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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Sponsor: Shire	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
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Study 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

Investigators and Study Centers:
A total of 19 investigators participated in the study in North America and countries within Europe.

Coordinating Investigator:

[redacted]

Publication (reference):
Ing, S.W., Mannstadt, M., Rejnmark. L., Takács, I., Song, I., Shapiro, H., He, P., and Finkelman, R.D. A Phase 1 PK/PD Study of Once vs Twice Daily Administration of rhPTH(1-84) in Patients With Hypoparathyroidism: Interim Analysis. Annual Meeting, American Society for Bone and Mineral Research, 2019.

Studied Period:
First subject consented: 04 Mar 2017

Last Subject completed: 08 Mar 2019

Study Phase: 1

Objectives:

Primary:

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

Secondary:

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

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Methodology:

This study consisted of the administrative screening period (up to 120 days prior to first dose, if needed); the clinical screening period (within 28 days prior to first dose); 2 treatment periods, the respective doses of which were separated by a washout (≥5 days but ≤30 days) between the administration of rhPTH(1-84) or the first administration of rhPTH(1-84) in each period for QD or BID dosing, respectively; and a follow-up visit [30±2 days after the last dose of rhPTH(1-84) was administered].

Clinical screening occurred within 28 days of the first dose. Subjects were enrolled into one of 4 sequential cohorts and received rhPTH(1-84) treatment according to the sequences presented in the treatment scheme below. Subjects who met the inclusion/exclusion criteria at clinical screening reported to the Clinical Research Center 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 on Day 1. Subjects were randomly assigned to 1 of 2 treatment sequences prior to administration of rhPTH(1-84) on Day 1 of Treatment Period 1, only after all entry criteria were confirmed. The treatment sequence assignments within each cohort were as follows:

Treatment Scheme				
Cohort		**Treatment Period 1 (Day 1)**	**Washout Period**	**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
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

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During Treatments A, B, and C (Cohorts 1 and 2), subjects were instructed to take their usual supplemental oral calcium and active vitamin D on Day -1, then these supplements were withheld starting on Day 1 (predose) through the completion of all study procedures on Day 2 for both the QD and BID dose regimens.

During Treatments D, E, and F (Cohorts 3 and 4), subjects were instructed to take their usual supplemental oral calcium and active vitamin D on Day -1 and withhold their usual active vitamin D starting on Day 1 through the completion of all study procedures on Day 2. Subjects were also instructed to take their usual dose(s) of supplemental oral calcium according to their usual regimen, regardless of the schedule/timing of rhPTH(1-84) administration(s). Critically, oral calcium supplementation was to be identical on Day -1, Day 1 and Day 2 in Treatment Period 1 and Treatment Period 2. On Day 2, subjects continued with their usual supplemental calcium regimen (ie, identical on Day -1 and Day 1) and, following the completion of all study procedures, subjects then re-started their active vitamin D at their next usual daily schedule.

For all treatments, rhPTH(1-84) was administered in the morning of Day 1 of each treatment period following an overnight fast of at least 8 hours. Subjects continued to fast until approximately 2 hours after rhPTH(1-84) administration, at which time a standardized meal was served. During the treatment period when subjects received the BID dose regimen, the evening dose of rhPTH(1-84) was administered 12 hours after the morning dose, and 2 hours prior to the evening meal. A snack or light meal could be provided to the subjects prior to the evening dose, provided it was consumed ≥2 hours prior to rhPTH(1-84) dose administration. During the washout period, subjects were instructed to take their usual doses of supplemental oral calcium and active vitamin D.

Serial blood samples for PK analyses were collected for the determination of parathyroid hormone (PTH) concentrations at predose and up to 24 hours postdose (Day 1/Day 2 - also referred to as Day 1/2) in each treatment period. For subjects randomized to the BID regimen, serial PK samples were collected up to 24 hours post the evening dose.

Serial blood and urine samples for PD analyses were collected over 24 hours on Day -1 and on Day 1 predose and following the administration of rhPTH(1-84) on Day 1/2. Pharmacodynamic markers planned for analysis included concentrations of serum calcium (total and albumin-corrected), phosphate, magnesium, 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D], creatinine, and fibroblast growth factor 23 (FGF23), and urinary excretion of calcium, phosphate, sodium, magnesium, citrate, cyclic adenosine monophosphate (cAMP), and creatinine.

Safety and tolerability were determined through assessment of adverse events (AEs), vital signs, electrocardiogram (ECG), and clinical laboratory evaluations throughout the study. Additional blood samples were collected for assessment of anti-PTH antibodies.

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A safety review was conducted at the completion of 8 subjects in each of Cohorts 1, 2, and 3 before any subject could be enrolled in the next cohort.

