STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP634-101
Protocol Title:	An Open-Label, Randomized, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Profiles of Once-Daily and Twice-Daily Dose Regimens of recombinant human Parathyroid Hormone (rhPTH[1-84]) Administered Subcutaneously to Subjects with Hypoparathyroidism.
Drug:	rhPTH(1-84)
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
Version No. and Date	Version 2.0, Date 16 May 2019

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ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BID	twice-daily
BMI	body mass index
CRC	clinical research centre
DMC	data monitoring committee
eCRF	electronic case report form
ECG	electrocardiogram
PCI	potentially clinically important
QD	once-daily
QRS	a time interval on an ECG trace that represents the depolarization of the ventricles
QT	a time interval on an ECG trace starting at the beginning of the QRS complex and finishing at the end of the T-wave (represents the time taken for the ventricles to depolarize & then repolarize)
QTcB	the QT interval on an ECG trace that has been corrected using Bazett's formula
QTcF	the QT interval on an ECG trace that has been corrected using Fridericia's formula
rhPTH(1-84)	recombinant human parathyroid hormone (1-84 amino acids)
RR	a time interval on an ECG trace starting at the peak of one R wave to the peak of the next R wave
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	system organ class
TEAE	treatment-emergent adverse event

1. Introduction

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic and pharmacodynamic data as described in the study protocol amendment 5 dated 18 Jun 2018. Specifications for tables, figures, and listings are contained in a separate document. Statistical analyses for pharmacokinetic/pharmacodynamic data are included in the SAP, as appropriate.

2. STUDY DESIGN

2.1 General Study Design

This study is an open-label, randomized, multi-center, 4 cohort, 2-period crossover study to characterize the effects of QD and BID dosing regimens of rhPTH(1-84) and the effect of adjunctive calcium (with no active vitamin D) in male and female adult subjects with a history of hypoparathyroidism for at least 12 months, post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia and serum intact PTH concentrations below the lower limit of the laboratory normal reference range as well as a requirement for both supplemental oral calcium ≥ 1000 mg/day and therapy with active forms of vitamin D at a minimum dose of ≥ 0.25 µg/day (i.e., 0.25 µg calcitriol or equivalent per day).

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

The treatment sequence assignments within each cohort are as follows:

Table 1: Treatment Scheme

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

BID=twice-daily; QD=once-daily; N= 32 subjects

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

Replacement subjects may be enrolled in the event that any subject does not complete each treatment (which would include the crossover dose) or have major protocol deviations such as not meeting inclusion/exclusion criteria. Replacement subjects may be enrolled on a case-by-case basis (as a subject is discontinued), and, if a subject is replaced, that subject will follow the same 2-period treatment sequence as the subject who discontinued (regardless of when the subject discontinued).

This study will consist of the Administrative Screening Period (within 120 days of Day 1 of Period 1) that includes the time required to authorize release and obtain medical records for subjects participating at sites outside their immediate care network (if applicable); the Clinical Screening Period;, 2 treatment periods which are to be separated by a washout (≥5 days but ≤30 days) between the dose or first dose of investigational product in each period (for QD or BID

dosing, respectively), and a follow-up visit (30±2 days after the last dose of investigational product is administered). The maximal total duration of study participation for a subject is 90 days (~3 months), if the maximum clinical screening, washout and follow-up visit durations are used. If the Administrative Screening Period is required, the maximum duration of study participation is 182 days.

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

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

Potentially eligible subjects who continue to meet all inclusion/exclusion criteria, but are unable to participate in the study due either to scheduling conflicts/timing (including the time required to obtain medical records release, if applicable) or appropriate slot availability at an investigational site, may be rescreened based on investigator discretion and sponsor approval should their availability to participate fall outside the screening window.

In these cases, a new screening number must be assigned for each subject who is rescreened and a new informed consent form must besigned. Number of screened subjects will reflect the number of unique subjects, rather than the number of unique screening IDs.

On Day 1 of Treatment Period 1:

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

On Day 1 of Treatment Period 2, subjects will receive the alternative treatment (according to the randomization schedule), following a washout period (≥5 days [ie, 120 hours] and ≤30 days) between administration of the dose or first dose ([for once-daily or twice-daily dosing,

respectively] of each treatment period). All investigational products will be administered via SC injection into alternating thighs at each administration.

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

For once-daily treatments (Treatments B and E), subjects will receive a single subcutaneous dose of rhPTH(1-84) in the morning on Day 1. For twice-daily treatments (Treatments A, C, D, and F), subjects will receive a subcutaneous dose of rhPTH(1-84) in the morning followed by the second dose 12 hours later on Day 1 (in the opposite thigh). If randomized to rhPTH(1-84) with calcium, subjects will take their supplemental oral calcium within 30 minutes prior to first dose administration. Prior to discharge from the CRC at each treatment period, subjects will be given specific instructions for when to resume taking their supplemental oral calcium and active vitamin D supplements during the day(s) when subjects are not in the CRC.

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

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

During Treatments D, E and F, subjects will take their usual dose of supplemental oral calcium (but withhold active vitamin D) in the morning on Day 1, prior to investigational product administration. On Day 2, following the completion of all study procedures, subjects will then re-start their active vitamin D at their next usual daily schedule.

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

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

For all dosing regimens, rhPTH(1-84) will be administered in the morning of Day 1 of each treatment period following an overnight fast of at least 8 hours. Subjects will continue to fast

until approximately 2 hours after rhPTH(1-84) administration, at which time a standardized meal will be served. For subjects assigned to the twice-daily dose regimen, the evening dose of investigational product will be administered 12 hours after the morning dose, and 2 hours prior to the evening meal. A snack or light meal may be provided to the subjects prior to the evening dose provided it is consumed ≥2 hours prior to investigational product dose administration.

Serial blood samples for pharmacokinetic analysis will be collected on Day 1 of each treatment period for the determination of PTH concentrations at pre-dose and up to 24 hours post morning dose (up to 24 hours post second dose for the twice-daily regimen). These blood samples will be collected according to the Schedule of Assessments (Table 3 and Table 4). Serial blood and urine samples for pharmacodynamic analysis will be collected on Day -1, pre-dose and on Day 1 following the administration of rhPTH(1-84) for the determination of concentrations of serum total calcium (uncorrected and corrected for serum albumin levels), phosphate, magnesium, creatinine, albumin, $1,25(OH)_2D_3$, and fibroblast growth factor 23 (FGF23), and urinary excretion of calcium, sodium, citrate, phosphate, cAMP, magnesium, and creatinine and the calcium-phosphate product will be determined. In addition, serum samples will be collected and analyzed for anti-PTH antibodies (for safety purposes) at the time points specified in **Error! Reference source not found.**, Table 3, and Table 4. Samples will be analyzed using a validated methodology

