Statistical Analysis Plan

NCT Number: NCT05137730

Title: A Randomized, Open-label, Single-center, Single-dose Study to Evaluate the Relative Bioavailability of a New Formulation Compared with the Approved Formulation of Recombinant Human Parathyroid Hormone (rhPTH[1-84]) and to Assess Dose Linearity of the New Formulation in Healthy Subjects

Study Number: TAK-834-1001

Document Version and Date: Final; 21 December 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-834-1001

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Phase 1

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Based on:

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Approval Signatures

Study Title: A Randomized, Open-label, Single-center, Single-dose Study to Evaluate the Relative Bioavailability of a New Formulation Compared with the Approved Formulation of Recombinant Human Parathyroid Hormone (rhPTH[1-84]) and to Assess Dose Linearity of the New Formulation in Healthy Subjects

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Study Title: A Randomized, Open-label, Single-center, Single-dose Study to Evaluate the Relative Bioavailability of a New Formulation Compared with the Approved Formulation of Recombinant Human Parathyroid Hormone (rhPTH[1-84]) and to Assess Dose Linearity of the New Formulation in Healthy Subjects

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ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
$AUC_{extrap}\%$	area under the curve from the last quantifiable concentration to infinity, expressed as a percentage of AUC_{∞}
$AUC_{extrap}\%_{obs}$	area under the curve from the last quantifiable concentration to infinity, calculated using the observed value of the last quantifiable concentration, expressed as a percentage of AUC_{∞}
$AUC_{extrap}\%_{pred}$	area under the curve from the last quantifiable concentration to infinity, calculated using the predicted value of the last quantifiable concentration, expressed as a percentage of AUC_{∞_pred}
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{∞_obs}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{∞_pred}	area under the concentration-time curve from time 0 to infinity, calculated using the predicted value of the last quantifiable concentration
AUC_{24}	area under the concentration-time curve from 0 to 24 hours postdose
BLQ	below the lower limit of quantitation
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CRU	clinical research unit
CV%	coefficient of variation
ECG	electrocardiogram
[redacted]	[redacted]
EOT	end of treatment
ET	early termination
Geom CV%	geometric percent coefficient of variation
Geom mean	geometric mean
GMR	geometric mean ratio
ICF	informed consent form
ISCV	intra-subject coefficient of variation
LSM	least-squares mean
mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations

[redacted]	[redacted]
PK	pharmacokinetic
PT	preferred term
PTH	parathyroid hormone
rhPTH	recombinant human parathyroid hormone
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
SOP	Standard Operating Procedures
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TFL	table, figure, and listing
t_{last}	time of the last measurable concentration
t_{max}	time of first occurrence of C_{max}
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Study Primary Objectives

Part I (Relative Bioavailability):

To evaluate the relative bioavailability of a new formulation (Formulation A; test) compared with the approved formulation (Formulation B; reference) of recombinant human parathyroid hormone (rhPTH) (1-84) following the administration of single subcutaneous (SC) doses of 100 µg rhPTH(1-84) in healthy subjects.

Part II (Dose Linearity):

To assess the dose linearity of the new formulation (Formulation A) of rhPTH(1-84) following the administration of SC doses of 25 µg, 50 µg, 75 µg, and 200 µg rhPTH(1-84) in healthy subjects.

1.1.2 Study Secondary Objectives

Part I (Relative Bioavailability):

To assess the safety and tolerability of SC injections of rhPTH(1-84) administered as Formulation A and Formulation B in healthy subjects.

Part II (Dose Linearity):

To assess the safety and tolerability of SC injections of rhPTH(1-84) administered as Formulation A in healthy subjects.

1.1.3 Study Exploratory Objectives

[redacted]

1.2 Endpoints

Note: AUC_{∞} and $AUC_{extrap}\%$ refer to AUC_{∞_obs} and $AUC_{extrap}\%_{\_obs}$ unless stated otherwise.

