CALCILYTIX THERAPEUTICS, INC

Abbreviated Title	CLTX-305 for treatment of ADH1
Protocol Number:	CLTX-305-201 NIH 20-D-0122
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Protocol Title:	A Phase 2b, Open-label Dose-ranging Study Evaluating the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics, and Efficacy of CLTX-305 (encaleret) in Autosomal Dominant Hypocalcemia Type 1 (ADH1).
Indication:	Autosomal Dominant Hypocalcemia Type 1 (ADH1)
Investigational Medicinal Product:	CLTX-305 (encaleret)
Sponsor/Manufacturer:	Calcilytix Therapeutics, Inc. 1800 Owens Street Suite C-1200 San Francisco CA, 94158
Key Sponsor Contacts:	[redacted]

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INVESTIGATOR'S STATEMENT

I agree to conduct the study (Study CLTX-305-201) in accordance with the protocol and with all applicable government regulations and Good Clinical Practice (GCP) guidance.

_____

Principal Investigator's Signature Date

_____

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SPONSOR'S AGREEMENT

I approve the attached protocol entitled "A Phase 2b, Open-label Dose-ranging Study Evaluating the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics, and Efficacy of CLTX-305 (encaleret) in Autosomal Dominant Hypocalcemia Type 1 (ADH1)" and agree to abide by all provisions set forth therein.

[redacted] 5/19/2023 | 10:46 AM PDT

[redacted] Date

[redacted]

Calcilytix Therapeutics, Inc.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADH1	Autosomal dominant hypocalcemia type 1 (ADH1)
AE	Adverse event
AESI	Adverse event of Special Interest
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
$AUC_{(0-inf)}$	AUC extrapolated to infinity
$AUC_{(0-t)}$	Area under the concentration-time curve from time 0 to the last measurable time point
$AUC_{(0-tau)}$	AUC over the dosing interval
BID	Twice daily
BMI	Body mass index
Ca	Calcium
CaSR	Calcium-sensing receptor
CaSR	Human gene encoding the CaSR
cCa	Albumin-corrected blood calcium
C_{max}	Maximum plasma concentration
Cr	Creatinine
C_{trough}	Trough concentration
CTx	Collagen cross-linked C-telopeptide
DL	Dose Level
DMC	Data Monitoring Committee
ECG	Electrocardiogram
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
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
Hr, hrs	Hour, Hours
ICF	Informed consent form
ICH	International Council for Harmonisation
IgM	Immunoglobulin M
IND	Investigational New Drug application
IMP	Investigational medicinal product: CLTX-305 (encaleret)
iPTH	Intact PTH
Kd	Dissociation constant

Abbreviation	Definition
LTE	Long-term Extension
M1	Metabolite of CLTX-305 (encaleret), ether glucuronide of the parent drug
M3	Metabolite of CLTX-305 (encaleret), acyl glucuronide of the parent drug
NIH	National Institutes of Health
P1NP	Procollagen type 1 N-propeptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
PTH	Parathyroid hormone
QD	Once daily
QT_c	QT interval corrected for changes in the heart rate
SOC	System organ class
$t_{½}$	Apparent terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
UVA/B	Ultraviolet A or B light
WOCBP	Women of childbearing potential

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on 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; a 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: A Phase 2b, Open-label Dose-ranging Study Evaluating the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics, and Efficacy of CLTX-305 (encaleret) in Autosomal Dominant Hypocalcemia Type 1 (ADH1)

Study Description: This will be a single-site, open-label, dose-ranging study to evaluate the safety, tolerability, and efficacy of CLTX-305 (encaleret) to maintain normalized albumin-corrected blood calcium (cCa) in participants with hypocalcemia due to ADH1. The study consists of 2 cohorts and 3 periods, followed by a Long-term Extension.

