Clinical Study Protocol

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 Protocol/Amendment 1; 18-Nov-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.

TAKEDA PHARMACEUTICALS PROTOCOL

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 Identifier: TAK-834-1001

Compound: rhPTH(1-84)

Date: 18-Nov-2021

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18-Nov-2021	Amendment 1	United States
15-Oct-2021	Initial version	United states

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1. STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 Telephone: +1 (617) 679-7000	rhPTH(1-84)
Study Identifier: TAK-834-1001	**Phase:** 1
Protocol 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 Design:

This is a randomized, open-label, single-center, two-part study to assess the relative bioavailability of a single subcutaneous (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 1.a.

Blood samples for plasma parathyroid hormone (PTH) pharmacokinetics (PK) and serum calcium and albumin concentrations will be collected predose and for 24 hours following each rhPTH(1-84) administration at the time points delineated in the Schedule of Study Procedures (Section 3).

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

Table 1.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

Treatment Definitions: a=100 µg rhPTH(1-84) Formulation A; b=100 µg rhPTH(1-84) Formulation B

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.

[redacted]

Safety and tolerability will be assessed by treatment-emergent adverse events (TEAEs) including injection site reaction assessments, laboratory evaluations, physical examinations, 12-lead electrocardiograms (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.

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 1.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 at the time points delineated in the Schedule of Study Procedures (Section 3).

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

Table 1.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

Treatment Definitions: c=25 µg rhPTH(1-84); d=50 µg rhPTH(1-84); e=75 µg rhPTH(1-84); f = 200 µg rhPTH(1-84)

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.

[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 AEs have occurred since the last study visit.

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 rhPTH(1-84) following the administration of single 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.

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.

Study Exploratory Objectives:

[redacted]

[redacted]	
Study Subject Population: Healthy male and female subjects aged 18 to 65 years, inclusive, at screening. Body mass index (BMI) 18.5-30.0 kg/m^2, inclusive, at screening. Attempts will be made to enroll at least 20% of each sex in each study part.	
Planned Number of Subjects: Part I (Relative Bioavailability): Approximately 84 subjects (42 subjects per sequence) will be enrolled to ensure at least 76 subjects complete Study Part I. Part II (Dose Linearity): Approximately 12 subjects (3 subjects per sequence) will be enrolled to ensure at least 8 subjects complete Study Part II.	**Planned Number of Sites:** 1
Dose Levels: Part I (Relative Bioavailability): a: 100 µg rhPTH(1-84) Formulation A (Test) b: 100 µg rhPTH(1-84) Formulation B (Reference) Part II (Dose Linearity): c: 25 µg rhPTH(1-84) Formulation A d: 50 µg rhPTH(1-84) Formulation A e: 75 µg rhPTH(1-84) Formulation A f: 200 µg rhPTH(1-84) Formulation A	**Route of Administration:** SC
Duration of Treatment: Part I (Relative Bioavailability): Single-dose on Day 1 of each period with 2 treatment periods. Part II (Dose Linearity): Single-dose on Day 1 of each period with 4 treatment periods.	**Planned Study Duration:** Part I (Relative Bioavailability): Approximately 58 days including screening period and follow-up. Part II (Dose Linearity): Approximately 60 days including screening period and follow-up.

Criteria for Inclusion:

Subjects must fulfill the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 18-65 years of age, inclusive, at screening. Attempts will be made to enroll at least 20% of each sex in each study part.
2. Continuous non-smoker who has not used nicotine containing products for at least 90 days prior to the first dosing and throughout the study, based on subject self-reporting.
3. BMI ≥18.5 and ≤30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee including the following:
   - Serum calcium, PTH, phosphate, and magnesium within laboratory normal limits at screening and check-in.
   - Vitamin D ($1,25(OH)_2D_3$) levels between lower limit of normal and up to 1.5 x upper limit of normal (ULN).
   - Seated blood pressure is ≥89/49 mmHg and ≤139/89 mmHg at screening.
   - Seated pulse rate is ≥40 bpm and ≤99 bpm at screening.
   - QT interval corrected for heart rate using Fridericia's formula (QTcF) interval is ≤450 msec (males) or ≤470 msec (females) or ECG findings considered normal or not clinically significant by the Investigator or designee at screening.
   - Estimated creatinine clearance ≥80 mL/minute at screening.
5. Agrees to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.
6. Understands the study procedures in the Informed Consent Form (ICF), be able to voluntarily provide written, signed, and dated informed consent, and be willing and able to comply with the protocol.

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study in the opinion of the Investigator or designee.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the study drug, or clinical or laboratory assessments.
4. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase (ALP), hereditary disorders predisposing to osteosarcoma or a prior history of external beam or implant radiation therapy involving the skeleton.
5. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
6. History or presence of alcoholism or drug abuse, in the opinion of the Investigator or designee, within the past 2 years prior to the first dosing.
7. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz alcohol).
8. Positive urine drug or alcohol results at screening or check-in.
9. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
10. History of abnormalities of calcium homeostasis including hyperparathyroidism, hypoparathyroidism, hyperthyroidism, Cushing's syndrome, hypercalcemia, hypocalcemia, osteoporosis, or any other calcium disorder.

11. Female subjects with a positive pregnancy test or who are lactating.
12. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
13. Has tattoo(s) or scarring at or near the site of injection or any other condition which may interfere with injection site examination, in the opinion of the Investigator or designee.
14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. A unit of caffeine is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars.
15. Prior screen failure, randomization, participation, or enrollment in this study or prior exposure to any exogenous PTH, PTH fragments or analogs 3 months prior to dosing with rhPTH(1-84).
16. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Excluded Medication, Supplements, and Dietary Products) for the prohibited time period.
17. Has been on a diet incompatible with the study diet or had any substantial changes in eating habits, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
18. Donation of blood or significant blood loss within 60 days prior to the first dosing.
19. Plasma donation within 7 days prior to the first dosing.
20. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Treatment Period 1 of the current study.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study:

<u>Parts I (Relative Bioavailability) and II (Dose Linearity)</u>:

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

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

The secondary endpoints will be assessed through evaluation of the following parameters:

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)
- Changes in vital signs, ECGs, and laboratory results (hematology, chemistry, and urinalysis) from baseline.

