PROTOCOL: SHP634-404

TITLE:	An Open-label Study Investigating the Safety and Efficacy of rhPTH(1-84) in Subjects with Hypoparathyroidism
DRUG:	rhPTH(1-84)
IND:	076514
EUDRACT NO.:	2017-003067-36
BLA:	125511
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	Multicenter study
PROTOCOL HISTORY:	Original Protocol: 30 Aug 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP634-404.

Title: An Open-label Study Investigating the Safety and Efficacy of rhPTH(1-84) in Subjects with Hypoparathyroidism

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International 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

Not applicable. This is Version 1.0 of the protocol.

See Appendix 1 for protocol history.

EMERGENCY CONTACT INFORMATION

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

Shire SAE e-mail: (for US and EU sites): [redacted]

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

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

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

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

For protocol- or safety-related issues, the investigator must contact the Medical Monitor (24-hour availability)

The Medical Monitors for this study are:

To be determined: Medical Monitor- North America
To be determined: Medical Monitor- Europe

By Electronic Protocol Inquiry Platform (ePIP) system: [redacted]
By telephone at:

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

The Shire Medical Monitor for this study is:

[redacted], MD
By telephone: [redacted]

PRODUCT QUALITY COMPLAINTS

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

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

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

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)
[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AE	adverse event
ACSC	albumin-corrected serum calcium
β-HCG	beta-human chorionic gonadotropin
CDK-epi	chronic kidney disease epidemiology
CI	confidence interval
CRF	case report form
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
EOS	end-of-study
ePIP	Electronic Protocol Inquiry Platform
[redacted]	[redacted]
[redacted]	[redacted]
EU	European Union
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ICH	International Council for Harmonisation
IRB	institutional review board
IRT	interactive response technology
[redacted]	[redacted]
[redacted]	[redacted]
PRO	patient-reported outcome
PTH	parathyroid hormone
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US(A)	United States of America
VAS	visual analog scale

STUDY SYNOPSIS

Protocol number: SHP634-404	**Drug:** rhPTH(1-84)
Title of the study: An Open-label Study Investigating the Safety and Efficacy of rhPTH(1-84) in Subjects with Hypoparathyroidism	
Number of subjects (total and for each treatment arm): Subjects who complete the SHP634-101 study will have the option to screen for this extension study (SHP634-404). Up to approximately 32 subjects are expected to enroll in this study.	
Investigator(s): Multicenter study	
Site(s) and region(s): This is a global study, with sites planned in North America and countries within Europe. Approximately 20-30 study sites are planned to participate in the study.	
Study period (planned): 2017–2020	**Clinical phase:** 3

Objectives:

Primary:

The primary objectives are as follows:

- To evaluate the proportion of subjects who achieve total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)–upper limit of normal (ULN).
- To further characterize the safety of rhPTH(1-84) in adult subjects with hypoparathyroidism.

Secondary:

The secondary objective is as follows:

- To evaluate biochemical responses to rhPTH(1-84) through 1 year of treatment.

Rationale:

This study is designed to evaluate the safety and efficacy of 52 weeks of once-daily subcutaneous (SC) rhPTH(1-84) for subjects who have previously been exposed to rhPTH(1-84) in the SHP634-101 study.

Investigational product, dose, and mode of administration:

- rhPTH(1-84) by SC injection, titrated within the dose range of 25-100 µg once daily (QD) based on biochemical response.

Methodology:

This study is a 52 week open-label study using rhPTH(1-84) for the treatment of adult male and female subjects with hypoparathyroidism. Subjects may be eligible to screen for the study if they have previously completed the SHP634-101 study.

- The study will consist of a screening period (Visit 1), a treatment period (Visits 2-9), and a 30 day safety follow-up period that includes an end-of-study (EOS) contact (Visit 10).
- All subjects will complete the 30 day follow-up period, including an EOS contact (Visit 10), as follows:
  - All subjects will have an EOS contact (Visit 10) 30 days following the last dose of investigational product.
  - Subjects who will not continue on rhPTH(1-84) following the end-of-treatment (EOT)/early

termination (ET) visit (Visit 9) will proceed with weekly follow-up visits with serum calcium (albumin-corrected), phosphate, and magnesium measurements until a maximum of 30 days has elapsed.

- Subjects who will be transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET visit (Visit 9) will proceed with weekly follow-up visits with serum calcium (albumin-corrected), phosphate, and magnesium measurements until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed.
- Subjects who transfer to commercial rhPTH(1-84) immediately after the EOT/ET visit (Visit 9) will have an EOS contact (Visit 10) 30 days following the last dose of investigational product.

- Treatment with investigational product will be initiated with 50 µg once daily as a SC injection in the thigh (alternate thigh every day). If albumin-corrected serum calcium (ACSC) is >2.25 mmol/L (>9.0 mg/dL), a starting dose of 25 µg can be considered.
- Subjects may have their rhPTH(1-84) dose increased in increments of 25 µg to a maximum of 100 µg SC QD by the investigator no more frequently than every 2 to 4 weeks, with the goal of achieving or maintaining ACSC levels in the range of 2-2.25 mmol/L (8.0-9.0 mg/dL). The rhPTH(1-84) dose may be adjusted downward at any time as needed to avoid hypercalcemia or due to any safety concerns. Total serum calcium should be measured 3-7 days after any adjustment of investigational product and/or supplements throughout the study.
- Once a subject achieves a stable albumin-corrected serum calcium (ACSC) (target: between 2-2.25 mmol/L [8.0-9.0 mg/dL]) and has minimized supplement doses, they will be maintained at that dose of rhPTH(1-84).
  - Within 2-5 days of achieving the maintenance dose the subject should have post-dose ACSC levels measured. The postdose levels should be drawn between 8-12 hours after the investigational product dosing. In general, if postdose ACSC results are abnormal, the postdose measurements should be repeated within 2-5 days.
- See Appendix 2 for additional information regarding dosing guidelines for active vitamin D supplements, calcium supplements, and investigational product.

Up to approximately 32 subjects are expected to enroll.

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. Site personnel will administer the [redacted] questionnaire, and subjects will be asked to complete patient-reported outcome (PRO) assessments [redacted] at the site at specified time points.

Safety assessments will include adverse event (AE) monitoring, serum chemistry, hematology, urinalysis, vital signs, electrocardiograms (ECGs), physical examinations, and measurement of anti-parathyroid hormone (PTH) antibodies.

Inclusion and exclusion criteria:

Inclusion criteria:

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

2. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
3. Previously completed the SHP634-101 study, including the 30-day follow-up.
4. Male or non-pregnant, non-lactating female subjects who agree to comply with applicable contraceptive requirements of the protocol or females of non-childbearing potential.

Exclusion criteria:

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

1. Received investigational study drug, aside from that received in study SHP634-101, within 3 months prior to the screening visit.
2. Presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine (with exception of the condition under study), or neurologic system(s) or psychiatric disease, that in the opinion of the investigator, would make the subject unsuitable for this study.
3. Received parathyroid hormone (PTH), PTH analog, or parathyroid hormone fragment 1-34 [PTH(1-34)] treatment within the last 30 days from the screening visit.
4. Subjects with a history of parathyroid hormone intolerance, based on investigator determination.
5. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis as determined by the investigator other than hypoparathyroidism, including but not limited to, active hyperthyroidism; poorly controlled insulin-dependent diabetes mellitus or type 2 diabetes mellitus; severe and chronic cardiac, liver or renal disease; Cushing's syndrome; neuromuscular disease such as rheumatoid arthritis; myeloma; pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy, bone metastases or a history of skeletal malignancies; primary or secondary hyperparathyroidism; a history of parathyroid carcinoma; hypopituitarism, acromegaly; or multiple endocrine neoplasia types 1 and 2 .
6. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase, young adult subjects with open epiphyses, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton.
7. Use of the following medications prior to administration of investigational product within:
    - 30 days-loop diuretics, lithium, systemic corticosteroids (medical judgment is required by the investigator. Primarily high doses of systemic corticosteroids [eg, prednisone] should be excluded. Stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable).
    - 3 months-cinacalcet hydrochloride
    - 6 months-fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin
    - 12 months-intravenous bisphosphonates, drug or alcohol abuse, as determined by the investigator
8. Presence of any clinically significant results from laboratory tests, vital signs assessments, or ECGs, that in the opinion of the investigator, would make the subject unsuitable for this study.
9. Any medical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for this study.
10. History of a clinically significant illness during the 4 weeks prior to dosing, that in the opinion of the investigator, would make the subject unsuitable for this study.
11. History of any clinically significant surgery or procedure within 8 weeks of first dose, as determined by the investigator or expected to undergo a major surgical procedure during the trial.
12. History of an allergic response(s) to PTH, PTH analogs, or PTH(1-34), or other clinically significant allergies, that in the opinion of the investigator, would make the subject unsuitable for this study.