Objectives:

Primary:

Periods 1 and 2: Evaluate the safety and tolerability of single and multiple doses of CLTX-305 (encaleret) in participants with ADH1

Period 3: Evaluate the safety, tolerability, and efficacy of CLTX-305 (encaleret) in participants with ADH1 for 24 weeks

Long-term Extension (LTE) following Period 3: Evaluate the longer-term (25 months or about 2 years) safety and tolerability of CLTX-305 (encaleret)

Secondary:

Periods 1 and 2:

- Evaluate the effect of CLTX-305 (encaleret) to increase serum iPTH levels after both single and multiple doses across a dose range in participants with ADH1

Periods 1, 2, and 3:

- Evaluate the pharmacodynamic (PD) effects of CLTX-305 (encaleret) on blood calcium concentrations
- Evaluate the PD effects of CLTX-305 (encaleret) on associated measures of calcium homeostasis including 1,25-$(OH)_2$ Vitamin D levels and urinary calcium excretion
- Evaluate the PD effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP)
- Evaluate the PK of both single and multiple ascending doses of CLTX-305 (encaleret) in participants with ADH1.

LTE:

- Obtain long-term data on efficacy (durability) of CLTX-305 (encaleret) on blood calcium concentrations
- Evaluate the long-term PD effects of CLTX-305 (encaleret) on associated measures of mineral homeostasis including iPTH, 1,25-$(OH)_2$ Vitamin D levels and urinary calcium excretion
- Evaluate the long-term PD effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP)

Endpoints:

Primary:

Periods 1, 2, and 3: Adverse events (AEs), clinical safety laboratory tests, vital signs, and electrocardiograms (ECGs)

Period 3: Albumin-corrected blood calcium concentrations (cCa) and 24-hr urinary calcium excretion after treatment with CLTX-305 (encaleret) for 24 weeks

LTE:

Adverse events (AEs), clinical safety laboratory tests, vital signs for approximately 25 months (approximately 2 years)

Secondary:

Periods 1 and 2: iPTH blood concentration profiles (24-hours) over time after single and multiple doses of CLTX-305 (encaleret)

Periods 1, 2, and 3:

- PK parameters: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), area under the concentration-time curve (AUC) from time 0 to the last measurable time point ($AUC_{(0\text{-}t)}$), AUC from time 0 to 24 hours ($AUC_{(0\text{-}24)}$), AUC extrapolated to infinity ($AUC_{(0\text{-}inf)}$) following single-doses.
- Determination of the steady state PK parameters: C_{max}, trough concentration (C_{trough}), and AUC over the dosing interval $AUC_{(0\text{-}tau)}$