1.2.1 Primary Endpoints

Parts I (Relative Bioavailability) and II (Dose Linearity):

The following pharmacokinetic (PK) parameters for baseline-adjusted plasma parathyroid hormone (PTH) concentrations for each treatment will be derived to evaluate relative bioavailability (Part I) and dose linearity (Part II):

- *Maximum observed concentration (C_{max})*
- *Area under the concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last})*
- *Area under the concentration-time curve from time 0 to infinity (AUC_{∞})*

1.2.2 Secondary Endpoints

The following safety endpoints will be recorded for both Part I (Relative Bioavailability) and Part II (Dose Linearity):

- *Number, severity, seriousness, and causality of treatment-emergent adverse events (TEAEs)*
- *Change in vital signs, electrocardiograms (ECGs), and laboratory results (hematology, chemistry, and urinalysis) from baseline*

1.2.3 Exploratory Endpoints

[redacted]

1.2.4 Additional Endpoints

Parts I (Relative Bioavailability) and II (Dose Linearity):

The following additional PK parameters will be estimated for unadjusted and baseline-adjusted plasma PTH concentrations for each single-dose treatment:

- *Area under the curve from the last quantifiable concentration to infinity, expressed as a percentage of AUC_∞ (AUC_{extrap}%)*
- *Time of first occurrence of C_{max} (t_{max})*
- *Time of the last measurable concentration (t_{last})*
- AUC_{∞_pred} (Part I only)
- $AUC_{extrap}\%_{\_pred}$ (Part I only)
- *Terminal disposition phase half-life* ($t_{1/2z}$; baseline-adjusted only)

The following additional PK parameters will be computed for unadjusted plasma PTH concentrations for each treatment:

- C_{max}
- AUC_{last}
- AUC_∞

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a randomized, open-label, single-center, two-part study to assess the relative bioavailability of a single SC dose of rhPTH(1-84) administered as the new formulation (Formulation A; test) and the approved formulation (Formulation B; reference) in Part I (Relative Bioavailability) of the study and to assess dose linearity of Formulation A in Part II (Dose Linearity) of the study. Both parts may be conducted concurrently.

Part I (Relative Bioavailability)

Part I (Relative Bioavailability) will be conducted as a randomized, two-sequence, two-period, crossover design.

Subjects in each treatment period will receive rhPTH(1-84) as a single 100 µg SC injection administered in the mid-thigh as either Formulation A or Formulation B depending on the randomized (1:1) treatment sequence as indicated in Table 2.a.

Blood samples for plasma PTH PK and serum calcium and albumin concentrations will be collected predose and for 24 hours following each rhPTH(1-84) administration.

There will be a drug washout of 96 (±1) hours between the administration of rhPTH(1-84) in each period.

Table 2.a Study Scheme for Part I (Relative Bioavailability)

Treatment Sequence	N	Treatment Period 1	Drug Washout (Hours)	Treatment Period 2
1	42	A	96 (±1)	B
2	42	B	96 (±1)	A

The planned dose levels of rhPTH(1-84) to be evaluated are outlined in Table 2.c.

Subjects will remain in the clinical research unit (CRU) until completion of the last postdose assessment on Day 2 of Treatment Period 2. If clinically significant findings are observed upon discharge, subjects may either be kept in the CRU for observation or return to the CRU for re-evaluation per Investigator's discretion.

Part II (Dose Linearity)

Part II (Dose Linearity) will be conducted as a randomized, four-sequence, four-period, crossover design.

Subjects in each treatment period will receive rhPTH(1-84) Formulation A as a single SC injection administered in the mid-thigh at a dose level depending on the randomized (1:1:1:1) treatment sequence as indicated in Table 2.b. *If possible, the same location in the same thigh will be used for all treatment periods. If the same thigh cannot be used, the alternative mid-thigh may be used.*

Blood samples for plasma PTH PK will be collected predose and for 24 hours following each rhPTH(1-84) administration.

There will be a drug washout of 48 (±1) hours between the administration of rhPTH(1-84) in each period.

Table 2.b Study Scheme for Part II (Dose Linearity)

Treatment Sequence	N	Treatment Period 1	Drug Washout (Hours)	Treatment Period 2	Drug Washout (Hours)	Treatment Period 3	Drug Washout (Hours)	Treatment Period 4
1	3	C	48 (±1)	D	48 (±1)	E	48 (±1)	F
2	3	D	48 (±1)	F	48 (±1)	C	48 (±1)	E
3	3	E	48 (±1)	C	48 (±1)	F	48 (±1)	D
4	3	F	48 (±1)	E	48 (±1)	D	48 (±1)	C

The planned dose levels of rhPTH(1-84) to be evaluated are outlined in Table 2.c.

Subjects will remain in the CRU until completion of the last postdose assessment on Day 2 of Treatment Period 4. If clinically significant findings are observed upon discharge, subjects may either be kept in the CRU for observation or return to the CRU for re-evaluation per Investigator's discretion.

