Abbreviated Title: PTH-Independent Effects of Encaleret

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Title: Phase 2 study of the PTH-independent Effects of Encaleret on Mineral Homeostasis in subjects with post-surgical hypoparathyroidism (PSH)

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Investigational Agents *(if applicable)***:**

Drug Name:	Encaleret
IND Number:	163887
Sponsor:	NIDCR
Manufacturer:	Calcilytix Therapeutics, Inc., a BridgeBio Company

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

Title: Phase 2 study of the PTH-independent Effects of Encaleret on Mineral Homeostasis in subjects with post-surgical hypoparathyroidism (PSH)

Study Description: This will be a single-site, proof-of-principle, open-label study to explore the PTH-independent effects of encaleret on calcium homeostasis in participants with low or undetectable PTH levels as a result of neck surgery (PSH).

Objectives:

Primary Objective:

- Evaluate the PTH-independent effects of encaleret on renal calcium handling in participants with PSH.

Secondary Objectives:

- Evaluate the ability of encaleret to normalize blood calcium while maintaining a normal urinary calcium in participants with PSH.

Tertiary/Exploratory Objectives:

- Evaluate the ability of encaleret to increase serum iPTH levels in participants with PSH.
- Evaluate the effect of encaleret on 1-alpha hydroxylase action by measuring 1,25-(OH)2 Vitamin D levels.
- Explore the dynamic effect of encaleret on blood and urinary calcium, iPTH, cAMP, 1,25-(OH)2 Vitamin D, and urinary citrate.
- Evaluate the effect of encaleret on bone turnover in participants with PSH.
- Evaluate the effect of encaleret on phosphate, magnesium, and FGF23 levels.
- Explore the effects of encaleret on 24-hour urine markers that impact stone formation
- Examine the PK of encaleret in participants with PSH and explore PK-PD interactions.
- Explore the effect of encaleret on bone and mineral homeostasis in the following sub-groups, *as defined in Section 9.3*:
    - Permanent hypoparathyroidism (Cohort 1)
    - Recent hypoparathyroidism (Cohort 2)
    - “PTH-Clamp” cohort
    - “Aparathyroid” cohort
    - Hyperthyroid cohort
    - Normothyroid cohort
    - Thyroid cancer cohort

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Primary Endpoint:

- Percent change in Fractional Excretion of Calcium (FECa) from baseline (Day -1) to the final day of treatment (Day 6 or the last measurement while on encaleret). FECa calculated using fasting blood levels and spot urine collection.

Secondary Endpoints:

- Proportion of participants who achieve a concomitant normal or elevated fasting blood calcium (albumin-corrected calcium >8.5 mg/dL) and a normal 24-hour urinary calcium level (<250 mg/24 hours for women, <300 mg/24 hours for men) on encaleret at any point between day 1 and day 5.

Tertiary/Exploratory Endpoints:

- Percent change in Fractional Excretion of Calcium (FECa) from baseline (Screening visit) to the final day of treatment (Day 6 or the last measurement while on encaleret). FECa calculated using fasting blood levels and spot urine collection.
- Change in blood iPTH comparing average baseline iPTH to average peak iPTH on encaleret. The average baseline iPTH will include all baseline iPTH levels from the screening visit, Day -1, and pre-dose on Day 1. The average peak iPTH will average the peak iPTH levels on every day the patient is on encaleret (days 1 to 5). An increase in iPTH will be considered clinically significant if there is an increase both by 50% AND by more than 10 pg/dL.
- Change in 1,25-(OH)2 Vitamin D on encaleret comparing the maximal level prior to receiving calcitriol (On Days 3-5) to baseline (Average of Day 1 Pre-dose levels). Increase will be considered significant if there is an increase of more than 50%. Participants who receive calcitriol prior to Day 3 will be excluded.
- Pharmacodynamic endpoints measured over 5 days of encaleret therapy:

- Blood iPTH – Absolute levels and change from baseline
- Albumin-corrected blood calcium – Absolute levels and change from baseline
- Ionized Calcium – Absolute levels and change from baseline
- Urinary calcium clearance (fractional excretion and 24-hour total excretion) – Absolute levels and change from baseline
- Serum levels of 1,25-(OH)2 Vitamin D – Absolute levels and change from baseline
- Blood intact FGF23 (iFGF23) and C-terminal FGF23 (cFGF23) – Absolute levels and change from baseline
- Urine cAMP and citrate – Absolute levels and change from baseline
- Blood bone resorption marker, collagen cross-linked C-telopeptide (CTx) – Absolute levels and change from baseline
- Blood bone formation marker, blood procollagen type 1 N-propeptide (P1NP) – Absolute levels and change from baseline

- PK parameters such as maximum plasma concentration Cmax), time to maximum plasma concentration (tmax), apparent terminal half-life (t½).
- Change in components of urine including: supersaturation, sodium, potassium, calcium, magnesium, chloride, phosphorus, sulfate, citrate excretion, oxalate, pH, uric acid, creatinine, osmolality, ammonium, urea nitrogen, protein catabolic rate

Study Population:	Enrollment up to 30 male or female participants to achieve 15 to enter the treatment phase. Two cohorts: **Cohort 1:** Permanent PSH (>1 year after surgery) with minimum of 7 and up to 10 participants **Cohort 2:** Recent PSH (<1 year after surgery) with up to 5 participants
Phase:	Phase 2
Description of Sites/Facilities Enrolling Participants:	National Institutes of Health (NIH) Clinical Center (CC)
Description of Study Intervention:	Encaleret will be provided as an oral film-coated tablet. Each tablet contains 54 mg of encaleret as 60 mg of encaleret sulfate (CLTX-305). Participants will receive 3 tablets twice a day (BID).

Study Duration:	Estimated time from when the study opens to enrollment until completion of data analyses is approximately 12 months.
Participant Duration:	Total duration of study participation will be 101 to 277days for each subject including between 4 and180 days between the screening visit and initiation of therapy, and 90 day follow up after discontinuation of the study drug.

1.2 Schema

Figure 1: Overall Study Schematic

<table>
<tr><td>Screening
(Day -90 to Day -2)</td><td>Day -2</td><td>Day -1</td><td>Day 1</td><td>Day 2</td><td>Day 3</td><td>Day 4</td><td>Day 5</td><td>Day 6</td><td>Day 8-12</td><td>30 ±7 days
and
90 ±7 days
after last dose</td></tr>
<tr><td rowspan="3">Screening/Nutritionist Evaluations</td><td rowspan="3">Participant travel to be local to the NIH</td><td>Admission to NIH</td><td colspan="6">Encaleret Therapy (Figure 2)</td><td rowspan="3">Discharge</td><td rowspan="3">Follow up labs and telephone contact</td><td rowspan="3">Follow up telephone contact</td></tr>
<tr><td>Baseline Fasting labs</td><td colspan="6">Safety and pharmacodynamic blood draws 4-8 times per day (Table B)</td></tr>
<tr><td colspan="7">Daily 24-hour urine collection:
Open Day -1 in AM
Close Day 6 in AM</td></tr>
</table>

PP = post-prandial

Figure 2: Treatment Schematic

<table>
<tr><td></td><td>Screening (Day -180 to Day -2)</td><td>Day -2</td><td>Day -1</td><td>Day 1</td><td>Day 2</td><td>Day 3</td><td>Day 4</td><td>Day 5</td><td>Day 6</td><td>Follow up Lab and Telephone Contact</td><td>30-Day Telephone Contact</td><td>90-Day Telephone Contact</td></tr>
<tr><td>Encaleret</td><td></td><td></td><td></td><td colspan="5">Encaleret every 12 hours</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="4">Calcium</td><td colspan="2">SOC Calcium</td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">SOC Calcium</td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="5">Calcium supplementation, individualized dosing</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="5">Dietary Calcium 1000 mg/day, adjusted as needed</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="5">Rescue Calcium PRN</td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Calcitriol</td><td colspan="2">SOC Calcitriol</td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">SOC Calcitriol</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="2">Calcitriol if cCa <8.5 mg/dL</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="6">Rescue Calcitiol PRN</td><td></td><td></td><td></td><td></td></tr>
</table>

SOC = Standard of care, BID = twice a day; TID = three times a day; PRN = as needed.

Rescue calcium and calcitriol and encaleret discontinuation per Table D.

1.3 Schedule of Activities (SOA)

Table A Schedule of Activities

	Screening	**NIH CC Inpatient Treatment Visit**							**Discharge**	**FU Lab[7]**	**Lab Phone FU[8]**	**30-Day Phone FU[9]**	**90-Day Phone FU[10]**
		Admission		**BID Dosing**									
Days	-180 to -2	-2 OR -1	-1	1	2	3	4	5	6	8-12	9-15	30 ± 7	90 ± 7
Informed Consent	X												
Admission to clinic/ inpatient floor[1]	X	X											
Demographics, Medical history	X												
Eligibility assessment	X												
Height	X												
Weight	X		X					X					
Vital signs[2]	X		X	X	X	X	X	X	X				
Physical examination	X		X					X					
Aes and SAEs, Prior/ Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	
NPO at midnight for morning fasting labs; water and medications ok			X	X	X	X	X	X	X				
Encaleret 162 mg q12h				X	X	X	X	X					
Calcium Carbonate, individualized dosages			X	X	X	X	X	X					
Nutritionist Visit	X												
Quantify dietary calcium intake			X	X	X	X	X	X					

Stop magnesium and potassium citrate (last doses on day -3)		X	X										
Stop activated vitamin D and baseline calcium supplements (last doses on day -2)[3]			X										
Start calcitriol if cCa < 8.5 mg/dL[3]						X	X	X					
Discharge, resume conventional therapy									X				
Telephone Contact											X	X	X
Screening Lab Tests[4]	X												
Safety laboratory testing[5]										X			
Evening mineral panel (Ca, Mg, PO4, albumin)			X										
Blood β-HCG pregnancy test (WOCBP only)	X		X							X			
BloodSampling[6]			X	X	X	X	X	X					
24-hour Urine (Ca, Mg, PO4, Cr, Na, K, Citrate, pH)	X		X	X	X	X	X	X					
Timed interval urine collections[7]				X	X	X	X	X					
Renal Ultrasound	X												
ECG, 12-lead	X		X	X	X	X	X	X					

Abbreviations: Adverse Event = AE; Albumin = Alb; Electrocardiogram = ECG; BID = Twice daily; Blood Pressure = BP; Calcium = Ca; Chloride = Cl; Concomitant Medication = Con. Meds; Creatinine = Cr; Early Termination = (ET); End of Treatment = EoT.

Follow-up = FU; Heart Rate = HR; Lactate Dehydrogenase = LDH; Intact Parathyroid Hormone = iPTH; Magnesium = Mg; NPO = Nothing by mouth; National Institute of Health Clinical Center = NIH CC; Parathyroid Hormone = PTH; Phosphate = PO_4; Phosphorus = P; Potassium = K; Prothrombin Time/ Prothrombin Time = PT/INR; Red Blood Cell Count = RBC; Thromboplastin Time = PTT; Serious Adverse Event = SAE; Women of Childbearing Potential = WOCBP

[1] Participants may complete the Screening Visit as outpatients or be housed overnight at NIH CC. Participants who complete the screening visit midweek have the option to stay overnight at NIH CC (or at local housing) during the intervening days prior to the start of Day -1. Participants also have the option of travel to be local to the NIH on day -2 and stay at NIH housing (e.g., The Edmond J. Safra Family Lodge) if available. Participants have the option of being admitted on Day -2 or Day -1.

[2] Vital signs include supine or sitting blood pressure (BP) by automated cuff, heart rate (HR), and respiratory rate, to be collected q8 hours during in-patient days.

[3] Algorithm for calcium/calcitriol titration and encaleret stopping criteria found in Table D

[4] Screening lab tests: CBC, Acute care panel, ionized calcium, eGFR, Liver Function Panel, mineral panel, iPTH, 25-OH Vitamin D, Lipid panel, CK, LDH, amylase, lipase, uric acid, Coagulation (PT/PTT/INR), urinalysis, HIV, Viral Hepatitis panel, FSH level test (postmenopausal women), spot urine: calcium, magnesium, phosphate, creatinine, and cAMP. TSH, Free T4

[5] Safety lab tests: BMP, calcium, albumin, magnesium, phosphate, iPTH.

[6] See Table B and C. Note attempts will be made to collect fasting calcium levels prior to the morning calcium dosage, however, calcium will be given to participants if clinically indicated (for example, in the setting of hypocalcemia).

[7] Participants instructed to obtain outpatient laboratory testing, approximately 3-7 days after discharge from NIH CC.

[8] Research team will contact the subject to review test results and provide guidance regarding clinical management as they transition to prior clinical care providers.

[9] All participants will receive a FU call within 30 ± 7 days after last dose of the encaleret. If subject discontinues from the study early (ET), they will resume prior medication regimen, and study team will arrange FU labs within 3-7 days and FU calls at 30 ± 7 days and 90 ± 7 days after the last dose of encaleret as long as subject agrees.

