hydroxyvitamin D
- Health status assessments (PGI-S for Hypoparathyroidism).

Subjects will be reminded to complete the HPT-SD, Most Bothersome Hypoparathyroidism-related Symptom, and health status assessments (PGI-S for Hypoparathyroidism, PGI-C for Hypoparathyroidism) at home before the Week -2 visit.

7.1.1.2 Week -2

The visit window for Week -2 will be ±2 days.

The core procedures and assessments will be performed, as well as the following additional procedures:

- 24-hour urine collection (to be completed the morning of the visit)
- Neurocognitive assessment training
- In-clinic neurocognitive assessment
- Review for completion
  - HPT-SD
  - Most Bothersome Hypoparathyroidism-related Symptom
  - Health status assessments (PGI-S for Hypoparathyroidism, PGI-C for Hypoparathyroidism).

After completion of these assessments, the subject will meet with a nutritionist (or other qualified individual in the opinion of the investigator) to review dietary (nonsupplement) calcium, phosphate, and sodium intake. At this evaluation the subject should be provided with recommended meal plans to match their usual baseline intake when performing study blood draws and urine collections. In particular, a specific standardized meal should be recommended for the subject to be consumed prior to study visits. The goal is to achieve consistency in the timing of the standardized meal and the study visit blood draw to the greatest extent possible.

Another electronic device containing the neurocognitive assessments (see Section 7.2.4.1), to be used at home and in the clinic, will be handed out and the subject will be taught how to use it.

The subject will be reminded to complete the neurocognitive assessments (CogState Brief Battery) at home twice daily on each of the 14 days before the next visit, ending 1 day before the visit.

7.1.2 Baseline

7.1.2.1 Day -2 Phone call

PRO instruments (including PGI-S for hypoparathyroidism and PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to baseline (Week 0) visit. Two days before the baseline (Week 0) visit, subjects should receive a phone call to remind them to complete their PRO instruments.

7.1.2.2 Baseline Visit (Week 0)

The visit window for Week 0 will be ±2 days.

At the visit, the HPT-SD will be reviewed for completion and eligibility to proceed with Baseline (Week 0) procedures will be confirmed based on the results of the HPT-SD administered during the period immediately prior to the Baseline (Week 0) visit (Day -14 to Day -1). The subject's Sum Score will be calculated for the HPT-SD at the visit. See Appendix 3 for HPT-SD and HPT-SD scoring for subject's eligibility in the study. At the visit, if the eligibility criteria for HPT-SD are confirmed, the inclusion and exclusion criteria will be confirmed and subjects will be randomized via IRT (see Section 6.2.2). Training for investigational product administration will take place.

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Clinical laboratory evaluations: serum chemistry (including serum calcium, albumin, phosphate, and magnesium), urine pregnancy test, serum PTH
- Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Plasma FGF-23
- Bone turnover markers
- Anti-PTH antibodies
- Healthcare resource utilization assessments (Baseline Visit version)
- Review for completion*
    - HPT-SD
    - At-home neurocognitive assessment
    - Focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)

- Health-related quality of life assessments (SF-36v2, EQ-5D-5L)
- WPAI:Hypoparathyroidism
- Health status assessments (PGI-S for Hypoparathyroidism, PGI-C for Hypoparathyroidism)

*Note: Subjects who did not complete the required PRO instruments prior to the baseline (Week 0) visit will not be randomized and can be rescreened starting at the Week -3 visit per the discretion of the investigator.

- Dispensing/administration of investigational product/supplements.

7.1.3 Treatment Period

The visit window will be ±2 days for Weeks 1-16 and ±3 days for Weeks 17-26.

7.1.3.1 Weeks 1, 2, 6, 10, 14, and 20

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Serum calcium, albumin, phosphate, and magnesium: to be completed per the investigator's discretion. Testing may be performed at a local laboratory.
- The dietary (nonsupplement) calcium, phosphate, and sodium intake will be reviewed (Week 6)
- The Week 1 and 2 visits may be conducted as a phone visit or an in-person visit.

7.1.3.2 Weeks 2, 8, 16

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Urine pregnancy test
- Serum calcium, albumin, phosphate, and magnesium
- Serum 25-hydroxyvitamin D
- 24-hour urine collection (except at Week 16 visit) (collection to be completed the morning of the visit)
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review HPT-SD for completion
- Dispensing/administration and accounting of investigational product/supplements.

7.1.3.3 Week 4

Phone Call Two Days Before the Week 4 Visit

PRO instruments (including PGI-S for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to the Week 4 visit. Two days before the Week 4 visit, subjects should receive a phone call to remind them to complete their PRO instruments.

The core procedures and assessments will be performed at the Week 4 visit, as well as the following additional procedures and assessments:

- Urine pregnancy test
- Serum calcium, albumin, phosphate, and magnesium
- Serum 25-hydroxyvitamin D
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review for completion
  - HPT-SD
  - Focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)
  - Health-related quality of life assessments (SF-36v2, EQ-5D-5L)
  - WPAI:Hypoparathyroidism
  - Health status assessments (PGI-S for Hypoparathyroidism)
- Dispensing/administration and accounting of investigational product/supplements.

7.1.3.4 Weeks 6, 10, 14 (Phone visits)

The core procedures and assessments will be performed (except for vital signs), as well as the following additional procedures and assessments:

- Urine pregnancy test
- Serum calcium, albumin, phosphate, and magnesium
- Serum 25-hydroxyvitamin D
- Healthcare resource utilization assessments (Follow-up Visit version)
- Dispensing/administration and accounting of investigational product/supplements.

7.1.3.5 Week 12

Phone Call Two Days Before the Week 12 Visit

PRO instruments (including PGI-S for hypoparathyroidism and PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to the Week 12 visit. Two days before the Week 12 visit, subjects should receive a phone call to remind them to complete their PRO instruments.

The core procedures and assessments will be performed at the Week 12 visit, as well as the following additional procedures and assessments:

- Serum calcium, albumin, phosphate, and magnesium: to be completed per the investigator's discretion. Testing may be performed at a local laboratory.
- Review HPT-SD for completion.

In addition:

- At Week 6 visit, the dietary (nonsupplement) calcium, phosphate, and sodium intake will be reviewed.
- At Week 10 visit, subject will be reminded to complete the at-home neurocognitive assessment twice daily on each of the 14 days before the next visit, ending 1 day before the visit.
- ECG (12-lead)
- Clinical laboratory evaluations: hematology, serum chemistry (including serum calcium, albumin, phosphate, and magnesium), urine pregnancy test
- Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Bone turnover markers
- Anti-PTH antibodies
- 24-hour urine collection (to be completed the morning of the visit)
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review for completion
  - HPT-SD
  - At-home neurocognitive assessment
  - Focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)
  - Health-related quality of life assessments (SF-36v2, EQ-5D-5L)
  - WPAI:Hypoparathyroidism
  - Health status assessments (PGI-S for Hypoparathyroidism and PGI-C for Hypoparathyroidism)
- Dispensing/administration and accounting of investigational product/supplements.
- The dietary (nonsupplement) calcium, phosphate, and sodium intake will be reviewed.

7.1.3.6 Week 20

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Urine pregnancy test
- Serum calcium, albumin, phosphate, and magnesium
- Serum 25-hydroxyvitamin D
- 24-hour urine collection (to be completed the day of the visit)
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review HPT-SD for completion
- Dispensing/administration and accounting of investigational product/supplements.

7.1.3.7 Week 24

Phone Call Two Days Before the Week 24 Visit

PRO instruments (including PGI-S for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to the Week 24 visit. Two days before the Week 24 visit, subjects should receive a phone call to remind them to complete their PRO instruments.

The core procedures and assessments will be performed at the Week 24 visit, as well as the following additional procedures and assessments:

- Urine pregnancy test
- In-clinic neurocognitive assessment
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review for completion
  - HPT-SD
  - Focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)
  - WPAI:Hypoparathyroidism
  - Health status assessments (PGI-S for Hypoparathyroidism)
- Dispensing and accounting of investigational product/supplements.

Subject will be reminded to complete the neurocognitive assessments at home twice daily on each of the 14 days before the next visit, ending 1 day before the visit.

7.1.3.8 Week 26

Phone Call the Day Before the Week 26 Visit

PRO instruments (including PGI-S for hypoparathyroidism and PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to the EOT (Week 26) visit. On the day before the Week 26 (EOT) visit, subjects should receive a phone call to remind them to complete their PRO instruments.

End-of-Treatment/Early-termination Visit (Week 26)

The visit window for the EOT/ET visit at Week 26 will be ±3 days.

The injection pen, mixing apparatus, PRO and neurocognitive assessment devices, and any unused investigational product will be collected.

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Physical examination
- ECG (12-lead)
- Clinical laboratory evaluations: hematology, serum chemistry (including serum calcium, albumin, phosphate, and magnesium), serum TSH, urinalysis, urine pregnancy test
- Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Plasma FGF-23
- Bone turnover markers
- Anti-PTH antibodies
- 24-hour urine collection (to be completed the morning of the visit)
- Healthcare resource utilization assessments (Follow-up Visit version)
- Review for completion
  - HPT-SD
  - At-home neurocognitive assessment
  - Focused hypoparathyroidism symptom assessments (FACT-Cog, FACIT-Fatigue)
  - Health-related quality of life assessments (SF-36v2, EQ-5D-5L)
  - WPAI:Hypoparathyroidism
  - Health status assessments (PGI-S for Hypoparathyroidism, PGI-C for Hypoparathyroidism)
- Accounting/administration of investigational product/supplements.

Subjects immediately transferring to commercial rhPTH(1-84) after the EOT (Week 26) visit will continue to be monitored under the care of a physician according to rhPTH(1-84) labeling instructions. All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

Subjects discontinuing treatment with rhPTH(1-84) will be prescribed appropriate oral calcium and/or active vitamin D supplements to compensate for the cessation of rhPTH(1-84) and will proceed with follow-up (see Section 7.1.4). Subjects transferring to commercial rhPTH(1-84) who experience a treatment gap of >7 days after the EOT (Week 26) visit will also proceed with follow-up until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed as described in Section 7.1.4.

All subjects will have an EOS contact (Week 30 contact) as described in Section 7.1.4.

7.1.4 Follow-up Period

The follow-up period for this protocol is 30 days. All subjects will have an EOS (Week 30) contact 30 days following the last dose of investigational product. The visit window for the follow-up visits will be ±2 days.

Weekly follow-up visits (Weeks 27 to 30) are scheduled for subjects discontinuing rhPTH(1-84) after the EOT visit (Week 26) or if ET. Subjects transferring to commercial rhPTH(1-84) with a treatment gap of >7 days after the EOT (Week 26) visit will proceed with weekly follow-up for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. If a subject transfers to commercial rhPTH(1-84) treatment before the EOS (Week 30) visit, assessments scheduled at the EOS (Week 30) visit should be performed at their last follow-up visit before transferring to commercial rhPTH(1-84); these subjects will have an EOS contact 30 days following their last dose of investigational product.

During weekly follow-up, subjects will be monitored for serum calcium levels, and adjustment of exogenous calcium and/or active vitamin D will be made, as necessary.

The EOS contact (Week 30 visit) is a safety follow-up telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments. Subjects who will be returning to the site for their last weekly follow-up visit can complete the EOS contact (Week 30 visit) at the site.

7.1.4.1 Weeks 27, 28, and 29

The core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Serum calcium, albumin, phosphate, and magnesium.

7.1.4.2 Week 30 (End-of-Study Contact)

All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 8.1).

The EOS contact (Week 30 visit) is a safety follow-up telephone call initiated by the site staff to query for adverse events (AEs) and concomitant treatments. Subjects who will be returning to the site for their last weekly follow-up visit can complete the EOS contact (Week 30 visit) at the site.

For subjects who are completing weekly follow-up visits, the core procedures and assessments will be performed, as well as the following additional procedures and assessments:

- Serum calcium, albumin, phosphate, and magnesium, and urine pregnancy test
- Anti-PTH antibodies
- Healthcare resource utilization assessments (Follow-up Visit version).

7.1.5 Additional Care of Subjects after the Study

No after care is planned for this study.

7.2 Study Evaluations and Procedures

Beginning with the baseline (Week 0) visit, a standardized meal (recommended at Week -2 visit) should be consumed before study visits. The goal is to achieve consistency in the timing of the standardized meal and the study visit blood draw to the greatest extent possible.

In general, subjects should not take active vitamin D or calcium supplements before reporting for visits starting with the baseline (Week 0) visit except at Week -2 and Week 24 visits in preparation for the in-clinic neurocognitive assessments: at Week -2 visit, subjects should take their usual active vitamin D and calcium supplement doses prior to the visit; and at Week 24 visit, subjects should take their usual active vitamin D, calcium supplement, and investigational product doses prior to the visit. If, in the opinion of the investigator, it is necessary for a subject to take active vitamin D and/or calcium supplements before reporting for the visit, the doses of the supplements taken before the blood draw should be the lowest dose necessary to maintain safety and should be used consistently at each visit to the greatest extent possible. The timing of any supplements taken before the blood draw with respect to the blood draw should also be consistent throughout the study to the greatest extent possible. Subjects should not take investigational product until the completion of the blood draw.

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics for each subject, such as date of birth, sex, and race (as allowed by local law), will be recorded in the source document at Week -3.

Medical history will be recorded in the source document for each subject. Medical history will include, but is not limited to:

- Etiology and duration of hypoparathyroidism, including detailed description of any previous neck surgery
- Any history of thyroid disease
- For postmenopausal women, menopausal history.

Clinical laboratory evaluations are described in Section 7.2.3.4.

7.2.2 Efficacy

7.2.2.1 Neurocognitive and Outcomes Research Assessments

See Section 7.2.4.1 and Section 7.2.4.2 for neurocognitive and PRO assessments, respectively.

7.2.2.2 Biochemical Evaluations

Serum calcium, albumin, phosphate, magnesium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and bone turnover markers, and plasma FGF-23 will be measured at the time points specified in Table 1.

Blood samples are to be collected in the morning prior to investigational product injection. In addition to protocol specified laboratory testing in the central laboratory, blood for the evaluation of serum calcium, albumin, phosphate, and magnesium levels obtained on scheduled visit days can be analyzed locally at the sites or other local laboratories that are authorized by the investigator. These values may be used for titration of investigational product and supplements. When these samples are drawn locally, these samples can be analyzed per local laboratory standards (eg, ionized or total serum or plasma calcium) and should be interpreted using the local laboratory normal values. If a local laboratory is used on scheduled study site visit days (ie, Weeks -3, -2, 0, 1, 2, 4, 8, 12, 16, 20, 24, 26, 27, 28, 29, 30), a duplicate sample must be collected and provided to the central laboratory.

Refer to the central laboratory manual for procedures including sample collection, handling, and storage. All samples collected will be discarded by the end of the study defined as finalization of CSR (Final Clinical Study Report).

Bone turnover markers will include serum bone-specific alkaline phosphatase, procollagen amino-terminal peptide, C-terminal telopeptide of type 1 collagen, and osteocalcin. Levels of FGF-23, a phosphaturic factor, are being measured to determine whether FGF-23 levels are affected by rhPTH(1-84) therapy (Gupta et al., 2004; Yamashita et al., 2007).

A 24-hour urine collection will be performed at each of the time points specified in Table 1 and the total volume recorded (the urine collection is to be completed the morning of the visit). Urine chemistry will be determined from the 24-hour urine collection. At the beginning of the study, the investigator should recommend an individualized dietary (non-supplement) calcium, phosphate, and sodium intake (based on usual consumption) for each subject to ingest consistently throughout the study and on 24-hour urine collection days.