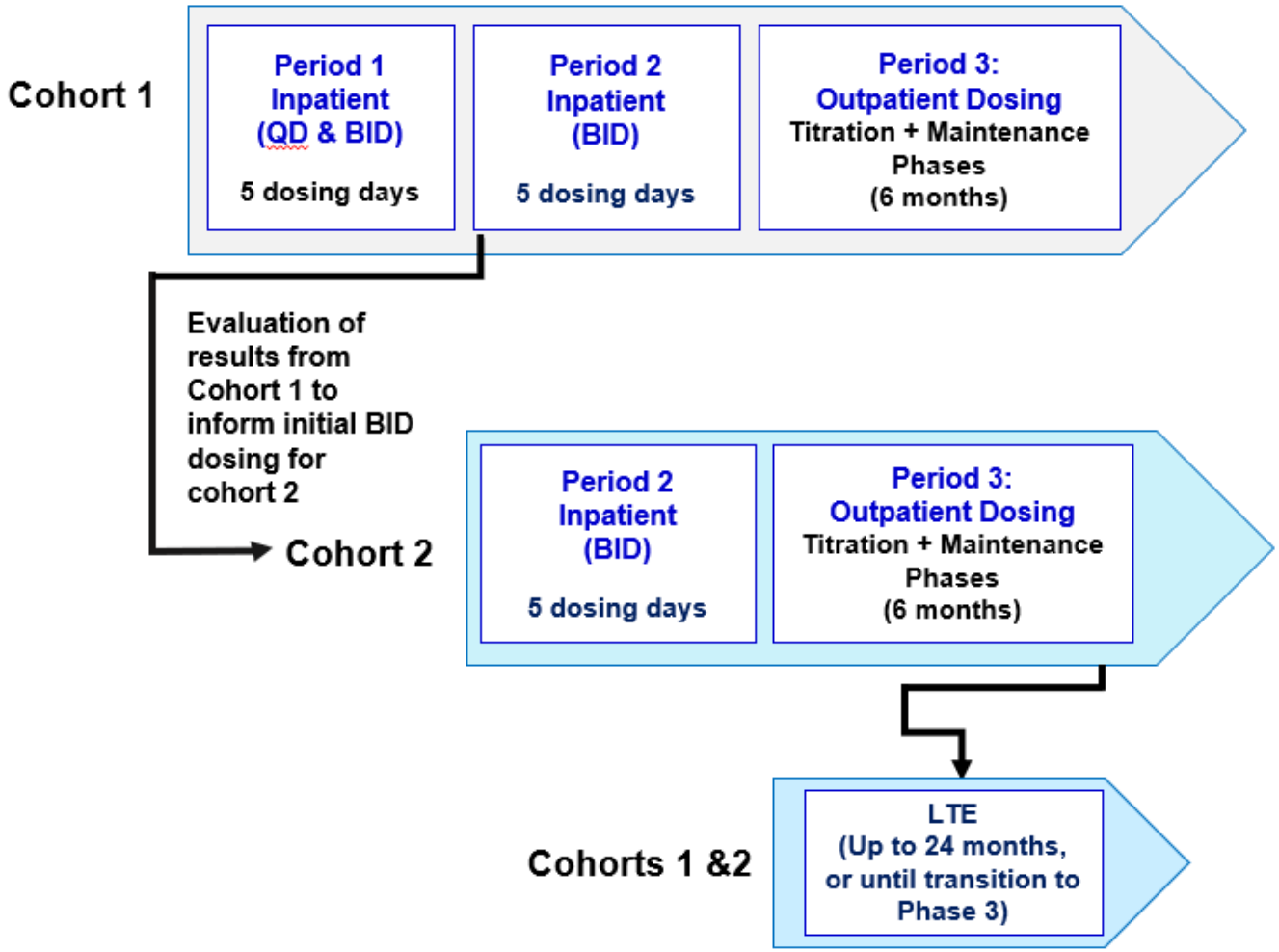
Periods 1, 2, 3, and LTE:

- Pharmacodynamic endpoints measured over time:
- Blood calcium - Absolute levels and change from baseline in cCa
- Urinary calcium clearance (fractional excretion and 24-hour total excretion)
- Renal function (eGFR)
- Serum levels of 1,25-$(OH)_2$ Vitamin D
- Blood samples for magnesium, phosphate, creatinine
- Urine samples for pH, magnesium, phosphate, sodium, potassium, creatinine, cAMP, citrate
- Bone resorption markers collagen cross-linked C-telopeptide (CTx)
- Bone formation markers – blood procollagen type 1 N-propeptide (P1NP)