Number of Subjects (Planned and Analyzed):

Approximately 32 subjects were expected to complete the study (Cohorts 1, 2, 3, and 4). A sufficient number of subjects was screened and enrolled to ensure that at least 8 subjects completed each treatment in their assigned cohort and provide sufficient data to meet study objectives.

A total of 34 subjects were screened and enrolled with 8 subjects each in Cohorts 1 and 3, and 9 subjects each in Cohorts 2 and 4. Thirty-three subjects completed the study, 34 were analyzed in the Safety Analysis Set and 33 were analyzed in the Pharmacokinetic Set and Pharmacodynamic Set. However, the following data were excluded from all PK and/or PD summary tables and figures:

- In Cohort 1: All data of one subject who did not meet all inclusion criteria were excluded from all PK and PD summary tables and figures.

- In Cohort 2: Treatment Period 2 data of one subject with a suspected dosing error or pen injection failure based on PTH concentrations reported as below the limit of quantification (BLQ) at all postdose timepoints were excluded from all PK and PD summary tables and figures; in addition, Treatment Period 2 data of one subject were excluded from all PD summary tables and figures for receiving calcium and vitamin D within 24 hours of dosing in Treatment Period 2.

- In Cohort 4: Treatment Period 1 data of 2 subjects were excluded from all PK and PD summary tables and figures due to sample mislabeling on Day 1; data from 3 subjects (Treatment Period 2 data from 2 subjects and Treatment Period 1 data from one subject) were excluded from all PK and PD summary tables and figures due to a suspected dosing error based on postdose PTH concentrations all reported as BLQ.

A posthoc analysis, where further PK and PD data were excluded due to extremely low PTH AUC_{0-24} (<300 pg*hr/mL) observed, was performed in addition to the planned analysis. The PK/PD data from 2 subjects receiving 50 µg BID dose regimen administered with calcium supplement (Cohort 4) were excluded in the posthoc analysis due to extremely low PTH AUC_{0-24} (<300 pg*hr/mL) observed for the specified treatment period, an indicator for likely partial dosing.

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Diagnosis and Main Criteria for Inclusion:

This study included adult men and women at least 18 years old with hypoparathyroidism for ≥12 months, post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia with concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range and a requirement for supplemental oral calcium treatment ≥1000 mg elemental calcium per day and active forms of vitamin D at a minimum dose of ≥0.25 µg per day (ie, ≥0.25 µg calcitriol or equivalent per day). Serum levels of calcium, magnesium, 25-hydroxyvitamin D [25(OH)D], and creatinine, as well as urinary excretion of calcium and renal clearance were also considered to determine subjects' eligibility.

Investigational Product, Dose and Mode of Administration, Lot Number(s):

The investigational product was rhPTH(1-84), which was provided as a multiple-dose, dual chamber, glass cartridge containing a sterile lyophilized powder and a sterile diluent for reconstitution at doses of 25 µg, 50 µg, and 100 µg. rhPTH(1-84) was administered subcutaneously using a Haselmeier injector pen into alternating thighs at each administration.

The lot numbers of product used in this study were:

- 25 µg doses: [redacted]
- 50 µg doses: [redacted]
- 100 µg doses: [redacted]

Reference Product(s), Dose and Mode of Administration, Lot Number:

None

Duration of Treatment:

The maximal total duration of study participation for a subject was 90 days if the maximum clinical screening, 2 treatment periods, washout, and follow-up visit durations were used. If the administrative screening period was required, the maximum duration of study participation was 182 days. Subjects were administered rhPTH(1-84) on Day 1 of each treatment period.

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Criteria for Evaluation:

Pharmacokinetics:

The PK parameters for PTH were estimated for each treatment period and included, but were not limited to:

- T_{max}: Time of maximum observed concentration sampled during a dosing interval (original and baseline-adjusted)
- C_{max}: Maximum observed concentration
- AUC_{last}: Area under the curve from the time of dosing to the last measurable concentration (original and baseline-adjusted)
- $AUC_{0\text{-}inf}$: Area under the curve extrapolated to infinity (baseline-adjusted only)
- $AUC_{0\text{-}24h}$: Area under the concentration curve from time zero to 24 hours post the first dose (original and baseline-adjusted)
- $AUC_{0\text{-}12h}$/ $AUC_{12\text{-}24h}$: Area under the concentration curve from time zero to 12 hours post the first dose/post the second dose (for BID treatment only, original and baseline-adjusted)
- λ_z: Elimination rate constant associated with the terminal (log-linear) portion of the curve (baseline-adjusted only)
- $t_{½}$: Terminal half-life (baseline-adjusted only)
- CL/F: Apparent total body clearance (baseline-adjusted only)
- Vss/F: Apparent volume of distribution at steady state (baseline-adjusted only)

Pharmacodynamics:

Pharmacodynamic parameters were estimated on both Day -1 and Day 1/2 in each treatment period (PD parameters for FGF23 were only estimated on Day 1/2).