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

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

Figure 1: Study Design Flow Chart

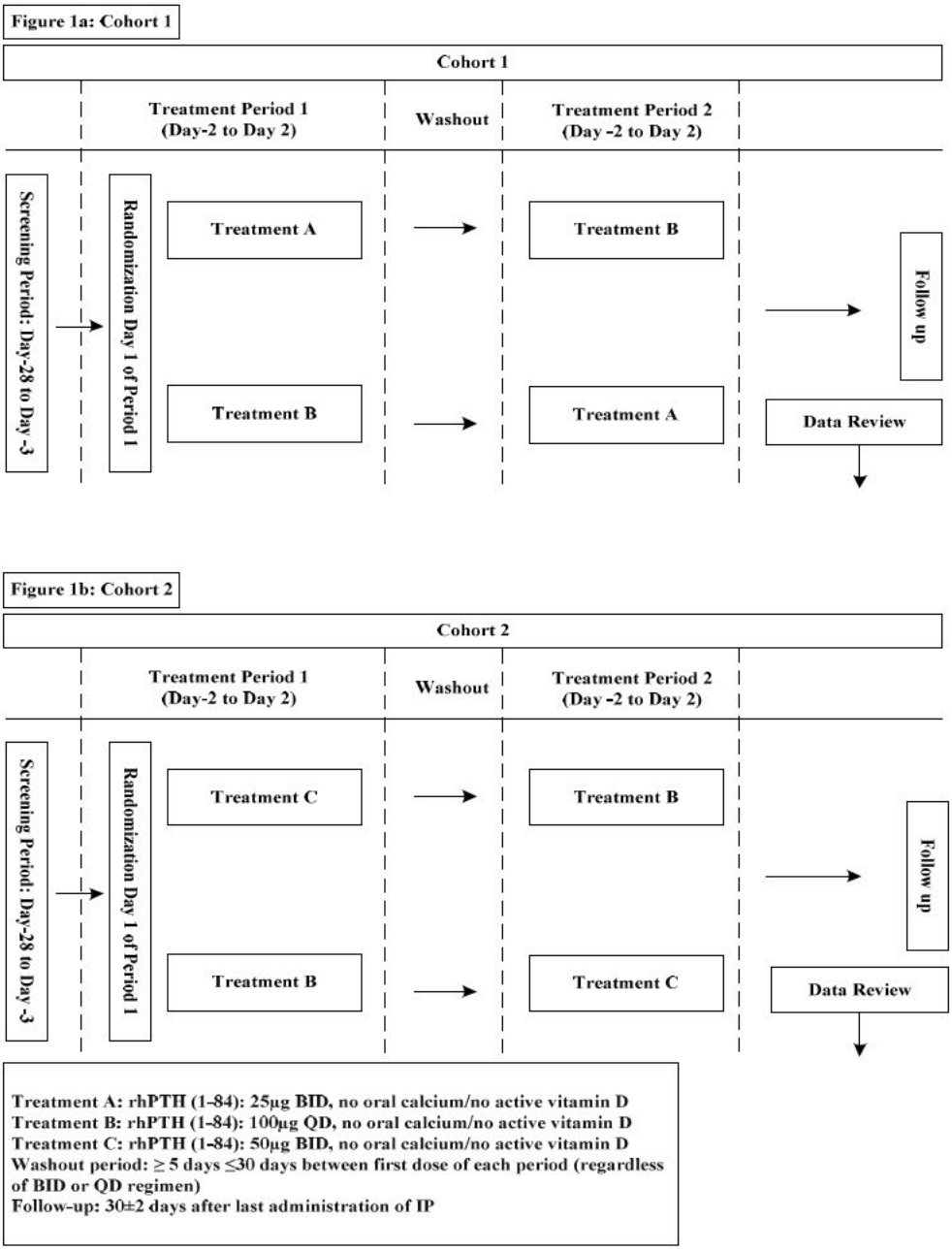


Figure 1c: Cohort 3

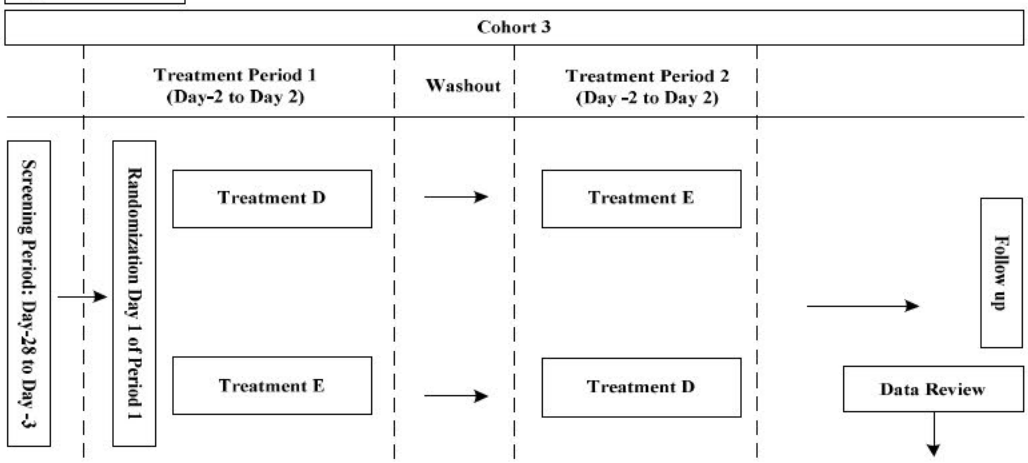
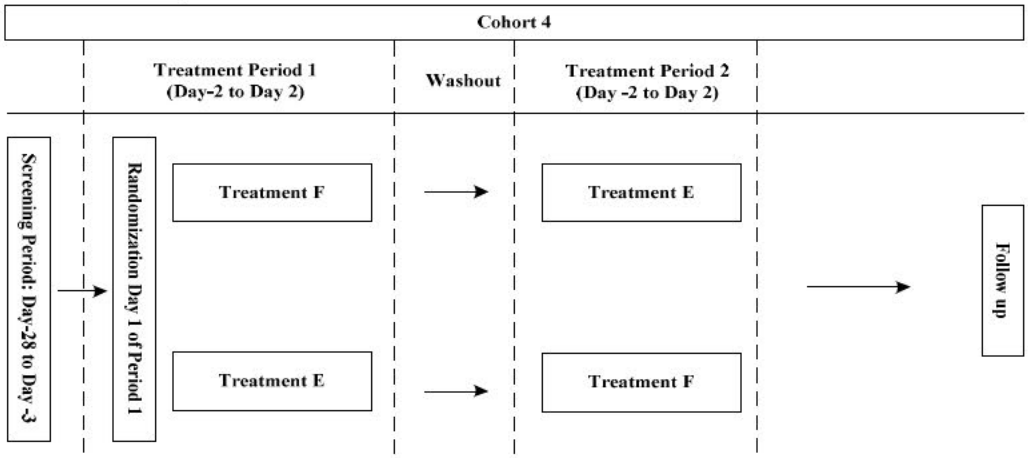


Figure 1d: Cohort 4



Treatment D: rhPTH (1-84): 25µg BID, with oral calcium/no active vitamin D
Treatment E: rhPTH (1-84): 100µg QD, with oral calcium/no active vitamin D
Treatment F: rhPTH (1-84): 50µg BID, with oral calcium/no active vitamin D
Washout period: ≥ 5 days ≤30 days between first dose of each period (regardless of BID or QD regimen)
Follow-up: 30±2 days after last administration of IP

2.2 Randomization

This is an open label, randomized, study. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting at 0001.

For screen failures, the screening number will be the identifying number used throughout the CRF.

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

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

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

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

2.3 Blinding

This is an open-label study, and, as such, there are no special handling considerations for blinded data.

2.4 Schedule of Assessments

STUDY SCHEDULE(S)

Table 2: Schedule of Assessments

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

Table 2: Schedule of Assessments

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

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Table 2: Schedule of Assessments

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

[a] Washout period should be ≥5 days (ie, 120 hours) and ≤30 days between first dose of each treatment period (whether dosing regimen is BID or QD).
[b] The investigator may elect to keep the subject in-clinic for the duration of the study, if the washout period is short (eg, 120-172 hours) and/or there are any safety concerns, and provided that there is a minimum washout of ≥120 hours between administration of IP in each treatment period.
[c] A follow-up visit must be completed 30±2 days after the last dose of IP.
[d] If applicable.
[e] Review and update medical history and re-confirm eligibility.
[f] In the event a subject is prematurely discontinued from the study, every attempt should be made to complete these assessments.
[g] The safety blood and urine assessments (Period 1 and Period 2), pregnancy test (for all females, Period 2), physical exam (Period 2), and weight (Period 2) should be collected after the scheduled serial PK and PD assessments have been completed on this study day, and prior to discharging the subject from the Clinical Research Center.
[h] Randomization will occur prior to administration of IP at Treatment Period 1, Day 1 only after all eligibility criteria have been confirmed/re-confirmed.
[i] Vital sign measurements should be collected in the supine position at each time point.
[j] See **Error! Not a valid bookmark self-reference.**, Table 3, and Table 4 for detailed collection time points.
[k] Weight measurement only.
[l] ECGs will be performed in triplicate measurement at each time point.
[m] Includes thyroid function tests, and estimated creatinine clearance (Cockcroft–Gault formula) at Clinical screening visit only.
[n] Serum β-HCG test at Screening is required for all females. Urine pregnancy test is required for all females at subsequent scheduled time points.
[o] Females only, to confirm menopausal status.
[p] At the end of the Clinical Screening Visit, subjects will be provided with a urine collection container to take home. Subjects will be given instructions to provide a 24-hour urine collection starting anytime during the Clinical Screening Period, but prior to their next admission to the CRC (eg, Day -3 and ending 24 hours later on Day -2). The sample must

Table 2: Schedule of Assessments

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

be kept in cold conditions (~4°C) and returned to the CRC upon collection, as per the instructions provided by the site.

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

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

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

[t] Supplemental oral calcium and active vitamin D will be withheld starting on day of dosing, and through the end of Day 1. Subjects will then resume their usual supplemental oral calcium and active vitamin D at their next usual daily schedule on Day 2.