Maximum duration of subject involvement in the study:

The maximum duration of subject participation in the study is expected to be approximately 57 weeks with

- Planned duration of screening period: 7 days
- Planned duration of treatment period: 52 weeks
- Planned duration of follow-up: 30 days [All subjects will complete an EOS contact (Visit 10) 30 days following the last dose of investigational product. Subjects who interrupt or will not continue with rhPTH(1-84) treatment after the EOT/ET visit (Visit 9) will have weekly visits until a maximum of 30 days has elapsed or until commercial rhPTH(1-84) treatment is started]

Endpoints and statistical analysis:

Analysis set:

Safety analysis population will consist of all enrolled subjects who have received at least 1 dose of rhPTH(1-84). Safety analysis population will be used for all efficacy and safety analyses for this study.

Primary efficacy endpoint:

Subject response status satisfying total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)-ULN at Visit 6 (Week 24) and at EOT/ET (Visit 9; Week 52).

Secondary efficacy endpoints:

- Change from baseline in ACSC concentration
- Change from baseline in serum phosphate concentration
- Change from baseline in ACSC-phosphate product
- Change from baseline in 24-hour urine calcium excretion
- Percentage changes from baseline in prescribed supplemental oral calcium dose
- Percentage changes from baseline in prescribed supplemental active vitamin D dose
- Percentage changes from baseline in markers of bone turnover

Safety variable :

- Adverse events including serious adverse events (SAEs)
- Laboratory safety data (eg, clinical chemistry, hematology, and urinalysis)
- Vital signs including body temperature, heart rate (beats per minute), and blood pressure (systolic and diastolic [mmHg])
- ECG parameters
- Measurements of estimated glomerular filtration rate (eGFR) and creatinine
- Change from baseline in anti-PTH antibodies

Exploratory Endpoints:

- [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]

Statistical Analyses:

Efficacy Analyses

Descriptive statistics will be used with a goal of summarizing the sample population. For the primary efficacy endpoint, the 95% confidence interval (CI) of the proportion of subjects with total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)–ULN will be provided. Secondary efficacy endpoints will be summarized with descriptive statistics at each assessment visit. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Safety Analyses

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. Treatment-emergent AE (TEAE) will be defined, and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the change and percent change from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Interim analyses:

There will be no Data Monitoring Committee for this open-label study; however, study data may be analyzed as necessary for safety monitoring or publication purposes.

STUDY SCHEDULES

Table 1: Schedule of Assessments (Visits 1-10)

Visit Number	1	2[a]	3	4	5	6	7	8	9	10[b]
Study Procedures/Study Week	Screening/-1	BL/0	4	8	16	24	32	40	EOT/ ET/52	EOS/56
Visit Windows	-7 days	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	30 ± 3 days
Visit Type (S=site/P=phone)	S	S	S	S	S	S	S	S	S	S or P
Informed Consent	X									
Review Inclusion/Exclusion Criteria	X	X								
Demographic information	X									
Medical History	X	X								
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X
Physical examination (height and weight)[c]	X	X							X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	
Electrocardiogram (12-lead)[e]	X								X	
Hematology[f]	X								X	
Serum chemistry[f]	X								X	
Serum TSH[f]	X									
Serum calcium, albumin, phosphate, and magnesium[f]	X	X[g,h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Serum 25-hydroxyvitamin D	X	X	X	X	X	X	X	X	X	
Serum 1,25-dihydroxyvitamin D	X	X				X			X	
Serum bone turnover markers[i]		X		X		X			X	
Estimated GFR (eGFR)[j]		X			X		X		X	
anti- PTH antibodies[k]		X				X			X	

Table 1: Schedule of Assessments (Visits 1-10)

Visit Number	1	2[a]	3	4	5	6	7	8	9	10[b]
Study Procedures/Study Week	Screening/-1	BL/0	4	8	16	24	32	40	EOT/ ET/52	EOS/56
Visit Windows	-7 days	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	30 ± 3 days
FSH[l]	X									
Serum pregnancy test (WOCBP only)	X								X	
Urine pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X	
Urinalysis[f]		X							X	
24-hour urine[f,m]		X			X		X		X	
Record supplement and IP history[n]		X	X	X	X	X	X	X	X	
Dispense/administration/accountability of investigational product and pen injectors/ ancillary supplies, as necessary		X	X	X	X	X	X	X	X	
Collect used/unused investigational product[o]			X	X	X	X	X	X	X	
[redacted]		X	X	X	X	X	X	X	X	
[redacted]									X	
[redacted]		X				X			X	
[redacted]		X	X	X	X	X	X	X	X	
[redacted]		X	X	X	X	X	X	X	X	

BL=baseline; [redacted] FSH=follicle stimulating hormone; GFR=glomerular filtration rate; EOT=end-of-treatment; EOS=end-of-study; ET=early termination; IP=investigational product; [redacted]; [redacted]; PTH=parathyroid hormone; TSH=thyroid stimulating hormone; WOCBP=women of child-bearing potential

[a] Final SHP634-101 study parameters may be used as screening parameters for this study if conducted within 30 days of screening. Serum calcium, albumin, phosphate, and magnesium levels must be re-measured if they were measured >1 week prior to screening in Study 634-404.

[b] All subjects will have an EOS contact (Visit 10) 30 days following the last dose of investigational product. The EOS contact (Visit 10) is a safety follow-up telephone call initiated by the site staff to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. See Table 2 for details related to the follow-up period for subjects who will not continue on rhPTH(1-84) or who experience a treatment gap following the EOT/ET visit (Visit 9).

[c] Height will be collected at screening only.

[d] Vital signs should be assessed prior to blood draws; see Section 7.2.4.4 for additional details related to the assessment of vital signs.

[e] Twelve-lead ECGs will be performed in triplicate with a minimum 2-minute gap between traces. The subject must be resting in the supine position for at least 5 minutes before

Table 1: Schedule of Assessments (Visits 1-10)

Visit Number	1	2[a]	3	4	5	6	7	8	9	10[b]
Study Procedures/Study Week	Screening/-1	BL/0	4	8	16	24	32	40	EOT/ ET/52	EOS/56
Visit Windows	-7 days	± 3 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	30 ± 3 days

collecting the ECG.

[f] See Section 7.2.4.5 for parameters included in clinical laboratory assessments.

[g] If the subject is hypercalcemic at baseline, delay initiation of rhPTH(1-84) administration until total serum calcium (albumin-corrected) levels are in the normal range. If initiation of investigational product is delayed by more than 2 weeks, contact the medical monitor.

[h] In addition to protocol specified laboratory testing processed in the central laboratory, serum calcium and albumin concentrations may be processed at local laboratories at scheduled study site visits or between visits to allow investigational product and/or supplements dose adjustments to be made at the time of the visit at the discretion of the investigator.

[i] Serum bone turnover markers will include, but are not limited to, bone-specific alkaline phosphatase, procollagen Type I N terminal propeptide, C-terminal telopeptide of type 1 collagen, N-terminal telopeptide of type 1 collagen, and total osteocalcin.

[j] The chronic kidney disease epidemiology (CDK-epi) formula will be used to calculate estimated glomerular filtration rate (eGFR).

[k] Blood draw for anti-PTH antibodies Blood samples for antibody testing should be collected at least 14 hours after dosing.

[l] Follicle stimulating hormone levels are required for newly menopausal women (see Section 4.4.1 for definition of postmenopausal).

[m] 24-hour urine collection includes the parameters specified in Section 7.2.4.5.

[n] Site personnel will record the time and actual dose of the last dose of calcium, active vitamin D, and investigational product that the subject has taken; a 24-hour recall period will be used.

[o] Subject is to return unused and used cartridges at each visit.

