STATISTICAL ANALYSIS PLAN

rhPTH(1-84)
PHASE IV

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

PROTOCOL IDENTIFIER: SHP634-404

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	29 Jul 2020	1. Add post-treatment medication/procedure definition to section 5.5 2. Updated analysis for prior/concomitant medication in section 5.4 and 5.5 3. Remove prior/concomitant therapies from section 5.4 and 5.5 4. Updated section 6.2.5, 6.2.6 and 6.3.4. The missing result will be imputed as 0 for each visit

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ABBREVIATIONS

ACSC	albumin-corrected serum calcium
AE	adverse event
BMI	body mass index
CDK-epi	CKD-epidemiology collaboration group
CI	confidence interval
CRF	case report form
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
EOS	end-of-study
[redacted]	[redacted]
ET	early termination
FSH	follicle stimulating hormone
[redacted]	[redacted]
MedDRA	Medical Dictionary for regulatory activities
PCS	potentially clinically significant
[redacted]	[redacted]
PT	preferred term
PTH	parathyroid hormone
QD	once a day
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
rhPTH(1-84)	recombinant human parathyroid hormone
RBC	red blood cell
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous
SI	système international
SOC	system organ class
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone

ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WHODrug	World Health Organization drug dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides technical details and elaboration of the statistical analyses of efficacy and safety data as described in the study protocol version 1 dated 30 Aug 2017. Specifications for tables, figures, and listings are contained in a separate document.

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.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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.

2.1.2 Secondary Objective(s)

The secondary objective is as follows:

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

2.2 Endpoints

2.2.1 Primary Efficacy Endpoint(s)

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 end-of-treatment (EOT)/early termination (ET) (Visit 9; Week 52).

2.2.2 Secondary Efficacy Endpoint(s)

- Change from baseline in ACSC (Albumin-corrected serum calcium) concentration at Week 24 and 52 (EOT).

- Change from baseline in serum phosphate concentration at Week 4, 8, 16, 24, 32, 40 and 52 (EOT).

- Change from baseline in ACSC-phosphate product at Week 4, 8, 16, 24, 32, 40 and 52 (EOT).

- Change from baseline in 24-hour urine calcium excretion at Week 16, 32 and 52 (EOT).

- Percentage changes from baseline in prescribed supplemental oral calcium dose at Week 4, 8, 16, 24, 32, 40, 52 (EOT) and 56 (EOS).

- Percentage changes from baseline in prescribed supplemental active vitamin D dose at Week 4, 8, 16, 24, 32, 40, 52 (EOT) and 56 (EOS).

- Percentage changes from baseline in markers of bone turnover at Week 8, 24 and 52 (EOT).

2.2.3 Exploratory Endpoint(s)

- [redacted]

[redacted]

2.2.4 Safety Variables

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

3. 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 subcutaneous (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.

- 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 (once a day) 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).

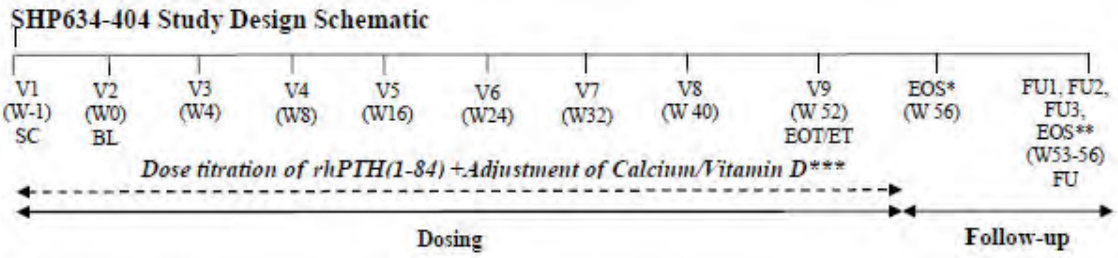
- Within 2-5 days of achieving the maintenance dose the subject should have post-dose ACSC levels measured. The postdose levels should be drawn between 8-12 hours after the investigational product dosing. In general, if postdose ACSC

results are abnormal, the postdose measurements should be repeated within 2-5 days.

3.1 General Description

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. Specific procedures at each study visit are summarized in Table 1.

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/W52) will have an EOS (Visit 10/W56) contact 30 days following the last dose of investigational product.