[u] Applies to subjects assigned to Treatment D, Treatment E and Treatment F only.

[v] Supplemental oral calcium should be taken according to the subject's usual daily regimen (but active vitamin D must be withheld).

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

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

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

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.
[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.
[c] These assessments should be performed within 30 minutes prior to the relative time of scheduled administration of IP on Day 1.
[d] Refer to Detailed Schedule of Assessments (Table 3 and Table 4) for collection time points (note: this time point is the same as the pre-dose collection time point on Day 1.
[e] ECGs will be performed in triplicate measurement at each time point.
[f] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.
[g] 24- hour urine collection for PD analysis will be collected according to the following collection intervals (relative to the Day 1 morning dose): pre-dose, 0-3 hours, 3-6 hours, 6-9 hours, 9-12 hours, 12-15 hours, 15-18 hours, 18-24 hours. 'X' denotes the start and stop of the entire urine collection period and '→' denotes continuous collection.
[h] PD urine collection assessments will include: calcium, sodium, citrate, phosphate, magnesium, cAMP and creatinine.
[i] The predose timepoint for PD urine sampling is used to signify the action that the subject needs to empty his/her bladder immediately before the start of the 0-3 urine collection based on the predicted dosing time of Day 1. It is not a separate pre-dose urine collection.

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

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

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.
[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.
[c] These assessments should be performed within 30 minutes prior to the scheduled time for IP dose administration on Day 1.
[d] ECGs will be performed in triplicate measurement at each time point.
[e] Randomization will occur prior to administration of IP of Treatment Period 1, Day 1 only (and only after all eligibility criteria have been confirmed/re-confirmed).
[f] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.
[g] The anti-PTH antibody sample should only be collected at Treatment Period 1, pre-dose (regardless of BID or QD regimen), and the sample collected within 30 mins prior to dosing.
[h] 24- hour urine collection for PD analysis will be collected according to the following collection intervals: 0-3 hours, 3-6 hours, 6-9 hours, 9-12 hours, 12-15 hours, 15-18 hours, 18-24 hours. 'X' denotes the start and stop of the entire urine collection period and '→' denotes continuous collection.
PD urine collection assessments will include: calcium, sodium, citrate, phosphate, magnesium, cAMP and creatinine.
[j] The last scheduled serial timepoint (i.e., 24 hours) will also serve as the discharge procedure for these assessments on Day 2.
[k] The urine sampling under pre-dose in this table is to signify the stop of Day -1, 18-24 hour PD urine collection period, and the start of the Day 1, 0-3 hour PD urine collection period. It is <u>not</u> a separate pre-dose collection.

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

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

[a] An attempt to perform these assessments and procedures should be made for any subject who withdraws or is removed from the study.
[b] Vital signs should be collected in the supine position at each time point. Subject should also be supine at least 5 minutes prior to vitals collection. Vital signs include blood pressure and pulse.
[c] These assessments should be performed within 30 minutes prior to the scheduled time for IP dose administration on Day 1.
[d] ECGs will be performed in triplicate measurement at each time point.
[e] Randomization will occur prior to administration of IP of Treatment Period 1, Day 1 only (and only after all eligibility criteria have been confirmed/re-confirmed).
[f] Pre-dose PK/PD collection for the second dose of the BID regimen should be completed within 15 minutes prior to the dose.
[g] PD blood sampling assessments will include: total serum calcium, magnesium, phosphate, albumin, creatinine, 1,25-dihyroxyvitamin D, and FGF23.
[h] The anti-PTH antibody sample should only be collected at Treatment Period 1, pre-dose (regardless of BID or QD regimen), and the sample collected within 30 mins prior to dosing.

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

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

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

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

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

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

2.5 Determination of Sample Size

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

2.6 Multiplicity Adjustments for Type I Error Control

Not applicable, as the statistical analyses are primarily descriptive with no hypothesis testing.

3. OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

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

4. SUBJECT POPULATION SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

4.2 All-Enrolled Set

The All-Enrolled Set consists of all subjects who sign the informed consent form and are randomized in the study.

4.3 Safety Analysis Set

The Safety Analysis Set includes enrolled subjects who have received at least 1 dose of rhPTH(1-84). All analyses of safety data will be based on this population.

4.4 Pharmacokinetic Set

The Pharmacokinetic Analysis Set consists of all enrolled subjects who do not have major protocol violations that affect the validity of the PK results, receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacokinetic concentration value available for 1 dose regimen. Subjects who do not meet the inclusion criterion for hypoparathyroidism will be excluded from the PK set. A listing of subjects excluded from the PK Set along with the reason for exclusion is to be generated. In the event of dosing error, proven or suspected based on PK data (extremely low post-dose PTH concentrations), PK data from the subject for the specific treatment period will be excluded from summary tables and figures. A listing of excluded PK data along with reason for exclusion will be generated.

4.5 Pharmacodynamic Set

The Pharmacodynamic Analysis Set consists of all enrolled subjects who do not have major protocol violations that affect the validity of the PD results, receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacodynamic value available for 1 dose regimen. Subjects who do not meet the inclusion criterion for hypoparathyroidism will be excluded from the PD set. A listing of subjects excluded from the PD Set along with the reason for exclusion is to be generated. In the event of dosing error, proven or suspected based on PK data (extremely low post-dose PTH concentrations), PD data from the subject for the specific treatment period will be excluded. During treatments A, B, and C, if a subject takes supplemental oral calcium/active vitamin D within 24 hours post the last rhPTH(1-84) dose, PD data from the subject for the specific treatment period will be excluded from summary tables and figures. A listing of excluded PD data along with the reason for exclusion will be generated.

5. SUBJECT DISPOSITION

A listing of all Screen Failures (ie, subjects who were screened but not randomized) will be presented along with reasons for screen fail and details of any AEs. Final subject numbers will be presented for subjects that had been re-screened.

The number of subjects included in each subject population set (ie, Screened, All-Enrolled, Safety, Pharmacokinetic, and Pharmacodynamic) will be summarized by treatment sequence, and by treatment.

For the summary by treatment sequence, the numbers and percentages of subjects who either completed or prematurely discontinued during the study will be presented for each treatment sequence and overall for the Safety Analysis Set. Reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) for each period (Period 1, Washout, Period 2, and Follow-up) by treatment sequence and overall for the Safety Analysis Set.

A similar summary table will be presented for the summary by treatment, with number and percentage of subjects who discontinued during that treatment period for the Safety Analysis Set.

All subjects who prematurely discontinued during the study period will be listed by discontinuation reason for the All-Enrolled Set.

6. PROTOCOL DEVIATIONS

A summary of the number and percentage of subjects in the All-Enrolled Set with protocol violations or deviations will be produced.

All protocol violation and deviation data will be listed for the All-Enrolled Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by treatment sequence and overall for the Safety Analysis Set.

The following demographic characteristics will be summarized in the following order in the tables: age, sex, ethnicity, race, weight, height, BMI, and BMI category (Underweight [<18.5 kg/m^2], Normal [18.5 to 24.99 kg/m^2], Overweight [25.0 to 29.99 kg/m^2], Obese [≥ 30.0 kg/m^2], Missing). In addition, other baseline characteristics will be summarized.

Height and weight at screening will be used to calculate BMI using the formula below:

$$\text{BMI} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

A listing will be created to show all the demographics and baseline characteristics for each enrolled subject.

A table for Parathyroid History will summarize the last record of active vitamin D or calcium supplementation prior to study medication. The dose of active vitamin D will be categorized as low (0-0.25 µg/day), medium (>0.25-0.5 µg/day) or high (>0.5 µg/day), and the dose of calcium supplementation will be categorized as 0-2000 mg/day or >2000 mg/day. The number and percentage of subjects in each category will be presented. Duration of hypoparathyroidism will be calculated from the date of informed consent and onset of hypoparathyroidism obtained from the medical history page. This will be summarized using standard summary statistics and also by number and percent of subjects in the categories <=5 years, >5-10 years, and >10 years.

Medical history will be coded using MedDRA version 19.0 or newer, and summarized by system organ class (SOC), preferred term (PT), and treatment sequence. Medical history will be listed for the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

A summary table showing number of subjects exposed and number of administrations received will be produced by period, overall and treatment for the Safety Analysis Set.

A listing will be created by subject number and visit giving the date and time of dose administration, for the Safety Analysis Set.