Blood PD markers of rhPTH(1-84) activity were serum calcium (total and albumin-corrected), phosphate, magnesium, $1,25(OH)_2D$, and creatinine, and plasma FGF23.

The PD parameters estimated from the raw serum concentration data included:

- $AUC_{0\text{-}24h}$: 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 were also calculated for the calcium-phosphate product.

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In addition, serum PD parameters were estimated based on baseline-adjusted serum concentration of PD markers as follows:

- AUC_{above}: Area under the concentration-time curve that was above the baseline, from time 0 hours to 24 hours
- AUC_{below}: Area under the concentration-time curve that was below the baseline, from time 0 hours to 24 hours
- AUC_{net}: AUC_{above} - AUC_{below}
- TE_{max}: Time to maximum effect
- E_{max}: Maximum effect
- TE_{min}: Time to minimum effect
- E_{min}: Minimum effect

The following PD urinary parameters were calculated for both Day -1 and Day 1/2 in each treatment period:

- Total amount of calcium, phosphate, sodium, magnesium, citrate, cAMP, and creatinine excreted in urine in each collection period.
- Total amount of calcium, phosphate, sodium, magnesium, citrate, and cAMP excreted in each collection period relative to the total amount of creatinine excreted in the same collection interval.
- Total amount of calcium, phosphate, sodium, magnesium, citrate, cAMP, and creatinine excreted in urine over 24 hours postdose.
- Total amount of calcium, phosphate, sodium, magnesium, citrate, and cAMP excreted in urine over 24 hours postdose relative to the total amount of creatinine excreted over 24 hours postdose.
- Renal clearance (CLr) of calcium, phosphate, magnesium, and creatinine (mL/min) in each collection period.
- Fractional excretion (FE) of calcium, phosphate, and magnesium in each collection period.

Statistical methods:

The analysis populations were defined as follows:

- The screened set consists of all subjects who signed informed consent.
- The all-enrolled set consists of all subjects who signed the informed consent form and were randomized in the study.
- The safety analysis set includes enrolled subjects who received at least 1 dose of rhPTH(1-84). All analyses of safety data were based on this population.

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- The PK analysis set consists of all enrolled subjects who did not have major protocol violations that affected the validity of the PK results, received at least 1 dose of rhPTH(1-84) and had at least 1 evaluable postdose PK concentration value available for 1 dose regimen. Subjects who did not meet the inclusion criterion for hypoparathyroidism were excluded from the PK set. In the event of dosing error, proven or suspected based on PK data (extremely low postdose PTH concentrations), PK data from the subject for the specific treatment period were excluded from summary tables and figures.
- The PD analysis set consists of all enrolled subjects who did not have major protocol violations that affected the validity of the PD results, received at least 1 dose of rhPTH(1-84) and had at least 1 evaluable postdose PD value available for 1 dose regimen. Subjects who did not meet the inclusion criterion for hypoparathyroidism were excluded from the PD set. In the event of dosing error, proven or suspected based on PK data (extremely low postdose PTH concentrations), PD data from the subject for the specific treatment period were excluded. During treatments A, B, and C, if a subject took 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 were excluded from summary tables and figures.

The sample size was determined based on a similar, prior PK/PD study. The number of subjects in this study was not based on statistical power considerations because the statistical analyses were primarily descriptive, and no hypothesis testing was specified in the study.

Individual PTH concentrations (raw and baseline-adjusted) were listed and summarized with descriptive statistics (number, arithmetic mean, standard deviation [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) were listed and summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by treatment.

For serum PD evaluations, concentrations (raw and baseline-adjusted) were summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment and day. There were 2 baseline definitions, one for Day -1 and one for Day 1. For Day -1, the baseline value was 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 was 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 PD markers were calculated by subtracting the appropriate baseline values from the raw concentrations at each time point.

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Pharmacodynamic parameters of serum total calcium and albumin-corrected calcium, phosphate, magnesium, $1,25(OH)_2D$, and calcium-phosphate product were summarized with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by treatment and day.

For urine PD evaluations, individual urinary excretion and amount relative to creatinine in each collection period as well as over 24 hours were listed and summarized with descriptive statistics by treatment and day (Day -1 and Day 1/2). In addition, the CLr of calcium, phosphate, magnesium, and creatinine and the FE of calcium, magnesium, and phosphate in each collection period were summarized with descriptive statistics by treatment and day. Individual and mean urine PD parameters over time (urine collection interval) were plotted on a linear scale, overlaid by treatment (both Day -1 and Day 1/2 were presented on the same plot).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0. An overall summary of the number of subjects with treatment-emergent adverse events (TEAEs) was presented by treatment group, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation of investigational product, severe TEAEs, and TEAEs leading to death.