[10] Final close out phone call will assess for any unintended pregnancies in either the patient or a sexual partner.

Table B: Urine Assays

	Day 1-5 Timepoints relative to AM dose +/- 20 min. PM dose given at +12 hrs +/- 30 min, given *after* 12 hr timepoint lab draw
Daily Urine Assays	
Spot Urine Measurement **Ca, Mg, PO4, Cr, cAMP**	Day -1 (fasting) Day 1, Time 0
Osmolality, cAMP	Day 1, Time 0 Day 1-5: 16-24 hr
Timed Interval Urine Ca, Mg, PO4, Crvolume	Day 1-5: 0-4 hr, 4-12 hr, 12-16 hr, 16-24 hr
24-Hour urine: Ca, Mg, PO4, Cr, Na, K, pH, Citrate Supersaturation Panel	Days -1 to 5 0-24 hrs (Start collection after first morning void and end 24 hours later) Day -1 and Day 5

Table C: Blood Sampling Days -1 to 5

Day -1: Baseline fasting labs including CBC, acute care panel, intact PTH, Ca, PO4, Mg, Cr, albumin, K, CK, Research blood, Bone turnover markers (CTX, P1NP), 25-(OH) Vitamin D, 1,25-(OH)2 Vitamin D, cAMP, ionized calcium, TSH, FT4

		-30 min	-15 min	30 min	1 hour	2 hour	4 hour	12 hour	16 hour	24 hour
Day 1	Mineral labs	X	X	X	X	X	X	X	X	
	Safety Labs		X					X		
	Ionized Calcium		X				X	X	X	
	Research Blood	X	X			X	X	X	X	
	Bone Turnover Markers		X							
	1,25D	X	X							
	cAMP		X							
	Pk		X			X	X			
Day 2-4	Mineral labs		X	X			X	X	X	
	Safety Labs		X					X		
	Ionized Calcium		X				X	X	X	
	Research Blood		X				X	X	X	
	Bone Turnover Markers		X							
	1,25D		X							
	cAMP		X							
	Pk		X							
Day 5	Mineral labs		X	X	X	X	X	X	X	X
	Safety Labs		X					X		
	Ionized Calcium		X				X	X	X	X
	Research Blood		X			X	X	X	X	X
	Bone Turnover Markers		X							
	1,25D		X							X
	cAMP		X							X
	Pk		X			X	X			

Mineral Labs: Intact PTH, Ca, PO4, Mg, Cr, Albumin
Safety Labs: Acute care panel (Na, K, Cl, CO2, BUN, Cr, eGFR), CK
Research Blood
Bone turnover Markers: CTX, P1NP
1,25-(OH)2 Vitamin D, cAMP

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2 INTRODUCTION

2.1 Study Rationale

This study will explore the PTH-independent effects of encaleret on calcium homeostasis in patients with low or undetectable PTH levels as a result of neck surgery (post-surgical hypoparathyroidism; PSH).

Hypoparathyroidism is characterized by an inappropriately low level of PTH which results in hypocalcemia. Inadequate PTH-secretion results in lower levels of endogenous 1,25-(OH)2 Vitamin D (decreasing calcium absorption from the gut), lower levels of calcium reabsorption in the kidney (leading to hypercalciuria), and decreased PTH-mediated bone resorption (decreasing calcium release from the bone).

Conventional therapy with oral calcium and calcitriol, often causes hypercalciuria, which is associated with long-term morbidity including nephrolithiasis, nephrocalcinosis and chronic kidney disease (Khan et al 2018, Li et al 2018). Managing patients with hypoparathyroidism is a challenging balance between increasing blood calcium while minimizing hypercalciuria (Gafni and Collins, 2019).

To avert symptoms of hypocalcemia, patients with PSH usually require a blood calcium in the normal range. This often results in hypercalciuria and renal calcification, which in some cases leads to loss of renal function, including the need for dialysis and transplantation. As such, there is a significant unmet need in treating patients with PSH.

Encaleret is a negative allosteric modulator of the calcium-sensing receptor (CaSR), also known as a calcilytic, which decreases the sensitivity of the CaSR to calcium, resulting in decreased renal calcium excretion, and in patients with intact parathyroid glands, increased PTH secretion. Pre-clinical studies have showed that calcilytics shift the IC50 of the calcium-PTH curve to the right (See IB Section 4.2.3 In Vivo Studies). In cellular and animal models of both post-surgical and genetic forms of hypoparathyroidism due to CaSR gain-of-function variants, calcilytics have been shown to shift the CaSR 'set-point' so as to increase renal reabsorption and PTH secretion (in animals with intact parathyroid glands), resulting in increased blood calcium (Loupy et al, 2012; Dong et al, 2015; Hannan et al, 2015).

Recent and ongoing phase 2 studies of encaleret in Autosomal Dominant Hypocalcemia type 1 (ADH1) due to gain-of-function variants in the CaSR, confirm the ability of encaleret to decrease urinary calcium and raise blood calcium. However, the net effect of encaleret on urinary and blood calcium in this situation is a result of the combined effect of both renal CaSR inactivation and increased PTH signaling. Patients with ADH1 have intact and functional parathyroid glands, so there is a rapid and robust increase in PTH secretion with encaleret therapy. To understand the PTH-independent effects of encaleret on calcium homeostasis, we will study patients with PSH treated with encaleret. The results of this study may also inform the potential role of encaleret in treating patients with PSH.

While it is predicted that calcilytics will act primarily at the kidneys in PSH to increase calcium reabsorption, this study also has the potential to inform the PTH-independent effects of encaleret on other aspects of bone and mineral homeostasis, such as active vitamin D (1,25 dihydroxyvitamin D) generation from action on 1-α hydroxylase, and/or bone turnover.

There is also the theoretical possibility that encaleret may have the ability to increase PTH secretion in patients with PSH with residual but clinically insufficient parathyroid function. If this occurs, it may even be the case that encaleret treatment could restore a normal level of parathyroid function over time.

In this exploratory proof-of-principle study, patients with PSH will be treated with encaleret in order to further our understanding of the PTH-independent effects of CaSR modulation. In addition, this study may provide clinically relevant information about how encaleret could be used as either an independent or adjuvant therapy for patients with PSH.

Our primary analyses will include all participants who received at least one dose of the study drug. However, because patients with PSH have variable residual parathyroid tissue, we will also perform sub-group analyses on a "PTH-Clamp" population defined as those whose iPTH do not increase more than 10 pg/mL on encaleret and a "Aparathyroid" population defined as those whose absolute iPTH level are less than 10 pg/dl throughout the study. The biochemical response of these subpopulations may more accurately reflect the PTH-independent effects of CaSR modulation.

A small cohort of patients who developed PSH within the last year, and have not proven to have permanent PSH, will also be included in this study. These patients may have reversible parathyroid gland damage. They are included to explore whether maximal PTH stimulation by a calcilytic can transiently increase PTH secretion in healing parathyroid glands.

2.2 Background

Encaleret (known previously as CLTX-305, JTT-305 or MK-5442), is an oral calcium-sensing receptor (CaSR) antagonist (calcilytic), currently in phase 2 study for the treatment of autosomal dominant hypocalcemia type 1 (ADH1).

Encaleret was initially developed as a treatment for osteoporosis by Japan Tobacco Inc., (JTI) and Merck, Sharp & Dohme Corp., (Merck); Healthy volunteers and postmenopausal women with osteoporosis participated in a 1,766-subject program of which 1,280 were exposed to encaleret in eight phase 1 and four phase 2 studies including exposures up to 52 weeks. No specific safety issues or signals were seen with acute dosing of encaleret sulfate up to 100 mg and chronic dosing up to 15 mg QD. Despite early data demonstrating a potential net benefit on bone formation, late phase trials failed to demonstrate efficacy on endpoints of bone mineral density (BMD) in postmenopausal women with osteoporosis and the drug was abandoned as a therapy for osteoporosis.

Hypercalcemia was identified as an on-target, dose-limiting side effect in the osteoporosis program. Increases in blood calcium that led to hypercalcemia were a safety issue in the osteoporosis program. However, increases in blood calcium would be therapeutic for patients with hypoparathyroidism. A recent phase 2 clinical trial of 13 patients with ADH1 over 24 weeks, followed by a 2-year long-term extension phase that is ongoing, has shown encaleret can increase blood PTH and calcium, and decrease urinary calcium excretion. In PSH, deficient parathyroid glands should limit the ability of encaleret to increase PTH. Thus, the primary therapeutic effect of encaleret in PSH is expected to be an increase in renal calcium reabsorption, although other effects on residual PTH secretion, activation of 25-hydroxy Vitamin D, and bone turnover, may also occur and are questions to be addressed in this study.

The goal of this proof-of-principle study is to directly study the physiologic effects of the negative allosteric modulator of the CaSR, encaleret on mineral homeostasis in the absence of a significant PTH effect. The results will inform whether negative modulation of the CaSR by encaleret is able to raise blood calcium while decreasing urinary calcium in patients with PSH. The results will inform the possibility that encaleret may be an effective standalone or adjuvant drug in the treatment of postsurgical hypoparathyroidism.

Pharmacokinetics and Product Metabolism

Encaleret (molecular formula (C29H33ClFNO4)2·H2SO4·H2O, molecular weight 1144.15) is formulated as 4.5, 9, 27 and 54 mg film-coated tablets. Each tablet contains 5, 10, 30, and 60 mg of encaleret sulfate (CLTX-305), respectively. The active agent inhibits the CaSR, via allosteric modulation, with an IC50 of 86.2 + 6.2 nM (in cell-based assays at 2 mM extracellular calcium). In humans, two major glucuronide metabolites (M1 and M3) occur. M1 (IC50 > 3000 nM) is inactive and M3 (IC50 67.3 + 6.6 nM) is active.

Encaleret is rapidly absorbed in humans (tmax median 1.5 hr. (range 0.75–3 h at most single doses or at steady-state). The elimination half-life (t1/2) was approximately 6.5 hours after single doses and 11-14 hours at steady state (14 days). Dose-proportional increases in plasma encaleret concentrations were documented over the encaleret sulfate dose range (5, 15, 30, 50 and 100 mg) in the fasted state without significant food effect. Encaleret showed minimal accumulation when administered once daily (QD) for two weeks in Japanese postmenopausal women. Based on non-clinical data, fecal excretion was the main route of elimination. In humans, excretion of unchanged encaleret and metabolites into urine was minimal (< 5% as total of parent and metabolite).

The two major glucuronide metabolites showed similar pharmacokinetics as the parent drug, with M1 median tmax approximately 2 hr. and M3 median tmax approximately 1.5 hr. For M1 (inactive), concentrations in plasma were approximately 2-fold higher than those of parent drug; M3 (active) concentrations were low (10% compared to parent). Neither M1 nor M3 showed prolonged elimination.

No significant age-related or race differences (US population vs. Japanese subjects) were observed in encaleret pharmacokinetics. AUC and Cmax values may be approximately 37% and 30% higher in females but these differences were not significant when body weight was taken into account. Hepatic and renal impairment studies have not been conducted. In a drug interaction study, co-administration with ketoconazole, a potent CYP3A4 inhibitor, resulted in approximately 1.67x increase in Cmax and approximately 2x increase in AUC0-24 with slightly less effect on M1 and M3.

For additional information see Investigator's Brochure (IB), Section 4.3 and Section 5.2.

Mineral Effects of Encaleret in Prior Clinical Trials

During the prior development program in osteoporosis, dose-related increases of endogenous serum parathyroid hormone (PTH) and blood calcium (Ca) were observed in subjects with presumed normal CaSR function (i.e., healthy volunteers and postmenopausal women with osteoporosis).

In healthy postmenopausal women, repeat encaleret sulfate doses of 15 or 20 mg resulted in consistent elevations in intact PTH (iPTH) over 3-4 hours after single daily dosing. Encaleret

sulfate dosing in phase 2 studies of normocalcemic subjects was limited to 15 mg once daily (QD) to minimize hypercalcemia.

With chronic once-daily dosing of encaleret sulfate up to 15 mg, albumin-corrected blood calcium (cCa) levels reached a plateau with up to 30% of subjects registering an elevated blood calcium above the upper limit of the laboratory reference range during long-term trials in postmenopausal women with normal systemic calcium homeostasis (normal CaSR sensitivity, normal parathyroid tissue). Such hypercalcemia was asymptomatic, modifiable by decreasing calcium/vitamin D supplementation, and/or resolved after stopping encaleret dosing. No serious adverse events (SAEs) related to either hyper- or hypocalcemia were observed in the encaleret program for osteoporosis in postmenopausal women (See IB Section 5.2).