[p] Subjects will be asked to complete the assessments at each applicable visit.

[q] To be administered by site personnel at each applicable visit.

Note: After initiating investigational product and after any adjustment of investigational product and/or supplemental calcium and active vitamin D doses, testing of total serum calcium (albumin-corrected) concentrations is required within 3-7 days after the adjustment, at the discretion of the investigator. This can be performed at a local laboratory.

Table 2: Schedule of Assessments (Follow-up visits for subjects who do not transfer to commercial treatment immediately following EOT/ET [Visit 9])

Visit Number	**FU1[a]**	**FU2[a]**	**FU3[a]**	**10[a]**
	Follow-up			
Study Procedures/Study Week	**53**	**54**	**55**	**EOS/56**
Visit Windows	**± 3 days**	**± 3 days**	**± 3 days**	**30 ± 3 days**
Visit Type (S=site/P=phone)	S	S	S	S or P
Prior/Concomitant medications	X	X	X	X
Adverse event monitoring	X	X	X	X
Vital signs[b]	X	X	X	X
Serum calcium, albumin, phosphate, and magnesium[c]	X[d]	X[d]	X[d]	X[d]

FU = follow up; EOS=end-of-study

[a] Weekly follow-up visits (Visits FU1, FU2, FU3, and 10) will be performed for subjects who will not continue on rhPTH(1-84) and for subjects transferring to commercial rhPTH(1-84) but experience a treatment gap following the EOT visit or the ET visit (Visit 9). These subjects will be prescribed appropriate oral calcium and/or active vitamin D supplements to compensate for the cessation of the rhPTH(1-84). Weekly follow-up visits will continue until a maximum of 30 days has elapsed or until commercial rhPTH(1-84) treatment is started . All subjects will complete an EOS contact (Visit 10) 30 days following the last dose investigational product. The EOS contact is a safety follow-up telephone call initiated by the site staff to query for serious adverse events (SAEs), 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 (Visit 10) at the site.

[b] Vital signs should be assessed prior to blood draws; see Section 7.2.4.4 for additional details related to the assessment of vital signs.

[c] See Section 7.2.4.5 for parameters included in clinical laboratory assessments.

[d] In addition to protocol specified laboratory testing processed in the central laboratory, serum calcium and albumin concentrations may be processed at local laboratories at scheduled study site visits or between visits to allow investigational product and/or supplements dose adjustments to be made at the time of the visit at the discretion of the investigator.

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 the amino acid sequence of which is identical to that of 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) administered in the dose range of 25 to 100 μg (SC) once daily (QD) is safe for use for the treatment of hypoparathyroidism. Very common adverse reactions (ie, reported in at least 1 in every 10 subjects) include hypocalcemia, hypercalcemia, headaches, hypoesthesia, paresthesia, diarrhea, nausea, vomiting, arthralgia, and muscle spasms. Common adverse reactions (ie, reported in at least 1 in every 100 subjects, but fewer than 1 in every 10 subjects) include hypomagnesemia, tetany, abdominal pain upper, anxiety, insomnia, palpitations, cough, muscle twitching, musculoskeletal pain, myalgia, neck pain, pain in extremity, hypercalciuria, pollakiuria, asthenia, chest pain, fatigue, injection site reactions, thirst, anti-PTH antibody positive, blood 25-hydroxycholecalciferol decreased, vitamin D decreased, somnolence, and hypertension.

No evidence for drug related objective laboratory or electrocardiogram (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; a risk to humans cannot be excluded. Therefore, administration of rhPTH(1-84) should be avoided in subjects who are considered to be at increased risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, 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 has not been established.

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

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This study is designed to evaluate the safety and efficacy of 52 weeks of once-daily SC rhPTH(1-84) for subjects who have previously been exposed to rhPTH(1-84) in the SHP634-101 study.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives are as follows:

- To evaluate the proportion of subjects who achieve total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L) – upper limit of normal (ULN).

- To further characterize the safety of rhPTH(1-84) in adult subjects with hypoparathyroidism.

2.2.2 Secondary Objectives

The secondary objective is as follows:

- To evaluate biochemical responses to rhPTH(1-84) through 1 year of treatment.

2.2.3 Exploratory Objectives

[redacted]

- [redacted]

3 STUDY DESIGN

3.1 Study Design and Flow Chart

3.1.1 Overall Study Design

This study is a 52 week open-label study using rhPTH(1-84) for the treatment of adult male and female subjects with hypoparathyroidism. Subjects may be eligible to screen for the study if they have previously completed the SHP634-101 study.

This study is designed to evaluate the safety and efficacy of 52 weeks of once-daily SC rhPTH(1-84) for subjects who have previously been exposed to rhPTH(1-84) in the SHP634-101 study.

- The study will consist of a screening period (Visit 1), a treatment period (Visits 2-9), and a 30 day safety follow-up period that includes an end-of-study (EOS) contact (Visit 10).
- All subjects will complete the 30 day follow-up period, including an EOS contact (Visit 10) as follows:
  - All subjects will have an EOS contact (Visit 10) 30 days following the last dose of investigational product.
  - Subjects who will not continue on rhPTH(1-84) following the end-of-treatment (EOT) or early termination (ET) visit (Visit 9) will proceed with weekly follow-up visits with serum calcium (albumin-corrected), phosphate, and magnesium measurements until a maximum of 30 days has elapsed.
  - Subjects who will be transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET visit (Visit 9) will proceed with weekly follow-up visits with serum calcium (albumin-corrected), phosphate, and magnesium measurements until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed.
  - Subjects who transfer to commercial rhPTH(1-84) immediately after the EOT/ET visit

(Visit 9) will have an EOS contact (Visit 10) 30 days following the last dose of investigational product.

- See Section 7.1.3 for additional details on the follow-up period.

- Treatment with investigational product will be initiated with 50 µg once daily as a subcutaneous injection in the thigh (alternate thigh every day). If albumin-corrected serum calcium (ACSC) is >2.25 mmol/L (>9.0 mg/dL), a starting dose of 25 µg can be considered.
- Subjects may have their rhPTH(1-84) dose increased in increments of 25 µg to a maximum of 100 µg SC QD by the investigator no more frequently than every 2 to 4 weeks, with the goal of achieving or maintaining ACSC levels in the range of 2-2.25 mmol/L (8.0-9.0 mg/dL). The rhPTH(1-84) dose may be adjusted downward at any time as needed to avoid hypercalcemia or due to any safety concerns. Total serum calcium should be measured 3-7 days after any adjustment of investigational product and/or supplements throughout the study.
- Once a subject achieves a stable ACSC (target: between 2-2.25 mmol/L [8.0-9.0 mg/dL]) and has minimized supplement doses, they will be maintained at that dose of rhPTH(1-84).
- Within 2-5 days of achieving the maintenance dose the subject should have post-dose ACSC levels measured. The postdose levels should be drawn between 8-12 hours after the investigational product dosing. In general, if postdose ACSC results are abnormal, the postdose measurements should be repeated within 2-5 days.
- See Appendix 2 for additional dosing guidelines for active vitamin D supplements, calcium supplements, and investigational product.

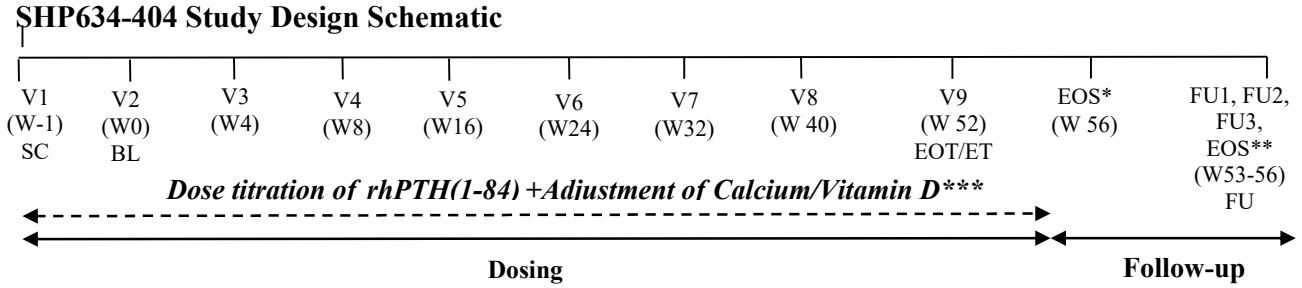
Up to approximately 32 subjects are expected to enroll.