The number and percentage of subjects reporting TEAEs and non-treatment emergent adverse events (non-TEAEs) for each treatment group was tabulated by system organ class (SOC) and preferred term (PT); and by SOC, PT, and maximum severity. Serious TEAEs, TEAEs leading to discontinuation of investigational product, severe TEAEs, and TEAEs leading to death were summarized by SOC, PT, and treatment group. The above summaries were repeated for non-TEAEs.

The number and percentage of subjects reporting TEAEs and non-TEAEs of special interest were summarized by preferred term.

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 were presented by treatment group for hematology, biochemistry, and urinalysis variables.

Descriptive statistics for vital signs (systolic and diastolic blood pressure and pulse rate) and their changes from baseline at each post-baseline time point were presented by treatment group.

Descriptive statistics for ECG variables (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point were presented by treatment group. Electrocardiogram interpretation by visit and treatment group was summarized for all visits.

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The number and percentage of subjects with clinical laboratory values, vital signs, and ECG variable values that were considered potentially clinically important (PCI) post-baseline were tabulated by time point and treatment group.

Demographic and Baseline Characteristics:

The mean (SD) age of all 34 subjects at study entry was 47.4 (11.5) years and demographics were similar between cohorts. The majority of subjects were female (30 [88.2%] subjects) and the majority were White (32 [94.1%] subjects), and no subjects were of Hispanic or Latino ethnicity. Mean (SD) baseline characteristics of weight and body mass index (BMI) were slightly higher in subjects in Cohort 1 and Cohort 4 than in Cohort 2 and Cohort 3. Fewer subjects were categorized as obese (BMI ≥30.0 kg/m^2) in Cohort 2 than in other cohorts. Subjects' height was slightly lower in Cohort 3 than in other cohorts. Subjects key baseline characteristics are presented in the table below:

Characteristics	Cohort 1 (N=9)	Cohort 2 (N=8)	Cohort 3 (N=9)	Cohort 4 (N=8)	Total (N=34)
Weight (kg)					
n	9	8	9	8	34
Mean (SD)	96.1 (32.9)	77.9 (10.5)	84.1 (13.5)	91.7 (35.9)	87.6 (25.6)
BMI (kg/m^2)[a]					
n	9	8	9	8	34
Mean (SD)	34.1 (11.5)	27.6 (5.2)	33.1 (7.0)	32.9 (13.0)	32.03 (9.6)
BMI Category [n (%)][b]					
Underweight (<18.5)	2 (22.2)	0	0	1 (12.5)	3 (8.8)
Normal (18.5 - <25.0)	0	2 (25.0)	1 (11.1)	1 (12.5)	4 (11.8)
Overweight (25.0 - <30.0)	1 (11.1)	4 (50.0)	2 (22.2)	1 (12.5)	8 (23.5)
Obese (≥30.0)	6 (66.7)	2 (25.0)	6 (66.7)	5 (62.5)	19 (55.9)

[a] BMI is calculated as [weight(kg) / height(m)^2].
[b] Centers for Disease Control BMI categories for adults.
Cohort 1 includes Sequence AB and BA. Cohort 2 includes Sequence CB and BC. Cohort 3 includes Sequence DE and ED, Cohort 4 includes Sequence FE and EF.
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.
Source: Section 14; Table 1.2.2

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Pharmacokinetic and Pharmacodynamic Results:

Pharmacokinetic Results:

High variability in plasma PTH concentrations was observed, likely due to PK assay variability and suspected rhPTH(1-84) dosing errors (see below).

Parathyroid hormone concentrations increased rapidly following SC administration (with QD dosing or after initial dose of BID dosing) of rhPTH(1-84) independently from adjunctive oral calcium supplement. A double peak concentration-time profile was typically observed with an initial peak occurring at 5 minutes to 30 minutes after the injection and a second peak at approximately 1 hour to 2 hours. Following achievement of peak levels, PTH concentrations declined steadily and fell below the lower limit of quantification (LLOQ) of the assay (10 pg/mL) by 12 hours to 24 hours postdose. Following the second administration for BID dosing, PTH concentrations increased to a peak at approximately 13 hours to 14 hours after the initial dose, decreasing gradually thereafter to below the LLOQ at approximately 20 hours after the initial dose.

Summaries of raw and baseline-adjusted PTH plasma PK parameters are presented by treatment in the tables below.