8.2 Measurement of Treatment Compliance

Since this is a Phase 1 study in which the study medication is administered at the Clinical Research Center (CRC), no summary of treatment compliance will be produced.

9. PRIOR AND CONCOMITANT MEDICATION

Version 2016MARDD (Basic) or newer of the WHODRUG will be used to classify prior and concomitant medications by therapeutic class. Medications will also be coded by the Anatomical Therapeutic Chemical (ATC) classification system.

Medications starting before the first dose of investigational product will be considered prior medications. Medications taken during Period 1 and stopping before the first dose of investigational product in Period 2 will be considered concomitant with Period 1. Medications taken after the first dose of investigational product in Period 2 will be considered concomitant with Period 2. If a medication is taken during Period 1 and Period 2 then it will be considered concomitant with both periods.

Both prior and concomitant medication usage will be summarized overall and by the number and proportion of subjects receiving each medication within each level 1 (anatomical main group) ATC group and preferred term for the Safety Analysis Set. Prior medication will be summarized by treatment sequence and concomitant medication will be summarized by treatment. Medications can be counted both as prior and concomitant medication, and concomitant medications can be counted under one or both treatments. Multiple medication usage by a subject in the same category will be counted only once. When calculating the number of subjects receiving medications overall for all treatments combined, each subject will be counted only once even if the medication is taken in both treatment periods.

All prior and concomitant medication will be listed.

A separate listing will be produced for the prior and concomitant medications of interest, which are calcium, vitamin D (any form), and thiazide diuretics.

10. EFFICACY ANALYSES

No efficacy analysis will be performed for this study.

10.1 Primary Efficacy Endpoint(s) and Analysis

Not applicable.

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

Not applicable.

10.3 Other Secondary Efficacy Endpoint(s) and Analysis

Not applicable.

10.4 Exploratory Efficacy Endpoint(s) and Analyses

Not applicable.

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Analysis Set. Safety variables include AEs and TEAEs, clinical episodes of hypocalcemia and/or hypercalcemia, and hypercalciuria, clinical laboratory variables, vital signs, and ECG variables. For clinical laboratory and vital sign variables, the last value collected before the first dose of investigational product in that period will be used as baseline for all analyses of that safety variable in that period.

Assessments at the follow-up visit will be assigned to the last treatment the patient received. Early termination visits will be summarized separately, and assigned to the treatment in Period 1 if prior to first dose of investigational product in Period 2, and assigned to treatment in Period 2 if after the first dose of investigational product in Period 2.

For handling of unscheduled visits, refer to Section 18.

11.1 Adverse Events

Adverse events will be coded using Version 19.0 or newer of MedDRA.

An AE (classified by preferred term) that occurs during the study will be considered a TEAE if it has a start date/time on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity on or after the date/time of the first dose of investigational product. If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study under the preferred term. An AE that occurs more than 5 days (120 hours) after the last dose of investigational product will not be counted as a TEAE.

Adverse events will be assigned to a treatment as follows. If the onset date of the AE is after first dose in Period 1, but prior to first dose in Period 2, and is ≤ 5 days after the date of last dose in Period 1 it will be counted as a Period 1 AE. If the onset date of the AE is after first dose in Period 2, and is ≤ 5 days after the date of last dose in Period 2 it will be counted as a Period 2 AE. Period 1 AEs will be assigned to the treatment received in Period 1, and Period 2 AEs will be assigned to the treatment received in Period 2. AEs with onset date > 5 days after the last dose in Period 1 and prior to the first dose in Period 2 will be counted as a Washout AE, not assigned to a treatment, and not considered a TEAE. AEs with onset date > 5 days after the last dose in Period 2 will be counted as a Follow-up AE, not assigned to a treatment, and not considered a TEAE.

When summarizing non-TEAEs by treatment, AEs occurring prior to first dose in Period 1 will be excluded, and other non-TEAEs will be assigned to the last treatment received.

An overall summary of the number of subjects with AEs will be presented by treatment and overall, including the number and percentage of subjects with any AEs, serious AEs, AEs related to investigational product, AEs leading to discontinuation of investigational product, severe AEs, and deaths. The number and percentage of subjects with TEAEs and non-TEAEs will be presented for the same categories.

The number and percentage of subjects reporting TEAEs for each treatment will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and maximum severity. TEAEs considered related to investigational product will also be 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. Severe TEAEs, Serious TEAEs and TEAEs leading to discontinuation of investigational product will be summarized by SOC, preferred term and treatment.

A summary table of TEAEs of special interest will be produced showing the number and percentage of subjects reporting TEAEs of special interest for each treatment tabulated by preferred term. The TEAEs of special interest are hypercalcemia, hypocalcemia and hypercalciuria.

The above summaries will be repeated for non-TEAEs. A separate summary of all AEs of special interest (including TEAEs and non-TEAEs) will also be produced.

Listings will be produced for all AEs (including pre-treatment AEs), SAEs, AEs considered related to investigational product, AEs leading to discontinuation of investigational product, deaths, and AEs of special interest.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented by treatment for the following clinical laboratory variables.

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell count – total and differential (WBC), total neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Biochemistry Sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, chloride, thyroid stimulating hormone (TSH)[a], thyroxine (T4 total)[a], triiodothyronine (T3)[a], 25(OH)D[a], phosphorus, total protein, total CO_2 (Bicarbonate), albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, uric acid, Creatinine clearance[a], β-HCG[b], FSH[b], Magnesium.

β-HCG=beta-human chorionic gonadotropin; FSH=follicle stimulating hormone; T3=triiodothyronine; TSH=thyroid stimulating hormone
a Tests done at Screening only and therefore will not appear in summary tables. They will be listed.
b Females only.

Urinalysis Glucose, specific gravity, blood, ketones, protein, calcium, bilirubin, pH, leukocyte esterase, and nitrites.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 5. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided for all results for the parameter with a PCI value for a subject, including the subject number, site, baseline, and post-baseline values.

Table 5: Criteria for Potentially Clinically Important Laboratory Tests

	Parameter	Unit	Lower Limit	Upper Limit
Chemistry	Albumin	g/L	<=20	>=90
	Alkaline Phosphatase	U/L	NA	>2*ULN
	ALT	U/L	NA	>3*ULN
	AST	U/L	NA	>3*ULN
	Bilirubin	µmol/L	NA	>2*ULN
	BUN	mmol/L	NA	>=10.7
	Chloride	mmol/L	<=80	>=125
	Creatinine	µmol/L	NA	>=177
	Glucose	mmol/L	<=1.7	>=13.9
	Gamma glutamyl transferase	U/L	NA	>=100
	Magnesium	mmol/L	<0.7	>1.4
	Phosphate (Phosphorus)	mmol/L	NA	>=2
	Potassium	mmol/L	<=2.5	>=6.5
	Sodium	mmol/L	<=120	>=165
	Uric acid	µmol/L	NA	>=624 (males)
			NA	>=505 (females)
Hematology	Hematocrit	fraction of 1	<=0.37 (males)	>0.54 (males)
			<=0.32 (females)	NA (females)
	Hemoglobin	g/L	<=115 (males)	NA
			<=95 (females)	NA
	Platelets	x10E9/L	<=75	>=700
	RBC count	x10E12/L	<=2.5 (males)	NA
			<=2.0 (females)	NA
	WBC count	x10E9/L	<=2.8	>=16.0
	Basophils/Leukocytes	L/L	NA	>=0.15

Table 5: Criteria for Potentially Clinically Important Laboratory Tests				
	Parameter	**Unit**	**Lower Limit**	**Upper Limit**
	Eosinophils/Leukocytes	L/L	NA	>=0.10
	Lymphocytes/Leukocytes	L/L	NA	>=0.80
	Monocytes/Leukocytes	L/L	NA	>=0.40
	Neutrophils/Leukocytes	L/L	<=0.15	NA
24-Hour urine	Urine calcium	mg	NA	>300 for men
		mg	NA	>250 for women

Listings for serum and urinary clinical laboratory results will be produced for all patients in the Safety Analysis Set.

11.3 Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each post-baseline assessment and at the end of study will be presented by treatment. All vital signs will be listed for each subject in the Safety Analysis Set.

