STATISTICAL ANALYSIS PLAN

rhPTH(1-84)
PHASE IV

A Phase 4, Open-Label, Single-Center Clinical Study of Extended use of rhPTH(1-84) in Hypoparathyroidism

PROTOCOL IDENTIFIER: SHP634-402

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REVISION HISTORY

Version No:	Document History Description of Update	Author(s)	Effective Date
Final 1.0	Final SAP	[redacted]	4 Dec 2019
Final 2.0	1. In Section 11.2.3 1) Calculate prescribed daily dose prior to target study day in each visit window; 2) Impute missing with 0 for both diary and prescribed daily dose; 3) Remove the condition of 9 minimal days of data when calculating the diary daily dose. 2. added section 11.3.3 3. Removed 'absolute change' from all analysis. 4. Updated SI unit and conventional unit for 24-hour calcium. 5. Added analysis for ACSC in conventional unit	[redacted]	14 Jul 2020
Final 3.0	1. Add condition #6 to section 15.3 2. Updated protocol deviation rules in section 7 3. Removed appendix 1 and indicated the software will be used for SF-36 scoring in section 11.2.8.	[redacted]	30 Oct 2020

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

ACSC	albumin-corrected serum calcium
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BMSi	bone material strength index
BSA	body surface area
BSAP	bone specific alkaline phosphatase
BUN	blood urea nitrogen
CKD-EPI	CKD-epidemiology collaboration group
CogQOL	impact on quality of life subscale
CogOth	comments from others subscale
CogPCA	perceived cognitive ability subscale
CogPCI	perceived cognitive impairments subscale
CRF	case report form
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
eGFR	estimated Glomerular Filtration Rate
EOT	end of treatment
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-Cog	Functional Assessment of Cancer Therapy - Cognitive Function
FSH	follicle-stimulating hormone
HADS	Hospital Anxiety and Depression Scale
HPT	hypoparathyroidism
HPT-SD	Hypoparathyroidism Symptom Diary
HRpQCT	high-resolution peripheral quantitative computerized tomography
MedDRA	Medical Dictionary of regulatory activities
mmHg	millimeters of mercury
P1NP	procollagen type I amino-terminal propeptide
PCI	potentially clinically important
PI	principle investigator
PT	preferred term
PTH	parathyroid hormone
RBC	red blood cell
rhPTH(1-84)	recombinant human parathyroid hormone
s-CTX	serum carboxy-terminal 4 telopeptide of type I collagen
SAE	serious adverse event

SAP	statistical analysis plan
SAS	Statistical Analysis System
SF-36	36-item Short Form Health Survey
SI	système international
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAP-5b	tartrate-resistant acid phosphate-5b
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization drug dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final study protocol SHP634-402 version 1.0 dated 27 May 2016 incorporating most recent amendment 2 dated 05 Sep 2018. Specifications for tables, figures, and listings are contained in a separate document.

Chronic hypoparathyroidism (HPT) is a life-long and irreversible disease for which the chronic administration of rhPTH(1-84) is a potential treatment option. Thus, long-term safety and efficacy data are important in evaluating the proper use of this treatment option in clinical practice.

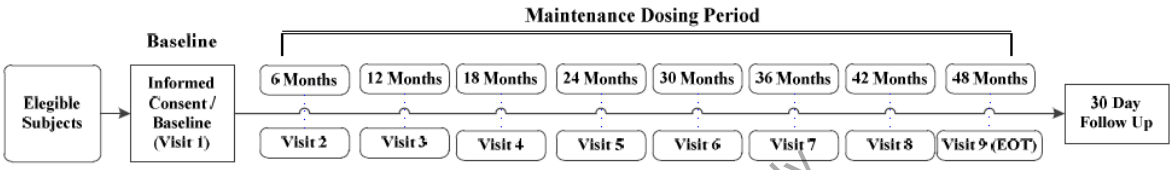
This study is investigating the effects of rhPTH(1-84) at doses of 25, 50, 75, and 100 μg for once daily subcutaneous injection to the thigh via a multidose pen injector device. The dose will be individualized to achieve a serum calcium level in the lower half of the normal range.

2. STUDY DESIGN

2.1 General Study Design

SHP634-402 is a single-center, open-label, single arm, Phase 4 study of rhPTH(1-84) treatment in adult subjects (up to 50 subjects) diagnosed with hypoparathyroidism. Subjects enrolled are currently or were previously enrolled in the core study (AAAE0544) and have maintained uninterrupted therapy with rhPTH(1-84). Study visits will be scheduled every 6 months up to the 48-month end of treatment visit. Specific procedures at each study visit are summarized in Table 1. A schematic of the study design is provided in Figure 1.