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 (see Table 1) to assess efficacy and safety. Site personnel will administer the [redacted], and subjects will be asked to complete patient-reported outcome (PRO) assessments [redacted] and [redacted] at the site at the time points specified in Table 1.

Safety assessments will include adverse event (AE) monitoring, serum chemistry, hematology, urinalysis, vital signs, ECGs, physical examinations, and measurement of anti-PTH antibodies.

A schematic representation of the study design and titration period is displayed in Figure 1. Figure 2 presents a flow chart of the study design.

Figure 1: Study Design Schematic

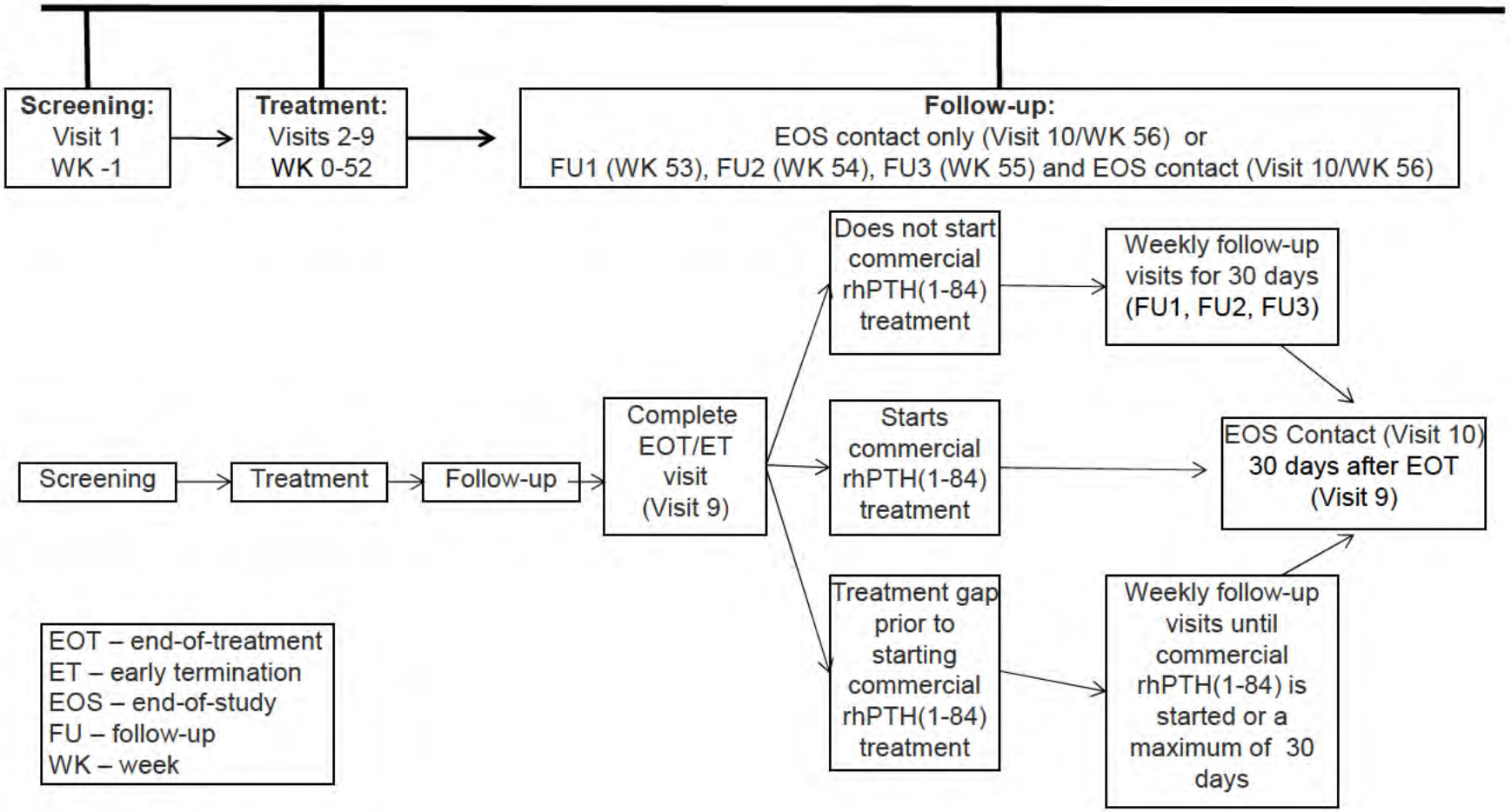


- All subjects will complete the 30 day follow-up period including an EOS contact (Visit 10) as follows:
  - *Subjects who transfer to commercial rhPTH(1-84) immediately after the EOT/ET visit (Visit 9) will have an EOS contact 30 days following the last dose of investigational product.
  - **Subjects who will not continue on rhPTH(1-84) following the EOT/ET visit (Visit 9) will proceed with weekly follow-up visits with serum calcium measurements until a maximum of 30 days has elapsed. All subjects will have an EOS contact (Visit 10) 30 days following the last dose of study drug.
  - **Subjects who will be transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET visit (Visit 9) will proceed with weekly follow-up visits with serum calcium measurements until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. All subjects will have an EOS contact (Visit 10) 30 days following the last dose of study drug.

***Total serum calcium should be measured 3-7 days after any adjustment of study drug and/or supplements.

BL– Baseline
EOT– End-of-Treatment
EOS– End-of-Study
ET– Early termination
FU – Follow-up
SC – Screening
W – Week

Figure 2: Study Design Flow Chart



3.1.2 Discussion of Study Design

This study will be open to subjects with hypoparathyroidism who complete the SHP634-101 study.

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 57 weeks (approximately 14 months). Subjects who do not continue on rhPTH(1-84) and subjects who will be transferring to commercial rhPTH(1-84) but experience a treatment gap following the EOT/ET (Visit 9) will proceed with weekly follow up visits with serum calcium measurements until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed. All subjects, including subjects who transfer to commercial rhPTH(1-84) immediately after the EOT/ET visit (Visit 9), will have an EOS contact (Visit 10) that is a safety follow-up contact, either a study clinic visit or a telephone call 30 days following the last dose of investigational product. The study will be completed in approximately 2-3 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 anticipated that this study will be a multisite, multicountry study. The regions to be targeted include North America and countries within Europe.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
3. Previously completed the SHP634-101 study, including the 30-day follow-up.

4. Male or non-pregnant, non-lactating female subjects who agree to comply with applicable contraceptive requirements of the protocol or females of non-childbearing potential.

4.2 Exclusion Criteria

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

1. Received investigational study drug, aside from that received in study SHP634-101, within 3 months prior to the screening visit.
2. Presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine (with exception of the condition under study), or neurologic system(s) or psychiatric disease, that in the opinion of the investigator, would make the subject unsuitable for this study.
3. Received parathyroid hormone (PTH), PTH analog, or parathyroid hormone fragment 1-34 [PTH(1-34)] treatment within the last 30 days from the screening visit.
4. Subjects with a history of parathyroid hormone intolerance, based on investigator determination.
5. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis as determined by the investigator other than hypoparathyroidism, including but not limited to, active hyperthyroidism; poorly controlled insulin-dependent diabetes mellitus or type 2 diabetes mellitus; severe and chronic cardiac, liver or renal disease; Cushing's syndrome; neuromuscular disease such as rheumatoid arthritis; myeloma; pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy, bone metastases or a history of skeletal malignancies; primary or secondary hyperparathyroidism; a history of parathyroid carcinoma; hypopituitarism, acromegaly; or multiple endocrine neoplasia types 1 and 2.
6. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase, young adult subjects with open epiphyses, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton.
7. Use of the following medications prior to administration of investigational product within:
    - 30 days–loop diuretics, lithium, systemic corticosteroids (medical judgment is required by the investigator. Primarily high doses of systemic corticosteroids [eg, prednisone] should be excluded. Stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable).
    - 3 months–cinacalcet hydrochloride
    - 6 months–fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin
    - 12 months–intravenous bisphosphonates, drug or alcohol abuse, as determined by the investigator

8. Presence of any clinically significant results from laboratory tests, vital signs assessments, or ECGs, that in the opinion of the investigator, would make the subject unsuitable for this study.
9. Any medical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for this study.
10. History of a clinically significant illness during the 4 weeks prior to dosing, that in the opinion of the investigator, would make the subject unsuitable for this study.
11. History of any clinically significant surgery or procedure within 8 weeks of first dose, as determined by the investigator or expected to undergo a major surgical procedure during the trial.
12. History of an allergic response(s) to PTH, PTH, or PTH(1-34) analogs, or other clinically significant allergies, that in the opinion of the investigator, would make the subject unsuitable for this study.