[redacted]

[redacted]

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 for each treatment regimen:

- The 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})

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

- Area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration (AUC_{last})
- Area under the plasma concentration-time curve from time zero to infinity (AUC_{∞})
- Maximum observed plasma concentration (C_{max})
- Terminal disposition phase half-life ($t_{1/2z}$).

Statistical Considerations:

Pharmacokinetics:

Part I (Relative Bioavailability):

The baseline-adjusted plasma PK parameters of the different formulations of rhPTH(1-84) will be compared for the relative bioavailability assessment. A linear mixed-effects model for crossover designs will be used on the natural log (ln)-transformed AUC_{last}, AUC_{∞}, and C_{max}. The 90% confidence intervals (CIs) for the central value ratios of AUC and C_{max} between the test and reference formulations will be constructed based on the 90% CIs of the difference in the least-squares means (LSMs) on the log scale.

Part II (Dose Linearity):

Apparent dose linearity of PK parameters (selected baseline-adjusted AUC and C_{max} parameters) will be assessed graphically. [redacted]

Safety:

TEAEs will be tabulated by treatment regimens. Summary statistics for vital signs, safety 12-lead ECGs, and laboratory assessments will be computed and provided.

[redacted]

Sample Size Justification:

Part I (Relative Bioavailability):

The sample size of 76 subjects was calculated to achieve 90% 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 for Part II (Dose Linearity) is not based on any statistical considerations but is considered sufficient for dose linearity evaluation. Part II (Dose Linearity) will enroll 12 subjects to ensure at least 8 subjects complete.

2. STUDY SCHEMATIC

Figure 1 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.

Figure 2 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. SCHEDULE OF STUDY PROCEDURES

Study Procedures	**S**[a]		**Study Days in Each Treatment Period**[b]																				**EOT or ET**[c]		**FU**[d]
Days →		**-1**	**1**																			**2**		16 (±2)[d]	32 (±2)[d]
Hours →		**C-I**[e]	-1	-0.5	-0.25	0						1	1.25	1.5	2	2.5	3	4	6	8	12	16[f]	24			
Minutes →							5	10	20	30	45															
Administrative Procedures																										
Informed Consent	X																									
Inclusion/Exclusion Criteria	X	X																								
Demographics and Medical History	X																									
Safety Evaluations																										
Full Physical Examination[g]	X	X																					X			
Height	X																									
Weight	X	X																					X			
12-lead Safety ECG[h]	X	X		X[i]								X						X		X			X	X		
Vital Signs (PR and BP)[j]	X	X		X[i]								X						X		X			X	X		
Vital Signs (T)	X	X										X						X		X			X	X		
Vital Signs (RR)	X	X																								
Hem, Serum Chem, and UA	X	X		X[i, k]																			X	X		
TSH and free T4	X																									
Serum Pregnancy Test (♀ only)	X	X																						X		
Serum FSH (♀ only)	X																									
Serum PTH[l]	X																									
Serum Vitamin D	X																									
Urine Drug and Alcohol Screen	X	X																								
HIV/Hepatitis Screen	X																									
AE Monitoring[m]	X												X											X	X	
ConMeds Monitoring	X												X											X	X	
Study Drug Administration / PK/[redacted]																										
Randomization			X																							

Study Procedures	**S**[a]		**Study Days in Each Treatment Period**[b]																				**EOT or ET**[c]		**FU**[d]
Days →		**-1**	**1**																			**2**		16 (±2)[d]	32 (±2)[d]
Hours →		**C-I**[e]	-1	-0.5	-0.25	0						1	1.25	1.5	2	2.5	3	4	6	8	12	16[f]	24			
Minutes →							5	10	20	30	45															
rhPTH(1-84) Administration[n]						X																				
Blood for PTH PK			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
[redacted]																										
Other Procedures																										
Admission in the CRU		X																								
Discharge from the CRU[p]																							X			
Visits	X																							X	X	

a Within 21 days prior to the first study drug administration.

b For Part I (Relative Bioavailability), there will be a washout period of 96 (±1) hours between doses. For Part II (Dose Linearity), there will be a washout period of 48 (±1) hours between doses.

c To be performed at the end of Treatment Period 2 for Part I (Relative Bioavailability) and end of Treatment Period 4 for Part II (Dose Linearity), or prior to early termination from the study. Assessments scheduled for both Day 2 and EOT/ET will not be conducted twice. 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.

d 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.

e Subjects will be admitted to the CRU on Day -1 of Treatment Period 1, at the time indicated by the CRU. Subjects may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements.

f The 16-hour postdose may be on either Day 1 or Day 2, depending on the time of dosing on Day 1.

g Full physical examinations will be performed at scheduled time points. Symptom driven physical examinations may be performed at the Investigator's or designee's discretion.

h 12-lead ECG should be performed within ±20 minutes of the planned time points. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG

i Assessments should be performed within ~30 minutes prior to dose administration.

j Vital signs will be obtained after the subject is seated for at least 5 minutes. Postdose assessments should be performed within a window of ±15 minutes of the scheduled time point.

k The urine collection may be the first void of the day (provided it is predose) but may be outside the 30-minute window if necessary.

l Parathyroid hormone at screening is for baseline eligibility use only and not for PK analysis.

m Abnormal findings in injection site reaction assessments will be reported as AEs.

n Subjects will fast for approximately 8 hours prior to dose administration in each treatment period for both Part I (Relative Bioavailability) and Part II (Dose Linearity) and continue fasting through at least 2 hours after administration of rhPTH(1-84). In each study part, treatment administration in consecutive treatment period (ie, Treatment Period 2 in Part I and Treatment Periods 2, 3, and 4 in Part II) will be administered at the same time of day (±1 hour) as treatment administration in Treatment Period 1.

[redacted]

p Subjects will remain in the CRU until completion of the last postdose assessment on Day 2 of Treatment Period 2 (Part I [Relative Bioavailability]) or Treatment Period 4 (Part II [Dose Linearity]).