Figure 1 Study Design Flow Chart



2.2 Schedule of Assessments

Table 1 Schedule of Assessments

Study Period	Baseline	Maintenance Dosing Period							End of Treatment	Follow-Up Call
Visit	1	2	3	4	5	6	7	8	EOT Visit[a]	
Study Month	0	6	12	18	24	30	36	42	48	49
Study Procedures		±1 Month								±7 Days
Informed Consent[b]	X									
Inclusion/Exclusion	X									
Medical history and demography	X									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X		X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	
Hematology	X				X				X	
Serum chemistry[d]	X	X	X	X	X	X	X	X	X	
Serum TSH	X									
Serum pregnancy test[e]	X									
Urine pregnancy test	X	X	X	X	X	X	X	X	X	
FSH level[f]	X									
Serum PTH antibodies[g]	X	X	X	X	X	X	X	X	X	
Serum 25-hydroxyvitamin D	X	X	X	X	X	X	X	X	X	
Serum 1,25-dihydroxyvitamin D	X	X	X	X	X	X	X	X	X	
Bone turnover markers[h]	X	X	X	X	X	X	X	X	X	
Urinalysis (dipstick)[i]	X				X				X	
24-hour urine		X	X	X	X	X	X	X	X	
Bone mineral density DXA	X	X	X	X	X	X	X	X	X	
Bone mineral density HRpQCT	X	X	X	X	X	X	X	X	X	
Bone biopsy (optional)[j]	X									
[redacted] (optional)[j]	X									
HPT-SD	X	X	X	X	X	X	X	X	X	
FACT-Cog assessment	X	X	X	X	X	X	X	X	X	
SF-36 RAND	X		X		X		X		X	
FACIT Fatigue Scale	X	X	X	X	X	X	X	X	X	
HADS assessment[k]	X	X	X	X	X	X	X	X	X	
[redacted]	X	X	X	X	X	X	X	X	X	
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X
Dispense/Account for study drug	X	X	X	X	X	X	X	X	X	
Collection of unused study drug & injection pen									X	
Record any use of Calcium, Calcitriol, and/or Vitamin D supplements[l]	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = Adverse event; DXA = dual-energy x-ray absorptiometry; HPT = Hypoparathyroidism; HPT-SD = Hypoparathyroidism Symptom Diary; SAE=Serious adverse event; SF-36 = RAND 36-Item Short Form Health Survey; HRpQCT = High-resolution peripheral quantitative computerized tomography.

[a] For subjects not continuing rhPTH[1-84] treatment, see protocol section 7.1.3.

[b] Remote consent allowed. Consent procedure must be complete prior to completing any baseline assessments

(can occur at baseline visit as long as complete prior to assessments).

[c] Vitals signs include: blood pressure, heart rate, body temperature, and respiration rate.

[d] Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP).

[e] Pregnancy tests for females of childbearing potential.

[f] FSH level required for newly menopausal women.

[g] Blood samples for antibody testing should be collected prior to dosing with PTH[1-84]. Any subject with newly developed PTH-specific antibodies at the end of treatment visit may require follow up. This will be discussed as necessary by the principle investigator (PI) and medical monitor on a case-by-case basis.

[h] Bone turnover markers include, but are not limited to, the following: serum carboxy-terminal 4 telopeptide of type I collagen (s-CTX), procollagen type I amino-terminal propeptide (P1NP), osteocalcin, bone specific alkaline phosphatase (BSAP), tartrate-resistant acid phosphate-5b (TRAP-5b), sclerostin.

[i] 24-hour urine collection includes urine calcium, creatinine, phosphate, magnesium and sodium analyses. Urine volume will be recorded. The 24-hour urine collections should generally be performed by the subject within 2 weeks prior to or within 2 days follow a study visit. These 24-hour urine collections may be analyzed in a local laboratory. To the greatest extent possible, the same laboratory should analyze the 24-hour urine collections throughout the study. Results from the last 24-hour urine collection obtained in Columbia protocol AAAE0544 will be used as the baseline assessment in this study. At the beginning of the study, the investigator should recommend an individualized target dietary (non-supplement) calcium intake for each subject to ingest consistently throughout the study 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 parent and active) and rhPTH(1-84) doses.

[j] This optional assessment may be performed up to 3 times during the study.

[k] The investigator must review responses to the HADS before the subject leaves the site and take any appropriate action that is clinically indicated based on the responses.

[l] Subjects will enter their actual doses of calcium taken for 14 days prior to each visit, following the baseline visit, in a home diary.

2.3 Determination of Sample Size

Approximately 50 subjects are anticipated to be enrolled. No formal sample size calculation was performed.

3. OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

- To evaluate albumin-corrected serum calcium (ACSC) while on rhPTH(1-84) treatment

3.1.2 Secondary Objectives

- To evaluate the proportion of subjects who achieve ACSC values above, below, or in the range of 7.5mg/dL to ULN
- To evaluate urinary calcium excretion and serum phosphate while on rhPTH(1-84) treatment
- To evaluate calcium and active vitamin D supplement doses while on rhPTH(1-84) treatment
- To evaluate patient reported-outcomes assessment including symptoms and impact of hypoparathyroidism (HPT-SD), fatigue (FACIT-Fatigue), cognitive function (FACT-Cog), anxiety and depression (HADS) and health-related quality-of-life (SF-36 v1) associated with long-term rhPTH(1-84) treatment
- To evaluate the skeletal actions of rhPTH(1-84): bone turnover markers, architecture, and histology (biopsy)

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint:

- Change in ACSC at Month 6, 12, 18, 24, 30, 36, 42, 48 (Baseline (402) as defined in Section 4)

3.2.2 Secondary Efficacy Endpoints:

- ACSC value above, below, or in the range of 7.5mg/dL to upper limit of normal (ULN) at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in urinary calcium and serum phosphate at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in calcium and active vitamin D supplement doses at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in HPT symptoms (as measured by the HPT-SD) at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) assessment (Version 3) at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in Functional Assessment of Chronic Illness Therapy (FACIT) (Fatigue Scale (Version 4)) at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in Hospital Anxiety and Depression Scale (HADS) at Month 6, 12, 18, 24, 30, 36, 42, 48