Summary of PTH Raw Plasma PK Parameters by Treatment (Pharmacokinetic Analysis Set)

PK Parameters	rhPTH(1-84) Treatment (NO CALCIUM)		
	25 µg BID (N=9) Cohort 1	50 µg BID (N=8) Cohort 2	100 µg QD (N=17) Cohort 1+2
Predose concentration (pg/mL) Mean (CV%)	n=8 8.64 (115)	n=8 1.25 (283)	n=14 13.0 (179)
Number of samples with predose concentrations that were BLQ	4	7	8
	GM (CV% of GM)		
C_{max} (pg/mL)	n=8 144 (52.7)	n=8 215 (51.8)	n=15 381 (94.4)
AUC_{0-24} (h*pg/mL)	1135 (38.5)	1388 (28.8)	1550 (48.6)

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PK Parameters	rhPTH(1-84) Treatment (WITH CALCIUM)			
	25 µg BID (N=8) Cohort 3	50 µg BID (N=8) Cohort 4	50 µg BID (N=8) Cohort 4 (Posthoc)[a]	100 µg QD (N=17) Cohort 3+4
Predose concentration (pg/mL) Mean (CV%)	n=8 2.71 (186)	n=7 10.4 (245)	n=4 15.6 (200)	n=14 0.00(<LLOQ[b])
Number of samples with predose concentrations that were BLQ	6	5	3	14
	GM (CV% of GM)			
	n=8	n=6	n=4	n=14
C_{max} (pg/mL)	125 (80.2)	101 (106.2)	159 (70.8)	241 (69.6)
AUC_{0-24} (h*pg/mL)	660 (70.7)	607 (135)	1082 (70.0)	n=13 1107 (59.3)

AUC_{0-24}=area under the concentration curve from time zero to 24 hours post the first dose; BID=twice daily; BLQ=below the limit of quantification; C_{max}=maximum observed concentration; CV%=coefficient of variation; GM=geometric mean; n=number of observations for the analysis; LLOQ=lower limit of quantification; QD=once daily.

[a] Data from 2 subjects receiving 50 µg BID dose regimen administered with calcium supplement (Cohort 4) were excluded in the posthoc analysis due to extremely low PTH AUC_{0-24} (<300 pg*hr/mL).

[b] LLOQ=10 pg/mL.

Cohort 1 includes Sequence AB and BA. Cohort 2 includes Sequence CB and BC. Cohort 3 includes Sequence DE and ED, Cohort 4 includes Sequence FE and EF.

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.

AUC_{0-24} parameter was excluded for Subject 115-0001 (Cohort 3) in the 100 µ QD treatment period due to the number of timepoints with missing data.

Source: Section 14; Table 2.1.1, Table 2.1.1b, Table 2.1.3, and Table 2.1.3b

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Summary of PTH Baseline-adjusted PK Parameters by Treatment (Pharmacokinetic Analysis Set)

PK Parameters	rhPTH(1-84) Treatment (NO CALCIUM)		
	25 µg BID (N=9) Cohort 1	50 µg BID (N=8) Cohort 2	100 µg QD (N=17) Cohorts 1 + 2
	GM (CV% of GM)		
C_{max} (pg/mL)	n=8 137 (50.9)	n=8 214 (51.6)	n=15 339 (138)
AUC_{0-24} (h*pg/mL)	n=8 945 (29.9)	n=8 1358 (31.3)	n=15 974 (335)

PK Parameters	rhPTH(1-84) Treatment (WITH CALCIUM)			
	25 µg BID (N=8) Cohort 3	50 µg BID (N=8) Cohort 4	50 µg BID (N=8) Cohort 4 (Posthoc)[a]	100 µg QD (N=17) Cohorts 3 + 4
	GM (CV% of GM)			
C_{max} (pg/mL)	n=8 121 (83.6)	n=6 101 (106)	n=4 159 (70.8)	n=14 241 (69.6)
AUC_{0-24} (h*pg/mL)	n=8 578 (94.3)	n=6 606 (135)	n=4 1079 (70.3)	n=13 1107 (59.3)

AUC_{0-24}=area under the concentration curve from time zero to 24 hours post the first dose; BID=twice daily; C_{max}=maximum observed concentration; CV%=coefficient of variation; GM=geometric mean; n=number of observations for the analysis; QD=once daily

[a] Data from 2 subjects receiving 50 µg BID dose regimen administered with calcium supplement (Cohort 4) were excluded in the posthoc analysis due to extremely low PTH AUC_{0-24} (<300 pg*hr/mL).

Cohort 1 includes Sequence AB and BA. Cohort 2 includes Sequence CB and BC. Cohort 3 includes Sequence DE and ED, Cohort 4 includes Sequence FE and EF.

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.

AUC_{0-24} parameter was excluded for Subject 115-0001 (Cohort 3) in the 100 µ QD treatment period due to the number of timepoints with missing data.

Source: Section 14; Table 2.1.4 and Table 2.1.4b

In summary, the AUC_{0-24} and C_{max} increased as rhPTH(1-84) dose increased. Dose proportionality, however, was not observed, and high PK variability was observed within a subject, within a cohort, as well as across cohorts.