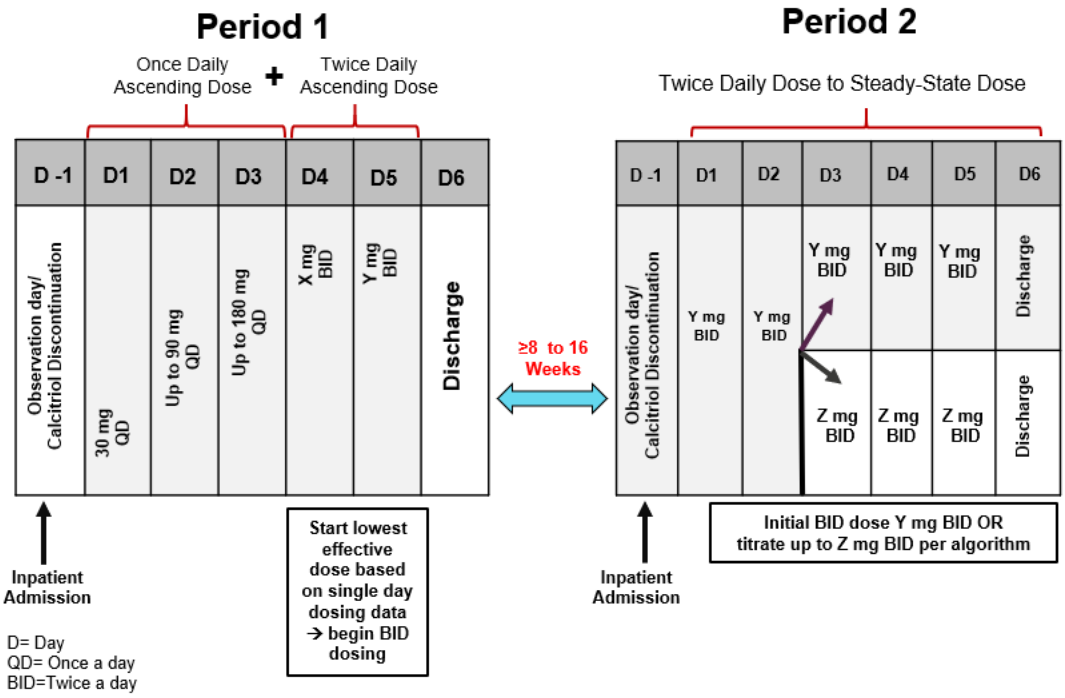
Study Population:	Up to 20 male or female participants (up to 16 to enter the treatment phase) with Autosomal Dominant Hypocalcemia Type 1 (ADH1)
Phase:	Phase 2b
Description of Sites/Facilities Enrolling Participants:	National Institutes of Health (NIH) Clinical Center (CC)
Description of Study Intervention:	CLTX-305 (encaleret) is an oral tablet containing the active ingredient encaleret provided in 5, 10, 30 and 60 mg doses.
Primary Study Duration:	Estimated time from when the study opens to enrollment until completion of Period 3 is approximately 16 months.
Participant Duration:	Total maximum duration of study participation, including Periods 1, 2, and 3, will be approximately 16 months for each participant, which includes up to 60 days between the screening visit and study drug initiation and up to 16 weeks between Periods 1 and 2. Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first.