Vital sign values will be considered PCI if they if they meet either the low or high PCI criteria listed in Table 6. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 6: Criteria for Potentially Clinically Significant Vital Signs			
Parameter	**Unit**	**Lower Limit**	**Upper Limit**
Systolic blood pressure	mmHg	A decrease from Baseline of ≥ 20 to a value ≤ 90	An increase from Baseline of ≥ 20 to a value ≥ 180
Diastolic blood pressure	mmHg	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 105
Pulse rate	bpm	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 120

11.4 Electrocardiogram (ECG)

At each timepoint, ECGs are collected in triplicate (any readings after the first three valid readings at a particular timepoint will be considered unscheduled). For numeric ECG variables, the mean of the valid values at each timepoint will be taken. For qualitative ECG results, the worst case will be used. Baseline for numeric ECG results is the mean of the available valid values at the last timepoint with any non-missing data prior to the first dose of investigational product in that period. For qualitative ECG results, baseline will be the worst case at the last timepoint with any non-missing data prior to the first dose of investigational product in that period.

Descriptive statistics for ECG variables (eg, heart rate, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by treatment. 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 timepoint for qualitative ECG results will be presented. All ECG results will be listed for each subject in the Safety Analysis Set.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 7. Assessment of whether a value is PCI will be based on the derived average at each timepoint for each subject. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment. The percentages will be calculated relative to the number of subjects with available non-PCI baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. A listing of all subjects with post-baseline PCI value will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 7: Criteria for Potentially Clinically Important ECG Values

Parameter	Upper Limit
QTcB	> 500 ms, > 480 ms, >450 ms
QTcF	> 500 ms, > 480 ms, >450 ms
QTcB	An increase from Baseline of >=60 ms and >= 30 ms
QTcF	An increase from Baseline of >=60 ms and >= 30 ms

11.5 Other Safety Variables

Anti-PTH antibodies will be assessed at Treatment Period 1 Day 1 (pre-dose) and at Follow-up. The results at each timepoint will be summarized for all subjects overall.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetics Population and Pharmacodynamic Population

The Pharmacokinetic Set consists of subjects who do not have major protocol violations that affect the validity of the PK results, receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacokinetic concentration value available for 1 dose regimen. See details in Section 4.4. A listing of subjects excluded from the PK set along with the reasons for exclusion will be generated.

The Pharmacodynamic Analysis Set consists of subjects who do not have major protocol violations that affect the validity of the PD results, receive at least 1 dose of rhPTH(1-84) and have at least 1 evaluable post-dose pharmacodynamic value available for 1 dose regimen. See details in Section 4.4. A listing of subjects excluded from the PD set along with the reasons for exclusion will be generated.

12.2 Handling BLQ and Missing Values

The following procedures will be used for raw plasma PTH concentrations, raw serum pharmacodynamic data, and raw urine pharmacodynamic data below the lower limit of quantification (LLOQ):

- Plasma samples that are BLQ are reported as <LLOQ on the data listings, where LLOQ is replaced by the actual value for LLOQ.
- Missing values may be imputed on a case-by-case basis

For plasma PTH concentrations the following guidance will be followed:

- Samples that are BLQ are treated as zero in the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma concentrations at individual time points.

- Mean concentrations are reported as zero if all values are BLQ, and no descriptive statistics are reported. If the calculated mean (± SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma concentration versus time plots.

- For calculation of area under the plasma concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into WinNonlin for pharmacokinetic analysis. WinNonlin uses the zero values that occur before the first time point with a concentration greater than LLOQ. Values that are BQL after the first measurable concentration are set to “missing” in the dataset loaded into WinNonlin

For serum PD concentrations the following guidance will be followed:

- Samples that are BLQ are treated as half the LLOQ in non-compartmental PD analysis and the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma concentrations at individual time points.

12.3 Pharmacokinetic Methods

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic Set. After database lock, a visual inspection of concentration-time profiles and pharmacokinetic parameters will be performed by PRA to determine dataset integrity and potential outliers. Descriptive statistics of pharmacokinetic parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by Shire for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

12.3.1 Raw PTH Concentration Data

For subjects and treatment periods when one dose is received, samples for pharmacokinetic analysis are taken at Predose, 10, 20 and 30 minutes, 1, 1.5, 2, 4, 8, 12, 16 and 24 hours. For subjects and treatment periods when two doses are received, samples for pharmacokinetic analysis are taken at Predose, 10, 20 and 30 minutes, 1, 1.5, 2, 4, and 8 hours. A second predose sample will be collected just before the second dose is administered 12 hours after the first dose, 10, 20 and 30 minutes following the second dose, and 13, 13.5, 14, 16, 20, 24, 28 and 36 hours after the first dose. Plasma concentrations of PTH(1-84) will be measured using a validated analytical method.

12.3.2 Baseline-adjusted PTH Concentration Data

Baseline-adjusted PTH concentrations (subject- and period-specific) are to be calculated by subtracting baseline endogenous PTH from the raw PTH concentrations. The baseline is defined as pre-morning-dose endogenous PTH level on Day 1 for each treatment period. Since rhPTH(1-84) is administered to subjects with hypoparathyroidism in this study, baseline endogenous PTH levels are expected to be low and likely below the lower limit of quantification (LLOQ) for PTH. If the baseline-adjusted PTH concentration gives a negative value then the baseline-adjusted PTH concentration should be set to zero. In the terminal phase (after the morning dose during the QD treatment and after the evening dose during the BID treatment), any positive baseline-adjusted PTH concentrations following a negative value will be assigned a value of zero.

If the pre-dose PTH value is missing, then this is set to 0 for the calculation of the baseline-adjusted PTH concentration for the purposes of calculating the baseline-adjusted pharmacokinetic parameters.

12.3.3 Pharmacokinetic Parameters

The pharmacokinetic analysis will be conducted by using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA). Pharmacokinetic

parameters will be determined from the plasma PTH concentration-time data by non-compartmental analysis. Pharmacokinetic analyses based on raw and baseline adjusted PTH concentrations will be performed. In each treatment period, all assessment dates will be related to the first day of rhPTH administration. This first day of investigational product administration is referred to as Day 1. Day-1 is the day that is preceding Day 1, and a Day 0 will not be defined.

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

- Time of maximum observed concentration sampled during a dosing interval (t_{max}), to be reported in the unit of hour (original and baseline-adjusted)
- Maximum observed concentration (C_{max}), to be reported in the unit of pg/mL (original and baseline-adjusted)
- Area under the curve from the time of dosing to the last measurable concentration (AUC_{last}). Calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (original and baseline-adjusted)
- Area under the curve extrapolated to infinity calculated as AUClast + Clast/λ_z ($AUC_{0\text{-}inf}$). Calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (baseline-adjusted only)
- % of AUC extrapolated from the last measurable concentration to infinity over AUC(0-inf) (%AUC extrapolated) (baseline-adjusted only)
- Area under the concentration curve from time zero to 24 hours post the first dose ($AUC_{0\text{-}24h}$), to be reported in the unit of pg.hr/mL (calculated using the linear up/log down method) (original and baseline-adjusted)
- Area under the concentration curve from time zero to 12 hours post the first dose ($AUC_{0\text{-}12h}$) calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (for BID treatment only, original and baseline-adjusted)
- Area under the concentration curve from the time of the second dose to 12 hours post the second dose ($AUC_{12\text{-}24h}$) calculated using the linear up/log down method, to be reported in the unit of pg.hr/mL (for BID treatment only, original and baseline-adjusted)
- Elimination rate constant associated with the terminal (log-linear) portion of the curve (λ_z) (baseline-adjusted only)
- Terminal half-life ($t_{½}$), calculated as 0.693/ λ_z (baseline-adjusted only)
- CL/F Apparent total body clearance, calculated as Dose/$AUC_{0\text{-}inf}$ (baseline-adjusted only)
- Vss/F Apparent volume of distribution at steady state, calculated as MRT xCL/F, where MRT is mean residence time calculated as AUMC0-inf/AUC0-inf and AUMC0-inf is the area under the first moment curve extrapolated to infinity. (baseline-adjusted only)

All pharmacokinetic parameter calculations will be performed using actual times calculated relative to the start of the study drug administration on Day 1 for each period. The pharmacokinetic parameters λ_z, $t_{1/2}$, $AUC_{0\text{-inf}}$, CL/F, and Vss/F will not be calculated for patients with PTH concentration-time profiles (baseline-adjusted) that do not exhibit a terminal log-linear phase.

If a pre-dose sample is missing, or if a 12 hour sample in the BID treatment is missing, then for the purposes of calculating the pharmacokinetic parameters, these values will be set to 0.