When collecting 24-hour urine specimens, subjects should be instructed to take their currently prescribed calcium, vitamin D (both native and active), and investigational product doses. On urine collection days, subjects should drink enough water to ensure that at least 1 liter of urine is collected over 24 hours. Subjects taking vitamin C or a multivitamin containing vitamin C must stop this medication for the 5 days prior to and during each 24-hour urine collection period.

7.2.3 Safety

7.2.3.1 Physical Examination (Including Height and Weight)

A physical examination including height and weight will be conducted at the time points specified in Table 1. Abnormalities identified at the baseline visit (Week 0) will be documented in the subject's source documents. Any clinically significant deviations from the baseline visit (Week 0) in physical examination findings that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.2 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.)

Additional information about AEs of hypocalcemia will be collected to allow categorization described in Section 8.1.4.

7.2.3.3 Vital Signs

Vital signs include blood pressure, pulse, body temperature, and respiratory rate. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from the baseline visit (Week 0) in vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.4 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Normal 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 that 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.

Serum Chemistry

Blood samples for serum chemistry will be collected at the time points specified in Table 1. The following parameters will be measured:

- Sodium
- Potassium
- Blood urea nitrogen
- Creatinine
- Chloride
- Total carbon dioxide (bicarbonate)
- Aspartate aminotransferase
- Alanine aminotransferase
- Alkaline phosphatase
- Uric acid

Additionally, serum levels of PTH will be measured at the Week -3 and Week 0 visits, and serum levels of TSH will be measured at the Week -3 and Week 26 visits. Female subjects who are newly menopausal will have their serum FSH levels tested at the Week -3 visit. Pregnancy testing is described in Section 7.2.3.5.

Creatinine clearance and glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] equation) will be estimated by the laboratory.

Urine Chemistry

24-hour urine samples for chemistry will be collected at the time points specified in Table 1. The following parameters will be measured:

- Calcium
- Phosphorus
- Creatinine
- Sodium
- Magnesium
- Potassium
- Chloride
- Citrate
- pH
- Urea nitrogen
- Oxalate
- Ammonium
- Uric acid
- Sulfate

The volume of the 24-hour urine collections will be captured.

The following will be calculated based on 24-hour urine collections:

- Calcium per Creatinine
- Calcium per Kg Body Weight
- Creatinine per Kg Body Weight
- Protein Catabolic Rate

In addition, 24-hour urine collections will have supersaturation calculated for the following parameters:

- Calcium oxalate
- Calcium phosphate (brushite)
- Uric acid

Hematology

Blood samples for hematology will be collected at the time points specified in Table 1. The following parameters will be measured:

- Hemoglobin
- Hematocrit
- Red blood cell count
- Platelet count
- White blood cell count.
- Automatic differential

Urinalysis

Urine samples for urinalysis (including microscopy [eg, crystals, bacteria, and cells] as needed if indicated by other parameters) will be collected at the time points specified in Table 1. The following parameters will be measured:

- pH
- Glucose
- Protein
- Blood
- Ketones
- Bilirubin
- Leukocyte esterase
- Specific gravity.

Urine creatinine and sodium will be determined from the 24-hour urine collections described in Section 7.2.2.2.

7.2.3.5 Pregnancy Test

Serum and urine β-HCG pregnancy tests will be performed on all female subjects of childbearing potential at the respective time points specified in Table 1, or if pregnancy is suspected, or on withdrawal of the subject from the study.

7.2.3.6 Electrocardiogram

A 12-lead ECG will be recorded at the time points specified in Table 1.

All ECGs will be performed in triplicate (with a minimum 2-minute gap between traces).

The following parameters will be provided to the sponsor or the sponsor representative by the central ECG reader: heart rate and PR, RR, QRS, and QT intervals. Information on T- and U-wave morphology should also be provided; U-waves should be captured as absent/normal or abnormal. The QT corrected for heart rate by the Bazett method and QT corrected for heart rate by the Fridericia method 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 or not the abnormality is clinically significant will be documented on the tracing and recorded in the source document.

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 30 minutes before collection. The subject must be resting in the supine position for at least 5 minutes before 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.

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 ECG obtained with the 3 assessments will be recorded in the source document. 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 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 used for data analysis.

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

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 medical monitor, reconfirms subject eligibility to continue.

7.2.3.7 Anti-parathyroid Hormone Antibodies

A blood sample for the detection of anti-PTH antibodies will be collected at each of the time points specified in Table 1. Blood samples for antibody testing should be collected before dosing with the investigational product (at least 14 hours after the prior dose of investigational product). Anti-PTH antibodies test results will be reported at the end of the study in order to maintain the study blind.

7.2.4 Neurocognitive, Health Economics, and Outcomes Research Assessments

Two electronic devices installed with neurocognitive assessments and PRO instruments will be provided to subjects at screening, and training in their use will be provided.

7.2.4.1 Neurocognitive Assessments

In-clinic Neurocognitive Assessments

In-clinic neurocognitive assessments will be administered at Week -2 and Week 24 visits. Subjects should take their usual active vitamin D and calcium supplement doses prior to the visit at Week -2 and should take their usual supplement and investigational product doses prior to the visit at Week 24. The neurocognitive test battery will include tests evaluating the frontal-executive domain, which encompasses functions attributable to the prefrontal cortex and its connections to the basal ganglia (mostly striatum). The tests will include the CogState Brief Battery, CogState Groton Maze Learning Test, CogState International Shopping List Task, and CogState International Shopping List Task-Delayed Recall.

At-home Neurocognitive Assessments

Subjects will complete the CogState Brief Battery twice daily on each of the days between the Week -2 visit and the baseline (Week 0) visit, and twice daily for 14-day period prior to the applicable visits specified in Table 1. Subjects will complete the testing once each morning after their morning routine (eg, dressing, eating, and taking medication) and once in the evening before dinner.

7.2.4.2 Patient-reported Outcomes Assessments

Subjects will be asked to complete PRO instruments as described in the subsections that follow. Subjects who meet the inclusion criteria and enroll in the study will take the device home and complete the instruments at home as follows:

- The Hypoparathyroidism Symptom Diary (HPT-SD) should be completed at a consistent time every day from the day of screening (Week -3) until the EOT/ET visit.
- All other PRO instruments should be completed at home once within the 2 days before each of the applicable visits specified in Table 1.

At home and during treatment with the investigational product, all PRO instruments should be completed approximately 5-12 hours after investigational product dosing.

Sites will be instructed to check and confirm that subjects have completed the required PRO instruments at each applicable visit.

Hypoparathyroidism Symptom Diary

Subjects will be asked to complete an HPT-SD daily at a consistent time from the day after the screening visit (Week -3) until the EOT/ET (Week 26) visit. During the screening period, the subject should record responses to the HPT-SD toward the end of the day or in the evening. During treatment with investigational product, it will be expected that subjects record responses approximately 5-12 hours after morning investigational product doses.

The HPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items:

- symptom subscale (items 1-7)
- anxiety (item 8)
- sadness and depression (item 9)
- impact subscale (items 10-13)

The 24-hour recall version of the instrument will be used in this study. See Appendix 3 for HPT SD and HPT-SD scoring for subject's eligibility in the study and scoring at baseline and during the treatment period.

The HPT-SD will include the "Most Bothersome Hypoparathyroidism-related Symptom" question once for the Week -2 visit (±2 days).

Focused Hypoparathyroidism Symptom Assessments

Subjects will be asked to complete the following symptom-specific instruments once within the 2 days before each of the visits specified in Table 1 and approximately 5-12 hours after investigational product dosing during treatment with investigational product:

- The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire contains 13 fatigue-related questions (Cella, 1997). The responses to the 13 items on the FACIT-Fatigue questionnaire are each measured on a 4-point Likert scale. Thus, the total score ranges from 0 to 52. High scores represent less fatigue.
- The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) assessment is a 37-item instrument (Wagner et al., 2004). The following 2 subscales (out of 4) were selected for the study: Perceived Cognitive Impairment, Impact on Quality of Life domains.

See Appendix 3 for focused hypoparathyroidism symptom instruments.

Health-related Quality of Life Assessment

Subjects will be asked to complete the 36-Item Short Form Health Survey version 2 (SF-36v2) and the EuroQol five dimensions questionnaire (EQ-5D) to assess health-related quality of life (HRQoL) and health status at home once within the 2 days before each of the visits specified in Table 1. During treatment with investigational product, the instruments should be completed approximately 5-12 hours after investigational product dosing.

The SF-36 and EQ-5D are validated instruments that question subjects about perceived physical and mental health and function. The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. The higher the score the less disability, ie, a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability. The 8 sections included in the SF-36 assessment are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Ware and Sherbourne, 1992). The SF-36v2 acute version with 1-week recall period will be used in this study.

The EQ-5D is a generic, multi-attribute, HRQoL instrument composed of a descriptive system and a visual analog scale (VAS) (EuroQol, 1990). The EQ-5D descriptive system has the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D 5-level version (EQ-5D-5L) will be used for this study.

See Appendix 3 for health-related quality of life instruments.

Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism

Subjects will be asked to complete the Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism) at home once within the 2 days before each of the applicable visits specified in Table 1. During treatment with investigational product, the instruments should be completed approximately 5-12 hours after investigational product dosing.

The WPAI:Hypoparathyroidism will be used to assess how hypoparathyroidism affects subjects' ability to work and perform regular activities. Concepts that the WPAI:Hypoparathyroidism measures include time missed from work and impairment of work and other regular activities due to specific health problems (Reilly et al., 1993).

See Appendix 3 for WPAI:Hypoparathyroidism instrument.

Health Status Assessments

Subjects will be asked to complete the Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism and the Patient Global Impression of Change (PGI-C) for Hypoparathyroidism assessments at home once within the 2 days before each of the applicable visits specified in Table 1. During treatment with investigational product, the instruments should be completed approximately 5-12 hours after investigational product dosing. See Appendix 3 for health status instrument.

7.2.4.3 Healthcare Resource Utilization Assessments

Measures of healthcare resource utilization will include encounters such as outpatient visits, laboratory tests, and procedures that are not scheduled in the protocol, emergency department visits, and hospitalizations. The reasons/diagnoses for each encounter (outpatient, emergency room, and inpatient) will be recorded. For hospitalizations, the start and stop dates of the stay will also be recorded. These questions will be asked directly of the subjects at the visits specified in Table 1; they will not appear in the subject's electronic device. Two versions of the healthcare resource utilization questionnaire will be used: the Baseline Visit version to be used at Baseline (Week 0) visit and the Follow-up Visit version to be used at applicable subsequent visits (Weeks 2, 4, 8, 12, 16, 20, 24, 26, and 30 [end-of study]). See Appendix 3 for healthcare resource utilization questionnaires.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

Treatment-emergent adverse events (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study drug. Events which occur more than 30 days after the last dose of study drug will not be considered treatment-emergent. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered treatment-emergent. Adverse events with completely missing onset dates and a stop date after the date of first dose (or unknown stop date) will also be considered treatment-emergent.

All AEs will be collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.4. 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 in the source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be documented.

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 will be performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

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

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/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. Outcomes are as follows:

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

8.1.4 Symptoms and Signs of the Disease Under Study

Symptoms and signs 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 and signs should be recorded as an AE.

The investigator should evaluate all AEs; if an AE is determined to be related to hypocalcemia the AE should be classified according to the following prespecified definitions:

Severe hypocalcemia (to be reported as SAEs)

Seizure, tetany, congestive heart failure, arrhythmia, or laryngospasm confirmed with low serum calcium measured at the time of symptoms and/or documentation of symptom resolution with calcium administration will be classed as severe hypocalcemia.

Self-treated hypocalcemia

Symptoms (specific, eg, muscle contractions; or nonspecific, eg, brain fog) for which the subject self-treats with additional calcium supplement will be classed as self-treated hypocalcemia. Hypocalcemia is confirmed by one of the following criteria:

- Low serum calcium measured at time of symptoms OR
- Resolution of symptoms with calcium supplementation.

Mild to moderate hypocalcemia other than self-treated

These symptoms may be specific (eg, muscle contractions) or nonspecific (eg, brain fog).

- Documented symptomatic – symptoms in the setting of a measured low serum calcium which resolve with calcium supplementation.
- Probable – no serum calcium at the time of typical symptoms available but resolve with calcium supplementation.
- Documented asymptomatic – biochemical hypocalcemia not associated with symptoms. These events will be derived from laboratory results, not subject diaries.

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 normal range, the duration until return to the normal 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 normal 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 normal 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 value 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 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to Shire Global Patient Safety Evaluation 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. It is not necessary to collect information regarding the pregnancy in the partner of a study participant.

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. The sponsor would like the following information to be collected during the pregnancy and after birth:

- Results of any diagnosis and/or laboratory tests taken prior to birth
- Details of any events or assessments during or after birth
- Details of any complications during the pregnancy
- Details of any relevant, concomitant medicinal products
- The outcome of the pregnancy
- Basic information regarding the newborn baby, including gestational age, weight, and general health/medical condition at birth
- General health/medical conditions regarding the baby at 30 days and 1 year of age.

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 nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a prespecified total daily dose of 100 μg of the product
- **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.

Acute accidental overdosage of rhPTH(1-84) can result in transient hypercalcemia and hypercalciuria. Treatment of suspected overdose should include temporary discontinuation of rhPTH(1-84), monitoring of serum calcium, and implementation of appropriate, supportive measures such as hydration. Due to the relatively short duration of the pharmacological activity of rhPTH(1-84), further measures should not be necessary.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator's brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Shire Global Patient Safety Evaluation and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

In the event of a serious adverse event (SAE), the investigator must enter SAE directly into the Electronic Data Capture (EDC) system by completing a SAE electronic Case Report Form (eCRF) or report via the paper SAE report form (only as back-up method, when EDC is down) within 24 hours to Shire Global Patient Safety Evaluation. In both cases Investigator signature should be present when submitting the forms. Applicable fax numbers and e-mail address (back-up method) can be found on the form (If SAE is submitted via fax, the SAE fax cover sheet including the site e-mail address details must be attached).

8.2.3 Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, 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 inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4 and must be reported to Shire Global Patient Safety Evaluation 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 Shire Global Patient Safety Evaluation 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

Shire will be responsible for notifying the relevant regulatory authorities/USA central institutional review boards (IRBs)/EU central ethics committees (ECs) of related, unexpected SAEs.

In addition, the CRO will be responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP634 program.

The investigator will be responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his/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 case report form (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.

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

This is a double-blind study in which the subject and investigator are blinded to treatment allocation. Data that may potentially unblind the treatment assignment (ie, antibodies to investigational product, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

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

All statistical analyses will be performed using SAS® software (SAS Institute, Cary, NC) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy, PRO, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, protocol deviations and exclusions from analysis sets, 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 before database lock. Any deviations from the SAP will be documented in the appropriate sections of the clinical study report.

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

An unblinded interim analysis for the primary endpoint will be performed after approximately 74% of all randomized subjects (N=approximately 68) have either completed 26 weeks of treatment (completed the study) or prematurely withdrawn from the study, whichever comes first. The purpose of this unblinded interim analysis is to reassess the appropriateness of assumptions used for the sample size calculation of the primary efficacy endpoint when the study was designed and to assess for futility. The reassessment of the sample size will utilize the conditional power approach under certain conditions that do not inflate the type I error (Mehta and Pocock, 2011). The planned interim analysis will be conducted by an external independent statistical group; the individuals involved in the day-to-day conduct of the trial will not be involved in the interim analysis or have access to the results of the interim analysis.