4.3 Restrictions

Subjects should strive to the greatest extent possible to maintain consistent daily dietary (nonsupplement) intake of calcium, phosphate, and sodium to ingest consistently throughout the study and during 24-hour urine collections.

4.4 Reproductive Potential

4.4.1 Female Contraception

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

Female subjects should be either:

- Postmenopausal as defined by 12 months of continuous amenorrhea and with serum follicle stimulating hormone levels >40 IU/L;
- Surgically sterile (having undergone1 of the following: 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 (. -HCG) pregnancy test at screening (Visit 1) and baseline (Visit 2). Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days before screening (Visit 1), plus condoms.
- Note: If a subject becomes sexually active during the study, she should use 1 of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

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). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for the EOT/ET visit (Visit 9) are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up (see Table 1 and Table 2). Comments (spontaneous or elicited) or complaints made by the subject must be documented in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be documented 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
- 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

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins and 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 must be documented.

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 end-of-study, as specified in the protocol), inclusive. Concomitant treatment information must be documented; this includes prescribed doses of active vitamin D and calcium.

5.2.1 Permitted Treatment

Thyroid hormone replacement therapy is permitted providing that the subject's serum thyroid-stimulating hormone (TSH) level is within the central laboratory normal range at baseline. A serum TSH level below the lower limit of the normal range but not undetectable in subjects treated with thyroid hormone may be allowed at the discretion of the investigator. 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 30 days before screening (Visit 1). The use of any other investigational drug or device is prohibited within 3 months before screening (Visit 1) except as used or administered in SHP634-101.

The washout periods for common prior treatments that are excluded medications for this study are shown in Table 3. Treatments not listed in Table 3 are considered allowable (see also Section 5.2.1).

Table 3: Common Excluded Treatments and Associated Washout Period

	Time Before First Dose			
Treatment	**1 month**	**3 months**	**6 months**	**12 months**
Loop diuretics	X			
Digoxin			X	
Lithium	X			
Methotrexate			X	
Systemic corticosteroids	X			
Fluoride supplements			X	
Cinacalcet hydrochloride		X		
Oral bisphosphonates			X	
Growth hormone			X	
Intravenous bisphosphonates				X

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

Subjects enrolled in this study may be taking active vitamin D to control serum calcium levels. Prior and concomitant prescribed doses of active vitamin D must be documented.

Subjects should receive native vitamin D to maintain the subject's serum 25(OH) vitamin D level in the range of ≥30 ng/mL and ≤ the upper limit of normal for the laboratory. Subjects with serum 25(OH) vitamin D levels below this range at screening should take vitamin D to reach levels within this range and to maintain serum 25(OH) vitamin D level in this range throughout the study. Prior and concomitant doses of native vitamin D must be documented.

Subjects enrolled in this study may be taking oral calcium supplements (either calcium carbonate or calcium citrate). Prior and concomitant prescribed doses of calcium must be documented.

Subjects with low serum magnesium should receive supplementation to keep the serum magnesium level in the normal range. Prior and concomitant doses of magnesium must be documented.

Subjects in this study may be taking thiazide diuretics (hydrochlorothiazide or chlorthalidone) to limit the extent and effect of hypercalciuria. Prior and concomitant prescribed doses of thiazide diuretics must be documented.

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.

6.1.1 Blinding the Treatment Assignment

Not Applicable.

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 enroll a subject into the study.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study.

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

Individual subject number(s) are automatically assigned via 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 visit (Visit 2).

Treatment with investigational product will be initiated with 50 µg once daily as a subcutaneous injection in the thigh (alternate thigh every day). If ACSC is >2.25mmol/L (>9.0mg/dL), a starting dose of 25 µg can be considered.

Subjects may have their rhPTH(1-84) dose increased in increments of 25 µg to a maximum of 100 µg SC QD by the investigator no more frequently than every 2 to 4 weeks, with the goal of achieving or maintaining ACSC levels in the range of 2-2.25 mmol/L (8.0-9.0 mg/dL). The

rhPTH(1-84) dose may be adjusted downward at any time as needed to avoid hypercalcemia or due to any safety concerns. Albumin-corrected serum calcium should be measured 3-7 days after any adjustment of investigational product and/or supplements throughout the study.

Once a subject achieves a stable ACSC (target: between 2-2.25 mmol/L [8.0-9.0 mg/dL]) and has minimized supplement doses, they will be maintained at that dose of rhPTH(1-84). Within 2-5 days of achieving the maintenance dose the subject should have post-dose ACSC levels measured. The postdose levels should be drawn between 8-12 hours after the investigational product dosing. In general, if postdose ACSC results are abnormal, the postdose measurements should be repeated within 2-5 days.

If the subject is hypercalcemic at baseline, the initiation of rhPTH(1-84) administration should be delayed until ACSC levels are in the normal range. If initiation of investigational product is delayed by more than 2 weeks, the medical monitor should be contacted.

All subjects will also take active vitamin D and calcium supplements (see Section 5.2.3) as appropriate. Active vitamin D and calcium supplements will not be supplied by the sponsor. Calcium supplement refers to prescribed nondietary oral calcium supplement.

See Appendix 2 for dosing guidelines for active vitamin D supplements, calcium supplements, and investigational product.

6.2.4 Unblinding the Treatment Assignment

Not Applicable.

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 written agreement.

6.3.2 Packaging

The study site will receive 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. In the event of drug expiries, a courier may ship drug supplies to subjects directly in between their study visits. Subjects may also use the courier service to return expired investigational product. Ancillary supplies, including single-use injection pen needles (31-gauge) and alcohol wipes, will be provided by the contract research organization (CRO) to the site.

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.

Prior to being dispensed to the subject, 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. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed 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 must 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. Subject is to return unused and used cartridges at each visit to the site for drug accountability purposes.

In the event an exchange of expiring investigational product kits is required in between scheduled site visits, a courier service may ship the investigational product kits directly to subjects and return the expiring investigational product to the site.

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

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

At the end of the study, or as instructed by the sponsor, all unused stock, 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 will be dispensed at each visit. Subjects must be instructed to bring their unused investigational product and their empty or used investigational product packaging to every visit. Additionally, subjects may use a courier service to return expired and empty/used investigational product. 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, calcium supplements, 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. See Table 2 for follow-up procedures for subjects will not continue on rhPTH(1-84) and for subjects transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET visit (Visit 9).

At site visits, procedures and assessments should be performed in the following order (as applicable at each visit [see Table 1]):

[redacted]

- Vital sign measurements (blood pressure, pulse, body temperature, and respiratory rate)
- Blood sample collection
- Other procedures and assessments

Site personnel will record the time and actual dose of the last dose of calcium, active vitamin D, and investigational product that the subject has taken at the visits specified in Table 1. A 24-hour recall period will be used.

Site personnel will administer the [redacted], and subjects will be asked to complete PRO assessments ([redacted]) at the visits specified in Table 1. Responses to PRO assessments will not be monitored for AEs.

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 administered investigational product(s). Screen failures will be captured in clinical database.

The window for the screening period will be 7 days. Subjects must sign an ICF for this study prior to having any study related procedures performed. Subjects will receive a jug for the baseline 24-hour urine collection at the screening visit (Visit 1).

7.1.2 Treatment Period

The visit window for the baseline visit (Visit 2) will be ±3 days; the visit window for Visits 3-9 will be ±7 days.

Final SHP634-101 study parameters may be used as screening parameters for this study if they were collected within 30 days of screening. However, serum calcium, albumin, phosphate, and magnesium levels must be re-measured if they were measured >1 week prior to screening in this study.

Subjects will receive treatment from the baseline visit (Visit 2) through the EOT/ET visit (Visit 9) during study SHP634-404.

Visit 9 will serve as EOT visit for all subjects.