- Change in health-related quality-of-life measured with the 36-item Short Form Health Survey (SF-36) at Month 6, 12, 18, 24, 30, 36, 42, 48
- Change in bone turnover markers (including, but not limited to, serum carboxy-terminal 4 telopeptide of type I collagen [s-CTX], procollagen type I amino-terminal propeptide [P1NP], osteocalcin, bone specific alkaline phosphatase [BSAP], TRAP-5b, sclerostin), architecture at Month 6, 12, 18, 24, 30, 36, 42, 48, and histology (biopsy)

3.2.3 Exploratory Efficacy Endpoint

- [redacted]

3.2.4 Safety Endpoints/Variables:

- AEs including SAEs
- Vital signs including body temperature (°C), heart rate (beats per minute), respiratory rate, and blood pressure (systolic and diastolic [mmHg])
- Estimated Glomerular Filtration Rate (eGFR) and creatinine clearance
- Measurements of Parathyroid hormone (PTH) antibody
- Laboratory safety data (e.g., clinical chemistry, hematology, and urinalysis)

4. GENERAL CONSIDERATIONS

No formal statistical testing will be conducted for this study. Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers. Ninety-five percent (95%) confidence intervals will be presented, where specified.

Baseline (402) is defined as the last available pre-dose value in SHP634-402.

Baseline (rhPTH) is defined as the last assessment value prior to the start of rhPTH(I-84) as determined from subject's medical records obtained from data collected retrospectively from the core study (AAAE0544).

For primary and selected secondary endpoints (specified in Section 11), the analysis will be performed with Baseline (402) as well as Baseline (rhPTH). For the analysis using Baseline (rhPTH), the retrospective data and data from prospective portion of SHP634-402 study will be combined.

End of treatment (EOT), defined as the last determination of response during the treatment period (from the date of first dose to the date of last dose + 1 day), will be analyzed in addition to the scheduled visits.

All summaries will be presented for rhPTH(1-84) only, unless otherwise specified.

4.1 Visit Window

Visits will be summarized based on the analysis visit windows as specified in Table 2. Since visit windows are being applied, month number instead of visit number will be used in the analysis presentations.

Table 2 Analysis Visit Window

For data using baseline (402), the analysis windows will be mapped as follows:

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1	<=1
Month 6	183	[153, 213], and ≤last dose day + 1
Month 12	365	[335, 395], and ≤last dose day + 1
Month 18	548	[518, 578], and ≤last dose day + 1
Month 24	730	[700, 760], and ≤last dose day + 1
Month 30	913	[883, 943], and ≤last dose day + 1
Month 36	1095	[1065, 1125], and ≤last dose day + 1
Month 42	1278	[1248, 1308], and ≤last dose day + 1
Month 48	1460	[1430, 1490], and ≤last dose day + 1

* The study day in Baseline (402) visit window is calculated from the date of first dose of investigational product in SHP634-402.

For data using baseline (rhPTH), the analysis windows will be mapped as follows:

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1	<=1
Month 6	183	(1, 274], and ≤last dose day + 1
Month 12	365	[275, 456], and ≤last dose day + 1
Month 18	548	[457, 639], and ≤last dose day + 1
Month 24	730	[640, 821], and ≤last dose day + 1
…	…	…
Month xx (rhPTH)	round(xx/12*365)	[target day of last analysis visit+92, target day+91) ,] , and ≤last dose day + 1

* The study day in Baseline (rhPTH) visit window is calculated from the date of first dose of of rhPTH from data collected retrospectively. Both retrospective data and data from SHP634-402 will be mapped into the analysis windows for Baseline (rhPTH).

The analysis visit will be mapped up to Month 48 for Baseline (402), as only concomitant medication and adverse events are collected at Month 49 (Follow-up visit). If there are more than one non-missing observations in the same analysis visit window, the following selection rules will be applied sequentially to determine which observation will be used for analysis:

- The observation that is closer to the target day will be used;
- If observations are equal-distance in days from the target day, the later one based on measurement date and time will be used.

4.2 Handling of Dropouts or Missing Data

For all variables, only the observed data from the subjects will be used in the statistical analyses, i.e., there is no plan to estimate (impute) missing data, unless otherwise specified.

4.3 Interim Analyses and Data Monitoring

A retrospective analysis of historical data captured from the medical records of subjects (e.g., since the start of rhPTH(1-84) treatment) was conducted separately, with details described in the separate Interim Analysis SAP Final 1.2, dated 12 January 2017.

There will be no Data Monitoring Committee for this unblinded exploratory study, however results of the prospective data portion of the study will be analyzed as necessary for safety monitoring and publication purposes.

5. SUBJECT POPULATION SETS

5.1 Enrolled Subjects

Enrolled Subjects consist of all subjects who have signed informed consent.

5.2 Safety Population

The Safety Population will be used for all analysis in this study and consists of all enrolled subjects who receive at least 1 dose of rhPTH(1-84) regardless of study (SHP634-402 or AAAE0544 core study).