The sponsor will only be notified by the external independent statistical group of their recommendations to (1) stop the trial early for futility, (2) maintain the sample size as outlined in the current study design, or (3) update the sample size from the conditional power calculation; this will be detailed in the pre-specified interim SAP.

9.6 Sample Size Calculation and Power Considerations

A total of 92 subjects (46 subjects per arm) are planned to be randomized in a 1:1 ratio to the rhPTH(1-84) and placebo treatment groups in order to have a total of approximately 78 subjects (39 subjects per arm) completing the study.

The sample size was estimated for the primary efficacy analysis on change from baseline to Week 26 in the HPT-SD symptom subscale. We assumed a mean difference of 0.4 units with a standard deviation of 0.6 units. A total of 39 completed subjects per treatment group will provide 82.5% power to detect a treatment difference of 0.67 between the rhPTH(1-84) and placebo treatment groups, based on a 1-sided, 2-sample t-test at the 0.025 level of significance. This takes into account a single interim analysis for futility at approximately 74% information with a non-binding stopping rule at conditional power under the alternative hypothesis less than approximately 10%. The power analysis and sample size estimation are calculated using East Version 6. Based on cross-sectional data from the HPT-SD psychometric evaluation study, a difference of 0.4 in HPT-SD would roughly correspond to a between-person one-unit difference in the patient global impression of severity for hypoparathyroidism (ie, the difference between ‘mild’ versus ‘moderate’ or ‘moderate’ versus ‘severe’). Based on data from HPT-SD psychometric evaluation study, an effect size of 0.67 is achieved approximately by a clinically meaningful between-treatment group difference of 0.4 in mean change in the HPT-SD. Approximately 92 subjects are planned to be randomized to compensate for the 15% of randomized subjects who will not complete the treatment phase.

This proposed sample size would also provide >70% power to detect a difference of 3.5 in change from baseline in the PCS derived from the SF-36v2, a key secondary endpoint, between the rhPTH(1-84) and placebo treatment groups and a standard deviation of 6.0.

9.7 Study Population

The **Intention-to-treat (ITT) Set** will consist of all randomized subjects. Subjects in the ITT Set will be analyzed in the treatment group assigned at randomization, regardless of the actual treatment received (analyzed as randomized).

The **Safety Set** will consist of all subjects who have taken at least 1 dose of investigational product. Subjects in the Safety Set will be analyzed in the treatment group corresponding to actual treatment received (analyzed as treated).

The **Per-protocol Set** (PPS) will consist of all subjects in the ITT Set who complete the study and who do not have predefined protocol deviations that impact the primary efficacy assessment. Subjects in the PPS will be analyzed as treated. Detailed specification of protocol deviations will be documented in the SAP.

9.8 Efficacy Analyses

All efficacy analyses will be based on the ITT Set unless otherwise specified.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Change in the HPT-SD symptom subscale score from baseline to Week 26

The null hypothesis for the primary efficacy endpoint is that there is no difference in symptom improvement at Week 26 from baseline between the rhPTH(1-84) and placebo treatment groups. The alternative hypothesis is that the rhPTH(1-84) treatment group shows superior symptom improvement compared with the placebo treatment group. See Appendix 3 for HPT-SD and HPT-SD scoring algorithm.

The primary efficacy analysis will be performed on subjects from the ITT Set using a mixed-effect model for repeated measures (MMRM) analysis at post-baseline visits (Weeks 2, 4, 8, 12, 16, 20, 24, 26), with change from baseline in the HPT-SD symptom subscale score as the outcome variable; treatment group, visit, and their interaction as fixed effect factors and subjects as a random effect, with adjustment for baseline HPT-SD symptom subscale score. The null hypothesis will be rejected if the statistical analysis results in a 1-sided p-value for treatment at Week 26 less than or equal to 0.025. In the model, visit will be treated as a class variable, assuming an unstructured covariance matrix to model the within-subject variability. If there is a convergence problem due to the use of unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. With a mixed effects model based on restricted maximum likelihood estimation used for the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed in the primary analysis.

The primary result obtained from the model will be the estimated main treatment effect at Week 26. The estimated main treatment effect of mean difference between rhPTH(1-84) and placebo, and a 95% confidence interval (CI) will be provided. In addition, least squares means estimated from the model for each treatment group at each post baseline visit, and the estimated treatment effect along with 2-sided 95% CI at each post baseline visit, will also be provided. Descriptive statistics for HPT-SD symptom subscale score at each assessment including baseline, Weeks 6, 10, and 14 and change from baseline at each post-baseline assessment will be reported.

Sensitivity analyses to explore the impact of missing data on the primary endpoint will be conducted. If data collection modalities change during the trial, sensitivity analyses may be performed to evaluate the impact of the alternate mode of data collection on the primary endpoint. Additional sensitivity analyses will also be conducted to explore the impact of adjustments to calcium and active vitamin D supplements on the primary endpoints. All sensitivity analyses will be described in the SAP.

Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, baseline calcium supplement dose, baseline active vitamin D dose, history of thyroid hormone replacement, and other important subgroups if feasible. A full list of subgroup analyses will be described in the SAP.

9.8.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Change in FACIT-Fatigue score at Week 26
- Change in the PCS derived from SF-36v2 scores at Week 26

The key secondary efficacy analyses will be conducted over the ITT Set. All tests will be performed as 1-sided tests at the 0.025 level of significance. Each key secondary endpoint will be analyzed similarly as the primary endpoint using MMRM model to compare treatment effect between the rhPTH(1-84) and placebo groups, with change in score from baseline at post-baseline visits as dependent variable; treatment group, visit, and their interaction as fixed effect factors and subjects as a random effect with adjustment for corresponding baseline score. Additionally, the statistical inference of interest is based on the p-value for treatment at Week 26.

Adjustment for Multiplicity

In order to maintain study-wide Type I error control, a hierarchical testing procedure will be used in the comparisons between rhPTH(1-84) and placebo on the primary and key secondary efficacy endpoints. Specifically, the testing will be conducted in the following order: primary endpoint, FACIT-Fatigue, and then PCS from the SF-36v2. A later test can only be reported as significant if all earlier tests are also found significant.

Multiplicity is not adjusted for other efficacy endpoints in this study.

9.8.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints assessed at Week 26 are:

- Change in the HPT-SD impact subscale score
- Change in score of individual HPT-SD impact items
- Change in the HPT-SD symptom item anxiety and symptom item sadness or depression individual item score
- Change in score of individual HPT-SD symptom items
- Response as defined as a 30% reduction in HPT symptom subscale score from Baseline to Week 26
- Change in the most bothersome symptom score
- Change in FACT-Cog score (Perceived Cognitive Impairment, Impact on Quality of Life domains)
- Change in score of individual domains of SF-36v2
- Change in score of mental component summary (MCS) of SF-36v2
- Change in Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism) score
- Change in scores of patient's assessment of overall health status using:
  - Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism
  - Patient Global Impression of Change (PGI-C) for Hypoparathyroidism
- Change in in-clinic neurocognitive assessment scores (assessed through Week 24) (CogState Brief Battery; CogState Groton Maze Learning Test, CogState International Shopping List Task, CogState International Shopping List Task-Delayed Recall)
- Change in at-home neurocognitive assessment scores (CogState Brief Battery)
- Change in 24-hour urine calcium excretion
- Change in serum phosphate level
- Changes in doses of active vitamin D and calcium supplements
- Albumin-corrected serum calcium control, defined as a concentration between 1.87 mmol/L (7.5 mg/dL) and ULN for the central laboratory normal range
- Composite endpoint, as defined as achieving all of the following:
  - Albumin-corrected serum calcium between 1.87 mmol/L (7.5 mg/dL) and the ULN for the central laboratory normal range
  - Dose of active vitamin D decreased by 50%
  - At least a 50% reduction from the baseline oral calcium supplement dose (this criterion will be considered met if the subject's baseline calcium dose is <1000 mg and it does not increase during the study).
- Change in bone turnover markers (see Section 7.2.2.2).

Secondary efficacy analyses will be performed on the ITT Set. Secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint using an MMRM model. Secondary efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by mean, standard deviation, minimum, maximum, and 95% confidence intervals (CIs). For categorical variables, statistical summaries will include number of subjects and percentages and 95% CIs for binary endpoints.

No multiplicity adjustment will be done on the secondary efficacy endpoints. Summary statistics including nominal p-values will be reported.

9.8.4 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Change in plasma FGF-23 levels
- Change in 24-hour urine phosphate, sodium, citrate, magnesium excretion
- Change in creatinine clearance
- Change in estimated glomerular filtration rate
- Change in EuroQol five dimensions questionnaire 5-level version (EQ-5D-5L): EQ-5D-5L index value, descriptive system, and EQ VAS measure
- Change in measures of healthcare resource utilization: frequency of encounters (outpatient visits, laboratory tests, and procedures not scheduled in the protocol; emergency room visits; hospitalization), length of stay (hospitalization), and reasons/diagnoses for the encounters.
- Change in dose of native vitamin D supplements (recorded as concomitant medications)

The analyses for these endpoints will be described in the SAP.

9.9 Safety Analyses

All safety analyses will be based on the Safety Set.

The following safety variables constitute the safety endpoints measured in this study:

- Adverse events
- Hypocalcemic AEs (see Section 8.1.4)
- Vital signs
- Laboratory safety data (serum chemistry, hematology, urinalysis)
- ECGs
- Anti-PTH antibodies.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent AEs 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. Hypocalcemic AEs, AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and/or listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed. Descriptive statistics will be presented by treatment group at each assessment visit for quantitative safety data as well as for the change from baseline, if applicable. Frequency counts and percentage will be calculated for the classification of qualitative safety data.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

Visits to sites will be conducted by representatives of the study sponsor and/or the CRO 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.

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

10.1.2 Indemnity/Liability and Insurance

Shire 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.

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

10.1.3 Public Posting of Study Information

Shire 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

Shire 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 EOS completion date for pediatric studies and within 1 year for nonpediatric studies as per guidance. Shire will provide the IRBs/ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

Shire 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.

Shire will make an EOS 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 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 before 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. Curricula vitae for investigators and subinvestigators will be 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 is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is 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 guideline 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 that accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms will be supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator will be responsible for maintaining adequate and accurate medical records from which accurate information will be 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 provided to the sponsor must be endorsed by the investigator.

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

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

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 clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form will include 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).

Nonstudy site personnel will not disclose any personal information or personal medical information.

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 USA Food and Drug Administration, European Medicines Agency, the United Kingdom 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 Food and Drug Administration (as well as other US national and local regulatory authorities), the European Medicines Agency, the United Kingdom 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 will be 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 will be 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; and any significant equity interest in the sponsor or subsidiaries as defined in Title 21 of the US Code of Federal Regulations 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It will be the responsibility of the investigator to obtain written informed consent from all study subjects before 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, will be 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 will provide 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 before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before 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 will be 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 before 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 investigator agreement.

Before 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. If required by local law, substantial protocol amendments must also be approved by the appropriate regulatory agency prior to implementation.

Investigational product supplies will not be released until the sponsor has received written regulatory agency and IRB/EC approval of all 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 as required by IRB/EC procedures.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996.
A site that is not a covered entity as defined by Health Insurance Portability and Accountability Act 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 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. Shire 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 will adhere to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee will be to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish before 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 before 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.

11 REFERENCES

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Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	04 Aug 2016	Global
Amendment 1	15 Jun 2017	Global
Amendment 2	03 May 2018	Global
Amendment 3	11 Nov 2020	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** 03 May 2018	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
The sponsor signatory was changed from [redacted], MD to [redacted], MD.		Protocol Signature Page
The EUDRACT number has been corrected to read EUDRACT NO.: 2017-000284-32 Per Administrative Change Memo #1 (dated 05 Jul 2017).		Title page
The interactive response technology (IRT) country-specific help desk phone numbers have been added to the emergency contact information page. These numbers are to be used in case an emergency unblinding of a subject's treatment assignment is required AND the IRT is out of order.		Emergency Contact Information
Per Administrative Change Memo #3 (dated 27 Nov 2017): • The title of health status assessments has been updated to "Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism" (formerly PGI-S) and "Patient Global Impression of Change (PGI-C) for Hypoparathyroidism" (formerly PGI-C). • The title of "Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)" has also been updated to "Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:Hypoparathyroidism)." Further updates were made to the title of "Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:Hypoparathyroidism)"; the revised title is now "Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism)."		Abbreviations; Synopsis; Table 1; Section 2.2.3; Section 7.1 (throughout); Section 7.2.4.2; Section 9.8.3; Appendix 3
The first blinded interim analysis has been removed. Only one planned interim analysis for the primary endpoint will take place after approximately 50% of all randomized subjects have either completed the study or prematurely withdrawn from the study, whichever comes first. It will be performed using unblinded data to reassess the appropriateness of assumptions used for the primary efficacy endpoint when the study was designed. The interim efficacy analysis will be performed by an external independent statistician. The sponsor will only be notified by the external independent statistical of their recommendation to (1) stop the trial early for futility, (2) maintain the sample size as outlined in the current study design, or (3) update the sample size from the conditional power calculation. The language in Section 9.6 has been updated for clarification.		Synopsis; Section 3.1.1; Section 9.5; Section 9.6

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** 03 May 2018	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
It has been clarified throughout the protocol that the EuroQol five dimensions questionnaire 5-level version (EQ-5D-5L) of the EuroQol five dimensions questionnaire (EQ-5D) will be used.		Synopsis, Table 1, Section 7.1, Section 7.1.2.1, Section 7.1.2.2, Section 7.1.3.3, Section 7.1.3.5, Section 7.1.3.8, Section 7.2.4.2, Section 9.8.4
It has been clarified that active vitamin D and/or calcium may be increased, decreased, and/or stopped during titration. It was also clarified that investigational product is given with active vitamin D and/or calcium supplements.		Synopsis; Section 3.1.1
The language in the primary objective and endpoint has been clarified. The primary efficacy analysis was revised to indicate that MMRM model fit using data at post-baseline visits for Weeks 2, 4, 8, 12, 16, 20, 24, and 26 with change from baseline in the HPT-SD symptom subscale score as the outcome variable; treatment group, visit, and their interaction as fixed effect factors and subjects as a random effect, with adjustment for baseline HPT-SD symptom subscale score. It was added that descriptive statistics for HPT-SD symptom subscale score at each assessment including Week 0 (baseline), Weeks 6, 10, and 14, and change from baseline at each post-baseline assessment will be reported. In addition the following was added: Sensitivity analyses to explore the impact of missing data on the primary endpoint will be conducted. Additional sensitivity analyses will also be conducted to explore the impact of adjustments to calcium and active vitamin D supplements on the primary. All sensitivity analyses will be described in the SAP. Prespecified subgroup analyses are planned for the primary endpoint including, but not limited to gender, baseline calcium supplement dose, baseline active vitamin D dose, history of thyroid hormone replacement, and other important subgroups if feasible. A full list of subgroup analyses will be described in the SAP.		Synopsis; Section 2.2; Section 9.8.1
The language in the key secondary objectives has been clarified. In addition, the key secondary analysis was updated to include additional details for MMRM analysis.		Synopsis; Section 2.2.2; Section 9.8.2
The language in the secondary objectives and endpoints and in the exploratory endpoints has been clarified. In addition: A secondary objective based on patient reported outcomes "Evaluate response to the HPT-SD symptom subscale (as measured by a ≥30% reduction in symptom subscale score)" was added; a corresponding secondary endpoint "Response as defined as a 30% reduction in HPT symptom subscale score from Baseline to Week 26" was added. The secondary endpoint "Metabolic control, as defined as achieving all of the following: • Albumin-corrected serum calcium between 1.87 mmol/L (7.5 mg/dL) and ULN for the central laboratory normal range		Synopsis; Section 2.2.3; Section 9.8.3; Section 9.8.4