Parts I (Relative Bioavailability) and II (Dose Linearity):

[redacted]

Safety and tolerability will be assessed by TEAEs including injection site reaction assessments, laboratory evaluations, physical examinations, 12-lead ECGs, and vital signs.

All subjects who received a dose of study drug (including subjects who terminate from the study early) will return to the CRU 16 (± 2) days (return visit) and 32 (± 2) days (follow-up visit) after the last study drug administration for collection of blood [redacted] *to determine if any adverse events (AEs) have occurred since the last study visit.*

The planned dose levels of rhPTH(1-84) to be evaluated in both study parts are outlined in Table 2.c.

Table 2.c Planned Dose Levels

Treatment	Formulation	Dose Level	Dose Form	Route of Administration
Part I (Relative Bioavailability)				
A	Formulation A (Test)	100 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh
B	Formulation B (Reference)	100 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh
Part II (Dose Linearity)				
C	Formulation A	25 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh
D	Formulation A	50 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh
E	Formulation A	75 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh
F	Formulation A	200 µg rhPTH(1-84)	Lyophilized powder to be reconstituted for SC dosing	SC injection in mid-thigh

The study schematic for Part I is presented in Figure 2.a:

Figure 2.a Study Schematic (Part I [Relative Bioavailability])

Pretreatment	Treatment Periods 1-2 (a)			Discharge (b)	Return Visit (c)	Follow up (c)
Screening	Predose Assessments	Dosing and Study Assessments	Safety and PK Assessments		Safety [redacted]	Safety [redacted]
Day -21 to first dosing	Day -1	Day 1	Days 1-2	Day 2 of last treatment period	16 (±2) days after last dose	32 (±2) days after last dose
	◄--------- Confinement (d) ---------►					

(a) There will be a washout period of 96 (±1) hours between rhPTH(1-84) dosing in each treatment period.
(b) If clinically significant findings are observed upon discharge, subjects may either be kept in the CRU for observation or return to the CRU for re-evaluation per Investigator's discretion.
(c) All subjects who received a dose of study drug (including subjects who terminate from the study early) will return to the CRU 16 (± 2) days (return visit) and 32 (± 2) days (follow-up visit) after the last study drug administration for collection of blood [redacted] to determine if any AEs have occurred since the last study visit.
(d) Subjects will start the confinement on Day -1 of Treatment Period 1 and remain confined until Day 2 of Treatment Period 2. Subjects may be admitted earlier for coronavirus disease 2019 (COVID-19) testing not related to study protocol as per CRU requirements.

The study schematic for Part II is presented in Figure 2.b:

Figure 2.b Study Schematic (Part II [Dose Linearity])

Pretreatment	Treatment Periods 1-4 (a)			Discharge (b)	Return Visit (c)	Follow up (c)
Screening	Predose Assessments	Dosing and Study Assessments	Safety and PK Assessments		Safety [redacted]	Safety [redacted]
Day -21 to first dosing	Day -1	Day 1	Days 1-2	Day 2 of last treatment period	16 (±2) days after last dose	32 (±2) days after last dose
	◄--------- Confinement (d) ---------►					

(a) There will be a washout period of 48 (±1) hours between rhPTH(1-84) dosing in each treatment period.
(b) If clinically significant findings are observed upon discharge, subjects may either be kept in the CRU for observation or return to the CRU for re-evaluation per Investigator's discretion.
(c) All subjects who received a dose of study drug (including subjects who terminate from the study early) will return to the CRU 16 (± 2) days (return visit) and 32 (± 2) days (follow-up visit) after the last study drug administration for collection of blood [redacted] to determine if any AEs have occurred since the last study visit..
(d) Subjects will start the confinement on Day -1 of Treatment Period 1 and remain confined until Day 2 of Treatment Period 4. Subjects may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

Part I (Relative Bioavailability):

The sample size of 76 subjects was calculated to achieve 90% confidence interval (CI) around the geometric mean ratio of the test and reference formulations within the limits of 0.80 to 1.25 for AUC and C_{max}. The true test to reference ratio was assumed to be 0.93, and 90% target power was used for the sample size determination. The intra-subject coefficient of variation (ISCV) was assumed to be 32.2%, the upper end of the two-sided 50% confidence limit of the ISCV for C_{max} estimated in study SHP634-103 (the ISCV observed in study SHP634-103 was higher for C_{max} than for AUC). Part I (Relative Bioavailability) will enroll 84 subjects to allow for up to eight dropouts.