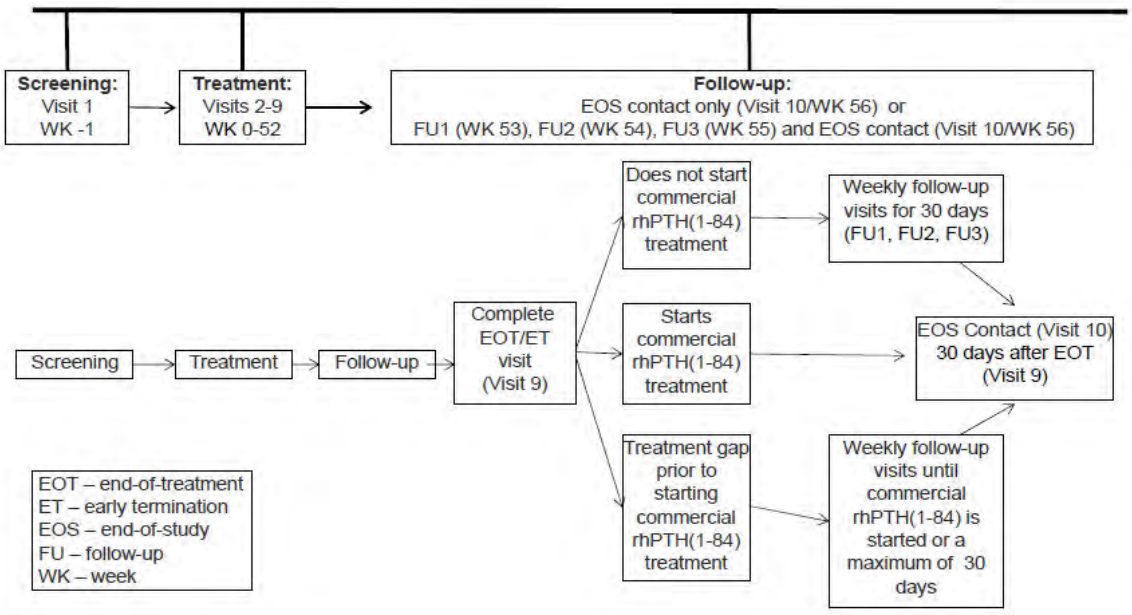
- **Subjects who will not continue on rhPTH(1-84) following the EOT/ET visit (Visit 9) will proceed with weekly follow-up visits (FU1/W53, FU2/W54 and FU3/W55) with serum calcium measurements until a maximum of 30 days has elapsed. All subjects will have an EOS contact (Visit 10/W56) 30 days following 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/W52) will proceed with weekly follow-up visits (FU1/W53, FU2/W54 and FU3/W55), 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/W56) 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 – Weekly follow-up visits (including FU1, FU2 and FU3); SC – Screening; W – Week

Figure 2: Study Design Flow Chart



3.2 Randomization

This is an open-label single arm study. Randomization is not applicable for this study.

3.3 Blinding

This is an open-label single arm study. Blinding is not applicable for this study.

3.4 Sample Size 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.

3.5 Schedule of Assessments

Table 1 Schedule of Assessment

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	

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[j]	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]; 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 Protocol 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 collecting the ECG.
[f] See Protocol 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 Protocol Section 4.4.1 for definition of postmenopausal).
[m] 24-hour urine collection includes the parameters specified in Protocol 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 Protocol Section 7.2.4.4 for additional details related to the assessment of vital signs.

[c] See Protocol 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.

4. STATISTICAL ANALYSIS SETS

4.1 Enrolled Set

Enrolled Set consists of all subjects who have signed informed consent excluding screen failures.

4.2 Safety Population

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

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A listing of all Screen Failures will be presented along with reasons for screen fail and details of any AEs. The listing will include the first screening data for re-screened subjects.

The number of subjects who were included in and excluded from each defined analysis set (i.e., Screened, Enrolled and Safety) will be summarized.

The number and percentage of subjects who completed and prematurely discontinued from the study and treatment will be presented. The study completion includes the completion of final protocol-defined assessment and follow-up visit or contact. Reasons for premature discontinuation from study as recorded on the study completion page of the electronic case report form (eCRF) will be summarized (number and percentage). All subjects who prematurely discontinued will be listed by discontinuation reason for Enrolled Set.

The number of subjects enrolled and completed will be tabulated by site and country. In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented. 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.