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• Dose of active vitamin D decreased by 50% • Dose of oral calcium supplement decreased by 50% or more." Was revised to "Composite endpoints, as defined as achieving all of the following: • Albumin-corrected serum calcium between 1.87 mmol/L (7.5 mg/dL) and the ULN for the central laboratory normal range • Dose of active vitamin D decreased by 50% • At least a 50% reduction from the baseline oral calcium supplement dose (this criterion will be considered met if the subject's baseline calcium dose is <1000 mg and it does not increase during the study)." The secondary endpoint "Markers of bone turnover" was revised to "Change in bone turnover marker" A secondary objective "To evaluate the effect of rhPTH(1-84) on bone turnover" has been added to support the existing secondary efficacy endpoint "Change in bone turnover markers." "The most bothersome symptom of hypoparathyroidism" has been added as a secondary objective and "Change in the most bothersome symptom score" as a secondary endpoint. The exploratory endpoint evaluating the effect of rhPTH(1-84) on change in the item score of the most burdensome symptom from baseline was removed due to the addition of the secondary objective and endpoint. Clarification has been made that the secondary efficacy endpoint "Change in in-clinic neurocognitive assessment scores (CogState Brief Battery; CogState Groton Maze Learning Test, CogState International Shopping List Task, CogState International Shopping List Task-Delayed Recall)" will be evaluated through Week 24 (not Week 26). A secondary efficacy endpoint "Percentage of subjects achieving the Minimal Clinical Important Difference (MCID) in the HPT-SD symptom subscale score" was removed. Secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint using an MMRM model. No multiplicity adjustment will be done on the secondary efficacy endpoints. Summary statistics including nominal p-values will be reported.		
The number of subjects anticipated to be enrolled at each site has been added: approximately 3 to 4 subjects.		Synopsis; Section 3.3
A section on early termination of the study was added. "Early Termination of the Study: After performance of the interim analysis an external independent statistical group may recommend that the sponsor stop the trial early for futility."		Section 3.4

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It has been clarified that the follow-up period will include an end-of-study contact for all subjects 30 days following the last dose of investigational product. The end-of-study contact is a safety follow-up telephone call initiated by the site staff to query for adverse events and concomitant treatments. Subjects who will be returning to the site for their last weekly follow-up visit can complete the EOS contact (Week 30 visit) at the site. It has also been clarified that subjects transferring to commercial rhPTH(1-84) who experience a treatment gap of >7 days following the EOT (Week 26) visit will proceed with weekly follow-up for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. If a subject transfers to commercial rhPTH(1-84) treatment before the EOS (Week 30) visit, assessments scheduled at the EOS (Week 30) visit should be performed at their last follow-up visit before transferring to commercial rhPTH(1-84); these subjects will have an EOS contact 30 days following their last dose of investigational product.		Synopsis; Table 1 (footnote 'c', formerly footnote 'b'); Section 3.1.1; Figure 1 (footnote 'a'); Section 3.2; Section 7.1.3.8; Section 7.1.4
It has been clarified that subjects 18-25 years of age must have evidence of epiphyseal closure based on bone age X-ray (single posteroanterior X-ray of left wrist and hand).		Synopsis; Table 1 (footnote 'e', formerly footnote 'd'); Section 4.1 (inclusion criterion #4); Section 7.1.1.1
Inclusion criterion #5 was revised to indicate that the subject has to have chronic hypoparathyroidism.		Synopsis, Section 4.1
Inclusion criterion #7 has been revised to the following: The subject must have a Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale Sum Score of ≥10 during the 14-day period immediately prior to the Week 0 visit (Day -14 to Day -1). In addition, the subject must have at least 4 HPT-SD diaries completed in the first 7 day period and at least 4 HPT-SD diaries completed in second 7 day period. See Appendix 3 for the calculation of the sum score. Corresponding text was revised as needed throughout the protocol.		Synopsis, Section 4.1, Section 7.1.2, Appendix 3
Inclusion criterion #8 was revised to the following: Must be treated with active vitamin D (calcitriol or alfacalcidol) alone or in conjunction with calcium supplements for at least 4 months prior to the screening visit. • The subject must be taking ≥0.5 µg/day of calcitriol or ≥1.0 µg/day of alfacalcidol. • If the subject is treated with a lower dose of active vitamin D the subject must also be taking calcium supplements of at least 800 mg/day of elemental calcium.		Synopsis, Section 4.1
Inclusion criterion #13 was revised to clarify that subjects must be willing to use oral active vitamin D and calcium supplements provided for the study unless they are directed to remain on supplements used prior to enrolment in the current study by the investigator after consultation with the medical monitor.		Synopsis, Section 4.1, Section 5.2.3

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Exclusion criterion #2 has been revised to define severe liver disease as a Child-Pugh score >9 (US FDA, 2003) and to clarify the example of hyperthyroidism as poorly controlled hyperthyroidism.		Synopsis; Section 4.2
Exclusion criterion #3 was revised to specify that subjects with very low or very high blood calcium level (eg, ACSC <1.87 mmol/L [<7.5 mg/dL] or ≥2.97 mmol/L [≥11.9 mg/dL]) at the Week -3 screening visit are to be excluded. It was also revised to indicate that the results from the central laboratory, not the local laboratory must be used for this assessment.		Synopsis; Section 4.2
Exclusion criterion #4 was revised to specify that subjects with blood calcium level above the upper limit of normal at the baseline (Week 0) visit are to be excluded.		Synopsis; Section 4.2
Exclusion criterion #11 was revised to include the following example: illness that is anticipated to be chronic and not transient.		Synopsis; Section 4.2
A new exclusion criterion has been added (#13) to exclude subjects with known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients. Refer to the investigator's brochure for the list of excipients.		Synopsis; Section 4.2
Exclusion #15 (formerly #14) was revised to indicate subjects with specific poorly controlled gastrointestinal diseases are to be excluded from the study.		Synopsis; Section 4.2
Exclusion criterion #16 (formerly #15) has been revised to define heart failure according to the New York Heart Association classification Class II to Class IV, as published in The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256. The reference has been added.		Synopsis; Section 4.2; Section 11
The mITT set was removed.		Synopsis; Section 9.7
The note at the beginning of the footnotes for Table 1 has been revised to include only a cross-reference to the corresponding sections for guidance about standardized meals and timing of active vitamin D, calcium supplements, and/or investigational product doses on study visit days.		Table 1 (Note)
A new footnote (a) has been added to 'Dose-titration period (Weeks 1-16)' in the schedule of assessment for clarity: the footnote reads "Changes in investigational product dose can occur approximately every 4 weeks up to and including Week 16. Active vitamin D and calcium supplements should be taken as determined by the investigator in order to achieve albumin-corrected serum calcium levels in the target range (see Appendix 2). Native vitamin D should be taken as determined by the investigator to target a serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the upper limit of normal (ULN). Magnesium supplements should be given, as appropriate, to achieve a serum magnesium concentration within the laboratory normal range." Text has also been clarified in the study design section and the dosing guidelines. It was also clarified that following Week 16 (maintenance dosing period [Weeks 17-26]), investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor		Table 1 (footnote 'a' and footnote 'b' [formerly footnote 'a']), Section 3.1.1, Section 6.2.3, Appendix 2

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A serum TSH level has been added as an assessment to be performed at the Week 26 visit (end-of-treatment visit).		Table 1, Section 7.1.3.8
Between visit predose nadir and post-dose peak levels have been added as assessments that are recommended to be performed during the treatment period following adjustment of investigational product, active vitamin D, and/or calcium supplements to aide in titration. If between visit predose nadir and post-dose peak levels are not assessed, the reason for not completing the measurements should be documented. Additional between visit blood draws can be completed at any time at the discretion of the investigator.		Table 1; Table 1 (footnote 'j'); Section 7.1; Appendix 2
A urine pregnancy test has been added as assessment to be performed at Week 30 visit (end-of-study visit).		Table 1; Section 7.1.4.2
It has been clarified that blood samples for the detection of anti-PTH antibodies must be collected prior to dosing with investigational product (at least 14 hours after the dose of investigational product).		Table 1 (footnote 'k', formerly footnote 'i'), Section 7.2.3.7
The completion of the "Most Bothersome Hypoparathyroidism-related Symptom" question, to occur once before the Week -2 visit, has been added. It supports the added secondary endpoint evaluating the most bothersome symptom of hypoparathyroidism. The Most Bothersome Hypoparathyroidism-related Symptom question should be completed at home once within the 2 days before the Week -2 visit; if the question was not completed at home prior to the Week-2 visit, it can be completed once at home within the 2 days after the scheduled visit. The question cannot be completed during the Week -2 visit.		Table 1; Table 1 (footnote 'n', formerly footnote 'l'); Section 7.1; Section 7.1.1.1; Section 7.1.1.2
The single version of Healthcare Resource Utilization assessments has been replaced with 2 versions: the Baseline Visit version to be used at the Baseline (Week 0) visit only; and the Follow-up Visit version to be used at subsequent visits (Weeks 2, 4, 8, 12, 16, 20, 24, 26, and 30 [end-of study]). Per Administrative Change Memo #3 (dated 27 Nov 2017).		Table 1(footnote 's'); Section 7.1.2; Section 7.1.3 (throughout); Section 7.1.4.2; Section 7.2.4.3; Appendix 3
Clarification has been made to the investigational product administration. In the schedule of assessments, the 'IP administration' row has been deleted and the 'Review subject records of active vitamin D, and calcium supplement doses' row edited to add 'records of IP doses'. The administration of investigational product has been added to appropriate sections of the study procedures.		Table 1 (including footnote 'o'); Section 7.1.2; Section 7.1.3.1; Section 7.1.3.2; Section 7.1.3.3; Section 7.1.3.5; Section 7.1.3.6; Section 7.1.3.8
The requirement for native vitamin D to be taken, as determined by the investigator, to target a serum 25 hydroxyvitamin D concentration of 75-250 nmol/L (30-100 ng/mL) has been revised to between 75 nmol/L (30 ng/mL) and the ULN.		Table 1 (footnote 'a'); Section 3.1.1; Section 5.2.3; Appendix 2
It has been clarified that the protocol allows local laboratories to be used for evaluation of blood albumin, calcium, phosphate, and magnesium concentrations. In addition to protocol specified laboratory testing in the central laboratory, blood for the evaluation of serum calcium, albumin, phosphate, and magnesium levels obtained on scheduled visit days can be analyzed locally at the sites or other local laboratories that are authorized by the investigator. These values may be used for titration of investigational product and supplements.		Table 1 (footnote 'i' formerly 'h'); Section 7.2, Section 7.2.2.2; Appendix 2

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When these samples are drawn locally, these samples can be analyzed per local laboratory standards (eg, ionized or total calcium or plasma calcium) and should be interpreted using the local laboratory normal values. If a local laboratory is used on scheduled study site visit days (ie, Weeks -3, -2, 0, 1, 2, 4, 8, 12, 16, 20, 24, 26, 27, 28, 29, 30), a duplicate sample must be collected and provided to the central laboratory.		
Language on dosing of active vitamin D, calcium supplements, and investigational product before reporting at Week -2 and Week 24 visits in preparation for the in-clinic neurocognitive assessments has been clarified: at Week -2 visit, subjects should take their usual active vitamin D and calcium supplement doses prior to the visit; and at Week 24 visit, subjects should take their usual active vitamin D, calcium supplement, and investigational product doses prior to the visit.		Section 7.1; Section 7.2
A clarification has been made that the 24-hour urine collection is to be completed the morning of the specified visits.		Table 1 (footnote 'l' formerly 'j'); Section 7.1.1.2; Section 7.1.3.2; Section 7.1.3.5; Section 7.1.3.6; Section 7.1.3.8; Section 7.2.2.2
The following restriction was added for 24-hour urine collection: "Subjects taking vitamin C or a multivitamin containing vitamin C must stop this medication for the 5 days prior to and during each 24-hour urine collection period."		Table 1 (footnote 'l' formerly 'j'); Section 5.2.2; Section 7.2.2.2
The following was clarified regarding the completion of PRO instruments: At the Week -3 visit, subjects should complete the PGI-S for hypoparathyroidism at the clinic after the subject has received and has been trained on the PRO device. PRO instruments (including PGI-S for hypoparathyroidism and PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L , and WPAI:hypoparathyroidism) should be completed once at home within the 2 days prior to baseline (Week 0) and Week 26 (EOT) visits. On the day before the baseline (Week 0) and the Week 26 (EOT) visits, subjects should receive a phone call to remind them to complete their PRO instruments. Subjects who do not complete their PRO instruments prior to the baseline (Week 0) visit will not be able to be randomized and can be rescreened starting at the Week -3 visit per the discretion of the investigator. Subjects should complete the PRO instruments for the Week -2 visit (including the most bothersome hypoparathyroidism-related symptom, PGI-S for hypoparathyroidism, and PGI-C for hypoparathyroidism) and for applicable visits between Week 1 and Week 24 (including PGI-S for hypoparathyroidism, PGI-C for hypoparathyroidism, Fact-Cog, FACIT-Fatigue, SF-36v2, EQ-5D-5L, and WPAI:hypoparathyroidism) once at home within the 2 days prior to the scheduled visit. If the PRO instruments are not completed prior to the scheduled visit, they can be completed once at home within the 2 days after the scheduled visit. PRO instruments cannot be completed during scheduled visits.		Table 1 (footnote 'r' formerly 'O'), Section 7.1, Section 7.1.1.1, Section 7.1.2.1, Section 7.1.2.2, Section 7.1.3.8

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A phone call has been added the day before the baseline (Week 0) visit and the day before the EOT (Week 26) visit to remind subjects to complete PROs prior to these visits.		Table 1 Section 7.1.2.1, and 7.1.3.8
Clarification has been made that subjects should be reminded at Week -3 visit to complete the HPT-SD, Most Bothersome Hypoparathyroidism-related Symptom, and health status assessments at home before the Week -2 visit.		Section 7.1.1.1; Section 7.1.1.2
Clarification has been made that subjects should be reminded at Week -2 visit to complete the Hypoparathyroidism Symptom Diary (HPT-SD). It has also been clarified the HPT-SD will be reviewed for completion at the baseline (Week 0) visit. The HPT-SD will be scored to confirm eligibility at the Week 0 visit.		Section 7.1.1.2, Section 7.1.2, Appendix 3
A benefit/risk assessment has been added to the protocol.		Section 1.3, Appendix 4
The double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam) have been removed as acceptable contraceptive methods. Only highly effective methods that have low user dependency and failure rate of <1% per year when used consistently and correctly are considered acceptable contraception methods.		Section 4.4.1
The following were added as examples of AEs that are symptoms of the disease under study that could lead to the discontinuation of a subject: persistent severe hypocalcemia or hypercalcemia that is not responsive to supplement or investigational product dose adjustment. The definition of severe hypercalcemia was added		Section 4.5.1
Denosumab has been added to the list of common excluded treatments, with an associated washout period of 4.25 months.		Section 5.2.2 (Table 2)
The procedures for unblinding a subject's treatment assignment have been clarified, and the back-up procedure when the IRT is out of order has been added.		Section 6.2.4
It has been indicated that a direct- to-subject service may be required to exchange the expiring study supplies between the site visits.		Section 6.3.2, Section 6.5
The schedule for completing the at-home neurocognitive assessment (CogState Brief Battery) has been updated for clarity and consistency within the protocol: Twice daily on each of the days between the Week -2 visit and the baseline (Week 0) visit, and twice daily on each of the 14 days before the Week 12 and Week 26 visits, ending 1 day before the visit.		Section 7.1; Section 7.2.4.1
A reference to the central laboratory manual for procedures including sample collection, handling, and storage has been added. Clarification has been made that all samples collected will be discarded by the end of the study.		Section 7.2
It was clarified that if active vitamin D and/or calcium supplements need to be taken, in the opinion of the investigator, prior to reporting for the visit, the lowest dose necessary to maintain safety should be taken and this dose should be used consistently at each visit to the greatest extent possible.		Section 7.2; Appendix 2
Uric acid was added to the serum chemistry parameters.		Section 7.2.3.4
Qualitative cystine has been removed from the urine chemistry parameters to be performed at baseline. This parameter is not necessary for the present study.		Section 7.2.3.4