12.3.4 Statistical Analysis of Pharmacokinetic Data

Individual PTH concentrations (raw and baseline-adjusted) will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, and maximum) by treatment and day. Pharmacokinetic parameters of PTH (based on raw and baseline-adjusted PTH concentrations) will be listed and summarized with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%) by treatment. CL/F and Vss/F will be listed, but not included in summary tables.

For Treatment B (repeated in Cohort 1 and Cohort 2) and Treatment E (repeated in Cohort 3 and Cohort 4), summary statistics (for both concentration data and pharmacokinetic parameters) will be prepared by cohort as well as for overall (combining different cohorts).

Figures of individual (overlaid by treatment) and mean (+/-SD) concentration-time profiles (overlaid by treatment as well as by rhPTH(1-84) dosing regimen) of raw and baseline-adjusted plasma PTH will be generated on linear and semi-log scales.

12.4 Pharmacodynamic Methods

All summaries and analyses of the pharmacodynamic data will be based on the Pharmacodynamic Set. After database lock, a visual inspection of concentration-time profiles and pharmacodynamic parameters will be performed by PRA to determine dataset integrity and potential outliers. Descriptive statistics of pharmacodynamic parameters may be calculated with and without subjects with potential outlier data. Subjects with potential outlier data will be reviewed by Shire for inclusion/exclusion from the descriptive statistics on a case-by-case basis. A listing of excluded subjects from the pharmacodynamic analysis will be provided.

12.4.1 Raw Pharmacodynamic Data

Serial blood and urine samples for pharmacodynamic analysis will be collected on Day -1, pre-dose and on Day 1 and Day 2 following the administration of rhPTH(1-84) for the determination of concentrations of serum calcium (uncorrected [total] and corrected for serum albumin levels), phosphate, magnesium, creatinine, albumin, $1,25(OH)_2D_3$, and fibroblast growth factor 23 (FGF23), and urinary excretion of calcium, sodium, citrate, phosphate, cAMP, magnesium, and creatinine.

The serum calcium-phosphate product will also be determined. This is calculated as serum calcium concentration (albumin corrected) x serum phosphate concentration.

For pharmacodynamic analyses, concentration values of serum total calcium and albumin-corrected serum calcium, phosphate, magnesium, albumin, creatinine, $1,25(OH)_2D_3$ and FGF23, reported as BLQ will be set to half the LLOQ.

12.4.2 Baseline-adjusted serum Pharmacodynamic Data

Individual serum concentrations of pharmacodynamic markers, calcium (uncorrected and corrected for albumin), phosphate, magnesium, $1,25(OH)_2D_3$, FGF23, and calcium-phosphate product will be baseline-adjusted at each time point. There will be two baseline definitions, one for Day -1 and one for Day 1. For Day -1, the baseline value is defined as the last non-missing value collected before the start of the active vitamin D administration on Day -1; for Day 1, the baseline value is defined as the last non-missing value collected before the administration of rhPTH(1-84) on Day 1 for each treatment period. Baseline-adjusted concentrations of pharmacodynamic markers are to be calculated by subtracting the appropriate baseline values from the raw concentrations at each time point.

12.4.3 Serum Pharmacodynamic Parameters

Pharmacodynamic parameters will be computed from the individual raw concentrations of serum calcium (mmol/L) (uncorrected and corrected for serum albumin levels), phosphate (mmol/L), magnesium (mmol/L), $1,25(OH)_2D_3$ (pmol/L) and FGF23 using a non-compartmental approach and actual times. pharmacodynamic parameters will be estimated for both Day -1 and Day 1 in each treatment period. Serum calcium will be corrected for serum albumin levels using the following equation:

Corrected calcium (mmol/L) = serum calcium (mmol/L) + 0.02 (40 - serum albumin (g/L)) (Parent X1, 2009)

The following parameters will be calculated from the raw serum concentration data using WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA):

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

The same parameters will also be calculated for the calcium-phosphate product.

In addition, serum pharmacodynamic parameters will be estimated based on baseline-adjusted serum concentration of pharmacodynamic markers as follows:

- AUCabove: Area under the concentration-time curve that is above the baseline, from time 0 to 24 hours, as calculated by the linear trapezoidal method
- AUCbelow: Area under the concentration-time curve that is below the baseline, from time 0 to 24 hours, as calculated by the linear trapezoidal method
- AUCnet: AUCabove - AUCbelow
- TE_{max}: time to maximum effect
- E_{max}: maximum effect
- TEmin: time to minimum effect
- Emin: minimum effect

12.4.4 Urinary Pharmacodynamic Parameters

The following parameters will be calculated for both Day -1 and Day 1/Day 2 in each treatment period:

- Total amount of sodium (mmol), calcium (mmol), magnesium (mmol), citrate (mmol), phosphate (mmol), cAMP (µmol) and creatinine (mmol) excreted in urine in each collection period where total amount = (total volume [L] of urine in each collection) × (concentration [mmol/L, mmol/L or µmol/L]) in pooled urine samples during a collection period
- Total amount of sodium, calcium, magnesium, citrate, cAMP and phosphate excreted in each collection period relative to the total amount of creatinine excreted in the same collection interval, mmol/mmol, nmol/mmol, or µmol/mmol
- Total amount of sodium, calcium, magnesium, citrate, phosphate, cAMP and creatinine excreted in urine over 24 hours post dose, mmol, nmol, or µmol
- Total amount of sodium, calcium, magnesium, citrate, phosphate and cAMP excreted in urine over 24 hours post dose relative to the total amount of creatinine excreted over 24 hours post dose, mmol/mmol, nmol/mmol, or µmol/mmol
- Renal clearance (CLr) of calcium, magnesium, creatinine and phosphate (mL/min) in each collection period where CLr = (Urine concentration) × (urine flow/serum concentration); urine flow is calculated as the total urine volume divided by time in the collection interval
- Fractional excretion (FE) of calcium, magnesium, and phosphate in each collection period, calculated as:

  100 × [Urine concentration of the analyte × Serum Creatinine]/[Serum concentration of the analyte × Urine Creatinine].

For the calculation of CLr and FE in each collection interval, the serum concentration value used is that which occurs at or closest to the middle of the urine collection period. For example, for the 0-3 hour urine collection, the serum values determined at the 1.5-hour serum sample is to be used. Calculation of these parameters will be by each time interval collected in

the CRF (0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-24 hours for QD, and for BID this will also include 24-30, and 30-36 hours).

The following table shows the urine collection period and the corresponding timepoint to be used for the serum concentration:

Urine Collection Period	**Timepoint of Collection of Serum Concentration**
0-3 hours	1.5 hours
3-6 hours	4 hours
6-9 hours	8 hours
9-12 hours	10 hours
12-15 hours	13.5 hours
15-18 hours	16 hours
18-24 hours	20 hours/24 hours[a]
24-30 hours[b]	28 hours
30-36 hours[b]	36 hours

[a] 20 hours for Day 1, 24 hours for Day -1
[b] For BID dose groups only.

12.4.5 Statistical Analysis of Pharmacodynamic Data

For serum pharmacodynamic evaluations, concentrations (raw and baseline-adjusted) of serum total calcium and albumin-corrected calcium, phosphate, creatinine, magnesium, $1,25(OH)_2D_3$ and FGF23 will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment and day. Pharmacodynamic parameters of serum total calcium and albumin-corrected calcium, phosphate, magnesium, $1,25(OH)_2D_3$ and FGF23 will be summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by treatment and day. This will be done for both raw and baseline-adjusted values, and will be done for both Day -1 and Day 1/2. Note for the Day -1 summaries, the treatment assigned will be the treatment the subject takes the following day.

Individual and mean concentration (raw and baseline-adjusted)-time plots of serum pharmacodynamic markers (serum total calcium and albumin-corrected calcium, phosphate, creatinine, magnesium, $1,25(OH)_2D_3$ and FGF23) will be generated on both linear and semilog scales. These figures will be generated as overlay plots by treatment.

For urine pharmacodynamic evaluations, the individual urinary excretion of calcium, sodium, citrate, magnesium, cAMP, and phosphate and amount relative to creatinine of calcium, sodium, citrate, magnesium, cAMP and phosphate in each collection period as well as over 24 hours will be listed and summarized with descriptive statistics by treatment and day (Day -1 and Day 1/2).

In addition, the renal clearance of calcium, magnesium,, creatinine and phosphate and fractional excretion of calcium, magnesium and phosphate in each collection period will be summarized with descriptive statistics by treatment and day.

Individual and mean urine pharmacodynamic parameters over time (urine collection interval) will be plotted on a linear scale, overlaid by treatment (both Day -1 and Days 1 and 2 will be presented on the same plot).