Abbreviations: ♀ = Females, [redacted] AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, ECG = Electrocardiogram, EOT/ET = End-of-Treatments or early termination, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, [redacted] PK = Pharmacokinetics, PR = Pulse rate, Preg = Pregnancy, PTH= Parathyroid hormone, RR = Respiratory rate, S = Screening, T = Temperature, T4 = Thyroxine, TSH = Thyroid stimulating hormone, UA = Urinalysis.

4. INTRODUCTION

4.1 Background

Parathyroid hormone (PTH) is synthesized and secreted by the parathyroid glands and is the principal regulator of calcium and phosphate homeostasis in humans (Brown, 1994; Silver and Kronenberg, 1996). Endogenous PTH is secreted in response to decreased plasma calcium and acts to restore normocalcemia through actions on kidney and bone, by increasing renal tubular reabsorption of calcium and the efflux of calcium from bone, both from the rapidly exchangeable calcium pool and by activating bone turnover and resorption. PTH also regulates the activity of the 25-hydroxyvitamin D-1α-hydroxylase enzyme, which stimulates the conversion of 25-hydroxyvitamin D to the active form of vitamin D, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$; calcitriol] which in turn increases intestinal calcium and phosphate absorption.

In hypoparathyroidism, impaired endogenous PTH secretory capacity results in chronic hypocalcemia and hyperphosphatemia, hypercalciuria, low $1,25(OH)_2D_3$ levels, decreased intestinal calcium absorption, and low bone turnover. Depending on its severity, chronic hypocalcemia can be associated with increased neuromuscular irritability, impaired cognitive function, mood disorders, seizures, cataracts, dry rough skin, coarse brittle hair, alopecia, and abnormal dentition. The low bone turnover leads to increased skeletal mineralization and high bone mineral density (Goltzman and Cole, 2006). Current therapies for hypoparathyroidism include calcium and calcitriol/1α-calcidol; the primary goal of treatment is to control symptoms of hypocalcemia while minimizing complications (Shoback, 2008).

Human recombinant parathyroid hormone [rhPTH(1-84)] has an identical amino acid sequence as the endogenous human 84-amino-acid hormone.

rhPTH(1-84) (Natpara®) received orphan designation for the treatment of hypoparathyroidism in the US in 2007, followed by approval of rhPTH(1-84) (Natpara®) as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism by the Food and Drug Administration (FDA) in 2015.

rhPTH(1-84) was granted marketing authorization on 24 April 2006 in the European Union (EU) for the therapeutic indication, "Treatment of osteoporosis in postmenopausal women at high risk of fractures," which was later retracted by the owning company for commercial reasons. Orphan designation for rhPTH(1-84) for the treatment of hypoparathyroidism was granted in the EU in 2013. rhPTH(1-84) was also granted approval as an adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone, by the European Medicines Agency in 2017, under the commercial name Natpar®.

Clinical summary

Up to Nov 2020, 16 clinical studies were conducted in which systemic concentrations of PTH(1-84) were measured following administration of rhPTH(1-84). In 11 of these studies, serum calcium levels were measured as a PD marker. Most of the studies in healthy subjects were single-dose investigations. PK and PD measurements were also made after 7 days, 12 months, and up to 18 months of daily dosing in subjects with hypoparathyroidism or

osteoporosis. The route of administration was SC for most studies. The site of SC administration was either the thigh or abdomen across all studies, but was restricted to the thigh for all studies in subjects with hypoparathyroidism. Four studies specifically investigated the PK/PD profiles in subjects with hypoparathyroidism.

Pharmacokinetics and Pharmacodynamics

The PK of PTH(1-84) following SC administration of rhPTH(1-84) in the thigh was similar in normal subjects, in postmenopausal women with or without osteoporosis, and in subjects with hypoparathyroidism. When injected in the thigh, the PK of PTH(1-84) is linear and dose proportional over a dose range of 50 to 100 µg and the response is reproducible across studies.

Administration to the thigh as opposed to the abdomen showed the same rapid initial increase in PTH concentrations, but with a lower peak level. The second peak concentration for the injection into the thigh was also lower than that for injection into the abdomen. Despite this longer duration, the amount of rhPTH(1-84) absorbed (systemic exposure) was slightly lower following SC injection in the thigh.

In Study CL1-11-013, the mean half-life was about 1.5 hours for SC injection.

In Study CL1-11-007, plasma concentrations of PTH approached baseline levels by 12 hours after dosing with both SC injection into the abdomen or thigh, however, the serum calcium profiles were different. The PD profile of dosing in the thigh showed a more-sustained increase in calcium levels (return to baseline in 24 hours) as compared to the abdomen (return to baseline in ±16 hours) Therefore, the thigh is the preferred administration site in the treatment of patients with hypoparathyroidism.

Multiple SC dosing of rhPTH(1-84) in the thigh for 7 days in healthy subjects showed that the plasma PTH(1-84) concentration-time profiles on the first and seventh day were similar. The plasma concentration data from the long-term studies in postmenopausal osteoporotic women and in subjects with hypoparathyroidism showed that there is no apparent change in the PK of PTH after up to 15 months of daily therapy.

In an open-label study, 7 subjects with hypoparathyroidism received rhPTH(1-84) 50 µg in the thigh followed 7 days later by a 100-µg SC dose. Both doses provided a 24-hour calcemic response. There was a dose-related increase in serum calcium levels, with maximum mean increases (approximately 0.5 to 0.8 mg/dL) observed at 12 hours. rhPTH(1-84) administration resulted in a substantial decrease in serum phosphate by markedly increasing urinary phosphate excretion, whereas calcitriol administration had little effect on urinary phosphate and tended to increase serum phosphate. As a result, rhPTH(1-84) administration decreased whereas calcitriol increased the serum calcium-phosphate product, an important determinant of soft-tissue calcification. Serum $1,25(OH)_2D_3$ increased to peak levels at 8 to 12 hours after rhPTH(1-84) administration.

Safety

Completed sponsor-initiated studies for the treatment of hypoparathyroidism include CL1-11-040 (REPLACE), PAR-C10-007 (RELAY), PAR-C10-009 (REPEAT), PAR-C10-008 (RACE), SHP634-101 (PARALLAX), SHP634-402, and SHP634-404. Ongoing sponsor-initiated studies in subjects with hypoparathyroidism include PAR-R13-001 (PARADIGHM) and SHP-634-401.