6. SUBJECT DISPOSITION

The number of subjects included in Enrolled Subjects and Safety Population will be summarized.

The number and percentage of subjects who completed and early terminated during the study will be presented. Reasons for early termination from the study as recorded on study completion page of the electronic case report form (eCRF) will be summarized (number and percentage). Subject disposition, subjects completing and prematurely discontinued during the study, and study analysis sets will be listed by subject for Enrolled Subjects.

7. PROTOCOL DEVIATIONS

Subjects with at least 1 protocol deviation for each deviation category will be summarized and listed. Protocol deviations will be identified programmatically as well as based on protocol deviations collected by the study monitors in protocol deviation log.

After the last subject exits the trial and prior to database lock, protocol deviations will be reviewed and summarized by category. The protocol deviation categories may include, but not limited to the following:

- ICF Process/Timing
- Investigator Record Keeping Source Documents
- Missing Endpoint Assessments
- Study Procedures/Assessments
- Study Treatment Admin/Dispense
- Visit Scheduling
- Use of Prohibited Concomitant Medications

All protocol deviations will be listed.

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety Population.

The following demographic characteristics will be summarized and listed: age (years), age category (18-44, 45-64, >=65), sex, ethnicity, race, height (cm), weight (kg), body mass index (BMI) (kg/m^2), prescribed vitamin D supplement (as continuous parameter and by categories of low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day), prescribed calcium supplement (as continuous parameter and by categories of 0-2000 mg/day, >2000 mg/day), study drug dose at baseline (mcg), duration of HPT (as continuous parameter and by categories of < =5 years, >5-10 years, > 10 years) . Duration of HPT is calculated as (date of informed consent - date of first diagnosis of HPT) + 1 where date of first diagnosis of HPT is captured in the Medical History CRF page.

Medical and surgical history will be coded using the Medical Dictionary of Regulatory Activities (MedDRA), Version 19.0. The history will be summarized by system organ class (SOC) and preferred term (PT) within system organ class for the Safety Population, with both SOC and PT sorted alphabetically. Medical history will be listed for the Safety Population.

9. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 Exposure to Investigational product

Exposure for the Safety Population during SHP634-402 will be summarized in terms of treatment duration in months, which is calculated as [(date of last dose - date of first dose in SHP634-402) + 1]/ 30.4375. The extent of exposure during SHP634-402 will also be categorized into months (<=1, >1-6, >6-12, >12-18, >18-24, >24-30, >30-36, >36-42, >42-48, >48 months) and tabulated. In addition, cumulative exposure to rhPTH(1-84) in years will also be calculated from the date of first rhPTH(1-84) as determined from subject's medical records and summarized categorically (<=1, >1-6, >6-12, >12 years). Descriptive statistics will be presented for exposure of study drug.

Exposure information will be listed for each subject.

10. PRIOR AND CONCOMITANT MEDICATION

Version Jun 2016 of the World Health Organization Drug Dictionary (WHODrug) will be used to classify prior and concomitant medications by therapeutic class.

Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product in prospective portion of SHP634-402.

For the prospective portion of the study, concomitant medications refers to all medicines taken between the dates of the first dose of rhPTH(1-84) in study SHP634-402 and the end of the follow-up period in the SHP634-402 study, inclusive. All available active vitamin D and calcium supplement doses from the beginning of rhPTH(1-84) will be recorded. Concomitant medication information must be recorded on the appropriate eCRF page.

Partial date imputation for medications is described in Section 15.3.

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication within each level of therapeutic class and preferred term. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same each level of therapeutic class and preferred term will be counted only once. Therapeutic classes will be sorted alphabetically while medication preferred terms will be sorted by decreased frequency within therapeutic class.

All prior and concomitant medications and medical/surgical procedures will be listed.

11. EFFICACY ANALYSES

The EOT value will be mapped to the visit windows as specified in Table 2 and summarized under the mapped visit. The EOT will also be included as a separate time point in the summary. No formal statistical hypothesis test will be conducted. The efficacy analysis will be performed using the Safety Population. For the analysis using Baseline (rhPTH), the retrospective data and data from prospective portion of SHP634-402 study will be combined.

11.1 Primary Efficacy Endpoint(s) and Analysis

The primary efficacy endpoint is defined as change in ACSC concentration (mmol/L) over time at each visit and EOT. ACSC concentration in SI unit (mmol/L) will be derived using the formula at the end of this section for retrospective data. For data from SHP634-402 study, ACSC concentration (mmol/L) derived by PPD global central laboratory will be used in the analysis.

The baseline serum calcium concentration is the final measurement taken prior to initiating investigational product in SHP634-402 (Baseline (402)). The analysis will be repeated using Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study. 95% CI will be provided for the means.

The observed values, changes and percentage changes from baseline (both Baseline (402) and Baseline (rhPTH)) in ACSC (mmol/L) and total serum calcium (mmol/L) will be summarized by visit and at EOT. The ACSC and total serum calcium over time will also be evaluated graphically using line graph. By-subject listings will be provided. The summary, figure and listing of ACSC will be repeated in conventional unit (mg/dL).

Albumin-corrected Serum Calcium in SI unit (mmol/L) = Total Serum Calcium (mmol/L) + 0.02 * [40 g/L - Albumin (g/L)], or

Albumin-corrected Serum Calcium in conventional unit (mg/dL) = Total Calcium (mg/dL) + 0.8 * [4 g/dL – Albumin (g/dL)].