In phase 1 osteoporosis trials, urinary calcium excretion decreased rapidly with encaleret, however, the effect only persisted for the first 12 hours. With once daily doses of 5 mg to 30 mg, 24-hour urinary calcium after 14 days of therapy was overall slightly increased (See IB Table 15 & 16, Figure 34). However, fractional excretion of calcium was lower than placebo at the 0-6 hour and 6-12 hour timepoints but elevated at the 12-24 hour timepoint. This suggests that the urinary calcium effect only persists for up to 12 hours and supports the use of every 12-hour dosing for maximal and sustainable urinary calcium effect. On the highest dosage of encaleret of 30 mg daily, despite blood calcium elevation above 11 mg/dL, urinary fractional excretion of calcium during the first 12 hours was suppressed. This suggests that encaleret may reduce urinary calcium excretion even during concomitant elevated blood calcium, supporting the hypothesis that encaleret has promise as a treatment for postsurgical hypoparathyroidism.

In period 1 of a phase 2 clinical trial of 13 individuals with ADH1, the dose of encaleret was escalated from 27 mg daily to 162 mg BID. In period 2, it was given at doses ranging between 4.5 mg to 171 mg BID based on individual patient response. Individualized dosing resulted in a rise in iPTH, normalization of mean blood calcium, and a decreased urinary calcium excretion in all patients (See IB Section 5.1.4). During this trial, mild transient hypocalcemia, hypercalcemia, and hypophosphatemia occurred during dose titration, however no moderate or severe electrolyte disturbances occurred. No serious adverse events (SAEs) occurred over 6 months of therapy. No participants discontinued the drug early, and all participants opted to enroll in the long-term extension of the trial.

In summary, data from the prior osteoporosis development program showed that once daily encaleret increases iPTH and blood calcium, but only transiently decreased urinary calcium excretion suggesting that 12-hour dosing is necessary to reduce overall renal calcium excretion. The Phase 2B trial in ADH1 showed that BID dosing can effectively decrease urinary calcium excretion and normalize blood calcium in patients with confirmed activating mutations of the calcium sensing receptor. In both patient cohorts (ADH1 and osteoporosis) the changes in blood and urinary calcium were due to a combined effect of increased blood iPTH levels, and direct modulation of CaSR at the kidney.

Subjects with PSH have inadequate parathyroid tissue, so encaleret's effect on PTH will likely be minimal; The primary effect will be through renal CaSR modulation, which is expected to decrease renal calcium excretion, resulting in an increase in blood calcium. Using encaleret in PSH will allow us to reveal PTH-independent mineral effects of CaSR action.

PSH: Clinical considerations

Hypoparathyroidism has a prevalence of approximately 77,000 adults in the United States with the most common cause, approximately 75%, due to complications from neck surgery (Mannstadt et al, 2017). PSH can be classified as transient (lasting <6 months) or permanent (lasting longer than 6 months). The true incidence of PSH is difficult to determine as it depends on numerous factors including the experience of the surgeon, extent of surgery, patient risk factors, and diagnosis criteria. Nevertheless, it is estimated that transient PSH affects up to 25-30% of patients undergoing total thyroidectomy, while permanent PSH occurs in up to 3% of patients (Mannstadt et al, 2018).

Hypoparathyroidism is characterized by an inappropriately low level of parathyroid hormone (PTH), hypocalcemia and hyperphosphatemia. Inadequate PTH-secretion results in lower levels of endogenous 1,25-(OH)2 Vitamin D (decreasing calcium absorption from the gut), lower levels of calcium reabsorption in the kidney (leading to hypercalciuria), and decreased PTH-mediated bone resorption (decreasing calcium release from the bone). Symptoms of hypocalcemia include paresthesias, muscle spasms, tetany, cramps, seizures, laryngospasm, neuromuscular irritability, cognitive impairment, personality disturbances, and prolonged QT intervals.

Conventional therapy with oral calcium and calcitriol, which includes a high pill burden and is cumbersome for patients, often causes hypercalciuria, which is associated with long-term morbidity including nephrolithiasis, nephrocalcinosis and chronic kidney disease (Khan et al 2018, Li et al 2018). Managing patients with hypoparathyroidism is a challenging balance between increasing blood calcium while minimizing hypercalciuria (Gafni and Collins, 2019). Practically, this is done by targeting the lowest blood calcium that still relieves symptoms of hypocalcemia to avoid hypercalciuria.

Recombinant human PTH 1-84 (Natpara, Takeda Inc.) was approved for the treatment of hypoparathyroidism, however, the effect on hypercalciuria, renal calcifications, and renal insufficiency is unclear (Gafni et al, 2018; Rubin et al, 2016) It is also currently unavailable in the US due to a prolonged recall. Long-acting PTH preparations are being developed and show promise, but will continue to require injections, which patients are often opposed to if comparable effective orally administered treatment is available.

Encaleret has the potential to fill the unmet need of an oral medication that can maintain eucalcemia without increasing the risk of renal calcification. By protecting patients from the main complications of conventional therapy (hypercalciuria, nephrolithiasis, nephrocalcinosis, and chronic kidney disease), encaleret could simplify the safe treatment of hypoparathyroidism and allow for higher serum calcium levels without higher iatrogenic risk.

PTH-Independent Mineral Effects of CaSR Modulation

The primary actions of the CaSR and PTH are closely interrelated. Because increased CaSR activity results in increased PTH production, identifying PTH-independent effects of CaSR activity is challenging. Patients with PSH, who are PTH-deficient, are the ideal group of patients to unravel this complicated physiology.

In rodents, the effect of CaSR modulation using calcilytics in PSH has been observed in a pre-clinical study of parathyroidectomized rats, in which a calcilytic NPS2143 increased blood calcium levels and decreased renal calcium excretion (Loupy et al. 2012). The same small study, using parathyroidectomized rats on stable supplemental PTH, suggested that, in rats at

least, dietary intake, 1,25D levels, fecal calcium excretion, and bone resorption were unchanged by the calcilytic, suggesting that the effect was primarily renal. Another pre-clinical study focused on surgical hypoparathyroid rats with remnant parathyroid tissue from hemi-parathyroidectomy or total parathyroidectomy with auto-transplantation (Lim et al, 2020). The calcilytic AXT914 increased iPTH and improved hypocalcemia, hyperphosphatemia, and hypercalciuria in both models.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Encaleret has been generally well tolerated in humans during chronic treatment up to and beyond 12 months. In a prior osteoporosis development program, encaleret was administered to over 1300 healthy men and post-menopausal women; no specific safety issues or signals were seen with acute dosing of encaleret sulfate up to 100 mg and chronic dosing up to 15 mg QD. No distinct patterns of adverse events (Aes) to suggest intolerance nor evidence of toxicity (on- or off-target) were seen with encaleret, except for its known, on-target pharmacological effect to stimulate endogenous PTH hormone release and dose-related hypercalcemia (in euparathyroid subjects) as described above.

In the ongoing phase 2 trial of encaleret in ADH1, encaleret was administered to 13 individuals with hypoparathyroidism at doses ranging from 4.5 mg to 171 mg BID for 24 weeks followed by an ongoing long-term extension. From the preliminary safety data (data cutoff date 27-OCT-2021), there have been no reported serious or severe Aes or discontinuations due to Aes. Seventeen Aes were considered related to study treatment by the Investigator which included mild hypophosphatemia (n=10), mild hypercalcemia (n=6), and mild hypocalcemia (n=2). Treatment-related Aes of hypophosphatemia, hypercalcemia, and hypophosphatemia were transient and resolved either spontaneously or with adjustment of the encaleret dose. Hypophosphatemia and hypercalcemia were due to on-target stimulation of PTH hormone release, while hypocalcemia was due to the patient's underlying hypoparathyroidism.

Details for all previous non-clinical and clinical studies with encaleret can be found in the encaleret Investigator's Brochure.

The most common adverse events reported in early phase trials included constipation, headache, dizziness, nausea, vomiting, abdominal pain, back pain, and dermatitis in addition to increased blood calcium concentrations. None of these adverse events occurred with differential frequency in the larger phase 2 trials where no specific pattern of adverse events or clear differences were evident in Aes by System, Organ, Class between encaleret and placebo or comparator arms (other than differences in calcium levels).

A thorough QT study in healthy subjects showed no clinically meaningful QTc prolongation following a single oral dose of up to 100 mg encaleret at any of the examined timepoints. In patients with ADH1, who are hypocalcemic at baseline, QTc decreased towards normal on encaleret, in parallel with normalization of calcium and magnesium level. Of note, although pre-encaleret cCa levels in this population ranged from 6.4 to 9 mg/dL, no subjects had QTcF or QTcB interval >480 msec.

In preclinical safety and toxicology studies, the dose-limiting effects of encaleret were related to mechanism-based elevations in serum calcium concentrations and effects on calcium

homeostasis. In contrast, no off-target or other tissue or organ-specific toxicities were identified.

The metabolism and elimination of encaleret in preclinical studies has been conducted. Based on non-clinical data, fecal excretion was the main route of elimination. In humans, excretion of unchanged encaleret and metabolites into urine was minimal (< 5% as total of parent and metabolite). The two major glucuronide metabolites (M1, M3) showed similar pharmacokinetics as the parent drug, with M1 median tmax ~2 hr. and M3 median tmax ~1.5 hr. For M1 (inactive), concentrations in plasma were approximately 2-fold higher than those of parent drug; M3 (active) concentrations were low (10% compared to parent). Neither M1 nor M3 showed prolonged elimination (see Investigator Brochure for details). Encaleret has not been formally studied in patients with severe to moderate renal impairment but significant dose adjustments in this population are not expected given elimination pathway and in the setting of the protocol dose escalation safety review process.

In a human drug interaction study, encaleret co-administration with ketoconazole, a potent CYP3A4 inhibitor, resulted in ~1.67x increase in Cmax and ~2x increase in AUC0-24 with slightly less effect on M1 and M3.

The potential for skin phototoxicity in humans is expected to be minimal based on the tissue distribution in rats and estimated human dosage, but participants may be at increased risk to natural or artificial sunlight (tanning beds or ultraviolet A/B light (UVA/B) treatment). Participants at increased risk to UV injury are encouraged to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment), wear sun-protective clothing, and use sunscreen that strongly absorbs ultraviolet A light (UVA). A carcinogenicity rat study showed an increased risk of osteosarcoma in rats receiving the highest exposure of encaleret (80 mg/kg/day) for more than a year. 360 rats were exposed to daily encaleret for up to 2 years during this study. No osteosarcoma was observed in the 10 mg/kg/day or 30 mg/kg/day dosage groups. In these wild-type rats, high encaleret doses resulted in excessive PTH secretion.

To put this in context, it's important to note that PTH analogs have also been shown to increase the incidence of osteosarcomas in rats in a dose-dependent manner (Vahle et al, 2002). A long-term study of PTH 1-34 in cynomolgus monkeys showed no evidence of bone tumors (Vahle et al, 2008). On the basis of the preclinical rat studies, pharmacologic PTH and PTH-like products included a black box warning about risk of osteosarcoma. A 15-year Osteosarcoma Surveillance Study did not identify an increase in osteosarcoma associated with use of PTH 1-34 (Gilsenan et al, 2021). The FDA removed the black box warning for teriparatide (PTH 1-34) and abaloparatide (a PTH-related drug) in 2021 and 2022 respectively. Nevertheless, due to the pre-clinical rat studies and the limitations of post-marketing studies, 'potential risk of osteosarcoma' is still included in the safety information for all PTH analogs.

Risk to participants in this study is likely very low. Participants in this study have insufficient parathyroid tissue, so encaleret is not expected to substantially increase PTH levels. In the first 6 participants with PSH exposed to encaleret, PTH remained in the low or low-normal range on encaleret. Participants are also exposed to encaleret for only 5 days in this study, much less than in the rat study (more than a year). Participants in this protocol will also receive an encaleret dose of 162 mg BID, a substantially lower exposure than the rats who developed osteosarcoma.

Furthermore, bone physiology in rats and humans are fundamentally different. Importantly, rats have open growth plates and experience longitudinal growth for most of their lives while human growth plates close prior to adulthood. Open growth plates are presumed to be a risk factor for the development of osteosarcomas. All participants in our study are adults with closed growth plates.

It is not possible to know conclusively whether bone cancer in rats was caused by encaleret or high PTH. It is also difficult to know if the findings in rats are relevant to humans because of differences between the bones of rats and humans. At this time, it is not known if there is truly an increased risk for osteosarcoma in humans treated with encaleret. In this study, the lower dose and duration of encaleret decreases the possible risk. As a precaution, this study does not allow people with an increased risk of osteosarcoma to participate.

It is not known if encaleret could have an effect on pregnancy or breastfeeding in humans. Encaleret may have potential teratogenic effects in humans based on the results of a reproductive toxicity study in rabbits where the incidence of skeletal anomalies (fusion of the sternebra) was increased in the fetuses at 30 mg/kg and above. Currently, Women of Childbearing Potential (WOCBP) will be consented to receive pregnancy testing at screening and at intervals throughout the trial and required to utilize contraception and agree to avoid pregnancy during the experimental treatment.