The following demographic characteristics will be summarized in the following order in the tables: age (years), age (categorical), sex, ethnicity, race, weight (kg), height (cm), and BMI (kg/m^2).

Age = (date of screening visit – date of birth+1)/365.25.

BMI = weight (kg)/(height (m))^2.

5.3 Medical History

Medical history will be collected at the Screening Visit (Visit 1) and will be coded using Medical Dictionary of Regulatory Activities (MedDRA) Version 20.1. A listing will be provided using the Safety Population.

The medical history will be summarized by system organ class (SOC) and preferred term (PT).

5.4 Prior Procedures and Medications

Prior medications will be coded using the World Health Organization Drug Dictionary (WHODrug) dated Sep 2017. Prior procedures will be coded using MedDRA Version 20.1.

Prior medication (procedures) is defined as any medication (procedures) with the start date prior to the date of the first dose of investigational product in SHP634-404.

The prior procedures will be summarized by the number and proportion of subjects within each preferred term and the prior medication usage will be summarized by the number and proportion of subjects within each therapeutic class and preferred term. Multiple medication usage by a subject in the same category will be counted only once.

All prior procedures and medication will be listed for the Safety Population.

5.5 Concomitant/Post-Treatment Procedures and Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) dated Sep 2017. Concomitant procedures will be coded using MedDRA Version 20.1.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product in SHP634-404 and continuing after the first dose of investigational product in SHP634-404 or with a start date between the dates of the first and last doses of investigational product, inclusive. Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of investigational product, inclusive. Any medication (procedure) with a start date after the date of the last dose of investigational product will not be considered a concomitant medication (procedure).

Post-Treatment medication (procedure) is defined as any medication (procedure) with a start date after the last dose of investigational product in SHP634-404. Post-Treatment (procedure) medication will be flagged in the listings only.

The concomitant procedure will be summarized by the number and proportion of subjects within each preferred term and the concomitant medication usage will be summarized by the number and proportion of subjects within each therapeutic class and preferred term.. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant and post-treatment procedures and medication will be listed for the Safety Population.

5.6 Exposure to Investigational Product

Exposure to investigational product will be summarized in terms of treatment duration in weeks, which is calculated as (date of the last dose of investigational product taken - date of first dose of investigational product taken in SHP634-404 + 1)/7. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented to describe the exposure to investigational product.

Exposure and dispense/account information will be listed for each subject.

5.7 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database and also be defined as major or minor.

Protocol deviations will be summarized by site and category. A complete listing will also be provided for all protocol deviations.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the Safety Population unless stated otherwise. Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product in SHP634-404 (based on dates or date/times). For early terminated subjects, the End of Treatment (EOT) measurements are presented at Week 52 (EOT).

Descriptive statistics will be used with a goal of summarizing the sample population. 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.

6.1 Analyses of Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the subject response satisfying total serum calcium (albumin-corrected) values in the range of 7.5 mg/dL (1.875 mmol/L)-ULN at Week 24 and at Week 52 (EOT). 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 (upper limit of normal) will be provided.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoint(s)

NA

6.1.2 Supplementary Analyses of Primary Efficacy Endpoint(s)

NA

6.2 Analyses of Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints will be summarized with descriptive statistics at each scheduled visit.

6.2.1 Change from baseline in Albumin-corrected Serum Calcium (mmol/L) concentration

The observed values, changes and percentage changes from baseline in Albumin-corrected Serum Calcium in SI unit (mmol/L) will be summarized at Screening, Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT). The ACSC 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).

6.2.2 Change from baseline in serum phosphate concentration (mmol/L)

The observed values, changes and percentage changes from baseline in serum phosphate (mmol/L) will be summarized at Screening, Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT). The serum phosphate over time will also be evaluated graphically using line graph. By-subject listings will be provided.

The proportion and 95% confidence interval (CI) of subjects with serum phosphate concentration (mmol/L) within the normal range will be provided at Screening, Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT) .

6.2.3 Change from baseline in ACSC-phosphate product ($mmol^2/L^2$)

The observed values, changes and percentage changes from baseline in ACSC-phosphate product will be summarized at Screening, Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT). The ACSC-phosphate product over time will also be evaluated graphically using line graph. By-subject listings will be provided.

ACSC-phosphate product will be calculated as ACSC (mmol/L)* serum phosphate (mmol/L).