11.2 Secondary Efficacy Endpoint(s) and Analysis

Secondary efficacy endpoints will be analyzed using Baseline (402). The same analysis will be performed for selected secondary endpoints where data are available using Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study. 95% CI will be provided for the means.

11.2.1 Albumin-corrected serum calcium value above, below, or in the range of 1.875mmol/L-ULN

The number and percentage of subjects with ACSC above, below, or in the range of 1.875mmol/L -ULN at each study visit will be tabulated. This analysis will be performed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from

retrospective data and data from prospective portion of SHP634-402 study. For retrospective data, the ULN of ACSC is derived from the ULN of calcium normal range. For data from SHP634-402 study, the ULN of ACSC is provided by PPD global central lab.

11.2.2 Change in Urinary Calcium (mmol/day) and Serum Phosphate (mmol/L)

The observed values, changes and percentage change from baseline (both Baseline (402) and Baseline (rhPTH)) in urinary calcium in SI unit (mmol/day) and serum phosphate in SI unit (mmol/L) will be summarized by visit and at EOT, and evaluated graphically using line graph. This analysis will be performed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study. Results from the last 24-hour urine collection obtained in Columbia protocol AAAE0544 will be used as the Baseline (402). By-subject listings will be provided. The summary and figure of urinary calcium and serum phosphate will be repeated in conventional unit (mg/day for urinary calcium and mg/dL for serum phosphate).

11.2.3 Change in Calcium and Active Vitamin D Supplement Doses

Efficacy endpoints based on the calcium and active vitamin D supplement will be derived using both the investigator prescribed data and subject diary data. The prescribed data will be collected in the Concomitant Medications CRF page and subject diary data will be collected in Supplemental Calcium and Active Vitamin D Dosing CRF page. Any medications that are taken in addition to the prescribed dose of calcium and active vitamin D supplement, diary data will be recorded in Supplemental Calcium and Active Vitamin D Dosing CRF page. Analysis based on the investigator prescribed data will be primary. Analysis based on the subject diary data will be considered as supportive.

The daily dose of calcium and active vitamin D supplement based on investigator prescription will be determined by using the latest prescribed dose prior to the target study day for each analysis visit. If no prescribed supplemental was taken on that analysis visit, the prescribed daily dose will be imputed as 0. The prescribed supplemental medication dose at the EOT for subjects who complete the treatment or Early Termination will be excluded from the derivation of the post-baseline prescribed dose.

The average daily dose of calcium and active vitamin D supplement based on subject diaries will be calculated as the average daily dose of a 14-day interval, i.e. total dose of the 14-day interval divided by 14 days. The 14-day interval for each analysis visit includes the dose reported during the 14 days on or prior to the assessment date of ACSC. However, this 14-day interval should not include or go beyond the assessment date of ACSC for the previous analysis visit. Diary data after the last dose date of study drug will be excluded from the derivation. A missing daily dose of calcium and active vitamin D supplement from subject diaries will be imputed as 0 on that date, as the diary data is collected only if a subject took additional calcium/vitamin D than prescribed dose.

The observed values, changes and percentage change from baseline in calcium and active vitamin D supplement will be summarized by visit and at EOT for prescribed daily dose, diary daily dose and total daily dose using Baseline (402), and for prescribed daily dose and total

daily dose using Baseline (rhPTH) too. The daily dose of calcium and active vitamin D supplement will be the sum of the prescribed daily dose of all calcium and all active vitamin D supplement medications respectively. In addition, the similar analysis will be repeated for the elemental calcium daily supplement medications. Change in calcium and active vitamin D supplement doses will be evaluated graphically using line graph. In addition, the frequency of dose change (0, 1-2, 3-5…) in prescribed calcium and active vitamin D supplement due to symptom of low calcium will be presented. By-subject listings will be provided.

11.2.4 Change in HPT symptoms (as measured by the Hypoparathyroidism Symptom Diary (HPT-SD))

The HPT-SD is a 13-item subject-reported outcomes instrument that insists of a symptom subscale (items 1-7, score range 0–4 for item 2-7 and score range 0-10 for item 1), anxiety (item 8, score range 0–4), sadness and depression (item 9, score range 0–4) and impact subscale (items 10-13, score range 0–2). The items 2-9 are reported in a 5-point scale: None (0), Mild (1), Moderate (2), Severe (3), Very severe (4). The item 10-13 are reported in a 3-point scale: Not at all (0), Somewhat (1), Very much (2). The 24-hour recall version of the instrument will be used in this study. The symptom subscale scores will be calculated as average score of the items 1-7 and the impact subscale scores will be calculated as average score of the items 1-13. 5 out of 7 symptom-focused items must be non-missing to compute the HPT-SD symptom score. Subjects must have non-missing responses to all 4 impact items to compute impact-focused subscales score. Individual item score will be examined as well as the scores of symptoms and impact subscales. The HPT-SD was only collected within the SHP634-402 study.

The observed values, changes and percentage change from baseline (Baseline (402)) in symptom subscale (item 1-7), anxiety item (item 8), sadness or depression item (item 9) and impact subscale (items 10-13) will be summarized by visit and at EOT. By-subject listings will be provided.