During this week-long inpatient study, hypoparathyroid participants on encaleret may experience fluctuations in their blood calcium levels including the potential for hypocalcemia and/or hypercalcemia. The long-term risk of such fluctuations with encaleret are not expected to be larger than the risk of current therapy, however it is possible such fluctuations may be more frequent during this proof-of-principle study. Notably, because these patients have insufficient functional parathyroid tissue, the risk for hypercalcemia is expected to be significantly less than the risk was in the previous studies of patients with ADH1 or premenopausal women. Similarly, hypophosphatemia that was induced by increased iPTH secretion in the previous study in patients with ADH1, is unlikely in this patient population. This study is designed to minimize the risk of untoward fluctuations in blood calcium and related serum chemistries: Participants will be supervised with frequent monitoring of blood calcium levels multiple times per day and may receive treatment for hypocalcemia or hypercalcemia, including oral or IV calcium and calcitriol as needed. To reduce the risk of symptomatic hypocalcemia or hypercalcemia, participants will be given a personalized robust calcium load based on their home calcium dosages and a starting dietary calcium of 1000 mg per day. Doses will be determined by an endocrinologist familiar with treating hypoparathyroidism and will be based on each participant's baseline requirements and blood calcium levels. Additional 'rescue' calcium and calcitriol will be added if the patients experience significant symptoms of hypocalcemia or an albumin-corrected blood calcium < 7 mg/dL (Table D). On day 3, if the albumin-corrected blood calcium continues to be persistently <8.5 mg/dL, calcitriol will be added at a dose determined by the investigators and based on the patient's pretreatment dosages and current blood calcium. Calcium and dietary calcium will be adjusted as need by physician investigators trained in endocrinology.

Additional risks and potential discomforts related to the frequent blood and urine sampling procedures in the supervised setting of the inpatient stays are addressed in the Informed Consent Document and include medical history, physical examination, renal ultrasound, and

ECG. During test days multiple blood and urine collections will occur introducing known common risks (discomfort, bruising) for blood draws and/or intravenous catheter placement introducing smaller risks of complications including fainting (usually a vasovagal response to sight or insertion of needles) or inflammation of the insertion site (including potentially pain and swelling) and the potential for infection or venous thrombosis. Central catheters (inserted via the arm or the neck) may be used to reduce subject burden during intensive sampling requirements. Blood sampling volumes will remain below the limits outlined in the NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009).

Based on the totality of the evidence acquired to date, no other organ-specific or adverse safety signals of potential clinical concern have been identified. Clinical trials in the new target population of patients with PSH will closely evaluate dose-related effects on calcium homeostasis and otherwise employ routine safety monitoring (For details on encaleret safety data, see IB Section 5.3).

2.3.2 Known Potential Benefits

There are no definitive currently known benefits of encaleret in the target population of PSH. However, this proof-of-principle study could possibly identify a novel therapeutic class for PSH, one which might allow patients with PSH maintain eucalcemia without increasing the risk of renal calcification. This study may possibly identify the PTH-independent effect of CaSR on renal calcium reabsorption, thereby contributing the greater body of knowledge and could inspire future therapeutic studies.

2.3.3 Assessment of Potential Risks and Benefits

This study is designed to minimize known potential risks (as described above) while allowing for the examination of the PTH-independent effect of CaSR on renal calcium reabsorption. This study will also address, in a proof-of-principle manner, the potential utility of encaleret as a therapy in patients with postsurgical hypoparathyroidism.

The primary known risk to patients of being enrolled in this study is the risk of hypercalcemia or hypocalcemia. To mitigate these risks, the study is entirely inpatient, calcium will be closely monitored, and supplementation will be adjusted as required. An algorithm for response to hyper/hypocalcemia is detailed in Table D including stopping criteria for Encaleret.

The risks of participation are reasonable relative to the medical knowledge that may be achieved.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the PTH-independent effects of encaleret on renal calcium	Percent change in Fractional Excretion of Calcium (FECa) from baseline (Day -1) to the final day	FECa reflects the relationship between blood calcium and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
handling in participants with PSH.	of treatment (Day 6 or the last measurement while on encaleret). FECa calculated using fasting blood levels and spot urine collections.	urinary calcium. CaSR modulation by encaleret is expected to directly affect FECa. If a patient stops encaleret early prior to Day 6, the last fasting FECa on encaleret 162 mg BID will be used for this endpoint.
Secondary		
Evaluate the ability of encaleret to normalize blood calcium while maintaining a normal urinary calcium in participants with PSH.	Proportion of participants who achieve a concomitant normal or elevated fasting blood calcium (albumin-corrected calcium >8.5 mg/dL) and a normal 24-hour urinary calcium level (<250 mg/24 hours for women, <300 mg/24 hours for men) on encaleret at any point between day 1 and day 5.	Clinically relevant endpoint to determine if encaleret can allow PSH to have both normal blood and urinary calcium.
Tertiary/Exploratory		
Evaluate the ability of encaleret to increase serum iPTH levels in participants with PSH.	Change in blood iPTH comparing average baseline iPTH to average peak iPTH on encaleret. The average baseline iPTH will include all baseline iPTH levels from the screening visit, Day -1, and pre-dose on Day 1. The average peak iPTH will average the peak iPTH levels on every day the patient is on encaleret (days 1 to 5). An increase in iPTH will be	Averaging iPTH will prevent spurious excursions from impacting outcomes

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	considered clinically significant if there is an increase both by 50% AND by more than 10 pg/dL.	
Evaluate the effect of encaleret on 1-alpha hydroxylase action by measuring 1,25-(OH)2 Vitamin D levels.	Change in 1,25-(OH)2 Vitamin D on encaleret comparing the maximal level prior to receiving calcitriol (On Days 3-5) to baseline (Average of Day 1 Pre-dose levels). Increase will be considered significant if there is an increase of more than 50%. Participants who receive calcitriol prior to Day 3 will be excluded.	
Explore the dynamic effect of encaleret on blood and urinary calcium and citrate, iPTH, cAMP, and 1,25-(OH)2 Vitamin D. Evaluate the effect of encaleret on bone turnover in participants with PSH. Evaluate the effect of encaleret on phosphate, magnesium, and FGF23 levels.	Percent change in Fractional Excretion of Calcium (FECa) from baseline (Screening visit) to the final day of treatment (Day 6 or the last measurement while on encaleret). FECa calculated using fasting blood levels and spot urine collection. Pharmacodynamic endpoints measured over time over 5 days of encaleret therapy: • Blood iPTH – Absolute levels and change from baseline • Albumin-corrected blood calcium - Absolute levels and change from baseline in cCa • Ionized Calcium – Absolute levels and change from baseline • Urinary calcium clearance (fractional excretion and 24-	These endpoints will allow us to further explore the effect of encaleret on other markers of bone and mineral metabolism and identify areas for future study.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Explore the effects of encaleret on 24-hour urine markers that impact stone formation	hour total excretion) - Absolute levels and change from baseline • Serum levels of 1,25-(OH)2 Vitamin D - Absolute levels and change from baseline • Blood iFGF23 and cFGF23 - Absolute levels and change from baseline • Urine cAMP and citrate - Absolute levels and change from baseline • Bone resorption markers collagen cross-linked C-telopeptide (CTx) - Absolute levels and change from baseline • Bone formation markers – blood procollagen type 1 N-propeptide (P1NP) - Absolute levels and change from baseline • Change in components of urine including: supersaturation, sodium, potassium, calcium, magnesium, chloride, phosphorus, sulfate, citrate excretion, oxalate, pH, uric acid, creatinine, osmolality, ammonium, urea nitrogen, protein catabolic rate	
• Examine the PK of encaleret in participants with PSH and explore PK-PD interactions.	• PK parameters such as maximum plasma concentration Cmax), time to maximum plasma concentration (tmax), apparent terminal half-life (t½)	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Explore the effect of encaleret on bone and mineral homeostasis in the following sub-groups, as defined in Section 9.3 Populations for analysis: • Permanent hypoparathyroid (Cohort 1) • Recent Hypoparathyroid (Cohort 2) • "PTH-Clamp" population • "Aparathyroid" population • Hyperthyroid cohort • Normothyroid cohort • Thyroid cancer cohort	• Subgroup analysis of other primary, secondary, and tertiary endpoints	Primary analysis of all endpoints will be performed on the entire population, but subgroup analysis will also be performed for exploratory and hypothesis-generating purposes.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-site, open-label, phase 2, proof-of-principle study to evaluate the PTH-independent effects of encaleret on renal calcium handling in participants with hypocalcemia due to PSH.

Up to 30 participants may be enrolled to support up to 15 participants entering the treatment phase of the study. Two main cohorts are planned:

Cohort 1: Permanent PSH with neck surgery ≥12 months ago (minimum 7, up to 10 participants)

Cohort 2: Recent PSH with neck surgery <12 months ago (up to 5 participants)

4.2 Scientific Rationale for Study Design

The current clinical trial is a small proof-of-principle trial designed to explore PTH-independent effects of encaleret on calcium homeostasis and to determine the ability of a calcilytic to decrease urinary calcium excretion and raise blood calcium in patients with PSH. Encaleret has the potential to fill the unmet need of an oral medication for PSH that can maintain eucalcemia without increasing the risk of hypercalciuria and renal calcifications.

Our primary analyses will include all participants who received at least one dose of the study drug. However, sub-group analysis will also be performed on patients with recent PSH (cohort 2) to explore whether maximal PTH stimulation by a calcilytic can transiently increase PTH secretion in healing parathyroid glands. Patients with recent PSH have the potential to either

have resolution of their hypoparathyroidism or progression to permanent hypoparathyroidism. They will likely respond to encaleret at the kidney level very similarly to cohort 1 in terms of the primary endpoint, FECa, because their kidneys presumably function the same. However, since these patients may have reversible parathyroid gland damage, they may be more likely to increase PTH secretion in response to maximal stimulation by encaleret. It should be noted that the dose of encaleret that is being used will be biologically sensed as profound hypocalcemia to a degree that would never be experienced by a patient with PSH and as such may function as a much more potent stimulator of PTH secretion.

Furthermore, because patients with PSH have variable residual parathyroid tissue, we will also perform exploratory sub-group analyses on a "PTH-Clamp" population whose iPTH did not increase more than 10 pg/mL on encaleret and a "Aparathyroid" population whose absolute iPTH level was less than 10 pg/dl throughout the study. The biochemical response of these subpopulations will likely more accurately reflect PTH-independent effects of CaSR modulation.

4.3 Justification for Dose

The current study proposes to initiate first-in-patient dosing in the new target population of participants with PSH with encaleret 162 mg BID over a 5-day inpatient admission.

Twice a day dosing is necessary to maximize and sustain the effect on renal calcium excretion. In previous studies in euparathyroid patients, once daily dosing did not normalize 24-hour urinary calcium excretion, however, calcium excretion was suppressed for the first 12 hours. In the ongoing Phase 2B study of patients with ADH1 due to activating CASR mutations, encaleret needed to be given twice daily to maintain 24-hour effects on blood and urine calcium.

The present PSH cohort is expected to be protected from hypercalcemia experienced by previous cohorts on encaleret (normal controls or patients with osteoporosis or ADH1). This is because patients with PSH, who have insufficient parathyroid tissue, are unlikely to have a robust PTH response to encaleret. On the other hand, because of the lack of functional parathyroids in this patient population, these patients may be at increased risk of symptomatic hypocalcemia during the course of the study. Thus, maximizing the encaleret dose in this population is both important for the safety of the patients, to reduce risk of hypocalcemia, as well as increasing the probability of establishing a definitive proof-of-principle which is the goal of this study.

A primary concern in this proof-of-principle study is to not make a type 2 error (not see an effect when one exists). Thus, we chose the highest dose that has been safely used previously in patients with hypoparathyroidism/ADH1 to increase the likelihood that we will see our predicted effect.