1.2 Schema

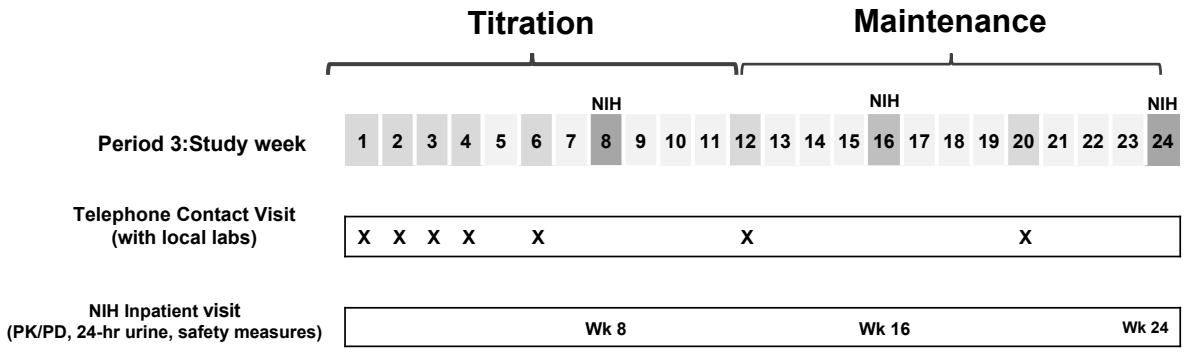
Overall Study Design



Schematic for Periods 1, 2, and 3



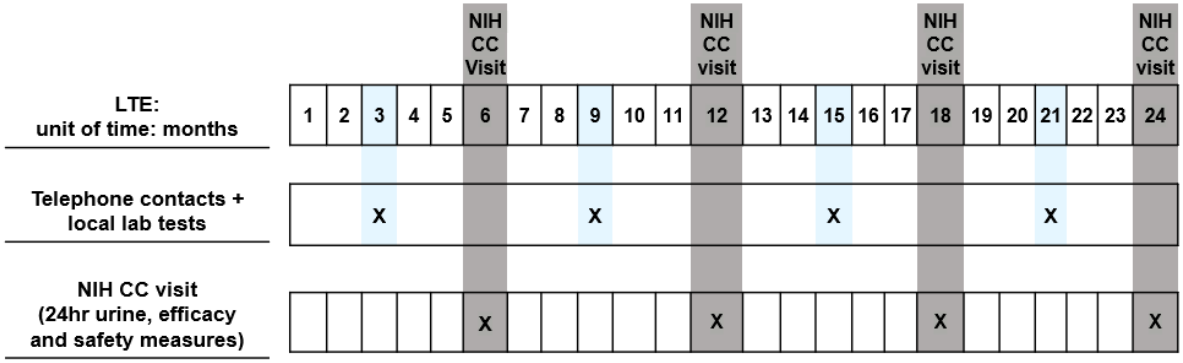
Period 3



Wk= Week

Shading to help visualization - Dark Grey (NIH visit), Light Grey (Telephone contact), as indicated

Long-term Extension (LTE)



Shading to help visualization - Dark Grey (NIH visit)

1.3 Schedule of Activities (SOA)

Table A Period 1 Schedule of Activities

Period 1	Screening[1]	Interval labs[12]	NIH CC inpatient Period 1						Discharge/ EoT/ET[2]	FU Lab[3]	FU Post last dose
			Admission	QD Dosing			BID Dosing				
Days	-60 to -2	-14 to-10	-1	1	2	3	4	5	6	7–8	9-11 30 ± 7
Informed Consent	X										
Admission to clinic	X		X								
Demographics, Medical history[4]	X										
Eligibility assessment	X										
Safety Lab Tests[5]	X		X								
Height[6] and weight	X		X					X	X		
Vital signs[7]	X		X	X	X	X	X	X	X		
Physical examination	X		X						X		
Renal Ultrasound, DXA Scan	X										
FSH level test (postmenopausal women)	X										
Blood β-HCG pregnancy test (WOCBP only)	X		X					X			
ECG, 12-lead	X		X					X			
AEs and SAEs, Prior/Concomitant meds[8]	X		X	←---------- →							
Study drug administration[9]				X	X	X	X	X			
PK/PD blood sample collection				Tables E, H, I, L						X	
24 hr. Urine[10]	X	X									
Outpatient laboratory testing		X[11]								X[3]	
Discharge[13]									X		
Telephone Contact[14, 15]											X