6.2.4 Change from baseline in 24-hour urine calcium excretion

The observed values, changes and percentage change from baseline in urinary calcium in SI unit (mmol/day) will be summarized at Week 0, 16, 32 and 52 (EOT). The urinary calcium over time will also be evaluated graphically using line graph. By-subject listings will be provided. The summary and figure of urinary calcium will be repeated in conventional unit (mg/day).

6.2.5 Percentage changes from baseline in prescribed supplemental oral calcium dose (mg)

Subjects enrolled in this study may be taking oral calcium supplements (either calcium carbonate or calcium citrate). The prescribed data will be collected in the Concomitant Medications CRF page. The daily dose of calcium supplement based on investigator prescription will be determined by the latest prescribed dose prior to each visit. In addition, the last actual dose taken prior to the site visit will be recorded in the Calcium and Vitamin D – Last Dose CRF page in the form of elemental calcium. The observed values, changes and percentage change from baseline in prescribed supplemental oral calcium dose will be summarized at Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT). The dose of calcium supplement will be the sum of the prescribed daily dose of all calcium

supplement medications. The similar analysis will be repeated for the elemental calcium daily supplement medications for both prescribed calcium daily dose and the last actual dose of calcium taken prior to each site visit. If no prescribed supplemental calcium was taken on that analysis visit, the prescribed and actual daily dose will be imputed as 0. By-subject listings will be provided.

6.2.6 Percentage changes from baseline in prescribed supplemental active vitamin D dose (mcg)

Subjects with serum 25(OH) vitamin D levels below the upper limit of normal for the laboratory at screening will take vitamin D to reach levels within the range of ≥30 ng/mL and ≤ the upper limit of normal (ULN) and to maintain serum 25(OH) vitamin D level in this range throughout the study. The prescribed data will be collected in the Concomitant Medications CRF page. The daily dose of active vitamin D supplement based on investigator prescription will be determined by the latest prescribed dose prior to each visit. In addition, the last actual dose taken prior to the site visit will be recorded in the Calcium and Vitamin D – Last Dose CRF page. The observed values, changes and percentage change from baseline in prescribed supplemental active vitamin D dose will be summarized at Week 0, 4, 8, 16, 24, 32, 40 and 52 (EOT) . The dose of active vitamin D supplement will be the sum of the prescribed daily dose of all active vitamin D supplement medications. The similar analysis will be repeated for the last actual dose of calcium taken prior to each site visit. If no prescribed supplemental vitamin D was taken on that analysis visit, the prescribed and actual daily dose will be imputed as 0. By-subject listings will be provided.

6.2.7 Percentage changes from baseline in markers of bone turnover

Bone turnover markers will include, but are not limited to, serum bone-specific alkaline phosphatase, urine procollagen Type I N terminal propeptide, serum C-terminal telopeptide of type 1 collagen, urine N-terminal telopeptide of type 1 collagen, and total serum osteocalcin. The observed values, changes and percentage change from baseline in bone turnover biomarkers will be summarized at Week 0, 8, 24 and 52 (EOT). By-subject listings will be provided.

6.3 Analyses of Exploratory Endpoint(s)

[redacted]

[redacted]

[redacted]

[redacted]

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Population. Safety variables include TEAEs, clinical laboratory variables, vital signs, ECG variables and PTH antibodies. For each safety variable, the last value collected before the first dose of investigational product in SHP634-404 will be used as baseline for all analyses of that safety variable.

7.1 Adverse Events

Adverse events will be coded using MedDRA Version 21.0 or latest.

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it has a start date on or after the first dose of investigational product in SHP634-404 or if it has a start date before the date of the first dose of investigational product in SHP634-404, but increases in severity on or after the date of the first dose of investigational product in SHP634-404. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, Hypocalcemic AEs, TEAEs related to investigational product and TEAEs leading to withdrawal, severity of serious TEAE, and deaths will be similarly summarized.
The number and percentage of subjects reporting TEAEs, as well as the number of events will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and maximum severity, by SOC, preferred term, and relationship. If more than 1 TEAE 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. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence. TEAEs related to investigational product, TEAEs leading to withdrawal, serious TEAEs and serious TEAEs leading to death, will be

summarized by SOC and preferred term. Listings will be provided for all AE, AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths. The number and percentage of subjects and events of hypocalcemia AEs reported in the study will be summarized by the following prespecified categories and preferred term: Severe hypocalcemia, Self-treated hypocalcemia, Mild to moderate hypocalcemia other than self-treated. Adverse event listings will provide the verbatim term as well as the SOC and PT for each recorded event.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory and changes from baseline at each assessment time point as well as shift tables from baseline to each scheduled visit for quantitative variables will be presented for the following clinical laboratory variables. 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.