5 STUDY POPULATION

5.1 Inclusion Criteria

Participants must meet the following criteria for inclusion during screening:

1. Be able to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.

2. Age ≥ 18 years
3. Postmenopausal women are allowed to participate in this study:
    a. Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to start of the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, shall she be considered not of childbearing potential.
4. Body mass index (BMI) ≥ 18.5 to < 39 kg/m^2
5. Have a diagnosis of PSH, either permanent PSH (Cohort 1, surgery >= 12 months ago) or recent PSH (Cohort 2, surgery < 12 months ago).
6. Participants must have achieved an albumin-corrected blood calcium level of 7.8-10.2 mg/dL on conventional therapy without significant symptoms of hypocalcemia or hypercalcemia.
7. Participants being treated with thiazide diuretics may be enrolled if they are willing and able to discontinue thiazides for at least 5 half-lives prior to initiation of encaleret and remain off during the study treatment period. (5 half-lives of hydrochlorothiazide = 75 hours; chlorothiazide = 10 hours; chlorthalidone = 12.5 days). If the thiazide is being used as an antihypertensive, as opposed to use as a urine calcium-lowering drug, alternative therapy will be offered.
8. Participants being treated with strong CYP3A4 inhibitors (including clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) may be enrolled if they are willing and able to discontinue these medications for at least 5 half-lives prior to initiation of encaleret and remain off during the study treatment period.
9. Participants being treated with magnesium or potassium citrate supplements should discontinue such treatment starting on Day -2.
10. Participants being treated with medications that have impacts on mineral metabolism which investigators believe may impact study endpoints may be enrolled if they are willing and safely able to discontinue the medication for at least 5 half-lives prior to initiation of encaleret and remain off during the study treatment period

5.2 Exclusion Criteria

Participants who meet any of the following criteria during Screening will not be eligible to participate in the study:

1. History of treatment with any PTH analog (i.e., PTH 1-84, PTH 1-34, TransCon PTH, etc.) within the previous 3 months
2. History of prior treatment with encaleret
3. History of hypocalcemic seizure within the past 3 months

4. Blood 25-OH Vitamin D level <25 or >60 ng/mL

    a. If subject has a blood 25-OH Vitamin D level < 25 ng/mL at the screening visit, they will be prescribed cholecalciferol or ergocalciferol supplementation. Once the 25-OH Vitamin D level is >= 25 ng/mL, the subject will be eligible to continue to the treatment phase of the study.

    b. If a subject has a blood 25-OH Vitamin D level >60 ng/mL at the screening visit, their vitamin D supplementation will be adjusted. Once the 25-OH Vitamin D level is <=60 ng/mL, the subject will be eligible to continue to the treatment phase of the study.

5. Participants with hemoglobin (Hgb) lower than the lower limit of normal.

    a. If subject has a low Hgb at the screening visit due to iron, B12, or folate deficiency, they will be prescribed supplementation. Once the Hgb level within the normal range, the subject will be eligible to continue to the treatment phase of the study.

6. Abnormal laboratory values which in the opinion of the investigator, would make the subject not suitable for participation in the study

7. Estimated glomerular filtration rate (eGFR) < 50 mL/minute/1.73 m^2 using CKD-EPI.

8. Insufficient hepatic function defined as one of the following:

    - Total Bilirubin > 1.5 x ULN OR

    - Aspartate transaminase (AST) > 2x ULN OR

    - Alanine transaminase (ALT) > 2x ULN

9. 12-lead resting electrocardiogram (ECG) with clinically significant abnormalities. Participants with screening QTcF (using the Frederica equation) > 450 milliseconds (ms) will not be eligible for the treatment phase of the study.

– If a participant has a prolonged QTcF during screening due to a reversible cause of long QT (for example hypocalcemia or QT-prolonging medications), the subject may be eligible for the treatment phase of the study if the reversible cause can be addressed, and repeat ECG shows QTcF ≤450 milliseconds.

10. Clinically significant cardiac disease including any of the following:

    – Congestive heart failure requiring treatment (NY Heart Association grade >= 2)

    - History of clinically significant cardiac arrythmias including ventricular arrhythmias, atrial fibrillation, or conduction abnormalities

    – History of unstable angina pectoris or acute myocardial infarction

11. Participants with positive hepatitis B surface antigen (HBsAg) or Hepatitis A immunoglobulin M (IgM) at the Screening Visit. Participants who are in complete remission from Hepatitis C as evidence by sensitive assay ≥12 weeks after completion of HCV therapy are allowed to participate in the study. Participants with human immunodeficiency virus (HIV) infection on a stable dose of anti-retroviral therapy who have an undetectable viral load are allowed to participate in the study.

12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum hCG laboratory test
13. Clinically significant abnormalities in thyroid function tests. This does not include participants with non-clinically significant or treated thyroid diseases (e.g. subclinical hypothyroidism, hypothyroidism on treatment, etc). Participants on TSH-suppression therapy for thyroid cancer are allowed to participate in this study regardless of TSH level.
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of the following (a+c or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
15. Sexually active male participants who are unwilling to use a condom during vaginal intercourse while taking the encaleret (study drug) and for 3 months after the last dose of the study drug. Participants should not father a child during active participation in the study starting with the first encaleret dose. Condoms are not required if the subject is vasectomized or if the subject's partner is not a woman of child-bearing potential.
16. Hypersensitivity to any active substance or excipient of encaleret
17. History of drug or alcohol dependency within 12 months preceding the Screening Visit
18. Current participation in other investigational drug studies

19. Unwillingness to refrain from blood donation within 12 weeks prior to admission visit through one year after the last dose of the study drug. If subject donated blood within 12 weeks of the screening visit, they will need to wait until 12 weeks have passed since blood donation for the admission visit.
20. Participants who have a history of diseases of mineral metabolism other than hypoparathyroidism or hyperparathyroidism which investigators believe may impact study endpoints (for example, X-linked hypophosphatemia, rickets, etc).
21. Participants with history of the following :
    - Any cancer except for thyroid cancer, basal cell skin cancer or squamous cell cancer in the last 5 years. Subjects with history of thyroid, basal cell or squamous cell cancers should have received definitive treatment for their malignancies prior to enrollment.
    - Skeletal malignancies
    - Bone metastases
    - Irradiation (radiotherapy) to the skeleton
    - Any other disease that increases the likelihood for osteosarcoma (ex. Paget's disease).
    - Unexplained elevations of alkaline phosphatase

5.3 Inclusion of Vulnerable Participants

5.3.1 Participation of NIH Staff or family members of study team members

NIH staff and family members of study team members may be enrolled in this study as this population meets the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.

The *NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research* will be made available. Please see section **10.1.3** for consent of NIH Staff.

5.4 Inclusion of Pregnant Women, fetuses, or neonates

Not applicable

5.5 Lifestyle Considerations

During this study, participants are asked to:

- Consume approximately 1000 mg of daily calcium from their diet, with assistance from a nutritionist.
- Refrain from donating blood at least 12 weeks prior to the admission visit to one year after the last dose of the drug.

- Refrain from eating food from midnight until the next morning during the admission visit

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently started on treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial because of failing to meet criteria may be rescreened to reassess the specific criteria that led to screen failure. Only the relevant criteria need to be repeated during rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

Individuals who meet criteria for participation in this trial but are unable to schedule an admission visit within 180 days of the screening visit, may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.7 Strategies for Recruitment and Retention

Hypoparathyroidism has an estimated prevalence of 77,000 adults in North America, with approximately 75% of which are from PSH (Mannstadt et al, 2017). Initial recruitment will include contacting participants with PSH known to NIH investigators. Additional recruitment may proceed through referrals from worldwide clinical and research experts involved in parathyroid surgery and hypoparathyroidism who may be contacted by investigators using a recruitment flier. Finally, outreach through patient advocacy organizations worldwide may also be pursued.

Up to 30 participants may be enrolled to support up to 15 participants entering the treatment phase of the study.

Potential participants will undergo the informed consent process and be screened during an admission or outpatient appointment at the NIH, when they will receive explanation of the clinical trial procedures and requirements. Participants will receive expert clinical oversight of their outpatient therapeutic regimen and management from NIH investigators during the period from screening to the in-house admission and throughout the clinical trial.

Participants will not be billed for any research or related clinical care that participants will receive at the NIH Clinical Center for this study.

5.7.1 Compensation

Participants will be compensated for participation in this clinical trial.

Maximum compensation will be $885 at the completion of the study with compensation broken down as follows:

Screening visit: $135

Admission visit: $720 ($120 per day x 6 days)

Telephone visits: $30 ($10 x 3 telephone visits)

If subject is unable to finish the study, he/she will receive adjusted compensation for part(s) completed also in accordance with NIH HRPP policy 3014-302 Subject Recruitment and Compensation.

Air/train/bus travel will be arranged by the NIH travel agency unless there are extenuating circumstances requiring the subject to book his/her own travel. Miscellaneous out-of-pocket travel expenses (e.g., baggage receipts, airport parking, taxis) will be reimbursed if a receipt is provided. Participants traveling by car from > 50 miles will be reimbursed mileage per NIH policies. Subject copays or co-insurance for local laboratories will be paid or reimbursed if an invoice or receipt is provided.

6 STUDY INTERVENTION

6.1 Study Interventions(s) Administration

6.1.1 Study Intervention Description

The investigational medicinal product (IMP), encaleret, will be provided as film-coated tablets containing the active ingredient encaleret provided in 54 mg dosage strength. Participants will receive encaleret 162 mg (3 tablets) BID per protocol with water.

6.1.2 Dosing and Administration

On Day -1/-2, participants who met eligibility criteria at the screening visit will be admitted to the NIH CC. Participants will not take their magnesium and potassium citrate starting on the morning of Day -2. Participants will not take their standard-of-care calcium or calcitriol starting on the morning of Day -1, and will instead start a personalized calcium supplementation, determined by investigators from their baseline calcium requirements and levels. They will start on a dietary daily calcium intake of approximately 1000 mg per day, which may be adjusted if needed.

Encaleret 162 mg twice a day will be administered to participants on Day 1 to 5. Additional calcium and/or calcitriol will be administered per algorithm (Table D) if required.

Calcium and calcitriol supplementation will be adjusted following the algorithm delineated in Table D with the primary goal of safety. Mild to moderate symptomatic hypocalcemia at any calcium level, cCa < 7 mg/dL, or borderline QT prolongation, would cause investigators to give oral calcium and/or calcitriol. Doses will be determined at the discretion of experienced investigator's understanding of the patient's prior supplement requirements and severity of hypocalcemia. IV calcium may be used for participants with severe hypocalcemic symptoms or QTcF > 500 ms. If a patient develops mild hypercalcemia, then calcium and calcitriol will be held until cCa is less than 9 mg/dL. If cCa has not trended down by 12 hours (or earlier per investigator discretion), encaleret will be stopped. If cCa is > 12 mg/dL, encaleret will be discontinued and calcium and calcitriol will be held until cCa is < 9 mg/dL, when home regimen is restarted.

On Day 3, investigators will add calcitriol supplementation if the albumin-corrected calcium remains < 8.5 mg/dL. The calcitriol dose will be determined by investigators, taking into account the current calcium level and the subject's baseline requirements.

The last dose of encaleret will be given on the night of Day 5. The patient will then resume calcium and calcitriol and be discharged home. If the patient is hypercalcaemic or hypocalcemic, their baseline calcium and calcitriol may be adjusted at discharge. If needed, they may remain at the NIH clinical center until their labs have stabilized to a safe level.

Table D: Titration algorithm:

		Encaleret Titration	Calcium supplementation titration*	Calcitriol titration*	Additional interventions/ monitoring
Hypocalcemia	**Severe symptomatic hypocalcemia (seizures, QTcF > 500)****	Continue encaleret	IV calcium until symptoms resolve, transition to oral calcium	Start or increase calcitriol	Monitor blood calcium every 4-6 hours until symptoms resolve
	Mild to moderate symptomatic hypocalcemia OR cCa < 7 mg/dL OR QTcF >480 OR Change in QTcF of >90 from baseline	Continue encaleret	Increase oral calcium and/or start or increase calcitriol		If QT prolonged, repeat ECG twice a day until QTc < 480 or <90 from baseline
	cCa 7-10.2 mg/dL without symptoms of hypo/hypercalcemia	Continue encaleret	Continue calcium	No change in dose until day 3. On day 3, if cCa remains < 8.5 mg/dL, start calcitriol.	
Hypercalcemia	**cCa 10.2 – 12 mg/dL**	Continue encaleret while holding calcium/calcitriol. Discontinue encaleret if cCa has not trended down up to 12 hours after holding calcium/calcitriol.	Hold calcium until cCa < 9 mg/dL, then restart calcium at a lower dose	Hold calcitriol if taking until cCa < 9 mg/dL, then consider restarting at a lower dose or discontinuing	
	cCa > 12 mg/dL	Discontinue encaleret	Hold calcium until safe to restart home regimen	Hold calcitriol until safe to restart home regimen	IV fluids, consideration of calcitonin therapy if hypercalcemia is prolonged

*This algorithm is meant as a guide and may not have considered all possible scenarios. Calcium and calcitriol titration will be determined by physician investigators specializing in endocrinology and will be based on the prior calcium/calcitriol dosage, the individual patient's prior response, and lab trends. Ultimate decisions regarding calcium and calcitriol changes will be made with the primary goal of patient safety even if this deviates from this algorithm.
**Note that severe hypocalcemia and hypercalcemia are not expected to occur during this study. Early intervention and close monitoring is in place to prevent these severe adverse outcomes from occurring.
cCa = Albumin-corrected blood calcium, QTcF = QT corrected using the Fridericia's correction equation, IV = intravenous

Drug Discontinuation

Encaleret will only be given at the 162 mg BID dosage during this study, but may be discontinued early in the setting of hypercalcemia per the algorithm in Table D.

Participants who develop abnormal clinical or laboratory assessments that indicate continuation of the treatment may put the subject at risk, may have their encaleret dosing interrupted at the discretion of the principal investigator.

Participants who met specific achievement thresholds for both the primary and secondary endpoints may be eligible for early drug discontinuation at the discretion of the principal investigator. The defined thresholds are as follows: The primary endpoint will be considered achieved if the fasting FECa has decreased by >40%. The secondary endpoint will be considered achieved if the participant has achieved concomitant normal or high blood calcium and normal urinary calcium. This approach aims to facilitate the evaluation of the PK-PD relationship (exploratory endpoint) during encaleret withdrawal.