All AEs and SAEs that are not resolved at the time of this visit will be followed to closure (see Section 7.1.3 and Section 8.1).

Subjects who will not continue on rhPTH(1-84) and subjects transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET visit (Visit 9) 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 7.1.3 for additional details).

7.1.3 Follow-up Period

The follow-up period for this protocol is 30 days; all subjects will complete the follow-up period including an EOS contact (Visit 10). The visit window for the EOS contact will be ±3 days.

Thirty days following the last dose of investigational product, all subjects, including subjects who transfer to commercial rhPTH(1-84) immediately after the EOT/ET visit (Visit 9), will have an EOS contact (Visit 10) that is a safety follow-up telephone call initiated by the site staff to query for serious adverse events (SAEs), adverse events (AEs), and concomitant treatments. Subjects who will be returning to the site for their last weekly follow up contact (Visit 10) can complete their EOS contact (Visit 10) at the site. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1).

Weekly follow-up visits (FU1, FU2, FU3, and EOS contact [Visit 10]) are scheduled for subjects who will not continue on rhPTH(1-84) and for subjects who will be transferring to commercial rhPTH(1-84) but experience a treatment gap after the EOT/ET (Visit 9). Follow-up visits will continue until a maximum of 30 days has elapsed or until commercial rhPTH(1-84) treatment is started. During follow-up, subjects will be monitored for ACSC, phosphate, and magnesium levels, and adjustment of exogenous calcium and/or active vitamin D will be made, as necessary.

7.1.4 Additional Care of Subjects after the Study

No after care is planned for this study post the follow-up period.

7.2 Study Evaluations and Procedures

Vitals signs should be assessed prior to blood draws.

Blood samples for antibody testing should be collected at least 14 hours after dosing.

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics for each subject will be collected at the screening visit (Visit 1). Information to be collected will include:

- Date of birth
- Sex
- Race and ethnicity

7.2.2 Efficacy

7.2.2.1 Biochemical Evaluations

Serum calcium, albumin, phosphate, magnesium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and bone turnover markers will be measured at the time points specified in Table 1 and Table 2. Bone turnover markers will include, but are not limited to, serum bone-specific alkaline phosphatase, procollagen Type I N terminal propeptide, C-terminal telopeptide of type 1 collagen, N-terminal telopeptide of type 1 collagen, and total osteocalcin.

A 24-hour urine collection will be performed at each of the time points specified in Table 1 and the total volume documented. Urine chemistry will be determined from the 24-hour urine collection. Parameters that will be measured are provided in Section 7.2.4.5. At the beginning of the study, the investigator should recommend an individualized target dietary (nonsupplement) calcium intake 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.

7.2.2.2 Outcomes Research Assessments

See Section 7.2.3.1 for PRO assessments.

7.2.3 Health Economics, and Outcomes Research Assessments

7.2.3.1 Patient-reported Outcomes Assessments

Subjects will be asked to complete the [redacted] and PRO assessments, as described in the subsections that follow, at the visits specified in Table 1.

[redacted]

[redacted]

See Appendix 3 for [redacted].

[redacted]

[redacted]

[redacted]

7.2.4 Safety

7.2.4.1 Medical and Medication History

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

- Recent use of medication (30 days prior to the first dose of investigational product)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

7.2.4.2 Physical Examination (Including Height and Weight)

A physical examination including height and weight will be conducted at the time points specified in Table 1. Height will be collected at baseline only. Abnormalities identified at the baseline visit (Visit 2) must be documented in the subject's source documents. Any clinically significant changes in physical examination findings that are deemed clinically significant in the opinion of the investigator are to be documented as an AE.

7.2.4.3 Adverse Event Collection

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

Adverse events will be collected from the signing of the informed consent through follow-up (see Section 8.1, Table 1, and Table 2).

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

7.2.4.4 Vital Signs

Vital signs include blood pressure, pulse, body temperature, and respiratory rate; vital signs will be conducted at the time points specified in Table 1 and Table 2. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Vital signs should be assessed prior to blood draws. Any clinically significant changes in vital signs that are deemed clinically significant in the opinion of the investigator are to be documented as an AE.

7.2.4.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's standard 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 whether the value(s) are 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. Any clinically significant changes in clinical laboratory evaluations that are deemed clinically significant in the opinion of the investigator are to be documented as an AE.

In addition to protocol specified laboratory testing processed in the central laboratory, serum calcium and albumin concentrations may be processed at local laboratories at scheduled study site visits (see Table 1 and Table 2) or between visits to allow investigational product and/or supplements dose adjustments to be made at the time of the visit, at the discretion of the investigator. The following clinical laboratory assessments will be performed:

Serum Chemistry

Blood samples for serum chemistry will be collected at the time points specified in Table 1 and Table 2. The following parameters will be measured:

- Albumin
- Alkaline phosphatase
- Alanine transaminase
- Aspartate transaminase
- Blood urea nitrogen
- Serum calcium
- Serum chloride
- Serum sodium
- Bicarbonate.
- Creatinine
- Direct bilirubin

- Glucose
- Magnesium
- Serum phosphorus
- Serum potassium
- Total bilirubin
- Total protein

Serum levels of thyroid-stimulating hormone (TSH) will be measured at screening only (Visit 1).

Female subjects who are newly menopausal will have their serum follicle stimulating hormone (FSH) levels tested at screening (Visit 1) unless their levels have been drawn within 3 months prior to enrollment. Pregnancy testing is described in Section 7.2.4.6.

Estimated creatinine clearance and glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] equation) will be calculated by the central 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:

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

In addition, total volume of the 24-hour urine collections will be captured.

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 cells
- Platelet count
- White blood cell count
- Automatic differential

Urinalysis

Urine samples for urinalysis 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

7.2.4.6 Pregnancy Test

Serum and/or 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.

7.2.4.7 Electrocardiogram

Twelve-lead ECGs will be documented at the time points specified in Table 1.

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

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 must be documented on the tracing and in the source document.

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 documented in the source document. The ECG parameters will be evaluated locally and the interpretation will be 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 will review ECGs for clinically meaningful changes.

7.2.4.8 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 at least 14 hours after dosing. Any subject with newly developed anti-PTH antibodies at the last study visit may require follow up. This will be discussed as necessary by the principal investigator and medical monitor on a case-by-case basis.

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]).

All AEs will be collected from the time the informed consent is signed until the defined follow-up period Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be documented. 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 documented 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 documented 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 documented 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 documented 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 of the Disease Under Study

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

Hypocalcemia AEs reported in the study are to be categorized 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 by1 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 (below the lower level of normal [LLN]) 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 (below LLN) 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 investigational product, 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 7.1.3.

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

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

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 250 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 ACSC, 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 the Shire Global Drug Safety Department 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.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

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 7.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

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

8.2.6 Fatal Outcome

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

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, Dose Reduced, Drug Withdrawn), the action taken with the investigational product should be documented as "Dose Not Changed" or "Not Applicable" (if the subject never received investigational product). The investigational product action of "Drug Withdrawn" should not be selected solely as a result of the subject's death.

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

The sponsor will be responsible for notifying the relevant regulatory authorities/USA central institutional review boards (IRBs)/European Union (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 electronic case report form (eCRF). A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF 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 an open-label study, and, as such, there are no special handling considerations for blinded data.

9.4 Statistical Analysis Process

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

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 must be documented in the appropriate sections of the clinical study report.

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

There will be no Data Monitoring Committee for this open-label study; however, study data may be analyzed as necessary for safety monitoring or publication purposes.

9.6 Sample Size Calculation and Power Considerations

Subjects who complete the SHP634-101 study may have the option to screen for this extension study (SHP634-404). Up to approximately 32 subjects are expected to enroll. Therefore, sample size and power considerations are not applicable to this study.

9.7 Study Population

The safety analysis population will consist of all subjects who have received at least 1 dose of rhPTH(1-84). The safety analysis population will be used for all efficacy and safety analyses for this study.

9.8 Efficacy Analyses

The safety analysis population will be used for all efficacy analyses for this study.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Subject response satisfying total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)-ULN at Visit 6 (Week 24) and at EOT/ET (Visit 9;Week 52).