A review of safety data across the hypoparathyroidism program to date indicated that rhPTH(1-84) administered in the dose range of 25 to 100 µg SC once daily (QD) is safe for use for the treatment of hypoparathyroidism. Very common adverse drug reactions (ie, reported in ≥10% of subjects) include hypocalcemia, hypercalcemia, headaches, hypoesthesia, paresthesia, diarrhea, nausea, vomiting, arthralgia, and muscle spasms. Common adverse drug reactions (ie, reported in ≥1% of subjects, but <10% of subjects) include hypomagnesemia, tetany, upper abdominal pain, anxiety, insomnia, palpitations, cough, muscle twitching, musculoskeletal pain, myalgia, neck pain, pain in extremity, hypercalciuria, pollakiuria, asthenia, chest pain, fatigue, injection site reactions, thirst, anti-PTH antibody positive, decrease in blood 25-hydroxycholecalciferol levels, decrease in vitamin D levels, somnolence, and hypertension.

There was no suggestion that rhPTH(1-84) causes drug-induced liver injury in humans. There were no renal-related AEs or abnormalities in renal function tests or urinalysis tests in clinical studies apart from changes expected from the mechanism of action of rhPTH(1-84). Despite significant increases in total serum calcium levels and improved calcium homeostasis, treatment with rhPTH(1-84) did not result in worsening of hypercalciuria.

Potential risks include those effects which are extensions of the pharmacologic actions of PTH including hypercalcemia.

Refer to the Investigator's Brochure (IB) for detailed background information on rhPTH(1-84) (rhPTH(I-84) Investigator's Brochure, Edition 11, 02 November 2020).

4.2 Rationale for the Proposed Study

A new formulation of rhPTH(1-84) has been developed to reduce the occurrence of atypical proteinaceous particles in reconstituted drug solution. The purpose of this study is to evaluate the PK of the new formulation in two parts:

Part I (Relative Bioavailability) will assess the relative bioavailability of the new formulation (Formulation A; test) compared with the approved formulation (Formulation B; reference) of rhPTH(1-84) following single-dose SC administration at 100 µg.

Part II (Dose Linearity) will assess the dose-linearity of Formulation A following single SC administrations in the dose range of 25 µg to 200 µg rhPTH(1-84).

Utilizing the relative bioavailability of Formulation A with respect to Formulation B at the 100 µg dose strength (Part I [Relative Bioavailability]) and the dose-exposure characteristics of

Formulation A, evaluated over a dose range of 25 µg to 200 µg (Part II [Dose Linearity]), will enable extrapolation of the relative bioavailability at different dose levels.

4.3 Benefit/Risk Profile

The initial therapeutic dose of rhPTH(1-84) is 50 µg QD, with a maximum recommended dose of 100 µg QD (Natpara® [parathyroid hormone], 2020). In the single ascending dose study PBR-930811, doses up to 5.0 µg/kg (equivalent to 350 µg for a 70 kg adult) were found safe and well tolerated (rhPTH(I-84) Investigator's Brochure Edition 11, 02 November 2020). The single doses of rhPTH(1-84) administered in this study are well below the highest safe and well tolerated doses and are not expected to pose any risk to the subjects.

There will be no direct health benefit for study subjects from receipt of study drugs. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, injection site reaction assessments, laboratory tests, AE questioning, and physical examinations) are adequate to protect the subject's safety and should detect all TEAEs.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

Not applicable

5.2 Study Objectives

5.2.1 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 rhPTH(1-84) following the administration of single 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.

5.2.2 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.

5.2.3 Study Exploratory Objectives

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoints

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

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

- AUC_{last}
- AUC_{∞}
- C_{max}

5.3.2 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 TEAEs
- Changes in vital signs, ECGs, and laboratory results (hematology, chemistry, and urinalysis) from baseline.

5.3.3 Exploratory Endpoints

[redacted]

5.3.4 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 regimen:

- $AUC_{\%extrap}$
- t_{max}

- t_{last}

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

- AUC_{last}
- AUC_{∞}
- C_{max}
- $t_{1/2z}$

6. STUDY DESIGN AND DESCRIPTION

6.1 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 6.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 at the time points delineated in the Schedule of Study Procedures (Section 3).

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

Table 6.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 6.c

Subjects will remain in the 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.

[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 AEs have occurred since the last study visit.

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 6.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 at the time points delineated in the Schedule of Study Procedures (Section 3).

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

Table 6.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 6.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.

[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 AEs have occurred since the last study visit.

The planned dose levels of rhPTH(1-84) to be evaluated are outlined in Table 6.c.

Table 6.c Planned Dose Levels

Regimen	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

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

Not applicable.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

The purpose of the study is to assess the relative bioavailability of the new rhPTH(1-84) formulation (Formulation A) compared with the currently used formulation (Formulation B) and the dose linearity of the new formulation. The relative bioavailability of Formulation A with respect to Formulation B at the 100 µg dose strength (Part I [Relative Bioavailability]) and the dose-exposure characteristics of Formulation A, evaluated over a dose range of 25 µg to 200 µg (Part II [Dose Linearity]), will enable extrapolation of the relative bioavailability of Formulation A to different dose levels.

By using healthy subjects, the study will mainly focus on the difference in the exposure between the formulations, and limit other factors on the dose-exposure response.

Subjects will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every subject acts as their own control.

Based on previous clinical data, following SC administration to the thigh of 100 µg rhPTH(1-84), PTH levels return to baseline within 16-24 hours and serum calcium levels return to baseline levels within 24 hours. Thus, the washout period between doses is considered sufficient to prevent carryover effects of the preceding treatment regimen.

[redacted]

[redacted]

6.4.2 Rationale for Dose

The recommended therapeutic dose range for rhPTH(1-84) (Natpara®) is 50 µg to 100 µg QD (Natpara® [parathyroid hormone], 2020). In study PBR 930811, a dose off up to 5.0 µg/kg, equivalent to an average dose of 350 µg for a 70 kg adult subject, was found safe and well tolerated. Thus, the dose of 100 µg was selected for the assessment of relative bioavailability of the new formulation in Part I.