Calcium and calcitriol supplementation and encaleret dose will be adjusted following the algorithm delineated in Table D with the primary goal of safety.

Drug Administration

Encaleret will be dispensed by the NIH Pharmacy. It will be provided as film-coated tablets containing the active ingredient encaleret provided in 54 mg dosage strength. Participants will receive encaleret 162 mg (3 tablets) every 12 hours per protocol with water.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The encaleret tablets used in this study will be supplied under a collaborative agreement with the manufacturer, Calcilytix Therapeutics, Inc. This drug will be received by the NIH pharmacy and dispensed to the study participants by NIH clinical center staff while participants are admitted at the NIH clinical center. The NIH pharmacy in collaboration with the PI is responsible for keeping accurate records of the amount of drug dispensed, returned, and remaining at the conclusion of the study.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The encaleret will be provided as film-coated tablets containing the active ingredient encaleret provided in 54 mg tablets.

The tablets contain the following excipients: mannitol, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, sucrose fatty acid esters, hydroxypropyl methylcellulose, magnesium stearate, macrogol, and titanium oxide.

6.2.3 Product Storage and Stability

Industry Partner and manufacturer, Calcilytix Therapeutics, Inc., will provide the study center with encaleret under a collaborative agreement. Encaleret will be stored at controlled room temperature between 20°C and 25°C with excursions permitted between 15°C and 30°C in the manufacturer-provided bottles.

All participants will receive encaleret only as dispensed and administered by staff at the NIH CC. All unused encaleret must be returned to the Industry Partner or destroyed on-site with approval by the Industry Partner, after a final encaleret accountability has been completed. If unused encaleret is not returned to the Industry Partner, proof of destruction must be provided to the Industry Partner.

6.2.4 Preparation

Not applicable

6.3 Measures to Minimize Bias: Randomization and Blinding

Not Applicable.

6.4 Study Intervention Compliance

Encaleret will be administered by NIH CC staff and recorded. The time of encaleret administration will be documented in the appropriate Case Report Form (CRF). Scheduled oral administration of study drug will occur at the study site under observation by study staff or designee, thus ensuring study drug compliance.

6.5 Concomitant Therapy

At Screening, the study staff at NIH will question each subject specifically on the use of all concomitant medications and record the medication and dosage in the appropriate CRF. In general, upon admission and throughout the study, NIH CC staff will monitor, record, and administer all concomitant medications during the inpatient stay.

Participants being treated with thiazide diuretics may be enrolled if they are willing and able to discontinue thiazides for 5 half-lives prior to initiation of encaleret and during the study treatment period. When the thiazide is being used an antihypertensive, alternative therapy will be offered.

Participants being treated with strong CYP3A4 inhibitors (including clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) must discontinue these medications during the screening period at least 5 half-lives prior to initiation of encaleret and during the study treatment period.

Participants being treated with magnesium or potassium citrate will be instructed to stop these at least 2 days prior to the treatment period (Day -2).

Participants being treated with medications (other than those used for treatment of hypoparathyroidism) that have strong impacts on mineral metabolism may need to stop these medications to continue in the study, if, in the expert opinion of the study investigators, these medications could influence the endpoints of the study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of the drug encaleret does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

When encaleret is discontinued, participants will be converted back to oral calcium and active Vitamin D. Serial blood and urine sampling may be continued for the remainder of the inpatient visit, at the discretion of the investigator. Additional blood or urine sampling may be obtained at the discretion of the investigator for safety monitoring and/or observation of PK/PD of encaleret withdrawal. Follow up laboratory testing within 1 week of discontinuing encaleret and the three follow up telephone contacts should be completed as indicated by the study protocol.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- AEs

- Protocol violation
- If it is discovered that the subject did not meet protocol entry criteria, and continued participation would present unacceptable risk to subject's health
- Non-compliance with administration of the investigational medicinal product encaleret (IMP)
- Withdrawal of consent: Participants may withdraw consent at any time for any reason without prejudice to future treatment. In the event of study withdrawal, the subject will be encouraged to undergo ET procedures as a final visit.
- Lost to follow-up
- Pregnancy at any time after signing the ICF.
- Study terminated by Sponsor
- Site closed by Sponsor
- PI's decision based on subject's safety

If participants discontinue participation or are terminated early from the study, and have received a dose of encaleret, they should have all follow up safety assessments as listed in the Schedules of Assessments (including one outpatient follow up laboratory assessment and three telephone contacts) if the subject agrees.

When participants are discontinued from study medication, they should be converted back to oral calcium and active Vitamin D. Participants will be instructed to undergo outpatient laboratory testing of their blood calcium within 1 week of discontinuing study medication and to have those results sent to NIH investigators for review. A telephone contact should be arranged for the investigative staff to review the blood results and advise on optimizing their outpatient clinical management.

All dosed participants who early terminate from the study, regardless of cause, should undergo a 30-day (± 7 days) and 90-day (± 7 days) follow-up telephone call after the last dose of encaleret. The reason for early termination from the study will be reflected in the CRF. If a subject early terminates from the study because of an AE, the PI/study staff must record the AE as the reason for subject discontinuation.

7.3 Lost to Follow-up

Lost to follow-up is an unlikely occurrence in this study because the treatment phase is entirely inpatient. Prior to admission, participants that are no longer able to be contacted will be considered screen failures. After discharge from the treatment phase, laboratory and telephone follow up encounters are for safety purposes. The investigator or designee will make every effort to regain contact with the participant following discharge from the treatment phase of the study for the patient's safety. Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Screening Procedures

8.1.1 Screening activities performed prior to obtaining informed consent

Prior to obtaining informed consent, prospective participants may be contacted via email, written, in person, video or telephone communications. With prospective subject's permission,

investigators may also review existing medical records including clinical notes, laboratory studies, imaging, photographs/video, pathology specimens/reports, or other relevant records.

8.1.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent this study: lab assessments, imaging, physical exam. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent form.

8.2 Study Evaluation & Procedures

The following procedures and imaging assessments will occur according to Section 1.3 Schedule of Activities.

All participants must sign the informed Consent Form (ICF) prior to any study-related procedures. Screening must be completed within 180 days prior to admission to the NIH CC (See Table A for Schedule of Activities).

Screening Visit: The first screening visit will be conducted at the NIH CC to determine subject eligibility, document current metabolic status, and assess dietary calcium intake. Participants may complete the screening assessments as outpatients or be housed overnight at NIH CC. Participants who complete the screening visit midweek have the option to stay overnight at NIH CC during the intervening days prior to Day -1. Each subject's current treatment regimen will be assessed by NIH investigators in relation to presence/absence and control of hypocalcemia-related complaints and symptoms, and assessment of blood and urine analytes including blood and urine calcium and phosphate. NIH investigators may recommend adjustments to a subject's outpatient regimen during the screening period, in accordance with the accepted goals of achieving cCa in the low normal range, while minimizing hypercalciuria. Unscheduled outpatient laboratory assessments, if required, will be arranged through outpatient laboratories with results transmitted to and reviewed by the investigators as standard of care. Participants who complete the screening process and meet inclusion/exclusion criteria, may be scheduled for admission for the treatment period of the protocol.

Procedures/evaluations planned as part of the screening visit include:

- History and Physical examination
- Height and Weight
- Vital Signs
- Nutritionist Assessment
- Blood laboratory assessment
- Electrocardiogram (ECG)
- 24-hour urine collection (may be performed after the visit if more convenient for the patient)

- Renal Ultrasound

After completing screening assessments, any AE/SAE reported by a subject, whether or not study drug has been administered, will be recorded by the investigators. Any AE/SAE prior to dosing will be categorized as "Baseline" and any AE/SAE after dosing will be categorized as "treatment-emergent."

Treatment Period:

Day -2 or Day -1 (Admission): Participants will be admitted to the NIH CC either the day prior to dosing or two days prior to dosing based on subject convenience. All participants will be instructed to stop taking calcitriol and home calcium dosage, with last doses on Day -2. Participants on magnesium or potassium citrate will be instructed to stop these supplements, with last doses on Day -3. Calcium supplementation with calcium carbonate(500 mg elemental calcium) three times a day will start on Day -1. Baseline 24-hour urine will be opened the morning of Day -1, and fasting laboratory assessment will be obtained. Attempts will be made to collect fasting calcium levels prior to the morning calcium dosage, however, calcium will be given to participants if clinically indicated (for example, in the setting of hypocalcemia).

Days 1 to 5: Encaleret 162 mg BID will be taken orally by the patient. Detailed summary of planned calcium and calcitriol therapy is presented in Figure 2 and a dosing algorithm is presented in Table D. Frequent blood and urine sampling for 24-hours will be performed for safety and outcome measures (see Table A and Table B). Encaleret will be administered in the morning and evening with water approximately 12 hours between each dose. The last dose of study medication will occur on the evening of Day 5. Daily ECG will be performed for monitoring of QT interval.

Day 6 (Discharge): After the blood sampling is collected on the morning of Day 6 and the 24-hour urine is closed, all participants will resume their prior conventional treatment regimen. During Day 6, cCa levels will be monitored until the patient is discharged. This admission can be extended if additional monitoring or treatment (e.g., to stabilize calcium) is needed prior to discharge.

Follow-up:

Outpatient testing done on day 8-12 (Less than 7 days after expected discharge from the NIH clinical center) will be collected either at the NIH CC or local laboratory. Blood samples collected will be evaluated for blood creatinine, albumin, calcium, magnesium, phosphate, and PTH. A telephone contact to the patient will be conducted once calcium results are available to be reviewed with investigative team. Additional outpatient testing to follow up safety issues will be performed as needed.

An additional two telephone contacts will be performed at 30-days (± 7 days) and 90-days (± 7 days) after the last encaleret dose for screening of AEs and pregnancies, respectively.

8.2.1 Biospecimen Evaluations

Screening visit and inpatient blood samples except for research samples and PK samples will be managed by the NIH Clinical Center laboratory. Urine samples will be either managed by the NIH laboratory or sent to LabCorp. Only exploratory end points, for example FGF23, will

be performed in non-CLIA certified labs on research samples. The primary endpoint assessments include evaluations of urinary excretion of calcium. The times for collection of these samples are detailed in the Schedule of Activities in Section 1.3.

All PK blood samples will be analyzed by a CRO contracted by the manufacturer. Details for sample processing and handling will be provided in a written SOP. The times for collection of these samples are detailed in the Table B and C.

The total blood volume collected for each subject will be less than the blood volume limits per subject as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). If a subject has a low body weight (<50 kg for adults), the blood volume taken will be reduced to remain within the NIH guidelines of 10.5mL/kg/8w.

In order to characterize both the pre-study calcemic status as well as changes associated with experimental interventions, the protocol will rely on frequent measurement of albumin-corrected blood calcium concentrations. Assays will be conducted according to specifications of the NIH Clinical Center Laboratory, Bethesda, MD. The main indicator of normal versus abnormal blood calcium levels will be based on the correction for serum or plasma albumin according to the formula corrected calcium (cCa) = measured total calcium (mg/dL) + 0.8(4 – albumin (g/dL)) OR measured total calcium (mmol/L) + 0.2(4 –albumin (g/dL)), recognizing that the total calcium reported in SI units (mmol/L) can be converted to conventional units (mg/dL) by multiplying by 4. Given that enrolled participants are expected to have both normal and stable albumin levels, the measures of total calcium and cCa are likely to be similar throughout the time course of this study. Ionized calcium assays will also be measured at the NIH Clinical Center and can be used to assess calcium status for dose adjustment decisions on a case by case basis in addition to the albumin corrected-calcium.

8.2.2 Correlative Studies for Research/Pharmacokinetic Studies

Not applicable

8.2.3 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Subject samples will be de-identified using a designated subject number and initials.

The clinical trial database, which may be shared with appropriate regulatory agencies, in addition to access from the NIDCR, NIDCR PI, and investigators, will contain clinical/demographic data on participants' age, ethnicity, sex, diagnosis, treatment, response to treatment, adverse events as per the standards of human clinical research. All shared data outside of the EDC will be de-identified without any link to individual identifying information. Safety and Other Assessments

Physical Examinations

At the times detailed in the Schedule of Activities in Section 1.2, participants will undergo a complete physical examination (PE), which is to be completed by a physician or an appropriately trained health professional. Any abnormal physical examination finding that is deemed clinically important (i.e., is associated with symptoms and/or requires medical intervention) will be recorded as an AE.

Vital Signs

Vital signs will be assessed in accordance to times and details indicated in the Schedule of Activities Table A, Section 1.2. Any abnormal vital sign that is deemed clinically significant (i.e., is associated with symptoms and/or requires medical intervention) will be recorded as an AE.

Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the times detailed in the Schedule of Activities. At Screening, the samples will be collected at the NIH Clinical Center. Additional testing during the Screening period may be conducted at an outpatient laboratory near the subject. All laboratory tests during the Treatment Period will be measured at the NIH Clinical Center.

Outpatient testing done on days 8-12 (Less than 7 days after expected discharge from the NIH clinical center) will be collected either at the NIH CC or local laboratory. Blood samples collected will be evaluated for blood creatinine, albumin, calcium, magnesium, phosphate, and PTH. This will allow for evaluation of calcium homeostasis after cessation of encaleret.

A telephone contact to the patient will be conducted once calcium results are available to be reviewed with investigative team.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page.

The investigator will assess the clinical significance of values outside the reference ranges provided by the laboratory.

Samples will be collected, processed, and stored according to the instructions provided in the Laboratory Manual.

The investigator or qualified sub-investigator will review all laboratory results for clinical significance. Any laboratory result deemed clinically significant (i.e., is associated with signs and symptoms and/or requires medical intervention) will be recorded as an AE.

Electrocardiograms

A standard 12-lead ECG will be assessed at the times detailed in the Schedule of Activities, Section 1.3. ECGs will be performed in the supine position after a 5-minute rest. The investigator or qualified sub-investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant (i.e., is associated with symptoms and/or requires medical intervention) will be reported as an AE.

Dietary Calcium

At screening visit participants will be educated by trained nutrition staff on aiming for dietary intake of 1000 mg calcium during inpatient admission. Throughout the inpatient admission at the clinical center, daily dietary intake of calcium will be assessed.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, an immediately life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other seriousness outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (e.g., elective procedures for preexisting conditions that did not worsen) are excluded from SAE reporting.

Note that death is an outcome of an AE and not an AE in itself. The event that was the proximate cause of death should be reported as the AE term.

8.3.3 Classification of an Adverse Event

Severity of Event

The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's CRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: A type of 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: A type of 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 subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and

his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

The PI may change the causality assessment at any time based on new accumulated information.

8.4.4 Expectedness

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the Investigator's Brochure for the study intervention. If an AE is considered unexpected, the sponsor will evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction. The suspected adverse reaction will then be reported expeditiously in an IND safety report if it also meets the definitions of serious and unexpected (21 CFR 312.32(c)(1)(i)).

8.3.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Investigators will record all reportable events with start dates occurring any time after informed consent is obtained until 30 ± 7 days after the last dose of encaleret.

Participants are to be queried regarding any AEs or SAEs at the time of each vital sign assessment, as well as at each visit, according to the Schedule of Activities (Section 1.3).

Participants will be asked to volunteer information with a nonleading question such as, "How do you feel?" Study center personnel will then record all pertinent information in the subject's CRF.

All AEs and SAEs reported by the subject (or subject representative) or observed or otherwise identified by the investigator (or other study center personnel) at a defined study visit or during any communication with the subject (or subject representative) occurring outside a defined study visit (from the time the subject signs the ICF to 30 ± 7 days after the last dose of encaleret must be documented. Any spontaneously reported SAE identified beyond 30 ± 7 days after the last dose of encaleret that is assessed as related to study treatment will be documented.

Events will be followed for outcome information until resolution or stabilization.

8.3.6 Adverse Event Reporting

Any untoward event that is reported from the time that the subject signs the ICF until study completion must be collected. Thus, any untoward medical occurrences or unfavorable and unintended signs, symptoms, or diseases that occur in the pretreatment, treatment, or posttreatment period are to be considered AEs (and SAEs if appropriate), and consequently recorded and reported as such.

Participants are to be queried regarding any AEs or SAEs at the time of each vital sign assessment, as well as at each visit, according to the Schedule of Activities (Section 1.3). Participants will be asked to volunteer information with a nonleading question such as, "How do you feel?" Study center personnel will then record all pertinent information in the subject's CRF.

All AEs and SAEs reported by the subject or guardian or observed or otherwise identified by the investigator (or other study center personnel) at a defined study visit or during any communication with the subject (or subject's legal representative) occurring outside a defined study visit (from the time the subject signs the ICF to study completion) must be documented.

All AEs must be recorded on the appropriate AE reporting page of the subject's CRF whether or not they are considered causally related to encaleret.

For every AE, the investigator must:

- Provide an assessment of the severity, causal relationship to encaleret, and seriousness of the event (i.e., whether it is a SAE)
- Document all actions taken with regard to encaleret
- Detail any other treatment measures taken for the AE
- Document resolution of the AE (with or without sequelae); ongoing; or lost to follow-up.

Reportable events will be tracked and submitted to the IRB as outlined in Policy 801.

8.3.7 Serious Adverse Event Reporting

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of all adverse events and shall report the results of such evaluation to the NIH Institutional Review Board (IRB) as per Policy 801. All SAEs will be reported to the DSMC at routine intervals or as indicated by the DSMC.

All SAEs, whether or not considered study intervention related, will be reported to the NIDCR Office of the Clinical Director within 7 days of investigator awareness. The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

All SAEs will also be reported to Calcilytix within 1 business day in order that Calcilytix may fulfill cross reporting requirements to the Calcilytix IND and all participating investigators under thaIND (21 CFR 312.32(c)(1)).

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

8.3.8 NIH Intramural IRB Reporting of IND Safety Reports

An IND annual safety report will be provided to the regulatory authorities and IRB. Only IND Safety Reports that meet the definition of an unanticipated problem (UP) or is new information that might affect the willingness of participants on the NIH study to enroll or remain in the study will need to be reported separately to the NIH Intramural IRB.

8.3.9 Events of Special Interest

Hypocalcemia in PSH

Hypocalcemia is not an expected side-effect of treatment with encaleret, but it is a complication of the underlying disease being treated. As such, hypocalcemia may develop whenever the underlying disease is inadequately treated and might occur due to either inadequate or missed doses of a specific, effective medication.

The current study involves reducing the dose of current maintenance medications or suspending their use entirely (i.e., oral calcium supplements and calcitriol), to facilitate evaluation of encaleret and potentially establishing clinical proof-of-principle. Under these circumstances there is a risk that participants could experience symptoms of hypocalcemia prior to reaching encaleret maximal effect. In order to mitigate this risk, the study design emphasizes safety foremost. All changes to oral maintenance medications in conjunction with encaleret dosing will be conducted with participants in residence at the Clinical Center, with multiple daily measurements of blood calcium and close supervision by health professionals with experience caring for individuals with hypoparathyroidism. In addition to these precautions, monitoring for and capture of events suggestive of or consistent with hypocalcemia will be reviewed as an AE of special interest as described below.

Adverse Events of Hypocalcemia: Symptomatic and Asymptomatic

Adverse events consistent with hypocalcemia will be classified as either symptomatic or asymptomatic, and assessed for severity, recognizing that there is a spectrum of clinical manifestations. Symptomatic hypocalcemia will be based on identification of new or worsening symptoms consistent with hypocalcemia such as numbness/tingling of hands, feet

or lips, muscle cramps/spasms/twitching, other weakness or lightheadedness and/or new or worsening anxiety, including anger or depression and neurocognitive signs of confusion/hallucinations accompanied by laboratory evidence of a drop in cCa. Many patients with PSH maintained on conventional therapy may have intermittent mild hypocalcemic symptoms on baseline therapy because of the need to balance blood calcium levels while minimizing urine calcium. In this case, symptomatic hypocalcemia will only be recorded if the symptoms are new or worse than the patient's baseline. Relevant symptoms will be documented as blood calcium levels are checked to confirm calcium status. A Case Report Form (CRF) for symptomatic hypocalcemia as an AE of special interest will capture the details of each hypocalcemic event including but not limited to symptoms, concomitant cCa concentrations, precipitating factors, treatment, resolution, and action taken regarding study medication.

Asymptomatic hypocalcemia will also be captured as an AE of special interest based on defining a threshold value for cCa < 7 mg/dL. Since cCa levels are sampled frequently throughout the inpatient period, asymptomatic low cCa results will be identified during routine cCa monitoring.

Clinical Evaluation and Treatment of Hypocalcemia:

Hypocalcemia can range in symptom severity from asymptomatic to life-threatening. Appropriate treatment and action regarding study medication and/or other interventions (e.g., urgent calcium supplementation) will primarily be based on clinical evaluation of severity and acuity. Cases of hypocalcemia in this trial, if they occur, are expected to be manageable with supportive treatment.

Different patients may have different sensitivities to low calcium levels but one advantage of conducting this initial proof-of-principle trial at the NIH is that the expert investigators have significant experience in managing these patients. The investigators performing the current study have decades of accumulated and institutional experience caring for these patients including management of hypocalcemia that is a consequence of the underlying disorder. This includes experience managing outpatient regimens of oral calcium and calcitriol to ensure patient functioning, well-being, and quality of life, based on outpatient laboratory monitoring and assessment of symptoms.

Appropriate evaluations may include serial cCa measures, initial, daily, and follow-up ECG as appropriate based on clinical assessment (bradycardia e.g.) and/or if cCa is persistently < 7 mg/dL.

Graded interventions according to the expert judgment of the NIH investigators will include standard measures such as oral calcium and/or calcitriol supplementation (see Table D) for mild-moderate events. In the case of unresolving or worsening hypocalcemia with more acute clinical manifestations including worsening neurocognitive deficits, seizures, tetany, hypotension, or cardiac dysfunction, for example, appropriate urgent intervention, also according with standards of care, will be undertaken by the site, including administration of intravenous calcium gluconate (See Table D).

Osteosarcoma as an Adverse Event of Special Interest:

The risk to participants in this study for developing osteosarcoma is very low. However, because a carcinogenicity study suggested high-dose, long-term encaleret increased the risk of

osteosarcoma in rats with intact parathyroid glands, we will also record any development of osteosarcoma in our participants as an adverse event of special interest.

8.3.10 Reporting of Pregnancy

Pregnancies in participants or partners at any time during the study will be reported. Study personnel must report every pregnancy from the time subject signs the ICF until 90 ± 7 days after the last dose of encaleret. Pregnancies in participants or partners will be reported to the NIDCR Office of the Clinical Director and Calcilytix within 7 days of investigator awareness.

The study team will make every effort to follow the pregnancy to its conclusion and report the outcome on the follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (e.g., if the female subject is hospitalized for hemorrhage), a separate SAE Form must be completed (in addition to the Pregnancy Form), with the appropriate serious criterion (e.g., hospitalization) indicated. The subject may also be asked to enroll on a research study to enable the collection of pregnancy related outcome data (for example, the NIH Intramural Research Program's Pregnancy Registry and/or an amended version of this protocol).

If a subject becomes pregnant, administration of the study drug(s) must be discontinued immediately.

If the partner of a male subject becomes pregnant after initiation of encaleret and within 90 ± 7 days of the last dose, the study team will inform the Sponsor, Calcilytix, and the medical monitor. If the pregnant partner agrees to be contacted, she may be asked to enroll on a research study to enable the collection of pregnancy related outcome data (for example, the NIH Intramural Research Program's Pregnancy Registry and/or an amended version of this protocol) with the intention of following the pregnancy to its conclusion and reporting the outcome on the follow-up Clinical Trial Pregnancy Form.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

Encaleret in PSH will decrease the fractional excretion of calcium comparing baseline (Day -1) to the last 24-hour period a patient was taking encaleret 162 mg BID. FECa will be calculated using 24-hour urine and 4-hour post-prandial blood levels.

9.2 Sample Size Determination

The proposed clinical trial is primarily exploratory and preliminary data is limited. The primary study endpoint is the percent decrease in FECa using the entire Treatment Population (all participants who received at least one dose of study drug). Participants withdrawing for any reason any time after receiving their first dose of the study drug will remain in the Treatment Population, and the final FECa used will be the last fasting timepoint during which the patient was taking encaleret 162 mg BID.

Power calculations were based on the prior experience with encaleret in ADH1. In the ADH1 cohort, during a 5-day dosage escalation study (period 1), when 6 subjects were on the maximal dose of 162 mg BID for 3 days, the Mean (Standard deviation) of the Day 6 change in fasting FECa from baseline was -66 (20) % (unpublished data). Using a two-tailed 0.05 level paired t-test, we found that 15 participants yielded 80% power to detect a percent change of 16%; 10 participants yielded 80% power to detect a percent change of 20% and 5 participants yielded 80% to detect a percent change of 34%. Given the mean reduction in FECa was 66% in the ADH1 cohort (and the kidneys of participants with PSH might be expected to respond even more robustly to encaleret), we anticipate even a sample size of 5 would be sufficient to confirm the proof-of-principle effect on FECa.

Nevertheless, we plan to enroll up to 15 participants in this study in order to increase the likelihood that we include participants with a range of residual parathyroid tissue and to include participants with recent hypoparathyroidism. This will allow for sub-group analysis (see Section 9.3), which will be exploratory and hypothesis generating.

Of note, we plan to enroll only 5 participants with recent PSH (Cohort 2), because we anticipate some challenges in enrolling this population. More than 5 participants may be impractical to enroll in a reasonable amount of time.