11.2.5 Change in FACT-Cog (Functional Assessment of Cancer Therapy - Cognitive Function) Assessment (Version 3)

The FACT-Cog assessment is a 37-item tool (Cella 1997) with each item rated on a 5-point scale ranging from 0 to 4. It includes 4 subscales: perceived cognitive impairments (20 items, Item #1 - #20, score range 0–72), impact of perceived cognitive impairments on quality of life (4 items, Item #34 – #37, score range 0–16), comments from others (4 items, Item #21 – #24, score range 0–16) and perceived cognitive ability (9 items, Item #25 - #33 score range 0–28). The item response of each question will be converted as described below to obtain an item score, except for perceived cognitive ability subscale. The subscale score is computed by multiplying the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. The higher the score, the better the quality of life. FACT-Cog was only collected in the SHP634-402 study.

Perceived cognitive impairments subscale (CogPCI):

The 18 items (item #1 - #18) from a total of 20 items in perceived cognitive impairments subscale are used, except for 2 questions, item #19 'I have trouble keeping track of what I am doing if am interrupted' and item #20 'I have trouble shifting back and forth between different activities that require thinking'. Compute the subscale score for the perceived cognitive impairments as follows:

CogPCI Subscale Score= [sum of (18-item response)]*18/ (#of items answered).

Impact on quality of life subscale (CogQOL):

The 4 items (Item #34 – #37) in impact on quality of life subscale are used. Compute the subscale score for the impact on quality of life as follows:

CogQOL Subscale Score = [sum of (4-item response)]*4/ (#of items answered).

Comments from others subscale (CogOth):

The 4 items (Item #21 – #24) in comments from others subscale are used. Compute the subscale score for the comments from others as follows:

CogOth Subscale Score = [sum of (4-item response)]*4/ (#of items answered)

Perceived cognitive ability subscale (CogPCA):

The 7 items (Item #25 - #31) from a total of 9 items in perceived cognitive ability subscale are used, except for 2 questions, item #32 'I am able to shift back and forth between two activities that require thinking' and item #33 'I am able to keep track of what I am doing, even if I am interrupted'. Compute the subscale score for the perceived cognitive ability as follows:

CogPCA Subscale Score = [sum of (7-item response)]*7/ (#of items answered).

The observed values, changes and percentage changes from baseline (Baseline (402)) in 4 subscale scores listed above will be summarized by visit and at EOT. By-subject listings will be provided.

11.2.6 Change in FACIT (Functional Assessment of Chronic Illness Therapy) Fatigue Scale (Version 4)

FACIT fatigue questionnaire contains 13 fatigue-related questions (Cella 1997). The responses to the 13 items on the FACIT fatigue questionnaire are each measured on a 4-point Likert scale (0-4). Thus, the total score ranges from 0 to 52. High scores represent less fatigue and better quality of life.

For 2 questions, item #7 'I have energy' and item #8 'I am able to do my usual activities', the item response from questionnaire will be used as item score and no conversion is needed. For the rest of 11 questions, item score is calculated as 4- item response. Compute the fatigue total score as follows:

Fatigue Total Score = [sum of (item scores)]*13/ (#of items answered).

The observed values, changes and percentage changes from baseline (Baseline (402)) in fatigue total score will be summarized by visit and at EOT. By-subject listings will be provided. FACIT fatigue scale was only collected in the SHP634-402 study.

11.2.7 Change in HADS (Hospital Anxiety and Depression Scale) Assessment

The HADS is a 14-item scale that generates ordinal data (Zigmond and Snaith 1983). Seven of the items relate to anxiety (Item # 1, 3, 5, 7, 9, 11 and13) and seven relate to depression (Item # 2, 4, 6, 8, 10, 12 and 14). The scale is designed to avoid reliance on aspects of conditions that are also common somatic symptoms of illness. Each item on the questionnaire is scored from 0-3 and anxiety or depression scale scores are calculated from the sum of 7 items in each scale, therefore a person can score between 0 and 21 for either anxiety or depression. Data returned from the HADS is ordinal. HADS was only collected in the SHP634-402 study.

The observed values, changes and percentage changes from baseline (Baseline (402)) in depression total score and anxiety total score will be summarized by visit and at EOT. By-subject listings will be provided.

11.2.8 Change in Health-Related Quality-of-Life Measured with RAND SF-36 Survey Over Time (Version 1)

The RAND (Research and Development) SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. The higher the score the less disability i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections included in the RAND SF-36 assessment are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The RAND SF-36 will be scored using the QualityMetric Health Outcomes™ Scoring Software.

The observed values, changes and percentage changes from baseline (both Baseline (402) and Baseline (rhPTH)) in 8 scale scores will be summarized by visit and at EOT. By-subject listings will be provided. This analysis will be performed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study.

11.2.9 Change in Bone Turnover Markers

The observed values, changes and percentage change from baseline (both Baseline (402) and Baseline (rhPTH)) in bone turnover biomarkers (including but not limited to s-CTX, P1NP, osteocalcin, BSAP, TRAP-5b, sclerostin) will be summarized by visit and at EOT. By-subject listings will be provided. Bone turnover markers will be analyzed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study.