Abbreviations: Adverse Event = AE; Albumin = Alb; Alanine aminotransferase = ALT Blood urea nitrogen = BUN; Aspartate aminotransferase = AST; Alkaline Phosphatase = Alk Phos;Electrocardiogram = ECG; BID = Twice daily; Blood Pressure = BP; Calcium = Ca; Calcium Sensing Receptor = CASR; Chloride = Cl; Concomitant Medication = Con. Meds; Creatinine = Cr; Dual-energy X-ray Absorptiometry = DXA; Early Termination = (ET); End of Treatment = EoT; Follow-up = FU; Follicle-Stimulating Hormone = FSH; Glucose = Glu; Heart Rate = HR; Hematocrit = Hct; Hemoglobin = Hgb; Lactate Dehydrogenase = LDH; Intact Parathyroid Hormone = iPTH; Magnesium = Mg; National Institute of Health Clinical Center = NIH CC; Parathyroid Hormone = PTH; Phosphate = PO_4; Phosphorus = P; Potassium = K; Pharmacodynamic = PD; Pharmacokinetic = PK; Prothrombin Time/ Prothrombin Time = PT/INR; Red Blood Cell Count = RBC; Thromboplastin Time = PTT; Serious Adverse Event = SAE; QD = Once daily; Total Bilirubin = Tbili; Triglycerides = TGL; White Blood Count = WBC; Women Of Child Bearing Potential = WOCBP

1. Screening Visit at NIH Clinical Center.
2. If participant discontinues from the study early (ET) or withdraws from taking the CLTX-305 (encaleret) (EoT), perform related assessments, resume prior medication regimen, arrange FU labs within 1-2 days, and a FU call within 30 ± 7 days after last dose of the CLTX-305 (encaleret).
3. Outpatient laboratory testing includes blood Cr, Ca, Alb, Mg, PO_4, iPTH, and PK sample collection on Day 7 or 8 after discharge from NIH CC on Day 6.
4. Including CaSR mutational analysis (if not documented).
5. Safety Labs – Chemistry (Na, K, Cl, bicarbonate, Glu, BUN, Cr, Alb, total protein, Ca, Mg, PO_4, iPTH, 25-OH Vitamin D, cholesterol, TG, AST, ALT, Tbili, Alk phos, LDH, amylase, lipase, uric acid), Hematology (RBC, Hgb, Hct, RBC indices, WBC, differential), Coagulation (PT/PTT/INR), urinalysis. HIV, viral hepatitis panel to be done at screening visit only.
6. Height measured at screening only.
7. 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. Orthostatic BP and HR will be assessed once at screening and once daily during Period 1.
8. Discontinue calcitriol on Day -1 during the admission.
9. On Days 1, 2, & 3 participants receive CLTX-305 (encaleret) per the dosing algorithm. On Day 4 & 5 participants receive BID doses based on Days 1-3.
10. 24-hour urine at the screening visit and 10-14 days prior to Day 1 dosing (Ca, Mg, PO_4, Cr, Na, K, Citrate, pH).
11. Outpatient laboratory testing on day -14-10 includes: blood Cr, calcium, albumin, magnesium, phosphate, 25-OH Vitamin D.
12. Interval lab tests at outpatient laboratory will be done in those for whom the screening visit is >21 days prior to Period 1.
13. After the last dose of CLTX-305 (encaleret), participants resume prior outpatient conventional treatment regimen prior to discharge.
14. Telephone contact: should occur on days 9 to 11 or once calcium results are available. PI/study staff to review results with participant.
15. Telephone contact: 30 ± 7 days after last dose of CLTX-305 (encaleret) in Period 1 to review AEs/Con meds

Table B Period 2 Schedule of Activities

Period 2	Screening[1]	Interval Labs [11]	NIH CC inpatient Period 2						Discharge/EoT/ET[2]	FU Post last dose
			Admission	BID Dosing						
Days	-60 to -2	-14 to -10	-1	1	2	3	4	5	6	
Informed Consent	X									
Admission to clinic	X		X							
Demographics, Medical history[3]	X									
Eligibility assessment	X									
Safety Lab Tests[4]	X		X							
Height[5] and weight	X		X					X	X	
Vital signs[6]	X		X	X	X	X	X	X	X	
Physical examination	X		X						X	
Renal Ultrasound, DXA Scan	X									
FSH (postmenopausal women)	X									
Blood β-HCG pregnancy test (WOCBP only)	X		X					X		
ECG, 12-lead	X		X	X[14]		X[14]		X[14]		
AEs and SAEs, Prior/Concomitant meds[7]	X		X	←----------						----------→
Study drug administration[8]				X	X	X	X	X		
PK/PD blood sample collection				Tables F, G, J, K						
24 hr. Urine[9]	X	X								
Outpatient laboratory testing		X[10]							X[2]	
Dispense study drug for Period 3, Discharge[12]									X	
Telephone Contact[13]										X