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell (WBC) count and automatic differential.

Serum chemistry 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, Thyroid-stimulating hormone (TSH), follicle stimulating hormone (FSH), Estimated creatinine clearance, eGFR(using the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] equation).

Urine chemistry Ammonium, Calcium, Chloride, Citrate, Creatinine, Magnesium, Oxalate, pH, Phosphate, Potassium, Sodium, Sulfate, Urea nitrogen, Uric acid, and total volume of the 24-hour urine collections.

Urinalysis pH, Glucose, Protein, Blood, Ketones, Bilirubin, Leukocyte esterase, Specific gravity.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 3. PCS values will be flagged in the

by–subject laboratory listings. All laboratory data, including pregnancy testing results will be listed for the Safety Population.

Table 3: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
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
Chloride	mmol/L	<=80	>=125
Creatinine	µmol/L	NA	>=177
Creatinine clearance	ml/min	<=60	NA
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

7.3 Vital Signs

Descriptive statistics for vital signs (height, weight, temperature, pulse rate, respiration rate, systolic and diastolic blood pressure) and their changes from baseline at each post-baseline visit and at the end of study will be presented.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline criteria listed in Table 4. PCS values will be flagged in the by – subject vital sign listing. All vital signs data will be listed for the Safety Population.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
	High	≥180	Increase of ≥20

Systolic blood pressure (mmHg)	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse (bpm)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15
Temperature (°C)	High	≥38.3	Increase of ≥0.8
	Low	-	-

[a] post-baseline value is considered as a PCS value if it meets both criteria for observed value and change from baseline.

7.4 Electrocardiogram (ECG)

For triplicate ECGs, the average value will be used. Descriptive statistics for ECG variables (eg, heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula. ECG interpretation will be summarized by visit. A shift table from baseline to each scheduled visit for qualitative ECG results will be presented.

Electrocardiogram variable values will be considered PCS if they meet or exceed the upper limit values listed in Table 5. PCS values will be flagged in the by – subject ECG listing.

Table 5: Criteria for Potentially Clinically Significant ECG Values

ECG Parameter	Unit	Higher Limit
QRS Interval	msec	≥150
PR Interval	msec	≥250
QTc Interval	msec	≥500

7.5 Estimated Glomerular Filtration rate (eGFR) (ml/min/1.73m^2) and Serum Creatinine (µmol/L)

Estimated glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-epi] equation) will be calculated by the central laboratory. Descriptive statistics for eGFR and serum creatinine and changes from baseline at each assessment time point will be tabulated similar to other clinical laboratory parameters.

7.6 PTH Antibodies

The number and percentage of subjects classified as having antibodies to PTH at each scheduled visit will be tabulated and listed.

8. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

N.A.

9. DATA HANDLING CONVENTIONS

9.1 General Data Reporting Conventions

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.

See Shire TFL Standards for rules on the number of decimal places to present data and p-values.

9.2 Definition of Baseline

Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product in SHP634-404 (based on dates or date/times).

9.3 Definition of Visit Windows

Assessments will be assigned to visits based on the completed CRF page.

9.4 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 is 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 PCS value determination and all assessments will be presented in the data listings.

9.5 Handling of Missing, Unused, and Spurious Data

9.5.1 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Population, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

9.5.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

9.5.2.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

9.5.2.1.1 Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

9.5.2.1.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

9.5.2.1.3 Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date

of the first dose of investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

9.5.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

9.5.2.2.1 Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

9.5.2.2.2 Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

9.5.2.2.3 Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

9.5.3 Missing Date Information for Adverse Events

For AEs, the start dates will be imputed following the same rules as in Section 9.5.2. Adverse events with completely missing onset dates and a stop date after the date of first dose (or unknown stop date) will also be considered treatment-emergent.

9.5.4 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 both the actual and the imputed values will be used in data listings.

9.5.5 Missing Relationship to Investigational 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 investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.5.6 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

Table 6: Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0
Chemistry: AST	<5	0
Chemistry: Total Bilirubin	<2	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0

10. ANALYSIS SOFTWARE

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

11. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

N.A.

12. REFERENCES

[redacted]