11.2.10 Change in Bone Mineral Density

The observed values, changes and percentage changes from baseline (both Baseline (402) and Baseline (rhPTH)) in Dual X-ray Absorptiometry (DXA) bone density results and High Resolution peripheral Quantitative Central Tomography (HRpQCT) results will be summarized by visit and at EOT. For HRpQCT results, bone mineral density from different locations (radius or tibia) will be summarized separately. By-subject listings will be provided. Bone architecture will be analyzed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study.

11.2.11 Change in Bone Histology (Biopsy)

An optional transiliac bone biopsy will be performed for willing subjects, at the discretion of the investigator a maximum of three time during the duration of the study. The observed values, changes and percentage changes from baseline (both Baseline (402) and Baseline (rhPTH)) in bone biopsy results (including but not limited to cancellous bone volume, cortical width, cancellous osteoid surface, cancellous osteoid thickness, cancellous eroded surface, cancellous mineralizing surface, cancellous mineral apposition rate, bone formation rate, and adjusted apposition rate) will be summarized by visit and at EOT. By-subject listings will be provided. Bone histology will be analyzed using Baseline (402) for data from SHP634-402 study and Baseline (rhPTH) for combined data from retrospective data and data from prospective portion of SHP634-402 study. If there is no sufficient data to summarize the change, the bone histology data will be listed only.

11.3 Exploratory Efficacy Endpoint(s) and Analyses

11.3.1 [redacted]

[redacted]

11.3.2 [redacted]

[redacted]

11.3.3 [redacted]

12. SAFETY ANALYSES

12.1 Adverse Events

Adverse events will be coded using Version 19.0 of MedDRA.

Treatment emergent adverse events (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the first dose of rhPTH(I-84) in SHP634-402 study drug and <= 30 days after last dose of study drug. If any AE records contain only partial dates, these will be handled by imputation as described in Section 15.3.

An overall summary of the number of subjects with TEAEs will be presented, including the number of events (except for summaries by highest category), number and percentage of subjects with any TEAEs, treatment-related TEAEs, TEAEs leading to withdrawal, severity of TEAEs (any and highest category), serious TEAE, relationship of serious TEAE to treatment, severity of serious TEAE, and TEAEs leading to death.

The number of events (except for summaries by highest category), number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and maximum severity; by SOC, preferred term, and relationship. TEAE related to investigational product, TEAE leading to withdrawal, SAEs, and deaths will be similarly summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

Listings will be provided for all AE, AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths. Adverse event listings will provide the verbatim term as well as the SOC and PT for each recorded event.

12.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in both SI and conventional units for 24-hour urine parameters and in SI unit for other parameters) and changes from baseline will be reported by visit and at EOT for quantitative parameters. The EOT value will be mapped to the visit windows as specified in Table 2 and summarized under the mapped visit. The EOT values will also be included as a separate time point in the summary. Change will only be reported if both baseline and the corresponding post-baseline time point are available. Additionally, shift tables will be presented, summarizing cross tabulations of low, normal, and high based on the parameter normal range, from baseline to each post-baseline visit and EOT. Percentages for shift tables will be based on the number of subjects with both baseline and post-baseline values at each visit. All the laboratory data below will be listed by parameter, subject and visit. Only scheduled laboratory parameters will be included in the laboratory summaries.

The following clinical laboratory parameters will be summarized, except for the parameters that are separately summarized in efficacy analysis:

Hematology	Hemoglobin, Platelet count, Hematocrit, White blood cell (WBC) count, Red blood cells (RBC), WBC differentials
Clinical chemistry	Sodium, Phosphate, Beta-human chorionic gonadotropin (β-HCG) (baseline only), Potassium, Magnesium, Follicle-stimulating hormone (FSH) (females only at baseline), Blood urea nitrogen (BUN), Total CO_2 (Bicarbonate), Creatinine, Albumin, Calcium, Aspartate transaminase (AST), Chloride, Alanine transaminase (ALT), Thyroid stimulating hormone (TSH) (baseline only), Alkaline phosphatase (ALP), 25-hydroxyvitamin D and 1,25-dihydoxyvitamin D levels, eGFR
Urinalysis	pH, Blood[a], Nitrites, Glucose, Ketones, Leukocyte esterase, Protein, Bilirubin, Specific gravity

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

24-Hour Urine	Calcium, Sodium, Creatinine, Total volume, Phosphate, Magnesium, Creatinine clearance

eGFR

eGFR (mL/min/1.73m^2) will be calculated from serum creatinine using the equation that the CKD-Epidemiology Collaboration group (CKD-EPI) developed and validated in 2009, which is called the CKD-EPI equation (Levey, 2009). The equation is as follows:

$$\text{eGFR} = 141 \times \min(S_{Cr}/k, 1)^{a} \times \max(S_{Cr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times b \times c$$

where S_{Cr} is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of S_{Cr}/k or 1, and max indicates the maximum of S_{Cr}/k or 1, b is 1.018 for females and 1 for males, c is 1.159 for blacks and 1 for others.

Creatinine clearance

Creatinine clearance (mL/min) = [Urine creatinine concentration (mg/dl) * Urine flow rate (L/day)] / Serum creatinine concentration (mg/dl)*1000/1440 (min/day). Then creatinine clearance will be normalized to a body surface area as CrCl * 1.73/BSA. The subject's BSA can be calculated with Dubois formula: $0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$.

Potentially Clinically Important Laboratory Test

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 3. The number and percentage of subjects with post-baseline PCI values will be tabulated. The percentages will be calculated relative to the number

of subjects with at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value.