9.3 Populations for Analyses

- **Treatment Population**: All participants who received at least one dose of study drug
- **Permanent hypoparathyroidism (Cohort 1):** Participants with long-standing hypoparathyroidism who received at least one dose of study drug
- **Recent Hypoparathyroid population (Cohort 2):** Participants with recent hypoparathyroidism who received at least one dose of study drug
- **"PTH-Clamp" Population**: Participants whose iPTH did not increase more than 10 pg/mL on encaleret

- **"Aparathyroid" Population:** Participants whose absolute iPTH level was less than 10 pg/dL throughout the study
- Hyperthyroid Population: Participants whose TSH is less than the lower limit of normal for the assay during the treatment phase of the study
- Normothyroid Population: Participants whose TSH is in the normal range during the treatment phase of the study
- Thyroid Cancer Population: Participants with a history of thyroid cancer

9.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with encaleret.

9.3.2 Evaluable for objective response

Not applicable.

9.3.3 Evaluable Non-Target Disease Response

Not applicable.

9.4 Statistical Analyses

9.4.1 General Approach

Categorical variables will be summarized by counts and percentages. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, median, inter-quartile range etc.). All analyses will be performed using SAS 9.4 (the SAS Institute, Cary NC).

9.4.2 Analysis of the Primary Endpoints

The primary endpoint is the percent change in FECa from baseline to the last day on encaleret 162 mg BID. If a subject stops encaleret early or decreases the dose, the FECa will be calculated using the last fasting labs when the patient was on encaleret 162 mg BID. For this primary endpoint, if the normality assumption holds, one-sample t-test will be used to analyze the data. Otherwise, the nonparametric alternative, the Wilcoxon signed-rank test will be used.

The primary endpoint analysis will be conducted in the Treatment Population.

9.4.3 Analysis of the Secondary Endpoint(s)

To analyze the proportion of participants who achieve a concomitant normal or elevated fasting blood calcium (albumin-corrected calcium >8.5 mg/dL) and a normal 24-hour urinary calcium level on encaleret (<250 mg/24 hours for women, <300 mg/24 hours for men) at any point between day 1 and day 5, the proportion along with its 95% confidence interval will be calculated using the exact binomial distribution.

9.4.4 Safety Analyses

Adverse events will be coded as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and each AE will be counted once only for a given participant. The

severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings. Each AE reported will include start date, stop date, severity, relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a separate table.

9.4.5 Baseline Descriptive Statistics

Descriptive statistics will be provided to summarize the characteristics of the participants at baseline.

9.4.6 Planned Interim Analyses

There is no planned interim analysis for this study.

9.4.7 Sub-Group Analyses

Due to small sample size and because this is a proof-of-principle study, primary and secondary endpoints will not be analyzed based on age, sex, race/ethnicity, or other demographic characteristics. Primary and secondary endpoints will be analyzed in each of the analysis populations listed in Section 9.3.

9.4.8 Tabulation of individual Participant Data

Individual participant data may be presented descriptively or graphically over time.

9.4.9 Exploratory Analyses

The pharmacodynamics variables will be analyzed in different analysis populations. Potentially linear mixed effects models may be used to analyze the repeated measures data if assumptions warrant.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 Informed Consent Process

10.1.1 Consent Procedures and Documentation

Standard Consent Procedures: The informed consent document will be provided as a physical or electronic document to the subject or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain, either in-person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) the procedures and tests involved in this study, and the associated risks, discomforts, and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the subject/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. When in person, consenting investigators and subject/consent designee, will be located in a private area (e.g., clinic consult room or private

inpatient room). When consent is conducted remotely, the subject/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If consent is obtained remotely, participants and investigators will view individual copies of the approved consent document at their respective locations.

For electronic consent: The study team will confirm with the participant that they are comfortable using the electronic consenting before proceeding with obtaining consent. If not, other methods will be utilized. When an electronic document with a digital signature is used for the documentation of consent, this study will use the iMedConsent™ platform which is 21 CFR, Part 11 compliant to obtain the required signatures. During the consent process, participants/LARs and investigators will view the same approved consent document simultaneously in their respective locations. The identity of the participant will be determined by verifying a government issued identification card via the telehealth platform, prior to obtaining the signature. iMedConsent will capture electronic signatures via the methods listed below:

• Using a smartphone: participants will be registering their signatures using their finger.

Participants will receive a secure link that leads them to secure "web pages" that will capture their electronic signatures using their finger.

• Using a computer/tablet/laptop: participants will be registering their signatures using a computer mouse or their finger/stylus (for touch/stylus enabled tablets and computer screens).

Participants will receive a secure link that leads them to secure "web pages" that will capture their electronic signatures using the aforementioned methods. Once the completed consent has been saved, it will post to CRIS within a few minutes. All consents completed in iMedConsent™ will post to both the Documents tab and the Consents tab in CRIS. If the research participant has a FollowMyHealth™ account a copy of the completed consent will be posted to their account within two business days. The study team will provide the research participant with a printed copy of the signed document.

10.1.2 Consent for minors when they reach the age of majority

Not applicable.

10.1.3 Considerations for Consent of NIH staff, or family members of study team members

Consent for NIH staff will be obtained as detailed above with following additional protections:

Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service in order to minimize the risk of undue pressure on the staff member.

10.1.4 Consent of Participants who are, or become, decisionally impaired

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that participants enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the participants will be withdrawn from the study.

10.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule and encaleret discontinuation procedures.

If a participant experiences severely symptomatic hypocalcemia (e.g., seizures, QTcF > 500 ms, IV calcium requirement) during the study, or severely symptomatic hypercalcemia (e.g., lethargy/stupor), recruitment will be paused and the DSMC will be consulted. At that time the DSMC will review the data to determine whether there is sufficient cause to terminate the study. The investigators may additionally propose amendments to the protocol to prevent recurrence of the event.

If three participants experience a Grade 3 or greater adverse event that is related to study treatment, recruitment will be paused and the DSMC will be consulted. At that time the DSMC will review the data to determine whether there is sufficient cause to terminate the study.

Additional circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and the Food and Drug Administration (FDA).

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical

records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All participants' records will only be identified by subject number. The investigator will keep a master subject list on which the subject number and the full name, address, and telephone number of each subject are listed. The subject's contact information will be securely stored at NIH Clinical Center for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or the Sponsor requirements.

Data collection will involve the use of a 21 CFR part 11 compliant EDC system, only authorized personnel will have access to the EDC system. All data collected in the context of this study will be stored in a secure location and evaluated according to regulatory requirements and applicable guidance for electronic records. Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents) will be retained at the NIH Clinical Center, along with adequate source documentation, according to local regulatory requirements and ICH requirements.

The investigator must retain a copy of all records that support CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, drug dispensing records) for a period of at least 15 years after study completion unless local regulations or NIH Clinical Center policies require a longer retention period.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the study center or to a suitably qualified and responsible third party.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 Future use of Stored Specimens and Data

A unique subject code will be used on the CRFs, and in the study database. A subject code log that links the names to identification numbers will be securely maintained at the NIH.

Data collected for this study will be analyzed and transmitted to Calcilytix via a secure, encrypted Internet connection and stored on a secure server.

All stored samples are coded and do not have personal identifiers. The codes for identifiers are contained in a subject code log that is maintained in secure research files at the NIH. Additional research samples collected for FGF23 and mid-molecule PTH may be stored at the NIH for use in future studies, with the participants' consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the NIH. These samples could be used to research the causes of PSH, its complications and other conditions for which individuals with PSH are at increased risk, and to improve treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage may not be possible after the study is completed. If participants are concurrently enrolled another NIH study (for example, the natural history protocol 01-D-0184), samples and data collected from this study may be transferred to the other study if the participant has consented for future use of their samples/data in both protocols.

10.5 Safety Oversight

The PI will be responsible for monitoring the data and accruing safety information. Serious adverse event (SAE) monitoring will be supported by an independent medical monitor in collaboration with the Office of Clinical Director and the Office of Clinical Trial Operations and Management (OCTOM), NIDCR.

The investigator will be responsible for monitoring the data and accruing safety information. The investigator is responsible for monitoring the study progress and study data. The investigator will also maintain responsibility for ensuring the accuracy, completeness, timeliness, and legibility of the data. The investigator and associate investigators are also required to keep accurate and timely records to ensure that the conduct of the study is fully documented. The investigator will review individual study participant data upon each patient encounter. Trends will be discussed to ensure subject safety, study compliance, and recruitment goals are met.

This study will be monitored by the NIDCR Division of Intramural Research Data and Safety Monitoring Committee (DSMC). Assessment and recommendations by the DSMC in relation to the study will be made to the NIDCR Clinical Director. The DSMC will include members with expertise in a broad range of areas, including human participants' protection, research ethics, clinical trial implementation, and medical bone and mineral metabolism. The PI and NIDCR OCD will receive assessments and recommendations from the DSMC following interval meetings. These assessments and recommendations will be submitted to the IRB at the time of Continuing Review, or as needed if safety concerns arise.

An independent study monitor on contract with NIDCR OCD DIR, NIH will review data and safety parameter of the study. Independent study monitors are qualified by training and experience to monitor the progress and safety of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct. The PI and NIDCR OCD will receive reports from the independent study monitor following interim monitoring visits. The results will be summarized for the DSMC at interval meetings and for the IRB at Continuing Review, or as needed if safety concerns arise.

10.6 Clinical Monitoring

Before the first subject is dosed in the study, designees from the Office of Clinical Director and the Office of Clinical Trial Operations and Management (OCTOM) will meet with the investigator and the investigator's staff to review the procedures for conducting the study. The

independent study monitor will routinely monitor the progress of the study by conducting on-site or virtual/remote visits thereafter. The monitor will also be able to review query statuses remotely, which may warrant more frequent communication with the NIH investigator and study staff. The investigator will make available to the study monitor the source documents, the signed consent forms, and all other study-related documents. The investigator will be responsible for reviewing eCRFs, resolving data queries generated by the study monitor via the system, providing missing or corrected data, approving all changes performed on the data, and endorsing the participants data within the EDC system.

Additional details of the process and procedures for clinical study research site monitoring will be documented in the Clinical Monitoring Plan (CMP).

10.7 Quality Assurance and Quality Control

Following written Standard Operating Procedures (SOPs), the clinical trial monitors will verify that the clinical trial is conducted, data are generated, biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). Additional details of monitoring (including Clinical, Safety, Data, Quality, and overall Trial monitoring) will be available in designated monitoring plan documents.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

10.8 Data Handling and Record Keeping

10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies or electronic copies of the study visit and outpatient lab results will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the electronic case report form (eCRF), derived from source documents, should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into CTDB, an electronic data capture system that is 21 CFR Part 11-compliant developed by NICHD for data collection, query management, and data analysis for NIH clinical studies. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered into the electronic data capture system directly from the source documents.

10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, and as per the NIH Intramural Records Retention Schedule.

10.9 Protocol Deviations and Non-Compliance

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of participants or others, or the scientific integrity or validity of the study.

10.10 Publication and Data Sharing Policy

10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Investigators will consider requests from qualified researchers for access to anonymized clinical data.

Results from this study may also be shared at scientific conferences.

10.10.2 Genomic Data Sharing Compliance

Not applicable.

10.11 Collaborative Agreements

10.11.1 Agreement Type

A Materials Cooperative Research and Development Agreement (MCRADA), between NIDCR and Calcilytix Therapeutics, Inc., the pharmaceutical company that produces Encaleret will be established. Calcilytix Therapeutics, Inc. will provide Encaleret for this study. They will also provide financial support for the protocol as detailed in the MCRADA. Calcilytix Therapeutics, Inc. is permitted to review manuscript(s) prior to publication.

10.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDCR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

ADH1	Autosomal dominant hypocalcemia type 1 (ADH1)
AE	Adverse Event
Alb	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{(0-24)}$	Area under the concentration-time curve from time 0 to 24 hours
BID	Twice daily
BMI	Body mass index
CaSR	Calcium-sensing receptor
cCa	Albumin-corrected blood calcium
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum plasma concentration
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
Cr	Creatinine
CRF	Case Report Form
CTx	Collagen cross-linked C-telopeptide
DCC	Data Coordinating Center
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
eGFR	Estimated glomerular filtration rate
ET	Early termination
EoT	End of Treatment
FDA	Food and Drug Administration

FGF23	Fibroblast growth factor-23
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IgM	Immunoglobulin M
IMP	Investigational medicinal product (encaleret)
iPTH	Intact PTH
IRB	Institutional Review Board
IRB	Institutional Review Board
M1	Metabolite of encaleret, ether glucuronide of the parent drug
M3	Metabolite of encaleret, acyl glucuronide of the parent drug
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health
P1NP	Procollagen type 1 N-pro-peptide
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PTH	Parathyroid hormone
QC	Quality Control
QD	Once daily
QT_c	QT interval corrected for changes in the heart rate
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
UP	Unanticipated Problem
WOCBP	Women of childbearing potential

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