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- When rhPTH(1-84) was administered without calcium supplement, raw and baseline-adjusted plasma PTH geometric mean C_{max} following the 100 µg QD dose were greater than those observed for the 50 µg and 25 µg BID dose regimens (approximately 1.6-fold and 2.5-fold greater, respectively). Raw and baseline-adjusted plasma PTH geometric mean AUC_{0-24} following the 100 µg QD dose without calcium supplement were 1.1- and 0.7-fold of those observed for the 50 µg BID dose regimen and were 1.4- and 1.0-fold greater than observed for the 25 µg BID dose regimen, respectively. Intersubject variability (CV% of geometric mean) in raw and baseline-adjusted PTH exposure, AUCs and C_{max}, was higher following the 100 µg QD dose regimen without calcium supplement than the BID dose regimens without calcium supplement.
- When rhPTH(1-84) was administered with calcium supplement, raw and baseline-adjusted plasma PTH geometric mean C_{max} following the 100 µg QD dose were greater than those observed for the 50 µg and 25 µg BID dose regimens (approximately 2.4-fold and 2.0-fold greater, respectively). Raw and baseline-adjusted plasma PTH geometric mean AUC_{0-24} following the 100 µg QD dose with calcium supplement were 1.8-fold of those observed for the 50 µg BID dose regimen and were approximately 1.9-fold greater than observed for the 25 µg BID dose regimen, respectively. Intersubject variability (CV% of geometric mean) in baseline-adjusted PTH exposure, AUCs and C_{max}, was significantly higher following the 50 µg BID dose regimen with calcium supplement than the 100 µg QD and the 25 µg BID dose regimens with calcium supplement.
- Two subjects in Cohort 4 (50 µg BID with calcium supplement) presented an AUC_{0-24} lower than 300 h*pg/mL, indicating only partial dose of rhPTH(1-84) may have been received by the subjects. After removing these 2 subjects (posthoc analysis), dose-proportional increase in AUC_{0-24} was observed: geometric means of AUC_{0-24} were similar between the 100 µg QD and 50 µg BID dose regimens and doubled from the 25 µg BID to 50 µg BID dose regimens.

Both the PTH assay as well as possibly dosing inaccuracy likely contributed to the high PK variability observed in this study.

- Historical PK data showed that baseline-adjusted PK parameters such as AUC demonstrated dose proportionality; however, this was not observed in this study. This difference was surmised to be partly due to variation in the PTH assay between cohorts (lower PTH concentrations in the standards used for Cohort 1 compared with those used in Cohort 2 sample testing) and partly due to PK variability in subjects between Cohort 1 and Cohort 2. While the preparation of standards for Cohort 3 was more accurate than those of Cohort 1 and Cohort 2, the underlying issue with the preparations of standards persisted for Cohorts 1 through 3. The revised procedure which included the preparation of independent quality controls in the PTH-depleted plasma was validated and implemented only in the preparation of Cohort 4 standards.

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Therefore, the standards used for Cohort 4 were accurate, and PTH PK data observed in Cohort 4 can be considered the most accurate.

- Based on observed PTH PK data, 3 (3/33 [10%]) subjects had confirmed dosing errors or partial dose received with complete missed dose based on all postdose PTH concentrations reported as BLQ or partial dose based on AUC_{0-24} <300 h*pg/mL. This suggests that dosing inaccuracy may have contributed to the variability in PTH concentrations. Differences were observed in PTH PK parameters for each rhPTH(1-84) dose (25 µg BID, 50 µg BID, and 100 µg QD) when rhPTH(1-84) was given with (Cohort 3 and Cohort 4) and without (Cohort 1 and Cohort 2) calcium supplements. At each rhPTH(1-84) dose regimen (25 µg BID, 50 µg BID, and 100 µg BID), PTH C_{max} and AUC_{0-24} were higher when calcium supplement was withheld on the day when rhPTH(1-84) was administered (Cohort 1 and Cohort 2) compared with when calcium supplement was not withheld (Cohort 3 and Cohort 4). Such difference is believed to be contributed to PTH assay variability by cohort due to the sequential enrollment by cohort.

Pharmacodynamic Results:

Descriptive summaries of PD results were presented by comparing PD parameters calculated at Day 1 when subjects were receiving rhPTH(1-84) with or without oral calcium supplement at 25 µg BID, 50 µg BID, or 100 µg QD dose regimens with Day -1 when subjects were receiving their usual regimen of supplemental oral calcium and active vitamin D.

Results of serum calcium and urinary excretion of calcium are presented in this synopsis; results on other PD markers are presented in the body of the clinical study report.