A series of doses ranging from 25 µg to 200 µg rhPTH(1-84) was selected for Part II (Dose Linearity) to acquire a PK profile of the new formulation for a wide dose range. Based on the safety profile of the drug, a dose of up to 350 µg is considered safe and well tolerated for a 70 kg adult, providing sufficient safety margin in case of higher bioavailability of the new formulation.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of relative bioavailability and dose linearity study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of AEs, vital signs, ECGs, laboratory assessments, and physical examinations.

6.4.3.3 [redacted]

[redacted]

6.4.3.4 [redacted]

[redacted]

6.4.4 Future Biomedical Research

Any residual plasma and urine samples will be stored by the Sponsor or Bioanalytical facility for up to 15 years, determined by the Sponsor following the last dosing. Tubes or containers will be identified with a barcode using an appropriate label.

No diseases/conditions, deoxyribonucleic acid, or ribonucleic acid will be the focus of these analyses. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses, and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the ICF, subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the CRU staff to request destruction of the residual samples once PK assessments required to meet the primary objectives of the study are completed. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

6.4.5 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the critical component is the blood collection for plasma concentrations of PTH and serum concentrations of calcium and albumin. The blood samples are to be collected as close to the scheduled times defined in this protocol as possible.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of the study drugs to any subject may not be modified. If necessary, a subject may be discontinued for the reasons described in Section 7.5.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3)

6.6.3 Definition of Study Completion

The end of the study is scheduled after completion of the evaluations in the follow-up visit for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.6.4 Definition of Study Discontinuation

The study will be completed as planned unless 1 or more of the criteria indicated in Section 6.6.5 are satisfied that require temporary suspension or early termination of the study.

6.6.5 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) compromises the ability to achieve the primary study objectives or compromises subject safety.
- A finding (eg, PK, [redacted]) from another nonclinical or clinical study using the study treatment results in the study being stopped for a nonsafety-related reason.
- Data from drug(s) of the same class or methodology(ies) used in this study become available and result in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.
- Unanticipated concerns of safety to the study subjects arise from this clinical study or additional nonclinical or clinical studies with rhPTH(1-84) or drug(s) of the same class.

6.6.6 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 18-65 years of age, inclusive, at screening. Attempts will be made to enroll at least 20% of each sex in each study part.
2. Continuous non-smoker who has not used nicotine containing products for at least 90 days prior to the first dosing and throughout the study, based on subject self-reporting.
3. BMI ≥18.5 and ≤30.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the Investigator or designee including the following:
   - Serum calcium, PTH, phosphate, and magnesium within laboratory normal limits at screening and check-in.
   - Vitamin D ($1,25(OH)_2D_3$) levels between lower limit of normal and up to 1.5x ULN.
   - Seated blood pressure is ≥89/49 mmHg and ≤139/89 mmHg at screening.
   - Seated pulse rate is ≥40 bpm and ≤99 bpm at screening.
   - QTcF interval is ≤450 msec (males) or ≤470 msec (females) or ECG findings considered normal or not clinically significant by the Investigator or designee at screening.
   - Estimated creatinine clearance ≥80 mL/minute at screening.
5. Agrees to comply with any applicable contraceptive requirements of the protocol as detailed in Appendix D.
6. Understands the study procedures in the ICF, be able to voluntarily provide written, signed, and dated informed consent, and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study in the opinion of the Investigator or designee.
2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the Investigator or designee.
3. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the study drug, or clinical or laboratory assessments.

4. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of ALP, hereditary disorders predisposing to osteosarcoma or a prior history of external beam or implant radiation therapy involving the skeleton.
5. History of any illness that, in the opinion of the Investigator or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
6. History or presence of alcoholism or drug abuse, in the opinion of the Investigator or designee, within the past 2 years prior to the first dosing.
7. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz alcohol).
8. Positive urine drug or alcohol results at screening or check-in.
9. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
10. History of abnormalities of calcium homeostasis including hyperparathyroidism, hypoparathyroidism, hyperthyroidism, Cushing's syndrome, hypercalcemia, hypocalcemia, osteoporosis, or any other calcium disorder.
11. Female subjects with a positive pregnancy test or who are lactating.
12. Positive results at screening for HIV, HBsAg, or HCV.
13. Has tattoo(s) or scarring at or near the site of injection or any other condition which may interfere with injection site examination, in the opinion of the Investigator or designee.
14. Routine consumption of more than 2 units of caffeine per day or subjects who experience caffeine withdrawal headaches. A unit of caffeine is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars.
15. Prior screen failure, randomization, participation, or enrollment in this study or prior exposure to any exogenous PTH, PTH fragments or analogs 3 months prior to dosing with rhPTH(1-84).
16. Unable to refrain from or anticipates the use of any medication or substance (including prescription or over-the-counter, vitamin supplements, natural or herbal supplements) as indicated in Section 7.3 (Excluded Medication, Supplements, and Dietary Products) for the prohibited time period.
17. Has been on a diet incompatible with the study diet or had any substantial changes in eating habits, in the opinion of the Investigator or designee, within the 30 days prior to the first dosing and throughout the study.
18. Donation of blood or significant blood loss within 60 days prior to the first dosing.
19. Plasma donation within 7 days prior to the first dosing.

20. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Treatment Period 1 of the current study.

7.3 Excluded Medications, Supplements, and Dietary Products

Concomitant medications will be prohibited as follows:

- Any drug, including prescription and or over-the-counter, vitamin supplements, natural or herbal supplements within 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Appendix D). After randomization, acetaminophen (up to 2 g per 24 hours), calcium gluconate and other medication for the treatment of AEs, may be administered at the discretion of the Investigator or designee.
- Thiazide diuretics within 14 days prior to the first dosing and throughout the study.
- Loop diuretics, lithium, antacids, systemic corticosteroids within 30 days prior to the first dosing and throughout the study (medical judgment is required by the Investigator). Primarily, high doses of systemic corticosteroids [eg, prednisone] and/or stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable at the Investigator's or designee's discretion.
- Calcitonin, cinacalcet hydrochloride, treatment with rhPTH(1-84) or N-terminal PTH or PTH-related peptide fragments or analogs within 3 months prior to the first dosing and throughout the study.
- For females: changes in hormone replacement therapy within 3 months prior to the first dosing and throughout the study are excluded. Stable (≥3 months) hormone replacement therapy is acceptable.
- Fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators within 6 month prior to the first dosing and throughout the study.
- Intravenous bisphosphonates within 12 month prior to the first dosing and throughout the study.