9.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline in ACSC concentration
- Change from baseline in serum phosphate concentration
- Change from baseline in ACSC-phosphate product
- Change from baseline in 24-hour urine calcium excretion
- Percentage changes from baseline in prescribed supplemental oral calcium dose
- Percentage changes from baseline in prescribed supplemental active vitamin D dose
- Percentage changes from baseline in markers of bone turnover

9.8.3 Statistical Methodology for Efficacy Endpoint(s)

Descriptive statistics will be used with a goal of summarizing the sample population. For the primary efficacy endpoint, the 95% confidence interval (CI) of the proportion of subjects with total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)–ULN will be provided. Secondary efficacy endpoints will be summarized with descriptive statistics at each assessment visit. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

9.8.4 Exploratory Endpoints

[redacted]

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 including SAEs
- Laboratory safety data (eg, clinical chemistry, hematology, and urinalysis)
- Vital signs including body temperature, heart rate (beats per minute), and blood pressure (systolic and diastolic [mmHg])
- ECG parameters
- Measurements of estimated glomerular filtration rate (eGFR) and creatinine
- Change from baseline in anti-PTH antibodies

9.9.1 Statistical Methodology for Safety Endpoint(s)

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened on or after the date and time of the first dose of investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term. 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 visit. Potentially clinically important findings will also be summarized or listed. Descriptive statistics will be presented by 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 R2, EU Directive 2001/20/EC and its updates, 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.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (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

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

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

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH E6, 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 must be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic case report forms (eCRFs) 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 documented onto eCRFs, which have been designed to document 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 documented directly onto the eCRF.

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 documented 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 eCRF 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.

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

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

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with 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. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, the sponsor 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 the sponsor. 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

[redacted]

12 APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	30 Aug 2017	Global

APPENDIX 2 DOSING GUIDELINES FOR ACTIVE VITAMIN D SUPPLEMENTS, CALCIUM SUPPLEMENTS, AND INVESTIGATIONAL PRODUCT

The dose of rhPTH(1-84) should be individualized based on total serum calcium (albumin-corrected) and 24-hour urinary calcium excretion. The recommended rhPTH(1-84) dose is the minimum dose required to prevent both hypocalcemia and hypercalciuria. This dose will generally be the dose that maintains total serum calcium (albumin-corrected) within the lower half of the normal range (ie, between 8 and 9 mg/dL [2.0 mmol/L and 2.25 mmol/L]) without the need for active forms of vitamin D and with calcium supplementation sufficient and individualized to meet the patient's daily requirements. Total serum calcium levels (albumin-corrected) between 2.25 mmol/L (9.0 mg/dL) and the upper limit of normal may also be acceptable if the 24-hour urine calcium excretion is not elevated and the post-dose total serum calcium (albumin-corrected), measured 8-12 hours after the dose of rhPTH(1-84), is not above the upper limit of the normal range.

Doses of active forms of vitamin D and calcium supplements will need to be adjusted when using rhPTH(1-84). Adjust dose of active vitamin D or calcium supplement or both based on serum calcium value and clinical assessment (ie, signs and symptoms of hypocalcemia or hypercalcemia). Suggested adjustments to active vitamin D and calcium supplement based on serum calcium levels are provided below.

Measure serum calcium concentration (albumin-corrected) within 3 to 7 days after initiation of rhPTH(1-84) and dose adjustments of rhPTH(1-84), calcium or active vitamin D.

If the subject does not require an investigational product dose change based on dose titration guidelines, and has not previously had a postdose evaluation on the current investigational product dose, the subject should have postdose ACSC levels measured within 2-5 days. The postdose levels should be drawn between 8-12 hours after the investigational product dosing. In general, if postdose ACSC results are abnormal, the postdose measurements should be repeated within 2-5 days. If values remain abnormal, please contact the medical monitor to discuss the case.

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 of 75-250 nmol/L (30-100 ng/mL). 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.

After initiation of rhPTH(1-84), blood samples should be drawn no later than 24 hours after the previous day's dose of investigational product.

At 2-4 week intervals rhPTH(1-84) may be increased in 25 μg increments to a maximal dose of 100 μg once daily (QD). At any time during the study as needed for safety reasons, rhPTH(1-84)

doses may be decreased in 25 μg decrements to a minimum of 25 μg QD. If the ACSC is >2.97 mmol/L (>11.9 mg/dL), then the investigational product should be stopped until the calcium level is corrected.

In addition to protocol specified laboratory testing processed in the central laboratory, serum calcium and albumin concentrations may be measured at local laboratories at scheduled study site visits so that the investigational product and/or supplements dose adjustments can be made at the time of the visit. Serum calcium and albumin concentrations should be obtained 2-5 days following any change in active vitamin D, calcium supplement, or investigational product doses. Therefore, unscheduled serum laboratory testing will be needed for many subjects between scheduled visits; they may also be performed at local laboratories.