Part II (Dose Linearity):

The sample size (N=12) *for Part II (Dose Linearity) is not based on any statistical considerations but is considered sufficient for dose linearity evaluation.*

5.0 ANALYSIS SETS

5.1 Safety Set

All subjects who received at least one dose of the study drug will be included in the safety evaluations.

5.2 Pharmacokinetic Set

All subjects who have at least one measurable predose (baseline) and one postdose concentration of PTH will be included in the statistical analyses.

Subjects who do not comply sufficiently with the protocol or who do not display an evaluable PK profile (eg, exposure to treatment, availability of measurements, and absence of major protocol violations) will be excluded from the descriptive statistics and statistical analyses.

Details on criteria for excluding subjects from the PK analysis will be described in the Clinical Pharmacology Analysis Plan (CPAP).

5.3 [redacted]

[redacted]

5.4 [redacted]

[redacted]

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All PK analyses will be conducted using Phoenix® WinNonLin® Version 8.1, or higher. All statistical analyses will be conducted using SAS® Version 9.4, or higher. All data recorded on the case report form (CRF) will be listed by subject. All tables, figures, and listings (TFLs) shells and numbering list will be included and specified in the TFL Shells document.

The number of observations (n) will be presented as an integer (no decimal places), arithmetic mean (mean), median, and geometric mean (geom mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (geom CV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be reported with 1 more level of precision than the individual data. The geometric mean ratios (GMRs) and 90% CIs around the ratios will be reported using 2 decimal places.

Concentration values below the lower limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. The BLQ values associated with PTH, calcium, and albumin concentrations will be set to ½ the lower limit of quantitation for the calculation of summary statistics, the generation of concentration plots, the calculation of albumin-corrected concentrations ([redacted] only), and the calculation of PK [redacted] parameters, as appropriate, in accordance with Celerion Standard Operating Procedures (SOPs).

A subject's PK parameter data will be included in the listings but may be excluded from the descriptive and inferential (analysis of variance [ANOVA]) statistics if one or more of the following criteria are met:

- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and Celerion Pharmacokinetic Scientist)

The details on PTH PK parameter calculations and TFLs will be outlined in the CPAP and TFL Shells document including specifics on the following:

- Insufficient data to determine a reliable $t_{½z}$ value and other λ_z-dependent parameters
- Unadjusted and baseline-adjusted PK parameters presented by part and treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables
- Unadjusted and baseline-adjusted concentration data presented by part and treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- Concentration data file used for PK analysis
- PK parameter WinNonlin® output file used to generate the TFLs
- ANOVA results presented in in-text and end-of-text tables (Part I only)
- The non-parametric analysis of t_{max} will be presented as end-of-text table (Part I only)
- Dose linearity analysis presented in in-text and end-of-text tables (Part II only)
- Dose linearity of PK parameters (baseline-adjusted AUC and C_{max}) will also be assessed graphically (Part II only)
- Mean unadjusted and baseline-adjusted concentration-time figures presented as in-text and end-of-text figures
- Individual unadjusted and baseline-adjusted concentration-time figures presented in Appendix 16.2.6.

The details on [redacted] TFLs will be outlined in the CPAP and TFL Shells document including specifics on the following:

- [redacted]

- Unadjusted and baseline-adjusted concentration data, [redacted] presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables
- [redacted]
- [redacted]
- ANOVA results presented in in-text and end-of-text tables
- Mean unadjusted and baseline-adjusted concentration-time figures, [redacted] presented as in-text and end-of-text figures
- Individual unadjusted and baseline-adjusted concentration-time figures, [redacted] presented in Appendix 16.2.6.

Continuous demographic and safety data will be summarized descriptively. For the categorical variables, the count and percentages of each value will be tabulated, where applicable. The denominator for the percent calculation will be the safety set for overall summaries, and the number of subjects dosed for each treatment in by-treatment summaries. For continuous variables, the number of observations, mean, SD, minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers. Study baseline is defined as the last observation prior to the first dose of the study, and period baseline is defined as the last observation prior to dosing in each period. When calculating change from baseline, period baseline will be used when available.

6.1.1 Handling of Treatment Misallocations

Subject data will be analyzed according to the treatments administered.