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It has been clarified that phosphorus, not phosphate will be measured for urine chemistry.		Section 7.2.3.4
Indicated that 24-hour urine collections will have supersaturation calculated for calcium oxalate, calcium phosphate (brushite), and uric acid. It was also indicated that the following will be calculated based on 24-hour urine collections: • Calcium per Creatinine • Calcium per Kg Body Weight • Creatinine per Kg Body Weight • Protein Catabolic Rate		Section 7.2.3.4
Indicated that urinalysis will include microscopy (eg, crystals, bacteria, and cells) as needed if indicated by other parameters.		Section 7.2.3.4
The protocol specifies that anti-PTH antibodies test results will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available (Section 9.3). Clarification has been made that anti-PTH antibodies test results will be reported at the end of the study.		Section 7.2.3.7
The following subscales were provided for the HPT-SD: The HPT-SD is a 13-item patient-reported outcomes instrument that consists of the following items: • symptom subscale (items 1-7) • anxiety (item 8) • sadness and depression (item 9) • impact subscale (items 10-13) It has been clarified that the HPT-SD will include the "Most Bothersome Hypoparathyroidism-related Symptom" question once for the Week -2 visit (±2 days).		Section 7.2.4.2
The following definition was added for a treatment-emergent adverse event: Treatment-emergent adverse events (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study drug. Events which occur more than 30 days after the last dose of study drug will not be considered treatment-emergent. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered treatment-emergent. Adverse events with completely missing onset dates and a stop date after the date of first dose (or unknown stop date) will also be considered treatment-emergent.		Section 8.1
Clarified that the investigator should evaluate all AEs; if an AE is determined to be related to hypocalcemia the AE should be classified according to the prespecified definitions.		Section 8.1.4

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The threshold for overdose has been changed to 100 µg for consistency with the standard definition of overdose as an intentional or unintentional intake of a dose of the investigational product exceeding a prespecified total daily dose. The maximum dose allowed in the study is 100 µg daily.		Section 8.1.7
Additional details were added to clarify sample size calculations and power considerations, including considering the single interim analysis for futility.		Section 9.6
Specification has been made that, if required by local law, substantial amendments must also be approved by the appropriate regulatory agency prior to implementation. It has been clarified that the investigational product supplies will not be released until the sponsor has received written regulatory agency and IRB/EC approval of all documents It has been clarified that as required by IRB/EC procedures, the investigator must also keep the local IRB/EC informed of any serious and significant AEs.		Section 10.3.2
The following definitions have been provided for the terms in the flowcharts related to predose calcium levels based on albumin-corrected serum calcium levels: Very Low: <1.87 mmol/L (<7.5 mg/dL) Low: 1.87 to <2.0 mmol/L (7.5 to <8.0 mg/dL) Low-normal: 2.0 to <2.25 mmol/L (8.0 to <9.0 mg/dL) High-normal: 2.25 to <2.55 mmol/L (9.0 to <10.2 mg/dL) High: 2.55 to <2.97 mmol/L (10.2 to <11.9 mg/dL) Very High: ≥2.97 mmol/L (≥11.9 mg/dL) The dosing guidelines flowcharts have been have been updated to reflect these levels.		Appendix 2
Minor corrections have been made to Figure B-1 "Dosing Guideline at Weeks 4, 8, 12, and 16 Visits for Very Low and Low Calcium Levels" and Figure C-1 "Dosing Guideline at Weeks 1, 2, 6, 10, and 14 Visits (and at any Unscheduled Laboratory Testing) for Very Low, Low, Low-normal, and High-normal Calcium Levels"		Appendix 2
Scoring of the HPT-SD appendix was revised to include the current method for scoring the HPT-SD for eligibility and scoring of the HPT-SD at baseline and during the treatment period (including individual item score and subscale scores). The corresponding numerical values of the verbal rating scale (including for items 1-9 and for items 10-13) were also added.		Appendix 3
The version of the Hypoparathyroidism Symptom Diary has been replaced with the 24-Hour Recall version (Version 1) to correct an error. Per Administrative Change Memo #2 (dated 16 Aug 2017).		Appendix 3

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A copy of the following patient reported outcome instruments has been added to the protocol Appendix 3: Most Bothersome Hypoparathyroidism-related Symptom© (Version 1); FACIT Fatigue Scale (Version 4); FACT-Cognitive Function (Version 3); SF-36v2® Health Survey Acute; EQ-5D-5L PDA version; WPAI:Hypoparathyroidism; PGI-S for Hypoparathyroidism® (Version 1); PGI-C for Hypoparathyroidism© (Version 1); and the Baseline Visit version and the Follow-up Visit version of the Healthcare Resources Utilization. A reference to Appendix 3 was added in the sections where these instruments are presented. Per Administrative Change Memo #3 (dated 27 Nov 2017).		Appendix 3
Appendix 5 was added; the appendix includes the following: United States Department of Agriculture national nutrient database for standard reference release for calcium, phosphorus, and sodium in milligrams measured by household and 100 grams.		Appendix 5

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Amendment Number 1	**Amendment Date** 15 Jun 2017	**Global/Country/Site Specific** Global
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Revised the study title to reflect the double-blind, adaptive, study design, and new primary objective evaluating symptom improvement. Deleted references to Phase 4 in the title as this study will be conducted in some regions where rhPTH(1-84) is not yet approved for marketing (now Phase 3b-4 study).		Title page; Protocol Signature Page; Synopsis
Updated the emergency contact information and the name of the 'Shire Global Pharmacovigilance and Risk Management Department' to 'Shire Global Drug Safety Department.'		Emergency contact information Section 8.1.6; Section 8.2.2; Section 8.2.4
Extended the planned study period to 2021.		Synopsis
Changed to a double–blind study design and the number of subjects to be enrolled to a minimum of 118 and no more than 150. Changed the primary objective of the study to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in symptoms of hypoparathyroidism assessed by the Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale score compared with standard therapy. Added key secondary objectives to test the hypotheses that rhPTH(1-84) treatment, compared with standard therapy, can result in superior improvements on the fatigue assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) and the physical component summary (PCS) derived from the 36-Item Short Form Health Survey version 2 (SF-36v2) acute version.		Synopsis; Section 2; Section 3.1; Section 6.1.1; Section 6.2.2; Section 9.5; Section 9.6; Section 9.8; deleted former Section 9.10

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Amendment Number 1	**Amendment Date** 15 Jun 2017	**Global/Country/Site Specific** Global
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Revised secondary objectives to include neurocognitive assessments, additional patient-reported outcomes, evaluations of metabolic control, and safety and tolerability of rhPTH(1-84). All endpoints were revised to support the new study objectives. Changes to the statistical analyses and sample size calculation were made, and 2 planned interim analyses will be performed. The first, blinded, interim analysis will be performed to assess the responsiveness of the HPT-SD and the second, unblinded, interim analysis to reassess the assumptions used for the sample size calculation of the primary efficacy endpoint and assess for futility. Based on the results of the second interim analysis, the number of subjects to be enrolled may be increased from 118 to up to 150, or the trial may be stopped due to futility.		
Changed the study visit schedule: reduced the duration of the treatment period in the study to 6 months (26 weeks); removed the flexible-dosing period; replaced several clinic visits with phone visits (Weeks 6, 10, and 14); and added weekly follow-up site visits during a 4-week period after the end-of-treatment visit (Week 26) or early termination visit for subjects discontinuing rhPTH(1-84). Subjects immediately transferring to commercial rhPTH(1-84) after the Week 26 visit, the end-of-treatment visit will serve as the end-of-study visit (no follow-up visits will be performed). Changed assessments time points according to the new treatment duration and endpoints, as appropriate.		Synopsis; Table 1; Section 3.1.1; Section 3.2; Figure 1; Section 5.2; Section 6.2.3; Section 7
Clarified that administration of the investigational product will take place in the morning and when injecting the investigational product, the subject should alternate the left and the right thighs each day.		Synopsis; Section 3.1.1; Section 6.2.3
Clarified that 'calcium supplement' refers to prescribed nondietary oral calcium supplement in the protocol.		Synopsis; Section 3.1.1; Section 6.2.3; Appendix 2
Removed renal ultrasounds and bone mineral density assessment as no longer relevant in a 6-month treatment study.		Synopsis; Table 1; Section 3.1.1; Section 3.1.2; Section 7.1.1.1; Section 7.1.2; Section 7.1.3.5; Section 7.1.3.8 (formerly 7.1.2.9); former Section 7.2.2.2; deleted former Section 7.2.2.3; Section 9.8.4 (formerly 9.8.3); Section 11
Revised eligibility criteria that define the diagnosis and status of hypoparathyroidism in subjects as follows: • Inclusion 5: Extended onset of hypoparathyroidism to at least 12 months before screening. Removed calcium/active vitamin supplements dependence as redundant with hypocalcemia. • Inclusion 6: Changed requirements of hypoparathyroidism symptoms for eligibility to at least 2 of the following symptoms related to hypoparathyroidism occurring within the Week -3 visit previous 2 weeks: muscle cramps, muscle spasms or twitching, tingling, numbness, heaviness in arms or legs, physical fatigue, or slowed or confused thinking (brain fog).		Synopsis; Section 4; Section 5.2.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** 15 Jun 2017	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
• Inclusion 7: Added requirements of hypoparathyroidism symptoms for eligibility based on the results of the HPT-SD administered during the first week of the screening period (from Week -3 to Week -2 visits) with occurrence of at least 2 symptoms (that average at least moderate in intensity) and a sum score of HPT-SD symptom subscale (items 1-7) measured ≥6. At least 4 responses must be entered for each symptom. • Inclusion 8: Changed requirements for treatment with active vitamin D supplement (alfacalcidol or calcitriol) alone or in conjunction with calcium supplements. Allow subjects treated with active vitamin D and/or calcium supplement at low doses to be eligible for the study if they have a history of inability to be successfully managed with higher doses. • Inclusion 9: Changed requirements for treatment with thyroid hormone replacement therapy. For subjects on thyroid hormone replacement therapy, the thyroid hormone dose must have been stable for at least 4 weeks before screening, and serum thyroid-stimulating hormone (TSH) level must be within the central laboratory normal range. A serum TSH level below the lower limit of the normal range but not undetectable in subjects treated with thyroid hormone may be allowed if there is no anticipated need for a change in thyroid hormone dose during the trial. • Inclusion 11: Allowed the inclusion of subjects with an estimated glomerular filtration rate >30 ml/min/1.73 m^2 using the CKD-epi equation (instead of serum creatinine <1.5 mg/dL). • Exclusion 1: Specified that history of hypoparathyroidism results from a known activating mutation in the *CaSR* gene. • Exclusion 2: Clarified which diseases that might affect calcium metabolism or calcium-phosphate homeostasis are excluded. • Exclusion 3: Newly added to exclude subjects with an albumin-corrected serum calcium level <1.875 mmol/L (7.5 mg/dL) or ≥2.56 mmol/L (10.3 mg/dL) at the Week -3 screening visit. • Exclusion 4: Newly added to exclude subjects with an albumin-corrected serum calcium level ≥2.56 mmol/L (10.3 mg/dL) at the baseline (Week 0) visit. • Exclusion 8 (formerly 6): Excluded the use of intravenous bisphosphonates preparations within the previous 24 months. • Exclusion 9 (formerly 7): Clarified history of seizure. • Former exclusion 12 on history of gout was deleted. • Exclusion 15: Changed 'cardiac insufficiency' to 'heart failure', revised the definition of bradycardia as resting heart rate of <60 beats/min to <50 beats/minute, and deleted 'hypotension'.		

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** 15 Jun 2017	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
Clarified other eligibility criteria as follows: • Inclusion 4: Specified radiological evidence of epiphyseal closure based on X-ray of left wrist and left hand for subjects 25 years of age or younger. • Inclusion 13: Newly added to ensure subjects are willing to use oral active vitamin D and calcium supplements provided for the study. • Inclusion 14 (formerly 13): Revised text for consistency with Section 4.4.1 on female contraception. • Exclusion 5 (formerly 3): Removed raloxifene hydrochloride, and estrogens and progestins for hormone replacement therapy from the list of prohibited medications. • Exclusion 10 (formerly 8): Replaced irradiation (radiotherapy) to the skeleton within 5 years before screening with increased baseline risk for osteosarcoma, such as with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or a prior history of external beam or implant radiation therapy involving the skeleton.		Synopsis; Section 4.1; Section 4.2; Section 5.2.2; Table 1; Table 2; Section 7.1.1.1
Active vitamin D and calcium supplements will be provided for the study		Synopsis; Section 3.1.1; Section 5.2.3; Section 6.2.3; Appendix 2
Added the EuroQol five dimensions questionnaire five levels (EQ-5D-5L) as a second health-related quality of life assessment and as exploratory endpoint.		Abbreviations; Table 1; Section 7.1; Section 7.1.2; Section 7.1.3.3; Section 7.1.3.5; Section 7.1.3.8; Section 7.2.4.2; Section 9.8.4
Deleted the Hospital Anxiety and Depression Scale (HADS) from PROs assessments to be performed in the study.		Abbreviations; Table 1; Section 7.2.4.2
Updated the background information on rhPTH(1-84), including the list of adverse reactions for consistency with the company core data sheet, and recent approval by the European Commission dated April 2017.		Section 1.1; Section 1.2
Revised language on data handling to account for double-blind study design.		Section 9.3
Clarified the measures of healthcare resource utilization: frequency covers encounters such as outpatient visits, laboratory tests, and procedures not scheduled in the protocol, emergency department visits, and hospitalizations.		Section 7.2.4.3; Section 9.8.4
Added follow-up dietary evaluations to assess the subjects' adherence to daily dietary (nonsupplement) intake of calcium, phosphate, and sodium prior to study blood draws, and during 24-hour urine collections.		Table 1; Section 4.3; Section 7.1.1.1; Section 7.1.3.5
Urinalysis will be analyzed via central laboratory rather than with a dipstick. Specified that glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] equation.		Table 1; Section 7.2.3.4
Specified that HPT-SD should be completed by the subject at a consistent time every day during the applicable period.		Table 1; Section 7.1; Section 7.2.4.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** 15 Jun 2017	**Global/Country/Site Specific** Global
Description of Change		**Section(s) Affected by Change**
Specified that the mixing apparatus will be collected at the end of treatment visit.		Table 1; Section 7.1.3.8
Corrected inconsistency in the period when prior medications will be collected.		Section 5
Minor edits to the information regarding magnesium supplements.		Section 5.2.3
Added procedure for unblinding a subject's treatment assignment to account for the double-blind study design.		Section 6.2.4
Clarified that single-use injection pen needles will be provided.		Section 6.3.2
Deleted a statement on health/safety concerns with returning the investigational product container.		Section 6.4
Added active vitamin D and calcium supplements to be distributed at each visit and also to be accounted for. Specified that native vitamin D and magnesium supplements will not be accounted for.		Section 6.5
Allowed subjects who fail to meet all inclusion/exclusion criteria to be rescreened, and only if the investigator assesses the reason for screen failure is transient and temporary. Also, eligible subjects who meet all inclusion/exclusion criteria, but are unable to participate in the study due to scheduling conflicts/timing, may be rescreened based on investigator discretion. Additionally the following was added: Subjects who did not complete all required PROs prior to the Week 0 (baseline) visit are allowed to be rescreened based on investigator discretion.		Section 7.1.1 (formerly in Section 7.1.1.1)
Clarified the definition of severe hypocalcemia as symptom of the disease under study to be reported as serious adverse event.		Section 8.1.4
Added dose of native vitamin D supplements (recorded as concomitant medications) and effect of rhPTH(1-84) on change in the item score of the most burdensome symptom from baseline as exploratory endpoints.		Section 9.1.4
Revised dosing guidelines for active vitamin D supplements, calcium supplements, and investigational product.		Appendix 2
Added new appendix presenting the following scales and assessments: Scoring of HPT-SD (scoring algorithm and for subject's eligibility in the study); HPT-SD; and Healthcare Resources Utilization.		Appendix 3
Minor changes have been made: • Patient to subject to be consistent with the sponsor writing standards • Conventional care to standard therapy, for consistency with product labelling • Laboratory reference range to central laboratory normal range • Albumin-adjusted to albumin-corrected • PTH antibodies to anti-PTH antibodies		