Similar serum calcium concentrations were observed between treatment regimens of rhPTH(1-84) and the usual regimen of supplemental oral calcium and active vitamin D in Cohort 1 and Cohort 2 (no oral calcium supplement). However, higher serum calcium concentrations were observed on day of rhPTH(1-84) dosing with oral calcium supplement (Cohort 3 and Cohort 4) as compared with those observed when subjects were receiving their usual regimen of supplemental oral calcium and active vitamin D. There were no clear differences in the serum calcium concentrations among the 3 dose regimens of rhPTH(1-84) (25 µg BID, 50 µg BID, and 100 µg QD). Serum calcium (albumin-corrected) concentrations above the upper limit of the laboratory reference range (2.55 mmol/L) were observed in 3 subjects (Cohorts 1, 3, and 4) during the usual regimen of supplemental oral calcium and active vitamin D and/or during the 25 µg BID, 50 µg BID, and/or 100 µg QD dose regimens of rhPTH(1-84). Persistent serum calcium (albumin-corrected) concentrations below 2 mmol/L were consistently observed in 9 subjects enrolled in Cohort 1 (2 subjects), Cohort 2 (5 subjects), and Cohort 3 (2 subjects).

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The administration of rhPTH(1-84) markedly reduced urinary excretion of calcium as compared with the usual regimen of supplemental oral calcium and active vitamin D, and the magnitude and duration of the effect were dependent on rhPTH(1-84) dose regimens. When rhPTH(1-84) was co-administered with supplemental oral calcium, its effect on reducing urinary calcium excretion was attenuated.

- The reduction in urinary calcium excretion began after dosing with rhPTH(1-84), with or without calcium supplement, and continued through 10 hours to 12 hours postdose for the 100 µg QD dose regimen. In contrast, the effect was sustained through 24 hours postdose for both the 25 µg BID and 50 µg BID dose regimens.
- When subjects were on their usual supplement treatment (Day -1), mean 24-hour urine calcium excretion values were all above the normal range (>7.5 mmol/24 hour), ranging from 8.88 mmol to 10.7 mmol. When subjects received rhPTH(1-84) doses (Day 1), mean 24-hour urine calcium excretion was reduced, ranging from 4.31 mmol to 8.81 mmol. For subjects who received no adjunctive calcium supplement during rhPTH(1-84) dosing, the mean 24-hour urine calcium excretion was lower in subjects who received BID dose regimens compared with the QD dose regimen (4.90 mmol/24 hours, 5.14 mmol/24 hours, and 6.04 mmol/24 hours for 25 µg BID, 50 µg BID, and 100 µg QD, respectively). For subjects who received adjunctive calcium supplement during rhPTH(1-84) dosing, the mean 24-hour urine calcium excretion was lower in subjects who received the 25 µg BID and 100 µg QD dose regimens compared with the 50 µg BID dose regimen (7.44 mmol/24 hours, 8.81 mmol/24 hours, and 7.93 mmol/24 hours for 25 µg BID, 50 µg BID, and 100 µg QD, respectively).
- Urinary calcium excretion over 24 hours (Day 1) was reduced by 47.6%, 49.6%, and 32.0% for the 25 µg BID, 50 µg BID, and 100 µg QD dose regimen without oral calcium supplement, respectively, in comparison with excretion observed when subjects were receiving their usual regimen of supplemental oral calcium and active vitamin D (Day -1). Urinary calcium excretion over 24 hours (Day 1) was reduced by 31.1%, 17.7%, and 18.4% for 25 µg BID, 50 µg BID, and 100 µg QD dose regimens with oral calcium supplement, respectively, in comparison with excretion observed in Day -1.
- Hypercalciuria (defined as calciuria >6.25 mmol/24 hour in female; >7.5 mmol/24 hour in male) was observed in 14 of the 17 (82%) subjects included in the PK/PD analysis of Cohorts 1 and 2 when subjects were receiving their usual regimen of supplemental oral calcium and active vitamin D. The rate of hypercalciuria, however, was reduced while on rhPTH(1-84) regimens without adjunctive calcium supplement: 29% (2/7 subjects) for 25 µg BID, 43% (3/7 subjects) for 50 µg BID, and 43% (6/14 subjects) for 100 µg QD dose regimens.

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Hypercalciuria was observed in 15 of the 17 (88%) subjects included in the PK/PD analysis of Cohort 3 and Cohort 4 when subjects were receiving their usual supplemental oral calcium and active vitamin D regimen. The rate of hypercalciuria, however, was reduced slightly while subjects were receiving rhPTH(1-84) regimens and calcium supplement with 75% (6/8 subjects) for 25 µg BID, 83% (5/6 subjects) for 50 µg BID, and 79% (11/14 subjects) for 100 µg QD dose regimens.