If deviations occur, the Investigator or designee in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 7.a.

Table 7.a Study Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -21 to predose [Day 1 of Treatment Period 1])	After First Dosing (Day 1 of Treatment Period 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited from first dosing until the end of PK collection in the last study period.
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing[a]	Prohibited from first dosing until the end of PK collection in the last study period.[a]
Medications	See Section 7.3	Prohibited from first dosing throughout the study.
Nicotine- and tobacco-containing and/or cannabis products	Prohibited from 90 days prior to first dosing	Prohibited from first dosing until the end of PK collection in the last study period.

(a) small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Water will be allowed ad libitum. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Subjects will fast overnight for at least 8 hours prior to each dosing. On Day 1 of each period, subjects will continue the fast for at least 2 hours postdose.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snack served at the CRU will be standardized, will be similar in caloric content and composition, and will be taken at approximately the same time in each period.

7.4.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

1. Pretreatment event (PTE) or AE: The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver Function Test (LFT) Abnormalities

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.2.9.1), if the following circumstances occur at any time during study drug treatment:

     - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x ULN, or
     - ALT or AST >3x ULN in conjunction with elevated bilirubin >2x ULN or international normalized ratio (INR) >1.5x ULN, or
     - ALT or AST >3x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), or
     - ALT >3x ULN twice consecutively at least 24 to 48 hours apart.

2. Significant protocol deviation: The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up: Attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal: The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the case report form (CRF).

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the CRF.
5. Study termination: The Sponsor, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), or regulatory agency terminates the study.
6. Pregnancy: as described in Appendix D.
7. Subjects may be withdrawn from the study by the Investigator or designee for the following reasons:

   - Positive drug or alcohol screen results.
   - Difficulties in blood collection

- Other. The specific reasons for discontinuation should be entered into the CRF including unavoidable circumstances such as the COVID-19 pandemic. Subjects may be withdrawn from the study at any time at the discretion of the Investigator or Sponsor for safety reasons which should be entered into the CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-treatments or early termination as described in Section 3.

7.7 Subject Replacement

Replacement of discontinued or withdrawn subjects due to any reason will be assessed on a case by case basis by the Sponsor and Investigator to ensure a minimum of 76 PK-evaluable subjects complete Part I (Relative Bioavailability) of the study, and a minimum of 8 PK-evaluable subjects complete Part II (Dose Linearity) of the study.

8. CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Product Name: rhPTH[1-84]

Strengths: 25 µg, 50 µg, 75 µg, 100 µg

The 200 µg dose will be achieved using two consecutive injections of the 100 µg

Dosage Form/Formulation: Lyophilized powder to be reconstituted for SC dosing.

Dosing regimen: Single dose

Route of Administration: SC injection in mid-thigh

Investigational product will be supplied as: multiple-dose, dual-chamber glass cartridges containing a sterile lyophilized powder and a diluent for reconstitution at a dose of either 25 µg, 50 µg, 75 µg, or 100 µg using the marketed mixing device. A commercially marketed injector pen will be used for SC dosing. A sterile, disposable pen needle will be used for each administration. Each individual injector pen will be used for only one subject.

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician according the treatment sequences indicated in Table 6.a (Part I [Relative Bioavailability]) and Table 6.b (Part II [Dose Linearity]).

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Not applicable.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused rhPTH(1-84) will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9. STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

Subjects in each study part will be randomized to treatment sequence according to Table 6.a (Part I [Relative Bioavailability]) and Table 6.b (Part II [Dose Linearity]).

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

All subjects will receive the treatments as detailed in Section 9.2.6.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited as listed in Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to subject safety.

For this study, collection of blood for plasma concentrations of PTH and serum concentrations of calcium and albumin is the critical parameter. Blood samples need to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior to or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

9.2.1 Full Physical Exam

Full physical examinations will be performed as outlined in the Schedule of Study Procedures (Section 3). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the Investigator or designee.

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3).

9.2.3 BMI

BMI (kg/m^2) will be calculated based on the height and weight measured at screening.

9.2.4 Vital Signs

Single measurements of temperature, respiratory rate, blood pressure, and pulse rate will be measured as outlined in the Schedule of Study Procedures (Section 3). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and pulse rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

Blood pressure and pulse rate will be measured within approximately 30 minutes prior to Day 1 dosing of each period for the predose time point. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3). Additional ECGs may be taken at any other times, if deemed necessary by the Investigator or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the Investigator or designee.

ECGs will be measured within approximately 30 minutes prior to Day 1 dosing of each period for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Injection Site Evaluation

In monitoring AEs, special attention will be paid to potential injection site reactions (ie, local tolerability). Any abnormal findings will be reported as AEs.

9.2.7 Study Drug Administration

rhPTH(1-84) formulations will be provided as described in Section 8.1.

Treatments will be administered as described in Table 6.c.

The pharmacy at the CRU will provide each dose in individual injector pen with a sterile, disposable pen needle. Each individual injector pen will be used for only one subject. To administer a 200 µg dose of Formulation A, two consecutive injections of the 100 µg strength of Formulation A will be administered using the same injector pen and disposable needle for each injection to the same subject. The consecutive injections must be administered as soon as possible, within no more than 5 minutes of each other, one in each thigh.

In Part I (Relative Bioavailability), the same location in the same thigh will be used for both treatment periods, if possible. In Part II (Dose Linearity), alternate thighs may be used in successive treatment periods.

All injections will be administered by a qualified designee, eg, a nurse. In the case of an incomplete dosing (eg, droplet(s) of study medication on the surface of the skin) as deemed by the Investigator and Sponsor or Sponsor's designee, the subject may be withdrawn.

Additional information regarding drug preparation and administration may be provided in a separate pharmacy manual.

The exact clock time of dosing will be recorded.