Appendix 2 Dosing Guidelines for Active Vitamin D Supplements, Calcium Supplements, and Investigational Product

In this study, the goal is to optimize rhPTH(1-84) dosing so as to reduce active vitamin D and calcium supplement doses to as low as safely possible, while maintaining serum calcium levels in a target range. In general, the target range is a stable serum calcium concentration measured before investigational product and supplement dosing ("predose") just below the lower end of the normal range and within the lower end of the normal range (eg, albumin-corrected serum calcium [ACSC] between 2.0 and 2.25 mmol/L [8.0-9.0 mg/dL] inclusive). Predose calcium levels in the mid-normal to upper-normal range (eg, ACSC between 2.25 mmol/L [9.0 mg/dL] and the upper limit of normal [ULN]) may also be acceptable if the 24-hour urine calcium excretion is not elevated. The ACSC and serum phosphate levels, measured 8-12 hours after investigational product dosing ("postdose"), are below the upper limit of the normal range. Table A1 provides predose and postdose target calcium levels.

Table A1 Target Calcium Levels

Timing of Measurement	Target Calcium Level	Example Acceptable Levels
Predose[a]	Slightly below the lower end of the normal range-within the lower level of the normal range OR	ACSC: 2.0-2.25 mmol/L (8.0-9.0 mg/dL
	Mid normal range-ULN if 24-hour urine calcium excretion is not elevated	ACSC: 2.25 mmol/L-ULN (9.0 mg/dL-ULN)
Postdose[b]	< ULN	ACSC:<ULN

Note: When these samples are drawn locally, these samples can be analyzed per local laboratory standards (eg, ionized or total calcium or plasma calcium) and can be used for this purpose as per the local laboratory standards and should be interpreted using the local laboratory normal values. If a local laboratory is used on scheduled study site visit days (ie, Weeks -3, -2, 0, 1, 2, 4, 8, 12, 16, 20, 24, 26, 27, 28, 29, 30), a duplicate sample must be collected and provided to the central laboratory. Ionized calcium, ACSC, or plasma calcium can be used to determine the calcium level.

ACSC=albumin-corrected serum calcium; ULN=upper limit of normal

a: To be measured prior to dosing with investigational product and supplements.

b: To be measured 8-12 hours after dosing with investigational product.

This section provides detailed guidelines for dose adjustments of active vitamin D supplements, calcium supplements (calcium supplement refers to prescribed non-dietary oral calcium supplement), and investigational product [rhPTH(1-84) or placebo] during the study. Active vitamin D (calcitriol or alfacalcidol) and calcium (calcium carbonate or calcium citrate) supplements will be provided for the study.

In addition, it is important to adjust native vitamin D and magnesium supplements throughout the study beginning with the screening visit. Native vitamin D supplements should be titrated to achieve a serum 25-hydroxyvitamin D concentration between 75 nmol/L (30 ng/mL) and the ULN for the laboratory. Subjects with low serum magnesium concentrations should receive magnesium supplementation, as appropriate, to achieve serum magnesium concentrations within the normal range. Native vitamin D and magnesium supplements will not be provided for the study.

Subjects eligible for randomization will be assigned to receive rhPTH(1-84) or placebo (both referred to as investigational product) in addition to active vitamin D and calcium supplements. The randomized treatment assignment will be blinded. Changes in investigational product dose can occur approximately every 4 weeks up to and including Week 16 in 25 µg increments up to a maximum dose of 100 µg QD. Following Week 16 (maintenance dosing period [Weeks 17-26]), investigational product doses are intended to remain relatively stable during the last 10 weeks of the treatment period; however, if the subject has not reached the optimal dose of investigational product, adjustments can be made following discussion with the medical monitor. Active vitamin D and calcium supplements may be titrated per investigator discretion to achieve biochemical targets during this period. At any time during the study as needed for safety reasons, investigational product doses may be decreased in 25 µg decrements to a minimum of 25 µg QD. If the serum calcium is significantly above the upper limit of the normal range (eg, >2.97 mmol/L [>11.9 mg/dL]), then the investigational product should be stopped until the calcium level is corrected (see Figure B-4 and Figure C-2). Active vitamin D and/or calcium supplement dose titrations may occur at any time.

In-clinic blood draws: Calcium, albumin, phosphate and magnesium

On study visit days blood draws should be measured in the morning before supplements and investigational product dosing and sent to the central laboratory If, in the opinion of the investigator, it is necessary for a subject to take active vitamin D and/or calcium supplements before reporting for the visit, the doses of the supplements taken before the blood draw should be the lowest dose necessary to maintain safety and should be used consistently at each visit to the greatest extent possible. The timing of any supplements taken before the blood draw with respect to the blood draw should also be consistent throughout the study to the greatest extent possible. Subjects should not take investigational product until the completion of the blood draw.

Immediately after the blood samples are obtained, the subject should take the usual dose of active vitamin D and calcium supplements and administer the most recently prescribed dose of investigational product. If the subject took partial doses of active vitamin D and calcium before traveling to the clinic, then any additional supplement doses needed to achieve the normal total dose should be administered following the blood draw. The remaining study procedures should occur after administration of supplements and investigational product (see Section 7.1).

In addition to protocol specified laboratory testing processed in the central laboratory, blood for the evaluation of serum calcium, albumin, phosphate, and magnesium levels obtained on scheduled visit days can be analyzed locally at the sites or other local laboratories that are authorized by the investigator. These values may be used for titration of investigational product and supplements. When these samples are drawn locally, these samples can be analyzed per local laboratory standards (eg, ionized or total calcium or plasma calcium) and should be interpreted using the local laboratory normal values. If a local laboratory is used on scheduled study site visit days (ie, Weeks -3, -2, 0, 1, 2, 4, 8, 12, 16, 20, 24, 26, 27, 28, 29, 30), a duplicate sample must be collected and provided to the central laboratory.

Between visit blood draws: Calcium, albumin, phosphate and magnesium

It is recommended that between visit predose nadir and post-dose peak levels should be assessed following the adjustment of investigational product, active vitamin D, and/or calcium supplements to aid in titration. If between visit predose nadir and post-dose peak levels are not assessed, the reason for not completing the measurements should be documented. Blood for the assessment of these levels should be collected approximately 2-5 days following any adjustment(s). The post-dose peak level blood draw for the evaluation of serum calcium, albumin, phosphate, and magnesium should be drawn approximately 8-12 hours following administration of the investigational product dose. The predose nadir level blood draw for the evaluation of serum calcium, phosphate, albumin, and magnesium should be drawn in the morning prior to the administration of the dose of investigational product that day, within 24 hours of the last dose of investigational product. Blood for predose nadir and post-dose peak levels can be drawn on the same day or different days as long as the blood draws are completed within the 2-5 day window and within the window specified for each level. Local laboratories can be used for these assessments; duplicate samples do not need to be sent to the central laboratory. Additional between visit blood draws can be completed at any time at the discretion of the investigator.

Dosing Guidelines:

Screening

During the screening period, subjects will use their pre-existing active vitamin D and calcium supplements. Supplement doses should only be changed during the screening period for safety reasons.

Initiation of Investigational Product

See Figure A for recommended dosing guideline at the initiation of the investigational product at baseline (Week 0) visit.

Treatment Period

See Figure B-1 for recommended dosing guideline at Weeks 4, 8, 12, and 16 visits for calcium levels below the lower limit of normal (eg, ACSC levels ≤2.0 mmol/L [≤8.0 mg/dL]).

See Figure B-2 for recommended dosing guideline at Weeks 4, 8, 12, and 16 visits for calcium levels in the lower part of the normal range to just below the normal range (eg, ACSC levels 2.0-2.25 mmol/L [8.0-9.0 mg/dL]).

See Figure B-3 for recommended dosing guideline at Weeks 4, 8, 12, and 16 visits for calcium levels in the mid-normal to upper part of the normal range (eg, ACSC levels 2.25-2.55 mmol/L [9.0-10.2 mg/dL]).

See Figure B-4 for recommended dosing guideline at Weeks 4, 8, 12, and 16 visits for calcium levels above the upper limit of the normal range (eg, ACSC >2.55 mmol/L [>10.2 mg/dL]).

See Figure C-1 for recommended dosing guideline at Weeks 1, 2, 6, 10, and 14 visits (and at any unscheduled laboratory testing) for calcium levels below the upper limit of the normal range (eg, ACSC levels ≤2.55 mmol/L [≤10.2 mg/dL]).

See Figure C-2 for recommended dosing guideline at Weeks 1, 2, 6, 10, and 14 visits (and at any unscheduled laboratory testing) for calcium levels above the upper limit of the normal range (eg, ACSC levels >2.55 mmol/L [>10.2 mg/dL]).

Please interpret the calcium values as per the normal values for the local laboratory used and for the analyte tested (eg, ionized or total calcium or plasma calcium). To aid in interpretation the following definitions are provided for the terms in the flowchart related to predose calcium levels based on albumin-corrected serum calcium levels.

Very Low: <1.87 mmol/L (<7.5 mg/dL)

Low: 1.87 to <2.0 mmol/L (7.5 to <8.0 mg/dL)

Low-normal: 2.0 to <2.25 mmol/L (8.0 to <9.0 mg/dL)

High-normal: 2.25 to <2.55 mmol/L (9.0 to <10.2 mg/dL)

High: 2.55 to <2.97 mmol/L (10.2 to <11.9 mg/dL)

Very High: ≥2.97 mmol/L (≥11.9 mg/dL)

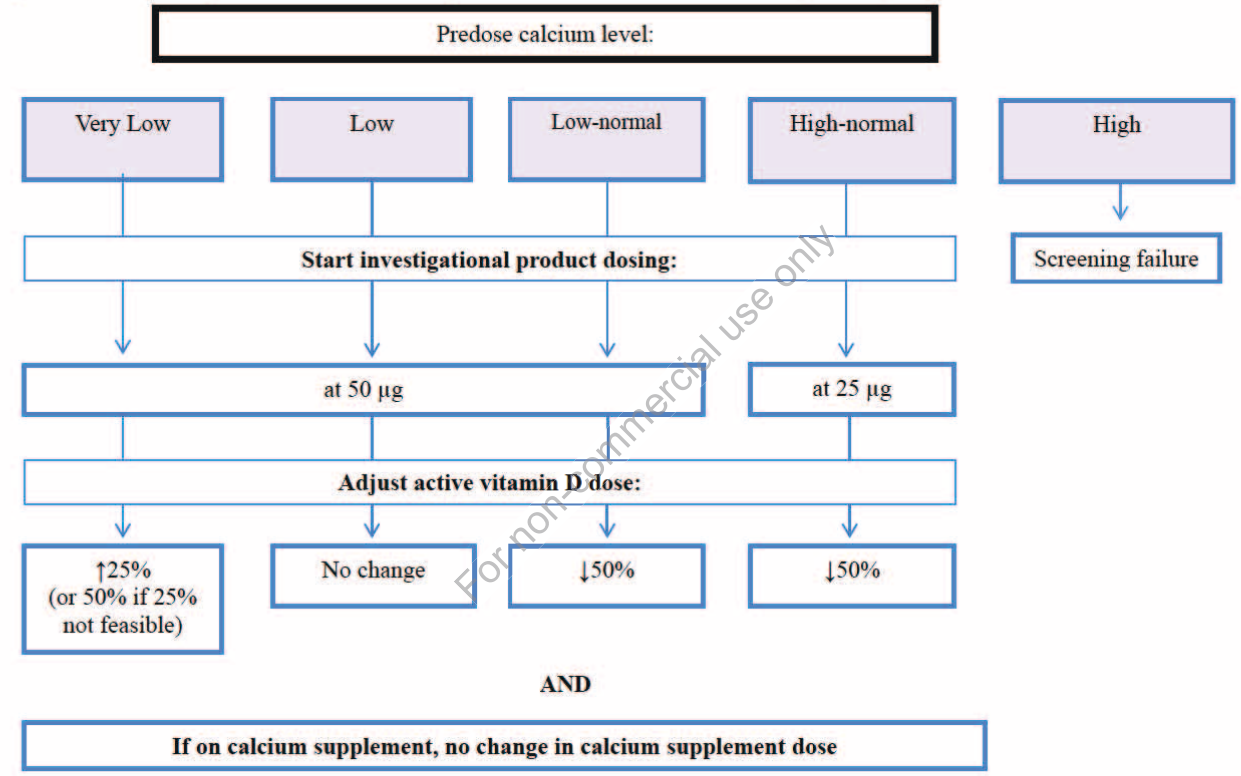
Missed dose

In the case of a missed dose, investigational product must be administered as soon as reasonably feasible and additional exogenous sources of calcium and/or active vitamin D should be taken based on symptoms of hypocalcemia.

Interruption or discontinuation of treatment

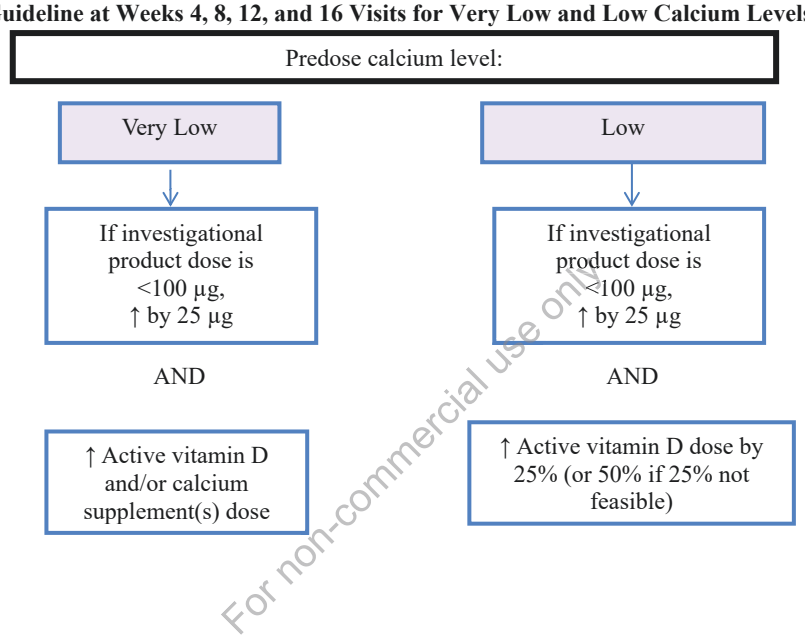
Abrupt interruption or discontinuation of rhPTH(1-84) can result in severe hypocalcemia. Temporary or permanent discontinuation of rhPTH(1-84) treatment must be accompanied by monitoring of serum calcium levels and adjustment, as necessary, of exogenous calcium and/or active vitamin D.