6.2 Study Information

A study information table will be generated including the following items for each study part: date of first subject's signed informed consent form, date of dosing, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Drug Dictionary, and SAS® version used for creating the datasets.

6.3 Disposition of Subjects

For each study part, disposition of subjects (number of subjects dosed, completed the study, discontinued from the study and/or study drug, and reason(s) for discontinuation(s)) will be summarized and listed by subject.

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographics

Demographic and baseline characteristics will be summarized by study part based on the safety set. Summary statistics (n, mean, SD, minimum, median, and maximum) will be generated for continuous variables (age, weight, height, and body mass index [BMI]) and the number and percentages of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI measured at screening will be used in the summaries. Demographic data will also be listed as recorded on the CRF, including the date of informed consent and protocol version.

6.4.2 Medical History and Concurrent Medical Conditions

Medical history to be recorded will include determining whether the subject has any significant conditions or diseases that resolved at or before signing the informed consent form (ICF). All medical history reported by the subject will be recorded regardless of how long ago it may have occurred. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed.

Any medical condition starting or worsening after taking the first dose of study drug will be classified as a TEAE. All medical history will be coded using MedDRA® Version 24.1. All medical history and concurrent medical conditions will be listed. If available, the medical history and concurrent medical condition listings will include the coded term (preferred term [PT] and system organ class [SOC]), start date (if known) and end date (if known) or whether the condition was ongoing, and a description of the condition or event. No summaries or statistical analysis will be performed for these data.

6.5 Medication History and Concomitant Medications

Medication history to be obtained includes any medication stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between ICF and the end of the study. All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Drug Dictionary Version 01Sep2021_b3 and listed. If available, the listings will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time (if known), or whether it continued after study completion, and indication for use. No summaries or statistical analysis will be performed for these data.

6.6 Efficacy Analysis

Not applicable.

6.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and relationship of TEAEs, and changes from baseline in the subjects' clinical laboratory results, vital signs, and 12-lead ECGs using the safety set. Clinically significant laboratory values, vital signs, and ECG results will be reported as AEs. All clinical safety data will be listed by study part, subject, period, and assessment time points, including rechecks, unscheduled assessments, and early termination (ET), chronologically. Subjects from both parts will be included in the same listing, but will be delineated by study part.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators. Summaries will be presented separately for each part.

6.7.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to study drug (related or not related), frequency, action relative to the study drug, and whether the AE is of special interest, as recorded in the CRF. All AEs occurring during this study will be coded using the MedDRA® Version 24.1. Only TEAEs will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after the first dose of study drug administered in the study. Each TEAE will be attributed to the treatment prior to and the closest to the AE based on the AE onset date and time.

If the onset time of an AE is missing and the onset date is the same as a treatment dosing date, then the AE will be counted under the treatment given on the same day. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent for the most recent treatment administered. If the onset date of an AE is missing, then the AE will be considered treatment emergent and attributed to the first treatment received. If severity is missing, the AE will be counted as severe, and if relationship is missing, the AE will be counted as related.

Summary of TEAEs will be presented for each study part. TEAEs will be tabulated by treatment (including overall), SOC, and PT. Summary tables will include number of subjects reporting the TEAE and as percent of safety set by treatment and overall. The most commonly reported non-serious TEAEs (ie, those events reported by >5% of subjects [or >1 subject if fewer than 20 subjects] in one or more treatments, excluding serious adverse events [SAEs]) will also be summarized. The denominators for percent calculations will be the number of subjects dosed for each treatment. In a similar way, TEAEs will be summarized as number of TEAEs and percentage of TEAEs for each treatment and overall.

Additional TEAE summary tables will be presented by severity and relationship to study drugs. If a subject has multiple TEAEs with different severity levels within the same PT, the subject will be counted in the most severe category only. If a subject has both related and unrelated TEAEs with the same PT, the subject will be counted as having related TEAEs.

An overview summary of TEAEs table, including number of subjects with TEAEs, SAEs, treatment-related TEAEs, treatment-related SAEs, TEAEs by severity, and AEs leading to discontinuation will be provided.

Should any SAEs (including all-cause mortalities) occur, they will be summarized the same way as TEAEs. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report.

6.7.2 Adverse Events of Special Interest (AESI) (if applicable)

The AESIs will include hyper- and hypocalcemia as determined by the investigator or designee. If applicable, AESIs will be summarized similarly to TEAEs in tables reporting number of subjects and number of events. AESIs will be identified in the listing and discussed in the text of the study report.