For Treatments a and b (Part I [Relative Bioavailability]), and Treatments c, d, and e (Part II [Dose Linearity]), Hour 0 will be define as the time of injection. For Treatment f (Part II [Dose Linearity]), Hour 0 will be define as the time of the second injection.

In each study part, treatment administration in consecutive treatment period (ie, Treatment Period 2 in Part I and Treatment Periods 2, 3, and 4 in Part II) will be administered time of day (±1 hour) as treatment administration in Treatment Period 1.

9.2.8 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10. [redacted]

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to when the serum chemistry sample being taken.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Albumin
Lipase	Potassium
Blood Urea Nitrogen	Chloride
Bilirubin (total and direct)	Glucose
Alkaline phosphatase (ALP)	Creatinine *
Aspartate aminotransferase (AST)	Magnesium
Alanine aminotransferase (ALT)	Sodium
Calcium	Phosphate

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen - Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone) - Amphetamines - Barbiturates - Benzodiazepines - Cocaine - Cannabinoids
HBsAg	
HCV (if antibody positive, confirm RNA negative)	
Urine alcohol screen	
Serum pregnancy test (for females only)	
FSH (for females only)	
Urine cotinine	
Vitamin D	
PTH	
COVID-19 testing (performed according to CRU standard procedures, provided in a separate document[s])	Thyroid stimulating hormone (TSH) Free thyroxine (T4)

9.3 Pharmacokinetics, [redacted]

Instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.3.1 PK Measurements

Samples from all subjects will be assayed even if the subjects do not complete the study. Samples for determination of plasma PTH, will be analyzed using validated bioanalytical methods.

Pharmacokinetic parameters of PTH will be calculated from the individual concentration-time profiles from all evaluable subjects using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma for PK Measurements

The following PK parameters will be calculated from unadjusted and baseline-adjusted plasma concentrations of PTH, unless otherwise specified:

AUC_{last}:	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
AUC_{∞}:	The area under the concentration-time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.
$AUC_{extrap\%}$:	The area under the curve from the last quantifiable concentration to infinity, expressed as a percentage of AUC_{∞}
C_{max}:	Maximum observed concentration.
t_{last}:	Time of the last measurable concentration.
t_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$t_{½z}$:	Terminal disposition phase half-life will be calculated as $0.693/\lambda_z$, where λ_z is the apparent first order terminal disposition phase rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares-regression analysis using the maximum number of points in the terminal log-linear phase (eg, three or more non-zero plasma concentrations).

No value for AUC_{∞}, $AUC_{extrap\%}$, or $t_{½z}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

No PK parameters will be calculated for subjects with detectable concentrations at 2 or fewer consecutive time points.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

9.3.2 [redacted]

[redacted]

9.3.2.1 [redacted]

[redacted]

[redacted]

9.3.3 [redacted]

[redacted]

9.3.4 Biomarker Measurements

Not applicable.

9.3.5 PGx Measurements

Not applicable.

9.3.6 Confinement

Subjects will be housed on Day -1 of Treatment Period 1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures in Treatment Period 2 (Part I [Relative Bioavailability]) or Treatment Period 4 (Part II [Dose Linearity]). Subjects may be admitted earlier for COVID-19 testing not related to study protocol as per CRU requirements.

At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

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.

10. ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).
    - Considered an IMPORTANT MEDICAL EVENT in the opinion of the investigator or designee.

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19 pneumonia	
COVID-19-related disease	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Section 10.1 and Section 10.1.1).

10.1.2 Special Interest AEs

The special interest AEs will include hyper- and hypocalcemia as determined by the investigator or designee.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit 32 ($\pm$2) days after the last dose of study drug. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or

not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours using the fax number or email address to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax or email it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting Special Interest AEs

When a special interest AE occurs through the AE collection period it should be reported within 24 hours using the fax number or email address to the attention of the contact listed in Section 14.1.1.

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.9.1 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11. STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 PK Set

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

11.1.1.2 Safety Set

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

11.1.1.3 [redacted]

[redacted]

11.1.1.4 [redacted]

[redacted]

11.1.2 Analysis of Demography and Other Baseline Characteristics

Continuous demographic data (ie, age, weight, height, and BMI) will be listed and summarized using appropriate summary statistics. Categorical demographic data (ie, gender, race, and ethnicity) will also be listed and tabulated.

11.1.3 PK Analysis

Statistical analysis of PK data will be based on the PK analysis data set.

Values will be reported for the unadjusted and baseline-adjusted PTH concentrations for each subject. Concentrations will be summarized by scheduled time points for PTH. PK parameters for the plasma concentrations will be calculated for each subject as described in Section 9.3.1.1. PK parameters for each subject will be listed and summarized by treatment using descriptive statistics.

11.1.3.1 Relative Bioavailability (Part I [Relative Bioavailability])

Analysis of Variance

A linear mixed-effects model will be used for the analysis on the ln-transformed AUC_{last}, AUC_{∞}, and C_{max} 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 regimen LSMs.

Ratios and Confidence Intervals

GMR and 90% CI, consistent with the two one-sided test (Schuirmann, 1987), will be calculated using the exponentiation of the difference between treatment regimen LSMs from the analyses on the ln-transformed AUC_{∞}, AUC_{last}, and C_{max} for PTH. These ratios will be expressed as a percentage relative to the appropriate reference formulation or treatment regimen.

11.1.3.2 Dose Linearity (Part II [Dose Linearity])

Apparent dose linearity of PK parameters (selected baseline-adjusted AUC and C_{max} parameters) will be assessed graphically. [redacted]

11.1.3.3 Non-Parametric Analysis

The PK parameter t_{max} will be analyzed using an appropriate nonparametric analysis; t_{max} will not be ln-transformed.

11.1.4 [redacted]

[redacted]

11.1.5 [redacted]

[redacted]

11.1.6 Safety Analysis

All safety data will be populated in the individual CRFs.

Dosing dates and times will be listed by subject.

Statistical analysis of safety data will be based on the safety analysis data set.

TEAEs will be tabulated. The remaining quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics.