The administration of rhPTH(1-84) markedly reduced serum phosphate levels and increased urinary phosphate excretion, in comparison with levels observed when the subjects were receiving their usual regimen of supplemental oral calcium and active vitamin D. The changes in mean serum phosphate concentrations following treatment with rhPTH(1-84) were consistent across rhPTH(1-84) dose regimens and independent from adjunctive calcium supplement.

Safety Results:

Overall, 18 (52.9%) subjects in Cohorts 1 through 4 experienced a total of 58 TEAEs during the study, 26 of which were considered to be related to the investigational product. When rhPTH(1-84) was administered without calcium supplement, 3 (33.3%) subjects reported 3 TEAEs during the 25 µg BID dosing, 1 (12.5%) subject reported 1 TEAE during the 50 µg BID dosing, and 4 (23.5%) subjects reported 9 TEAEs during the 100 µg QD dosing. When rhPTH(1-84) was administered with calcium supplement, 5 (62.5%) subjects reported 10 TEAEs during the 25 µg BID dosing, 3 (37.5%) subjects reported 15 TEAE during the 50 µg BID dosing, and 7 (41.2%) subjects reported 20 TEAEs during the 100 µg QD dosing. Higher percentages of subjects reporting TEAEs were observed in subjects receiving rhPTH(1-84) with adjunctive calcium supplement, regardless of the dose regimens, compared with subjects receiving rhPTH(1-84) without calcium supplement. The clinical significance of the observation is unclear. Serum calcium concentrations tended to be higher when adjunctive calcium was administered on the day of rhPTH(1-84) dosing, although generally remaining within the normal range.

Overall, the most commonly reported TEAEs were nausea with 7 events in 7 (20.6%) subjects, dizziness with 6 events in 6 (17.6%) subjects, headache with 10 events in 4 (11.8%) subjects, hot flush with 4 events in 4 (11.8%) subjects, and hypoaesthesia and tachycardia with 2 events in 2 (5.9%) subjects each. All other TEAEs were only reported by 1 subject each. Of the 58 TEAEs reported, 45 were mild and 13 moderate in severity. No subjects experienced a severe TEAE. All reported TEAEs but 2 (pain in extremity and fatigue) had outcomes of recovered/resolved at the time of study completion. No TEAEs of special interest (hypercalcaemia, hypocalcaemia, and hypercalciuria) were reported during this study.

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No serious TEAEs were reported, and there were no reports of TEAEs that resulted in death or led to the discontinuation of rhPTH(1-84).

A total of 9 (26.5%) subjects reported 18 non-TEAEs in all treatments group except in the 25 µg BID dose regimen without calcium supplement. The most common non-TEAEs were headache with 6 events in 6 (17.6%) subjects and nausea with 2 events in 2 (5.9%) subjects. All other non-TEAEs were only reported by 1 subject each.

In general, there were no clinically meaningful changes from baseline or apparent differences between treatment groups in clinical laboratory test results, vital sign measurements, and 12-lead ECG results. One PCI clinical laboratory test result of haematocrite decreased was reported as TEAE which was deemed moderate in intensity and not related to study drug and resolved in 23 days. No vital sign measurements or 12-lead ECG results were reported as TEAEs.

One subject presented a confirmed positive anti-drug antibody (ADA) result at follow-up. No apparent impact on PTH concentrations or on PD parameters was observed. No injection site reaction or signs and symptoms consistent with hypersensitivity reaction were reported for this subject at any point in the study.

Administration of rhPTH(1-84), whether administered as QD or BID dose regimens, was generally safe and well tolerated by subjects taking part in this study.

CONCLUSIONS

- No clear differences in serum calcium concentrations were observed among the 3 rhPTH(1-84) dose regimens (25 µg BID, 50 µg BID, and 100 µg QD). For rhPTH(1-84) administered alone, similar serum calcium concentrations were observed during treatment compared with the usual regimen of supplemental oral calcium and active vitamin D, while for rhPTH(1-84) co-administered with supplemental oral calcium, higher serum calcium concentrations were observed during treatment compared with the usual regimen of supplemental oral calcium and active vitamin D.
- Twenty-four hour urinary calcium was incrementally lower during rhPTH(1-84) BID dose regimens compared with the QD dose regimen. rhPTH(1-84) markedly reduced the urinary calcium excretion and the rate of hypercalciuria compared with supplemental oral calcium and active vitamin D. The effect of rhPTH(1-84) to reduce urinary calcium excretion was attenuated when rhPTH(1 84) was co-administered with supplemental oral calcium.
- High PK variability was seen and dose proportionality of PK was not observed in this study. This was likely due to PK assay variability and suspected rhPTH(1-84) dosing errors.
- The safety profile, whether administered as QD or BID dose regimens, is similar to what is known of rhPTH(1-84). There were no reports of severe AEs or TESAEs.

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