6.7.3 Clinical Laboratory Evaluation

In each study part, serum chemistry, hematology, and urinalysis will be performed at screening, check-in, at predose and 24 hours postdose in each period, and at end of treatment (EOT) (or ET, if applicable).

Urine drug screening will be carried out at screening and Period 1 Day -1 only, in both study parts. TSH, free T4, PTH, and serum Vitamin D will be tested at screening. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the investigator.

For baseline and post-baseline laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for laboratory test results and change from period baseline by time point of collection for each study part. Period baseline is defined as the last assessment including rechecks or unscheduled assessments taken prior to the first dose in each period. Post-baseline unscheduled or recheck assessments will not be used in analysis. All clinical laboratory data will be listed by study part and subject.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. For each laboratory test, a shift table will be developed comparing the frequency and percentage of the results at baseline (above reference range [H], within reference range [N], or below reference range [L]) with the postdose time points for each treatment. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

6.7.4 Vital Signs

In each study part, vital sign measurements of pulse rate and blood pressure will be recorded at screening, check-in, at predose and 1, 4, 8, and 24 hours postdose in each period, and at EOT (or ET, if applicable). Temperature will be recorded at screening, check-in, at 1, 4, 8, and 24 hours postdose in each period, and at EOT (or ET if applicable). Respiration rate will be recorded at screening and check-in. Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the investigator.

For baseline and post-baseline, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for pulse rate and blood pressure results and change from period baseline by time point of collection for each study part. Period baseline is defined as the last assessment including rechecks or unscheduled assessments taken prior to the first dose in each period. Post-baseline unscheduled or recheck assessments will not be used in analysis. Vital sign data will be listed by study part and subject.

6.7.5 12-Lead Electrocardiogram

In each study part, single 12-lead ECGs will be collected at screening, check-in, at predose and 1, 4, 8, and 24 hours postdose in each period, and at EOT (or ET, if applicable). Additional unscheduled ECGs may be taken at other times, if deemed necessary by the investigator.

For baseline and post-baseline, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for ECG results and change from period baseline by time point of collection for each study part. Period baseline is defined as the last assessment including rechecks or unscheduled assessments taken prior to the first dose in each period. Post-baseline unscheduled or recheck assessments will not be used in analysis. ECG data will also be listed by study part and subject.

6.7.6 Physical Examination

In each study part, a full physical examination will be performed at screening, check-in and at EOT (or ET, if applicable). Symptom-driven physical examinations may be performed at other times at the discretion of the investigator. Physical examination findings will be presented in the data listings by study part and subject.

6.7.7 [redacted]

[redacted]

[redacted]

6.7.8 Overdose

All cases of overdose will be presented in a data listing by study part and subject. Any AEs associated with overdose will be documented.

6.7.9 Extent of Exposure and Compliance

The dates, times, and dosages of rhPTH(1-84) will be listed by study part and subject.

6.8 Pharmacokinetic [redacted] Analyses

6.8.1 Pharmacokinetic Analysis

Blood samples for assessment of plasma PTH concentrations will be collected as outlined in Table 6.a below:

Table 6.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Period	Scheduled Time (Hours)*
PTH	Plasma	1, 2, 3, and 4#	Predose (-1, -0.5, and -0.25 hours) and 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours postdose.

*The actual date and time of sample collection will be recorded on the source document in the CRF.
#Periods 1 and 2 (for Part I) and 1, 2, 3, and 4 (for Part II)

Unadjusted and baseline-adjusted PTH concentrations will be listed and summarized descriptively by part and either treatment (for Part I) or dose level (for Part II), and PK sampling time using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, and maximum. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive statistics.

Individual subject unadjusted and baseline-adjusted concentration-time curves will be plotted by part on linear and semi-log scales. The mean profiles of the unadjusted and baseline-adjusted concentration-time data will be plotted by part on linear (with and without SD) and semi-log scales. For summary statistics and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

The PK parameters will be calculated from unadjusted and baseline-adjusted PTH concentration-time profiles using non-compartmental analysis methods where all calculations will be based on actual sampling times after dosing. The PK parameters will be summarized by part and treatment using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, median, maximum, geom mean, and geom CV%. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from descriptive statistics.