Figure A **Investigational Product Dosing Initiation Guideline for Baseline (Week 0) Visit**



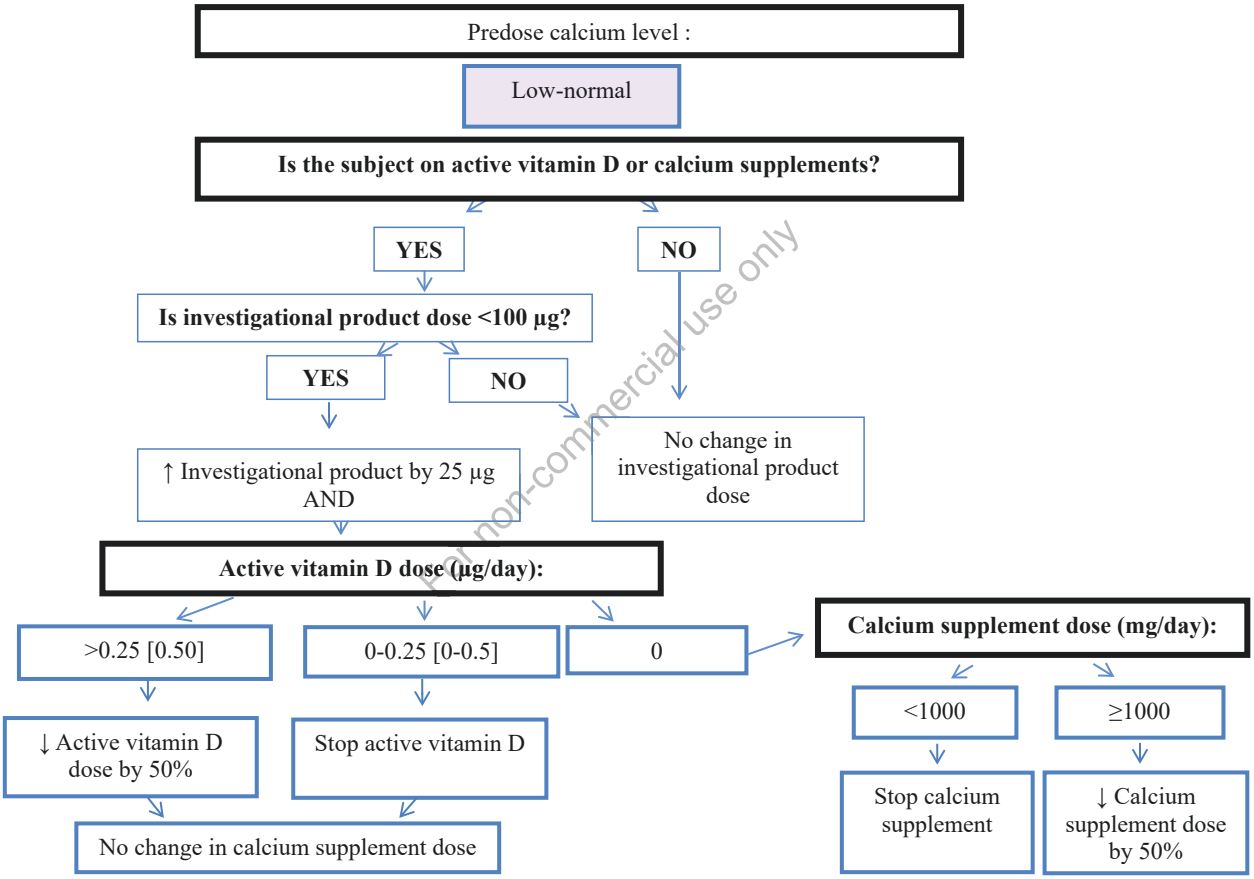
Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to alfacalcidol and calcitriol.

Figure B-1 Dosing Guideline at Weeks 4, 8, 12, and 16 Visits for Very Low and Low Calcium Levels



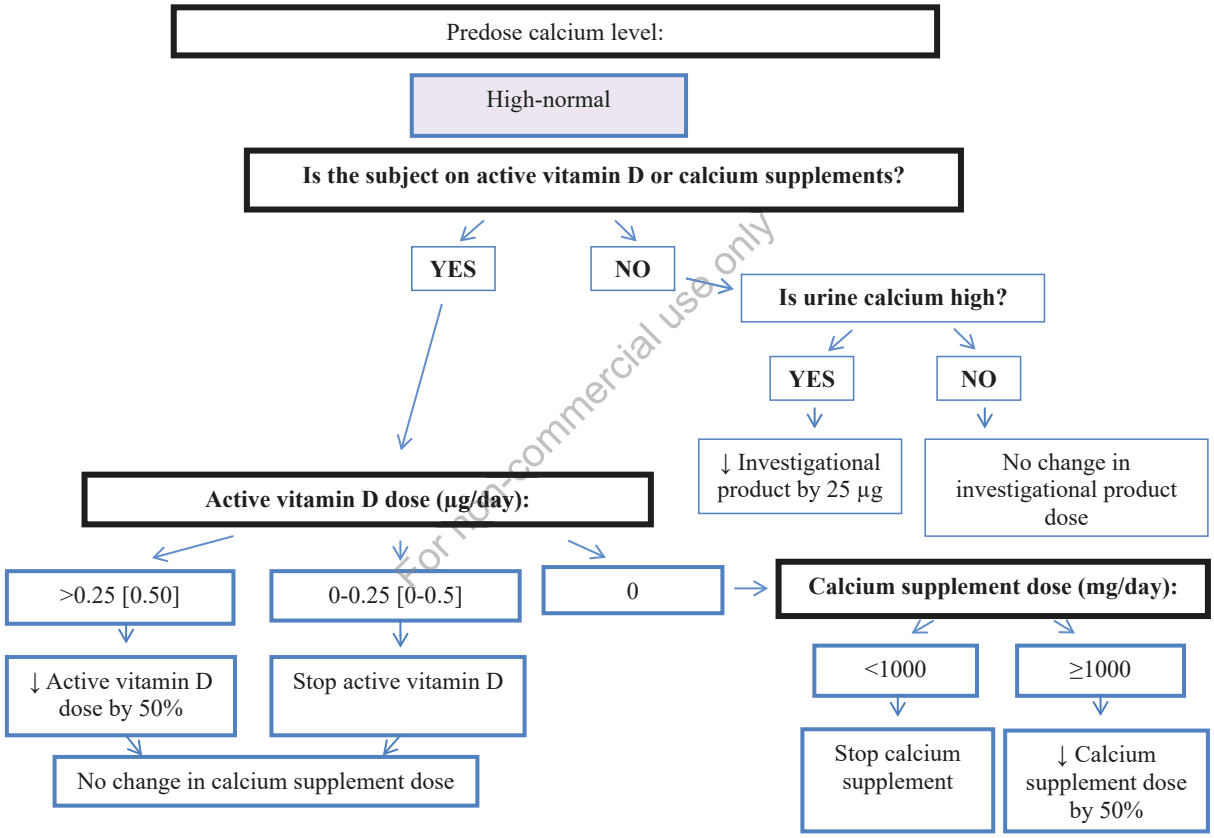
Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol and alfacalcidol

Figure B-2 Dosing Guideline at Weeks 4, 8, 12, and 16 Visits for Low-normal Calcium Levels



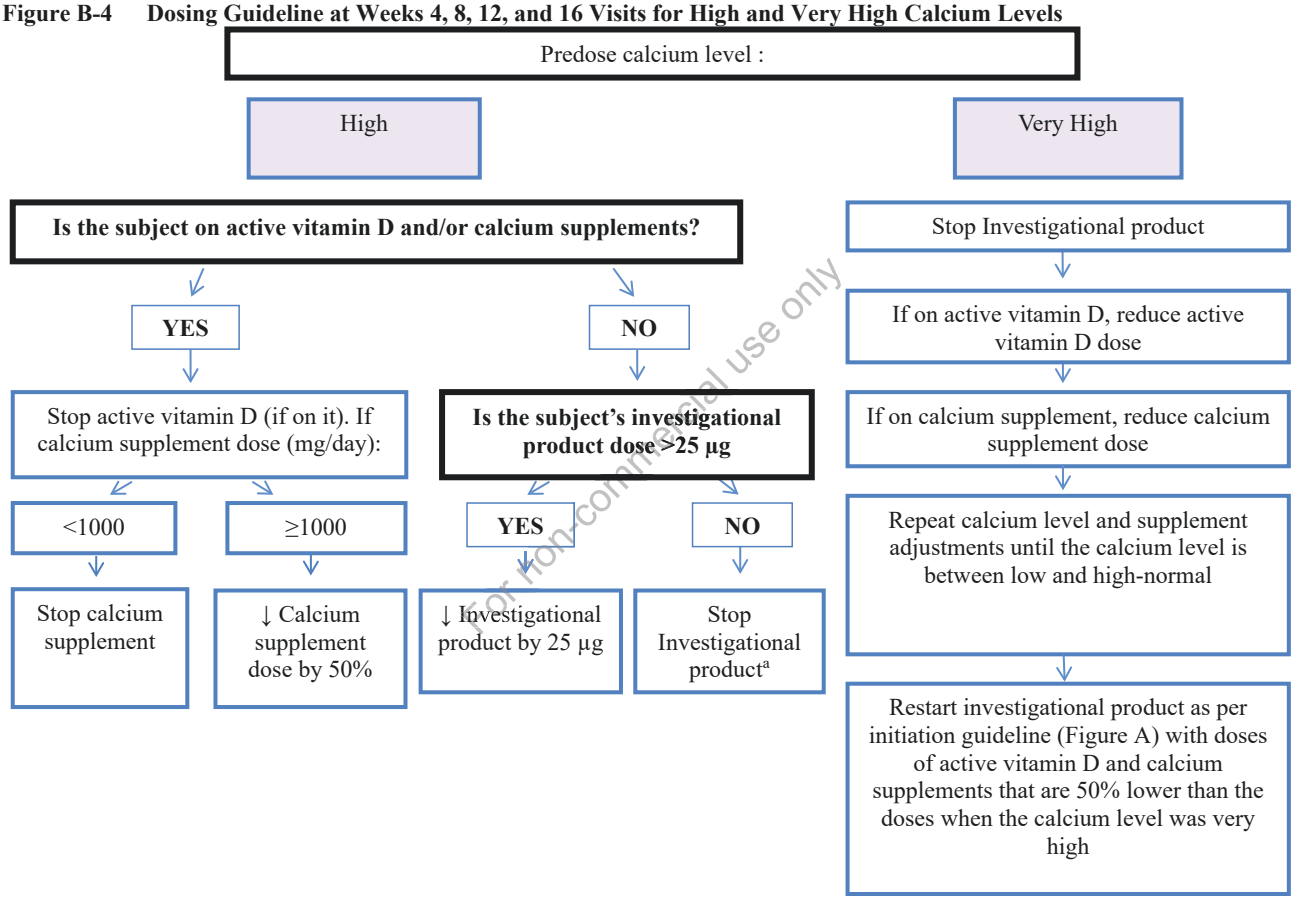
Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol [alfacalcidol].

Figure B-3 Dosing Guideline at Weeks 4, 8, 12, and 16 Visits for High-normal Calcium Levels



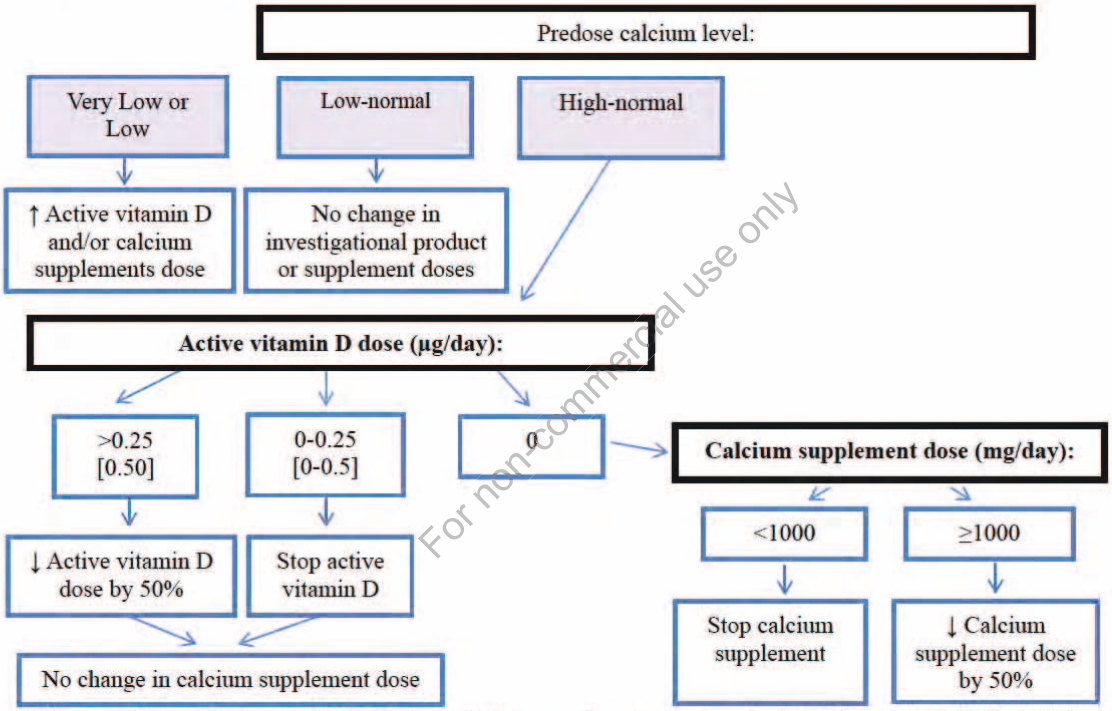
Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol [alfacalcidol].