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 Initiation

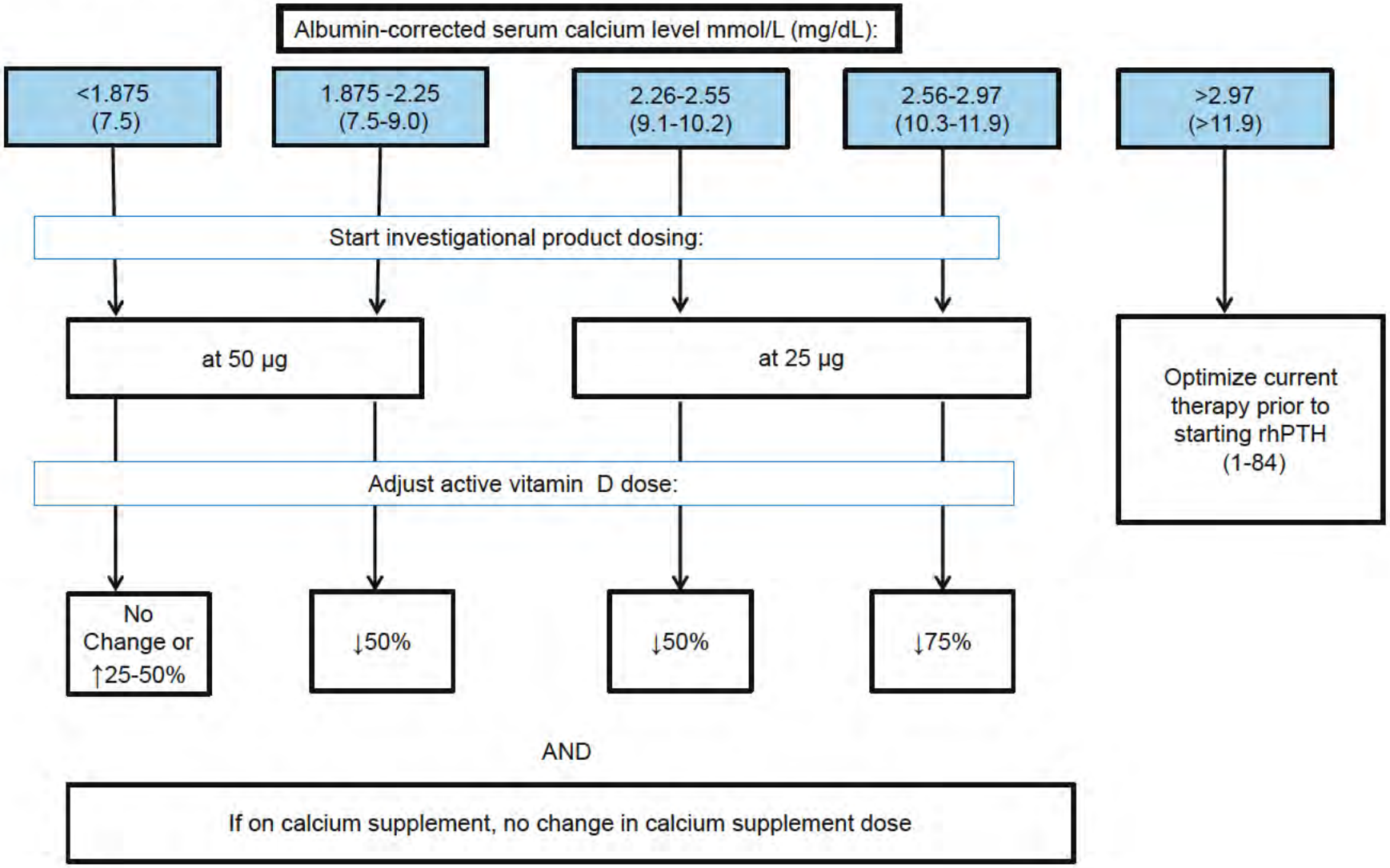
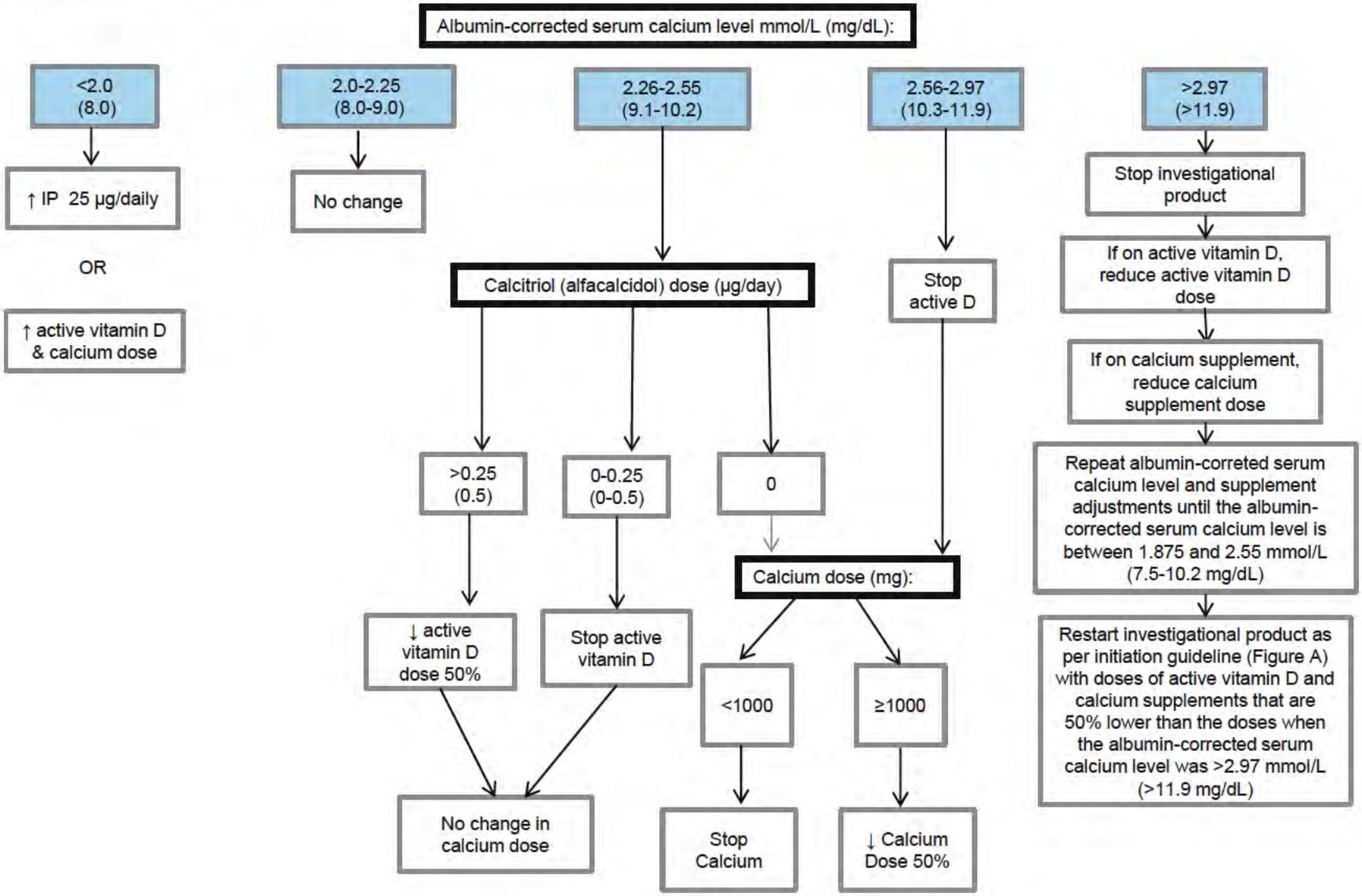


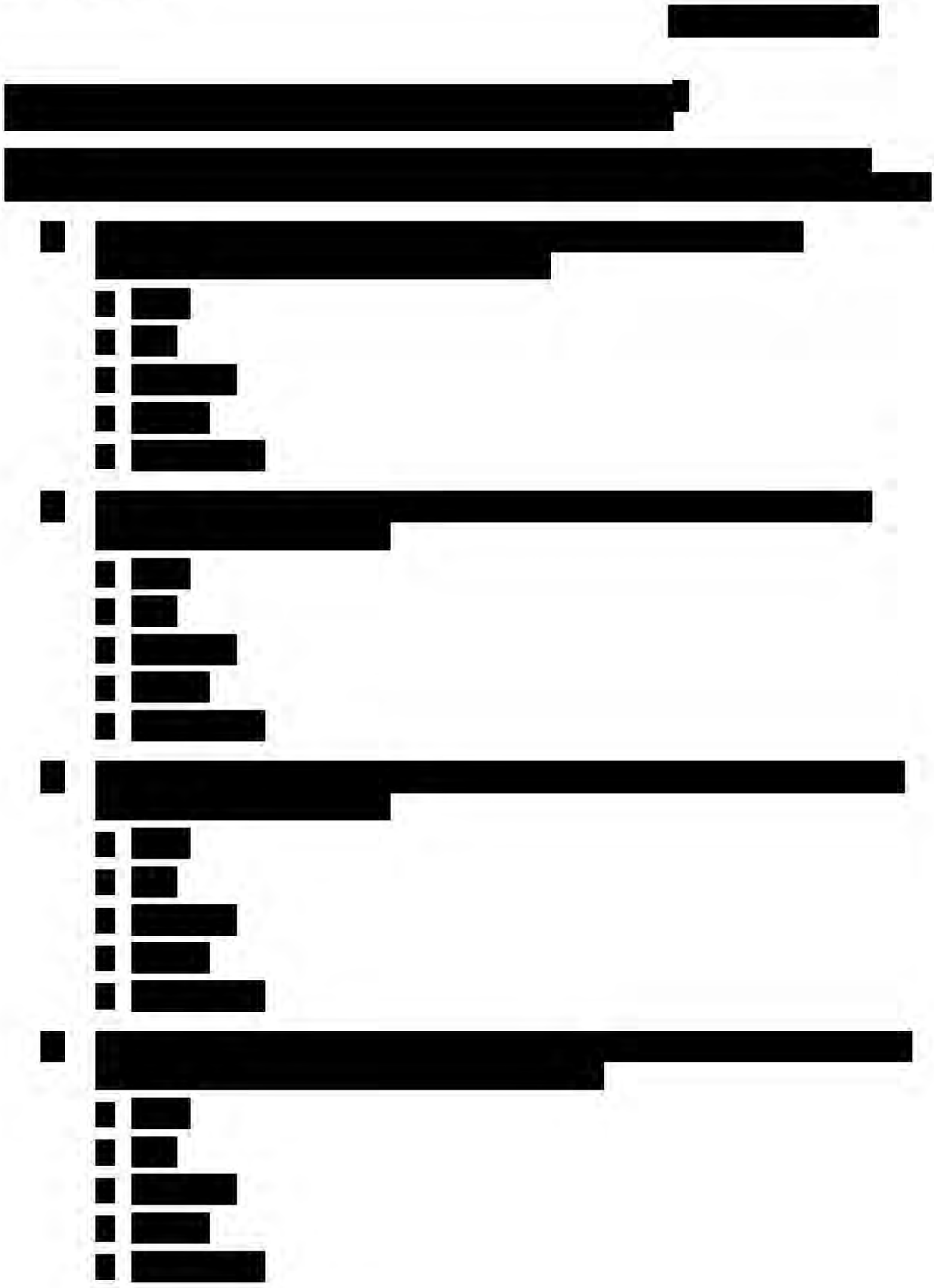
Figure B: Ongoing investigational product, active vitamin D, and calcium Adjustments



APPENDIX 3 SCALES AND ASSESSMENTS

The following scales and assessments are presented:

- [redacted]
- [redacted]
- [redacted]
- [redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]