Baseline-adjusted PTH concentrations will be calculated by subtracting the average of the measured PTH values from the 3 predose time points (-1, -0.5, and -0.25 hours) from all postdose PTH concentrations. Negative baseline-adjusted PTH values will be set to 0, and any positive baseline-adjusted PTH concentration following occurrence of the first negative baseline-adjusted concentration will also be set to 0.

Relative Bioavailability (Part I Only)

For the evaluation of relative bioavailability in Part I, a linear mixed-effects model will be used for the analysis on the ln-transformed unadjusted and baseline-adjusted C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred} for PTH. The model will include sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The analysis will include calculation of LSMs as well as the difference between treatment LSMs. The GMR and 90% CI will be calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed unadjusted and baseline-adjusted C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞_pred} for PTH. These ratios will be expressed as a ratio relative to the reference formulation.

The comparison of interest is as follows:

- Formulation A (Test) compared to Formulation B (Reference)

The 90% CIs around the GMRs for plasma C_{max}, AUC_{last}, and AUC_{∞} will be assessed whether they fall within the 0.80-1.25 limits.

The following SAS® code will be used to perform the analysis in Part I:

```
PROC MIXED DATA=xxx;
CLASS TREAT SEQUENCE PERIOD SUBJECT;
MODEL ln(<param>) = TREAT SEQUENCE PERIOD;
RANDOM SUBJECT(SEQUENCE);
ESTIMATE "Treatment A vs. Treatment B" TREAT 1 -1 / CL ALPHA=0.1 E;
LSMEANS TREAT / CL ALPHA=0.05;
RUN;
```

Non-Parametric Analysis of t_{max} (Part I Only)

The t_{max} will be analyzed using nonparametric analysis for paired samples (the Wilcoxon Signed Rank Test statistic). The difference of medians (treatment effect) and the corresponding 90% CI will be estimated using the Hodges-Lehmann method and Walsh Averages. The t_{max} will not be ln-transformed. The comparison of interest is the same as for the relative bioavailability assessment listed above.

Dose Linearity (Part II Only)

For the evaluation of dose linearity in Part II, a linear regression model will be used for the analysis on the ln-transformed unadjusted and baseline-adjusted C_{max}, AUC_{last}, and AUC_{∞} for PTH. The model will include sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect, with ln(dose) as a covariate.

As a first step, the significance of a quadratic term, $[\ln(dose)]^2$, will be tested. If the quadratic term is not significant, then it will be noted in the table and discussed. Secondly, the quadratic term will be removed from the model and the final model will be used to assess the linear relationship between ln-transformed PK parameters and ln(dose).

The following SAS® code will be used to perform the analysis in Part II:

Step 1: Check significance of the quadratic term:

```
PROC MIXED DATA=xxx;
CLASS SEQUENCE PERIOD SUBJECT;
MODEL LNPKPARAM = LNDOSE LNDOSE*LNDOSE SEQUENCE PERIOD / DDFM =
KR SOLUTION CL ALPHA=0.10;
RANDOM SUBJECT(SEQUENCE);
```

Step 2: assess dose linearity:

```
PROC MIXED DATA=xxx;
```

CLASS SEQUENCE PERIOD SUBJECT;
MODEL LNPKPARAM = LNDOSE SEQUENCE PERIOD / DDFM = KR SOLUTION CL ALPHA=0.10;
RANDOM SUBJECT(SEQUENCE);

[redacted]

6.8.2 [redacted]

[redacted]

Table 6.b [redacted]

[redacted]				
[redacted]				

[redacted]

[redacted]

[redacted]

6.9 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.10 Preliminary Analysis

A preliminary PK analysis will be completed after database lock as described in the CPAP and Section 6.8.1 of the SAP, with the following changes: 1) unblinded QCed data will be used (unless the QAed data is available, in which case the QAed data will be used); 2) nominal times will be used for the calculation of PK parameters (not actual sampling times); 3) tables and figures will be created using Phoenix® WinNonlin® Version 8.1 or higher, except for the ANOVA tables which will be generated using SAS® Version 9.4 or higher.

6.11 Interim Analyses

No formal interim analysis is planned for this study.

6.12 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

[redacted]

Based on the study design in Part 2, a linear regression model will be used to account for the effects of period, sequence, and subject in the dose proportionality analysis, which is not the power model.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Analysis Software

SAS® Version 9.4 or higher will be used for all statistical analyses provided in the clinical study report.