Table 3 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/L	<=20	>=90
Alkaline Phosphatase	U/L	NA	>2*ULN
ALT	U/L	NA	>3*ULN
AST	U/L	NA	>3*ULN
BUN	mmol/L	NA	>=10.7
Calcium (total)	mmol/L	<=2.1	>=3.0
Chloride	mmol/L	<=80	>=125
Creatinine	µmol/L	NA	>=177
Phosphate	mmol/L	NA	>=2
Potassium	mmol/L	<=2.5	>=6.5
Sodium	mmol/L	<=120	>=165
Hematology			
Hematocrit	L/L	<=0.37 (males) <=0.32 (females)	>0.54 (males) NA (females)
Hemoglobin	g/L	<=115 (males) <=95 (females)	NA
Platelets	10^9/L	<=75	>=700
RBC	10^12/L	<=2.5 (males) <=2.0 (females)	NA
WBC	10^9/L	<=2.8	>=16.0
24-Hour urine			
Urine calcium	mmol/day	NA	>7.5 for men >6.25 for women
Creatinine clearance	ml/min	<=60	NA

12.3 Vital Signs

Descriptive statistics for vital signs (blood pressure, heart rate, body temperature, and respiration rate) and their changes from baseline at each post-baseline visit and at EOT will be presented. The EOT value will be mapped to the visit windows as specified in Table 2 and summarized under the mapped visit. The EOT values will also be included as a separate time point in the summary.

12.4 Physical Examination

Physical examination results will be listed.

12.5 Serum and Urine Pregnancy

Categorical urinalysis findings and urine pregnancy results will be listed only.

12.6 PTH Antibodies

The number and percentage of subjects classified as having antibodies to PTH at each visit and at EOT will be tabulated and listed. The EOT value will be mapped to the visit windows as specified in Table 2 and summarized under the mapped visit. The EOT values will also be included as a separate time point in the summary.

13. COMPUTER METHODS

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

14. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

[redacted] is described in Section 13.3.3.

15. DATA HANDLING CONVENTIONS

15.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers.

For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values, see below:

1. For measures of median and mean, use 1 decimal place beyond those used for the measurement.
2. For measures of standard deviation and standard error, use 2 decimal places beyond those used for the measurement.
3. For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
4. >=5 is rounded up away from zero, whereas <5 is rounded down toward zero to account for rounding of negative numbers.
5. For p-values use 3 decimal places.
6. Presentation of p-values, display p-values that would round to 0.000 as <0.001.
7. BMI should be rounded to 1 decimal place for reporting.
8. Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
9. Averaged laboratory results e.g. Diastolic/Systolic Blood Pressure and Pulse (when taken in triplicate) should be rounded to 1 decimal place for reporting.

15.2 Repeated or Unscheduled Assessments of Safety Parameters

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

15.3 Missing Date Information

Complete dates will be imputed from partial dates of adverse events and medications solely for the purpose of defining treatment emergence for adverse events and prior/concomitant status for medications for data from SHP634-402 study. Dates will be defined using the hierarchy of derivations below.

Adverse event or medication start date:

1. If year and month are known, and it is the month and year of the first dose date, use the first dose date.

2. If year and month are known, and it is the month and year of the informed consent, use the informed consent date.

3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.

4. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.

5. If only year is known, and it is the year of the informed consent, use the informed consent date.

6. If only year is known, and it is after year of the informed consent, use December 31st of that year.

7. Should any of the previous start dates created be after a complete stop date provided, use the stop date instead of the date that would otherwise be created.

8. Otherwise, if start date is unknown leave as missing.

Medication stop date:

1. If year and month are known and study medication stopped during that month and year, use the stop date of study medication.

2. If year and month are known and informed consent was provided during that month and year, use the date of informed consent.

3. If year and month are known and study medication stopped after the date of informed consent and not in the month that medication stopped, use the last day of the month.

4. If year and month are known and are prior to the month of informed consent, use the first day of the month.

5. If only year is known and study medication stopped during that year, use the stop date of study medication.

6. If only year is known and study medication stopped after that year, use December 31stof that year.

7. If only year is known and study medication stopped prior to that year, use the first day of the year.

8. Should any of the previous stop dates created be before a start date, either a complete date or an imputed one, use the (imputed) start date instead of the date that would otherwise be created.

9. Otherwise, if stop date is unknown leave as missing.

For retrospective data, the partial dates from clinical laboratory, RAND SF-36, bone mineral density, bone turnover biomarker and bone histology, the partial dates will be imputed as follows: If only year exist, then impute the missing month and date with ‘July-01’; if year and month exist, then impute the missing day with ‘15’.

15.4 Missing Severity Assessment for Adverse Events

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

15.5 Missing Relationship to Investigation Product for Adverse Events

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

16. REFERENCES

Cella, D. 1997. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system. Evanston, IL: Center on Outcomes, Research and Education (CORE).
Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., Coresh, J. C. I. N. N., Dec, P. C. a. I. M. & Author Reply, P. 2009. A new equation to estimate glomerular filtration rate. Annals of internal medicine, 150, 604-12.
Zigmond, A. S. & Snaith, R. P. 1983. The hospital anxiety and depression scale. Acta Psychiatr Scand, 67, 361-70.