12.5 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic-pharmacodynamic correlations may be assessed using scatter plot figures of selected rhPTH pharmacokinetic parameters (such as but not limited to AUC_{0-24}, C_{max}, time above threshold of 17.2 pg/mL, AUC above threshold of 17.2 pg/mL, time above threshold of 25 pg/mL, and AUC above threshold of 25 pg/mL) against time-matched selected pharmacodynamic parameters of serum total calcium and albumin-corrected calcium, phosphate, creatinine, magnesium, $1,25(OH)_2D_3$ and FGF23 values and selected urine pharmacodynamic parameters. Appropriate correlation or regression analysis may be explored.

12.6 Population Pharmacokinetic and Quantitative System Pharmacology Modeling and Simulation

This will be covered in a separate SAP.

13. OTHER ANALYSES

13.1 Quality of Life Analyses

Not applicable.

13.2 Health Economics and Outcomes Research Analyses

Not applicable.

14. INTERIM ANALYSIS

An interim analysis is planned for this study. A separate Interim Analysis SAP will be developed to describe the interim analysis. At the end of each cohort a safety review will be performed before proceeding to the next cohort. The review will include, at a minimum, the Coordinating Investigator and the Shire Medical Monitors. The requirements for the data presentations to be used for this safety review will be documented separately.

15. DATA MONITORING/REVIEW COMMITTEE

Not applicable, as no data monitoring review is planned for this study.

16. COMPUTER METHODS

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

WinNonlin Phoenix version 6.3 or higher (Pharsight Corporation, Mountain View, California, USA) will be used for calculating pharmacokinetic and pharmacodynamics parameters.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There were no changes to the analysis planned in the latest version of the protocol.

18. DATA HANDLING CONVENTIONS

18.1 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. Percentages will be presented to 1 decimal place.

The rules for the number of decimal places to present data and p-values are listed 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.

18.2 Derived Efficacy Endpoints

Not applicable.

18.3 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. In addition to determination of baseline, unscheduled visits will be included in PCI value determination. However, for all other summaries only scheduled visits will be used.

All assessments (including unscheduled) will be presented in the data listings.

18.4 Missing Date of Investigational Product

Since the investigational products will be administered during in-patient confinement at a CRC, there should not be any missing dates of investigational product.

18.5 Missing Date and Time Information for Prior or Concomitant Medications

For prior or concomitant 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.

18.5.1 Incomplete Start Date and Time

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.

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. The exception to this would be if the year of the start date is the same as the year of the treatment period 2 dose, in which case the day and month of the first dose of investigational product in period 2 will be assigned to the missing fields.

Missing month only

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

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. The exception to this would be if the month of the start date is the same as the month of the treatment period 2 dose, in which case the day of the first dose of investigational product in period 2 will be assigned to the missing fields.

Missing/Incomplete Time

If the time is missing and the date is complete and is the same as the date of the first dose of investigational product in either period, or the date is imputed to be one of these dates, then

the time will be set to the time of the first dose of investigational product on that day. Otherwise, missing times will be imputed as 00:00.

If the minutes are given but the hour is not, then the time will be regarded as completely missing and handled as above. If the hour is given but the minutes are not, then if the hour is the same as the hour of a dose of investigational product on that day, then the minutes of that dose of investigational product will be assigned to the missing fields. Otherwise 00 will be assigned to the missing minutes.

18.5.2 Incomplete Stop Date and Time

The following rules will be applied to impute the missing numerical fields. 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.

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.

Missing month only

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

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.

Missing Time

- If the time is missing it will be imputed as 23:59.

18.6 Missing Date Information for Adverse Events

For AEs, only incomplete (i.e., partially missing) start dates will be imputed. Incomplete stop dates will not be imputed.

18.6.1 Incomplete Start Date

Follow same rules as in Section 18.5.1.

18.6.2 Incomplete Stop Date

Not applicable.

18.7 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.

18.8 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 the investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 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 (e.g. <5), then 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 5: 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

19. References

Parent X1, Spielmann C, Hanser AM. 2009. ["Corrected" calcium: calcium status underestimation in non-hypoalbuminemic patients and in hypercalcemic patients]. Ann Biol Clin (Paris). [Online]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19654080

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4.3.4	Severe Non-Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.3.5	Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.3.6	Non-Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.3.7	Treatment-emergent Adverse Events Not Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.4.1	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.4.2	Serious Non-Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.4.3	Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.4.4	Non-Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Product by System Organ Class, Preferred Term and Treatment (Safety Analysis Set)	Y
4.5.1	Treatment-emergent Adverse Events of Special Interest by Preferred Term and Treatment (Safety Analysis Set)	N
4.5.2	Non-Treatment-emergent Adverse Events of Special Interest by Preferred Term and Treatment (Safety Analysis Set)	N
4.5.3	Adverse Events of Special Interest by Preferred Term and Treatment (Safety Analysis Set)	N
4.6.1	Quantitative Clinical Laboratory Results by Treatment: Hematology (Safety Analysis Set)	Y
4.6.2	Shift from Baseline in Clinical Laboratory Results by Treatment: Hematology (Safety Analysis Set)	Y
4.6.3	Potentially Clinically Important (PCI) Laboratory Results by Treatment: Hematology (Safety Analysis Set)	Y
4.6.4	Quantitative Clinical Laboratory Results by Treatment: Biochemistry (Safety Analysis Set)	Y
4.6.5	Shift from Baseline in Clinical Laboratory Results by Treatment: Biochemistry (Safety Analysis Set)	Y

Table	Title	Shire Std
4.6.6	Potentially Clinically Important (PCI) Laboratory Results by Treatment: Biochemistry (Safety Analysis Set)	Y
4.6.7	Quantitative Clinical Laboratory Results by Treatment: Urinalysis (Safety Analysis Set)	Y
4.6.8	Qualitative Clinical Laboratory Results by Treatment: Urinalysis (Safety Analysis Set)	Y
4.6.9	Shift from Baseline in Clinical Laboratory Results by Treatment: Urinalysis (Safety Analysis Set)	Y
4.6.10	Potentially Clinically Important (PCI) Laboratory Results by Treatment: Urinalysis (Safety Analysis Set)	Y
4.7.1	Actual Values and Change from Baseline in Vital Signs by Treatment (Safety Analysis Set)	Y
4.7.2	Potentially Clinically Important Vital Signs Results by Timepoint and Treatment (Safety Analysis Set)	Y
4.8.1	Actual Values and Change from Baseline in ECG by Timepoint and Treatment (Safety Analysis Set)	Y
4.8.2	ECG Interpretation by Timepoint and Treatment (Safety Analysis Set)	Y
4.8.3	Shift from Baseline to Post-Baseline Timepoint in Qualitative ECG Results by Treatment (Safety Analysis Set)	Y
4.8.4	Potentially Clinically Important ECG Results by Timepoint and Treatment (Safety Analysis Set)	Y
4.9.1	Immunogenicity (Anti-PTH Antibody) (Safety Analysis Set)	N

Figures	Title	Shire Std
2.1.1	Plot of Raw Mean Plasma PTH Concentrations versus Time by Treatment on a Linear Axis (Pharmacokinetic Analysis Set)	N
2.1.2	Plot of Raw Mean Plasma PTH Concentrations versus Time by Treatment on a Semi-log Axis (Pharmacokinetic Analysis Set)	N
2.1.3	Plot of Baseline Adjusted Mean Plasma PTH Concentrations versus Time by Treatment on a Linear Axis (Pharmacokinetic Analysis Set)	N
2.1.4	Plot of Baseline Adjusted Mean Plasma PTH Concentrations versus Time by Treatment on a Semi-log Axis (Pharmacokinetic Analysis Set)	N
2.1.5	Plot of Baseline Adjusted Individual Plasma PTH Concentrations versus Time by Treatment on a Linear Axis (Pharmacokinetic Analysis Set)	N
2.1.6	Plot of Baseline Adjusted Individual Plasma PTH Concentrations versus Time by Treatment on a Semi-log Axis (Pharmacokinetic Analysis Set)	N
2.4.1	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (uncorrected) (Pharmacodynamic Analysis Set)	N
2.4.3	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (albumin-corrected) (Pharmacodynamic Analysis Set)	N