Figure B-4 Dosing Guideline at Weeks 4, 8, 12, and 16 Visits for High and Very High Calcium Levels



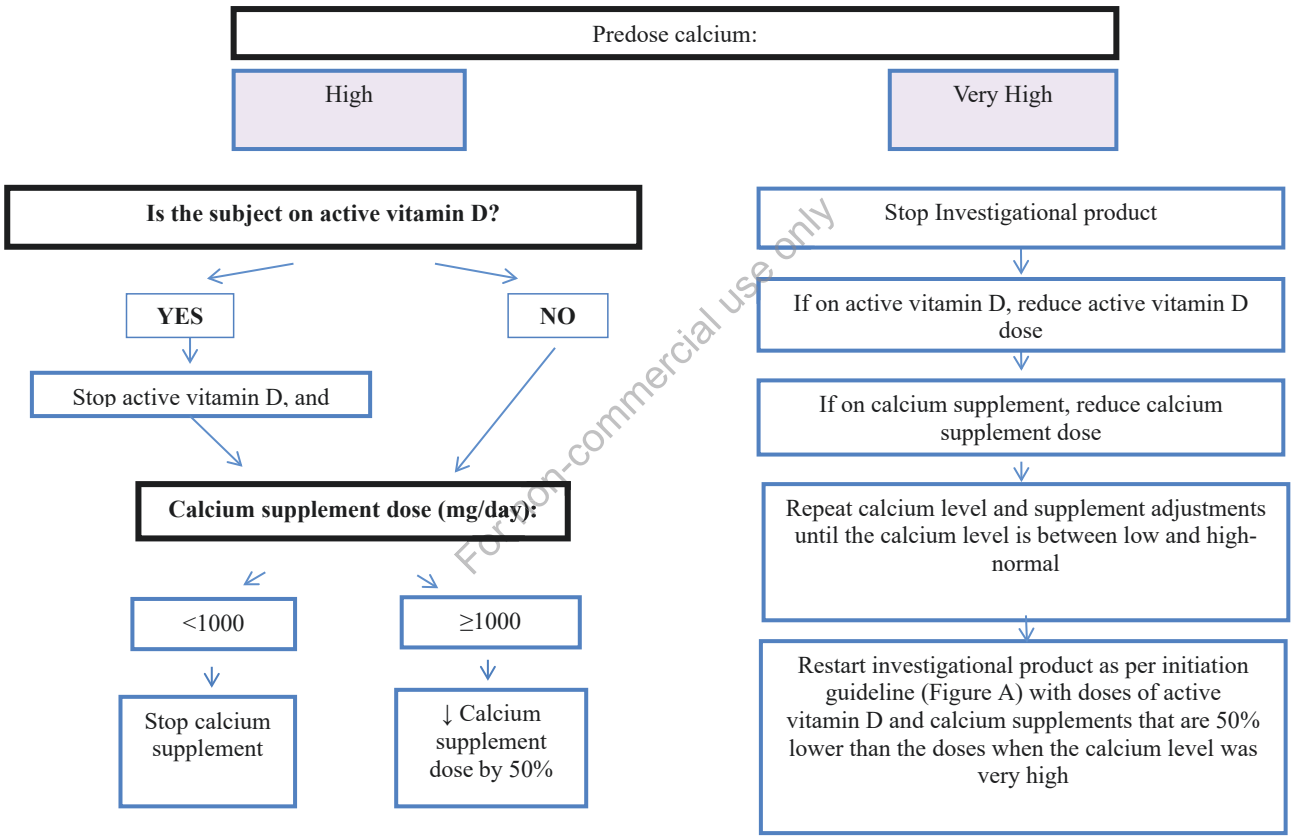
Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol and alfacalcidol.
[a] Contact the medical monitor.

Figure C-1 Dosing Guideline at Weeks 1, 2, 6, 10, and 14 Visits (and at any Unscheduled Laboratory Testing) for Very Low, Low, Low-normal, and High-normal Calcium Levels



Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol [alfacalcidol].

Figure C-2 Dosing Guideline at Weeks 1, 2, 6, 10, and 14 Visits (and at any Unscheduled Laboratory Testing) for High and Very High Calcium Levels



Note: Calcium supplement refers to prescribed nondietary oral calcium supplement and active vitamin D refers to calcitriol and alfacalcidol.

Appendix 3 Scales and Assessments

In the case of an unplanned event that disallows/prevents the administration of the PRO on a device, for reasons including but not limited to, device outage or other technical limitation, subjects may record on a paper version of the assessments that is provided by the CRO or PRO vendor.

The following scales and assessments are presented:

- Scoring of Hypoparathyroidism Symptom Diary
- Hypoparathyroidism Symptom Diary® (Version 1)
- Most Bothersome Hypoparathyroidism-related Symptom© (Version 1)
- FACIT Fatigue Scale (Version 4)
- FACT-Cognitive Function (Version 3)
- SF-36v2® Health Survey Acute
- EQ-5D-5L PDA version
- Work Productivity and Activity Impairment Questionnaire: Hypoparathyroidism (WPAI:Hypoparathyroidism)
- Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism® (Version 1)
- Patient Global Impression of Change (PGI-C) for Hypoparathyroidism© (Version 1)

Healthcare Resources Utilization (Baseline Visit version and Follow-up Visit version)

SCORING OF HYPOPARATHYROIDISM SYMPTOM DIARY

Scoring of the HPT-SD for Eligibility

Eligibility will be determined using the HPT-SD responses from the 14-day period immediately prior to the Week 0 (Baseline) visit ending the day before the Week 0 visit (Day -1 to -14 from the Week 0 visit). For scoring of the Sum Score, the subject must have at least 4 HPT-SD diaries completed in the first 7 day period and at least 4 HPT-SD diaries completed in second 7 day period. Sum score of the symptom subscale (7 items) from the HPT-SD responses will be calculated at the Week 0 visit. Eligibility based on the HPT-SD results will be available for site assessment at the Week 0 visit through the ERT study portal.

The sum score will be calculated from the HPT-SD responses as follows:

Step 1: Eligibility requires at least 4 out of 7 completed daily diaries for first and second 7 day periods within the 14 day period immediately prior to the baseline visit. If fewer than 4 responses are available in either 7 day period, then the subject is not eligible for the study.

Step 2: If step 1 is met, compute an item-level average for each of the 7 symptoms (items) in the symptom subscale over the 14 day period.

Step 3: To calculate the Sum Score add together the 7 item-level averages calculated in Step 2.

Scoring of the HPT-SD at Baseline and during the Treatment Period

Scoring of Hypoparathyroidism Symptom Diary will be done over a 14-day period. The steps are the following for calculation of the scores:

For individual item scores:

Step 1: Data must be available for at least 4 out of 7 days (for all items in HPT-SD) during each of the two 7-day periods within the 14-day period. If the data availability criterion is not met, then set the individual item score to missing.

Step 2: If Step 1 is met, compute an individual item score by taking the average of the scores over the 14-day period for each of the 13 items.

For subscale (symptom [items 1-7] and impact [items 10-13]) scores:

For symptom subscale: calculate the average score of the symptom items 1-7 over the 14-day period

For Impact subscale: calculate the average score of the impact items 10-13 over the 14-day period

Note: Corresponding numerical values of the verbal rating scale are:

- For items 1-9:
  - None=0
  - Mild=1
  - Moderate=2
  - Severe=3
  - Very severe=4
- For items 10-13
  - Not at all=0
  - Somewhat=1
  - Very much=2

HYPOPARATHYROIDISM SYMPTOM DIARY© (VERSION 1)

For each of the following questions, please choose the one answer that best describes your experiences related to hypoparathyroidism during the past 24 hours.

1. **How would you rate any muscle cramps you experienced during the past 24 hours?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

2. **How would you rate any tingling you experienced during the past 24 hours?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

3. **How would you rate any numbness you experienced during the past 24 hours?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

4. **How would you rate any muscle spasms or twitching you experienced during the past 24 hours?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

5. How would you rate any feelings of heaviness you experienced in your arms or legs during the past 24 hours?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

6. How would you rate any physical fatigue you experienced during the past 24 hours?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

7. How would you rate any slowed or confused thinking, sometimes called brain fog, you experienced during the past 24 hours?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

8. How would you rate any anxiety you felt during the past 24 hours?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

9. How would you rate any sadness or depression you felt during the past 24 hours?

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

10. How did your hypoparathyroidism impact your sleep last night?

- ☐ Not at all
- ☐ Somewhat
- ☐ Very much

11. How did your hypoparathyroidism impact your ability to exercise in the past 24 hours?

- ☐ Not at all
- ☐ Somewhat
- ☐ Very much

12. How did your hypoparathyroidism impact your ability to complete your work (for example, at school, at home or at a job) in the past 24 hours?

- ☐ Not at all
- ☐ Somewhat
- ☐ Very much

13. How did your hypoparathyroidism impact your relationships with your family members in the past 24 hours?

- ☐ Not at all
- ☐ Somewhat
- ☐ Very much

Most Bothersome Hypoparathyroidism-related Symptom© (Version 1)

Which symptom is the most bothersome to you? Please select only one response:

- ☐ Muscle cramps
- ☐ Tingling
- ☐ Numbness
- ☐ Muscle spasms or twitching
- ☐ Feelings of heaviness in your arms or legs
- ☐ Physical fatigue
- ☐ Slowed or confused thinking, sometimes called brain fog

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please select one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please select one number per line to indicate your response as it applies to the past 7 days.**

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

Please select one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please select one number per line to indicate your response as it applies to the past 7 days.

	COMMENTS FROM OTHERS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
CogO4	Other people have told me I seemed confused	0	1	2	3	4

FACT-Cog (Version 3)

Please select one number per line to indicate your response as it applies to the past 7 days.

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please select one number per line to indicate your response as it applies to the past 7 days.

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one response that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago
Somewhat better now than one week ago
About the same as one week ago
Somewhat worse now than one week ago
Much worse now than one week ago

The following questions are about activities you might do during a typical day.

Does your health now limit you in these activities? If so, how much?

Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in climbing several flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in climbing one flight of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in walking more than a mile? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

Does your health now limit you in walking several hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in walking one hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
During the past week, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, how much of the time have you accomplished less than you would like as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time

During the past week, how much of the time were you limited in the kind of work or other activities as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, how much of the time have you had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
During the past week, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)? All of the time Most of the time Some of the time A little of the time None of the time

During the past week, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Not at all Slightly Moderately Quite a bit Extremely
How much bodily pain have you had during the past week? None Very mild Mild Moderate Severe Very severe
During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely
These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past week did you feel full of life? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week have you been very nervous? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week have you felt so down in the dumps that nothing could cheer you up? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week have you felt calm and peaceful? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week did you have a lot of energy? All of the time Most of the time Some of the time A little of the time None of the time

How much of the time during the past week have you felt downhearted and depressed? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week did you feel worn out? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week have you been happy? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past week did you feel tired? All of the time Most of the time Some of the time A little of the time None of the time
During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? All of the time Most of the time Some of the time A little of the time None of the time

How TRUE or FALSE is <u>each</u> of the following statements for you?
I seem to get sick a little easier than other people. Definitely true Mostly true Don't know Mostly false Definitely false
I am as healthy as anybody I know. Definitely true Mostly true Don't know Mostly false Definitely false
I expect my health to get worse. Definitely true Mostly true Don't know Mostly false Definitely false
My health is excellent. Definitely true Mostly true Don't know Mostly false Definitely false

EQ-5D-5L	
EQ-5D-5L PDA version	
English (USA)	Country (Language)
Health Questionnaire	Health Questionnaire
English version for the USA	Version (Target Language)
	Version (English)
On the following screens please tap the statement that best describes your health TODAY.	Instruction
Your mobility TODAY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
Your self-care TODAY	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
Your usual activities TODAY (*e.g. work, study, housework, family or leisure activities*)	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
Your pain / discomfort TODAY	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
Your anxiety / depression TODAY	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
On the next screen you will see a scale numbered 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI: Hypoparathyroidism)

The following questions ask about the effect of your HYPOPARATHYROIDISM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your HYPOPARATHYROIDISM? *Include hours you missed on sick days, times you went in late, left early, etc., because of your HYPOPARATHYROIDISM. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your HYPOPARATHYROIDISM affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If HYPOPARATHYROIDISM affected your work only a little, choose a low number. Choose a high number if HYPOPARATHYROIDISM affected your work a great deal.

Consider only how much HYPOPARATHYROIDISM affected productivity while you were working.

HYPOPARATHYROIDISM had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	HYPOPARATHYROIDISM completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your HYPOPARATHYROIDISM affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If HYPOPARATHYROIDISM affected your activities only a little, choose a low number. Choose a high number if HYPOPARATHYROIDISM affected your activities a great deal.

Consider only how much HYPOPARATHYROIDISM affected your ability to do your regular daily activities, other than work at a job.

HYPOPARATHYROIDISM had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	HYPOPARATHYROIDISM completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Patient Global Impression of Severity (PGI-S) for Hypoparathyroidism® (Version 1)

Please complete the following question. Please choose only 1 answer.

Overall, how would you rate your current hypoparathyroidism-related symptoms?

- No symptoms
- Mild
- Moderate
- Severe
- Very severe

Patient Global Impression of Change (PGI-C) for Hypoparathyroidism© (Version 1)

Please complete the following question. Please choose only 1 answer.

Compared to the beginning of this study, how would you rate your hypoparathyroidism-related symptoms now?

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

Questions to Ask (at Baseline):	Answers:
During the past 12 months, how many times have you seen your doctor or other health care professional about your own health at a DOCTOR'S OFFICE, URGENT CARE, A CLINIC, OR SOME OTHER PLACE? Do not include times you were hospitalized overnight, visits to the hospital emergency rooms, home visits, dental visits, or telephone calls.	_____ times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
During the past 12 months, how many times have you gone to a HOSPITAL EMERGENCY ROOM about your own health (include only emergency room visits of less than 24 hours duration)?	_____ times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
During the past 12 months, were you a patient in a hospital overnight? Include emergency room visits that	

were equal to or more than 24 hours.	times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
If yes, list each admission date, discharge date, and duration for each hospitalization as well as the Diagnosis/Reason for each hospitalization	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	

Questions to Ask (at Follow-up Visits):	Answers:
Since the last time assessed (**Study coordinator to provide subject the reference from the last assessment**), how many times have you seen your doctor or other health care professional about your own health at a DOCTOR'S OFFICE, URGENT CARE, A CLINIC, OR SOME OTHER PLACE? Do not include times you were hospitalized overnight, visits to the hospital emergency rooms, home visits, dental visits,	_____ times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
Since the last study visit, how many times have you gone to a HOSPITAL EMERGENCY ROOM about your own health (include only emergency room visits of less than 24 hours duration)?	_____ times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
Since the last study visit, were you a patient in a hospital overnight? Include emergency room visits that	

were equal to or more than 24 hours.	times total
How many were for: High blood calcium (hypercalcemia)	_____ times
How many were for: Low blood calcium (hypocalcemia)	_____ times
How many were for: Kidney stones	_____ times
How many were for: Other kidney problems	_____ times
How many were for: Other, please specify: _____	_____ times
If yes, list each admission date, discharge date, and duration for each hospitalization as well as the Diagnosis/Reason for each hospitalization	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	
Diagnosis/Reason	
Admission Date	
Discharge Date	
Duration (in days)	

Appendix 4 Benefit/Risk Assessment

The assessment of benefit/risk for this clinical trial (SHP634-401) includes a consideration of the known benefits and risks of treatment with rhPTH(1-84) as outlined in the investigator's brochure , the risks of placebo, the risks associated with switching to supplements supplied by the study supplied, and the risks of the procedures of the study. There is a risk of hypercalcemia or hypocalcemia particularly during the dose titration phase of the study. These risks are minimized by frequent monitoring of serum calcium throughout the study, frequent clinical assessments, and by standardized dosing instructions found in the protocol. All subjects will be asked to use calcium and active vitamin D supplements provided by the study, which may result in a change to previous supplements used and thereby some risk of hypo- or hypercalcemia. This risk is minimized by frequent monitoring of serum calcium throughout the study, frequent clinical assessments, and by standardized dosing instructions found in the protocol. For those subjects who receive rhPTH(1-84) during the study and discontinue rhPTH(1-84) during or at the end of the study there is a risk of hypocalcemia. This risk will be mitigated by close monitoring of the subjects' calcium levels and careful titration of active vitamin D and calcium doses for 4 weeks after discontinuation of rhPTH(1-84). The risks associated with procedures are known for blood and urine collections, ECGs, and a possible X-Ray. The risk associated with diaries, PROs, and neurocognitive assessments are minimal. The benefits from participating in this trial for subjects treated with rhPTH(1-84) may be an improvement of the symptoms and neurocognitive function associated with hypoparathyroidism in addition to the known effect of treatment with rhPTH(1-84) compared to standard of care (supplementation). Shire believes the benefit-risk profile for this study is favorable.