11.1.6.1 AEs

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

11.1.6.2 Clinical Laboratory Evaluation

Clinical laboratory results will be summarized by treatment and point of time of collection and a shift table describing out of normal range shifts will be provided.

11.1.6.3 Vital Signs

Vital signs assessments will be summarized by treatment and point of time of collection.

11.1.6.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection.

Medical history, and concurrent conditions will be coded using the MedDRA® and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary and will be listed by subject.

11.2 Interim Analysis and Criteria for Early Termination

In Part I (Relative Bioavailability), an interim PK analysis will be conducted following completion of Treatment Period 2 for approximately 25 subjects. Full details will be described in the SAP.

The interim analyses will be conducted for informational purposes only and to provide preliminary study results. No changes to the design or conduct will be made as a result of interim analysis.

11.3 Determination of Sample Size

Part I (Relative Bioavailability):

The sample size of 76 subjects was calculated to achieve 90% 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 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 for Part II (Dose Linearity) is not based on any statistical considerations but is considered sufficient for dose linearity evaluation.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

For COVID-19-related protocol deviations, the specific protocol deviation, the reason for the deviation, and the relationship to COVID-19 should be documented using CRU standard processes.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICF s must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

Any investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14. ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 1-484-595-8155 Email: GPSE@takeda.com

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

µg	Microgram(s)
$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3
[redacted]	[redacted]
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_∞	The area under the concentration-time curve, from time 0 to infinity
$AUC_{extrap\%}$	Percent of AUC_∞ extrapolated
AUC_{24}	The area under the concentration-time curve, from time 0 to 24 hours postdose
AUC_{last}	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
BMI	Body mass index
bpm	Beats per minute
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeter
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CRU	Clinical Research Unit
ECG	Electrocardiogram
[redacted]	[redacted]
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
Ig	Immunoglobulin(s)
INR	International normalized ratio
IRB	Institutional Review Board
ISCV	Intra-subject coefficient of variation
kg	Kilogram
L	Liter
LFT	Liver function test
ln	Natural log
LSM	Least-squares means
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
oz	Ounce
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PTE	Pretreatment event
PTH	Parathyroid hormone
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
rhPTH	Recombinant human parathyroid hormone
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SUSAR	Suspected unexpected serious adverse reaction
$t_{½z}$	Terminal disposition phase half-life
T4	Thyroxine
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
t_{last}	Time of the last measurable concentration
t_{max}	Time of first occurrence of C_{max}
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USA	United States of America
WHO	World Health Organization

15. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA®. Drugs will be coded using the WHO Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Completed CRFs are required for each subject who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs must be completed in English. Data are transcribed directly onto CRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from

regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16. REFERENCES

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Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the Investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective/effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 28 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects.
25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 28 days after last dose of study drug, female subjects of childbearing potential** who are sexually active with a nonsterilized male partner* must use a highly effective/effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

** A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) will be used to confirm a post-menopausal state including in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy.

A female of non-childbearing potential, must have undergone one of the following sterilization procedures at least 6 months prior to the first dosing:

- hysteroscopic sterilization;
- bilateral tubal ligation or bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and FSH serum levels consistent with postmenopausal status. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) will be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly)":
   - Non-Hormonal Methods:
     - Intrauterine device at least 3 months prior to the first dosing.
     - Bilateral tubal occlusion.
     - Vasectomised partner * (provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success).
     - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 28 days after last dose.
   - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method (Evaluate on compound-by-compound and protocol –by-protocol basis and obtain clinical pharmacology justification).
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
       - Oral.
       - Intravaginal (eg, ring).
       - transdermal.
     - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
       - oral.
       - Injectable.
       - Implantable.
2. Effective methods of contraception methods of contraception are defined as "those, alone or in combination, that may result in a failure rate less than 1%":
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).

- Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, {and sperm donation} during the course of the study.
5. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is “yes”)
      iv. Is there a chance you could be pregnant?
6. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses; with the exception of female subjects using a protocol acceptable contraception method that has a known side effect of delayed or irregular menses). In addition, subjects must also have a negative serum hCG pregnancy test within 1 day prior to receiving first dose of study drug as close as possible and prior to first dose of study drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
  - Is there a chance you could be pregnant?

Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose, should also be recorded following authorization from the subject's partner.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Summary of Changes from Previous Version

The protocol is amended to address updates as requested by The Food and Drug Administration based on the communication dated 03 Nov 2021.

A summary of changes incorporated into Amendment 1 is provided in the table below.

Summary of Changes(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
The protocol is updated to include assessment of [redacted]	Section 1 (Study Summary) Section 2 (Study Schematic) Section 3 (Schedule of Study Procedures) Section 5.2.3 ([redacted]) Section 5.3.3 ([redacted]) Section 6.1 (Study Design) Section 6.4.1 (Rationale of Study Design) Section 6.4.3.4 ([redacted]) (new section) Section 7.3 (Excluded Medications, Supplements, Dietary Products) Section 9.2.8 (AE Monitoring) Section 9.3 (Pharmacokinetics, [redacted]) Section 9.3.3 ([redacted]) (new section) Section 9.3.6 (Confinement) Section 10.2.8.1 (Collection Period) Section 11.1.1.4 ([redacted]) (new section) Section 11.1.5 ([redacted]) (new section) Section 14.1.4 (List of Abbreviations) Section 16 (References)

Summary of Changes(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
The protocol is updated to include baseline-adjusted C_{max} in the primary endpoints of the study.	Section 1 (Study Summary) Section 5.3.1 (Primary Endpoints) Section 5.3.4 (Additional Endpoints) Section 11.1.3.1 (Relative Bioavailability ([Part I (Relative Bioavailability)]))
Sample size for Part I was increased from 80 to 84 subjects to conform with the inclusion of C_{max} as a primary endpoint of the study.	Section 1 (Study Summary) Section 6.1 (Study Design) Section 7.7 (Subject Replacement) Section 11.3 (Determination of Sample Size)
Resting position prior to vital signs measurements was updated from supine to seated position.	Section 3 (Schedule of Study Procedures)
List of prohibited medication and supplements was updated to align with the indication in the exclusion criterion.	Section 7.3 (Excluded Medication, Supplements, Dietary Products)