Figures	Title	Shire Std
2.4.5	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Phosphate (Pharmacodynamic Analysis Set)	N
2.4.7	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Magnesium (Pharmacodynamic Analysis Set)	N
2.4.9	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Creatinine (Pharmacodynamic Analysis Set)	N
2.4.11	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – $1,25(OH)_2D_3$ (Pharmacodynamic Analysis Set)	N
2.4.13	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – FGF23 (Pharmacodynamic Analysis Set)	N
2.4.15	Plot of Raw Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Albumin Corrected Calcium-Phosphate Product (Pharmacodynamic Analysis Set)	N
2.5.1	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (uncorrected) (Pharmacodynamic Analysis Set)	N
2.5.3	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (albumin-corrected) (Pharmacodynamic Analysis Set)	N
2.5.5	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Phosphate (Pharmacodynamic Analysis Set)	N
2.5.7	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Magnesium (Pharmacodynamic Analysis Set)	N
2.5.9	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Creatinine (Pharmacodynamic Analysis Set)	N
2.5.11	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – $1,25(OH)_2D_3$ (Pharmacodynamic Analysis Set)	N
2.5.13	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – FGF23 (Pharmacodynamic Analysis Set)	N
2.5.15	Plot of Baseline-adjusted Individual Concentrations versus Time by Treatment and Day on a Linear Axis – Albumin Corrected Calcium-Phosphate Product (Pharmacodynamic Analysis Set)	N
2.6.1	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (uncorrected) (Pharmacodynamic Analysis Set)	N
2.6.3	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (albumin-corrected) (Pharmacodynamic Analysis Set)	N
2.6.5	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Phosphate (Pharmacodynamic Analysis Set)	N
2.6.7	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Magnesium (Pharmacodynamic Analysis Set)	N
2.6.9	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Creatinine (Pharmacodynamic Analysis Set)	N
2.6.11	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – $1,25(OH)_2D_3$ (Pharmacodynamic Analysis Set)	N
2.6.13	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – FGF23 (Pharmacodynamic Analysis Set)	N

Figures	Title	Shire Std
2.6.15	Plot of Raw Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Albumin Corrected Calcium-Phosphate Product (Pharmacodynamic Analysis Set)	N
2.7.1	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (uncorrected) (Pharmacodynamic Analysis Set)	N
2.7.3	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Calcium (albumin-corrected) (Pharmacodynamic Analysis Set)	N
2.7.5	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Serum Phosphate (Pharmacodynamic Analysis Set)	N
2.7.7	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Magnesium (Pharmacodynamic Analysis Set)	N
2.7.9	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – $1,25(OH)_2D_3$ (Pharmacodynamic Analysis Set)	N
2.7.11	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – FGF23 (Pharmacodynamic Analysis Set)	N
2.7.13	Plot of Baseline-adjusted Mean Concentrations versus Time by Treatment and Day on a Linear Axis – Albumin Corrected Calcium-Phosphate Product (Pharmacodynamic Analysis Set)	N
2.8.1.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Sodium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.1.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Sodium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.2.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Calcium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.2.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Calcium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.2.3	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Calcium (Pharmacodynamic Analysis Set)	N
2.8.2.4	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Calcium (Pharmacodynamic Analysis Set)	N
2.8.3.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Magnesium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.3.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Magnesium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.3.3	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Magnesium (Pharmacodynamic Analysis Set)	N
2.8.3.4	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Magnesium (Pharmacodynamic Analysis Set)	N
2.8.4.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Citrate Amount Excreted (Pharmacodynamic Analysis Set)	N

Figures	Title	Shire Std
2.8.4.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Citrate amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.5.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Phosphate Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.5.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Phosphate amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.5.3	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Phosphate (Pharmacodynamic Analysis Set)	N
2.8.5.4	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Phosphate (Pharmacodynamic Analysis Set)	N
2.8.6.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day –cAMP Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.6.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day –cAMP amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.8.7.1	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Creatinine Amount Excreted (Pharmacodynamic Analysis Set)	N
2.8.7.2	Plot of Individual Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Creatinine (Pharmacodynamic Analysis Set)	N
2.9.1.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Sodium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.1.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Sodium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.2.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Calcium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.2.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Calcium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.2.3	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Calcium (Pharmacodynamic Analysis Set)	N
2.9.2.4	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Calcium (Pharmacodynamic Analysis Set)	N
2.9.3.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Magnesium Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.3.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Magnesium amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.3.3	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Magnesium (Pharmacodynamic Analysis Set)	N
2.9.3.4	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Magnesium (Pharmacodynamic Analysis Set)	N
2.9.4.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Citrate Amount Excreted (Pharmacodynamic Analysis Set)	N

Figures	Title	Shire Std
2.9.4.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Citrate amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.5.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Phosphate Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.5.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Phosphate amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.5.3	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Phosphate (Pharmacodynamic Analysis Set)	N
2.9.5.4	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Fractional Excretion of Phosphate (Pharmacodynamic Analysis Set)	N
2.9.6.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –cAMP Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.6.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –cAMP amount excreted relative to Creatinine (Pharmacodynamic Analysis Set)	N
2.9.7.1	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day –Creatinine Amount Excreted (Pharmacodynamic Analysis Set)	N
2.9.7.2	Plot of Mean Urine Pharmacodynamic Parameters over Time by Treatment and Day – Renal Clearance of Creatinine (Pharmacodynamic Analysis Set)	N

Listing	Title	Shire Std
	Listing of Subject Data for Screen Failures	Y
16.1.7	Randomization Assignments (All-Enrolled Set)	Y
1.1	Subject Disposition (All-Enrolled Set)	Y
1.2	Subjects Who Discontinued from the Study (Safety Analysis Set)	Y
1.3	Study Analysis Set Classification (Enrolled Set)	Y
2.1	Listing of Protocol Deviations (All-Enrolled Set)	Y
4.1	Subject Demographics (Safety Analysis Set)	Y
4.2	Subject Baseline Characteristics (Safety Analysis Set)	Y
4.3	Parathyroid History (Safety Analysis Set)	N
4.4	Medical History (Safety Analysis Set)	Y
4.5	Prior and Concomitant Medications (Safety Analysis Set)	Y
4.6	Prior and Concomitant Medications of Special Interest (Safety Analysis Set)	Y
5.1	Investigational Product Exposure (Safety Analysis Set)	Y
5.2	Pharmacokinetic Blood Sampling and PTH Concentrations (Pharmacokinetic Analysis Set)	Y
5.3	Raw PTH Pharmacokinetic Parameters (Pharmacokinetic Analysis Set)	N
5.4	Baseline-adjusted PTH Pharmacokinetic Parameters (Pharmacokinetic Analysis Set)	N

Listing	Title	Shire Std
5.5	Pharmacodynamic Blood Sampling (Pharmacodynamic Analysis Set)	Y
5.6	Pharmacodynamic Concentrations (Pharmacodynamic Analysis Set)	N
5.7	Raw Pharmacodynamic Parameters (Pharmacodynamic Analysis Set)	N
5.8	Baseline-adjusted Pharmacodynamic Parameters (Pharmacodynamic Analysis Set)	N
5.9	Pharmacodynamic Urine Sampling (Pharmacodynamic Analysis Set)	Y
5.10	Pharmacodynamic Urine Parameters (Pharmacodynamic Analysis Set)	N
5.11	Data Excluded from Pharmacokinetic and Pharmacodynamic Analysis	N
7.1	Adverse Events (Safety Analysis Set)	Y
7.2	Serious Adverse Events (Safety Analysis Set)	Y
7.3	Adverse Events Considered Related to Investigational Product (Safety Analysis Set)	Y
7.4	Adverse Events Leading to Discontinuation of Investigational Product (Safety Analysis Set)	Y
7.5	Adverse Events with Fatal Outcome (Safety Analysis Set)	Y
7.6	Adverse Events of Special Interest (Safety Analysis Set)	Y
8.1.1	Serum Clinical Laboratory Test Results (Safety Analysis Set)	N
8.1.2	Urinary Clinical Laboratory Test Results (Safety Analysis Set)	N
8.1.3	Subjects with Potentially Clinically Important Laboratory Test Results (Safety Analysis Set)	Y
8.2.1	Vital Signs (Safety Analysis Set)	Y
8.2.2	Subjects with Potentially Clinically Important Vital Signs (Safety Analysis Set)	Y
8.3.1	12-lead ECG Results and Investigator's Interpretation (Safety Analysis Set)	Y
8.3.2	Subjects with Potentially Clinically Important ECG Results (Safety Analysis Set)	Y
8.5.1	Immunogenicity (Anti-PTH Antibody) Results (Safety Analysis Set)	N