Abbreviations: Adverse Event = AE; Albumin = Alb; Alanine aminotransferase = ALT; Blood urea nitrogen = BUN; Aspartate aminotransferase = AST; Alkaline Phosphatase = Alk Phos; Electrocardiogram = ECG; BID = Twice daily; Blood Pressure = BP; Calcium = Ca; Calcium Sensing Receptor = CaSR; Chloride = Cl; Concomitant medication = Con. meds; Creatinine = Cr ; Dual-energy X-ray Absorptiometry = DXA; Early Termination = (ET); End of Treatment = EoT; Follow-up = FU; Follicle-Stimulating Hormone = FSH; Glucose = Glu; Heart Rate = HR; Hematocrit = Hct; Hemoglobin = Hgb; Lactate Dehydrogenase = LDH; Intact Parathyroid Hormone = iPTH; Magnesium = Mg; National Institute of Health Clinical Center = NIH CC; Parathyroid Hormone = PTH; Phosphate = PO_4; Phosphorus = P; Potassium = K; Pharmacodynamic = PD; Pharmacokinetic = PK; Prothrombin Time/ Prothrombin Time = PT/INR; Red Blood Cell Count = RBC; Thromboplastin Time = PTT; Serious Adverse Event = SAE; QD = Once daily; Total Bilirubin = Tbili; Triglycerides = TGL; White Blood Count = WBC; Women Of Child Bearing Potential = WOCBP

1 Screening Visit at NIH CC for Cohort 2 participants. Participants may complete the Screening Visit as outpatients or be housed overnight at NIH CC. Cohort 1 participants do not require re-screening assessments. Participants who complete the screening visit midweek have the option to stay overnight at NIH CC during the intervening days prior to the start of Period 2, Day -1.

2 If participant discontinues from the study early (ET) or withdraws from taking CLTX-305 (encaleret) (EoT), perform related assessments, resume prior medication regimen, arrange FU labs within 1-2 days. Participants instructed to obtain outpatient laboratory testing (See Footnote 10) approximately 1-2 days after discharge from NIH CC. PI/Site

staff should contact the participant within 3-5 days to review test results and provide guidance regarding clinical management as they transition to prior clinical care providers. Optionally, participants may stay in the NIH CC overnight to complete assessments.

[3] Including CaSR mutational analysis (if not documented).

[4] Safety Labs – Chemistry (Na, K, Cl, bicarbonate, Glu, BUN, Cr, alb, total protein, Ca, Mg, PO_4, iPTH, 25-OH Vitamin D, cholesterol, TG, AST, ALT, Tbili, Alk phos, LDH, amylase, lipase, uric acid), Hematology (RBC, Hgb, Hct, RBC indices, WBC, diff), Coagulation (PT/PTT/INR), urinalysis. HIV, viral hepatitis panel, and iron panel to be done at screening visit only unless repeat measures are clinically indicated.

[5] Height measured at screening only.

[6] 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. Orthostatic BP and HR will be assessed once at screening and once daily during Period 2.

[7] Discontinue calcitriol on Day -1 during the admission.

[8] Initial dose (Days 1 & 2) of CLTX-305 (encaleret) BID based on results from Period 1. If calcium has not increased into the normal range, then the CLTX-305 (encaleret) dose will be increased for Days 3-5. Participants will undergo frequent PK/PD sampling over 24h on Day 5.

[9] 24-hour urine at the screening visit 14 to 10 days prior to Day 1 dosing (Ca, Mg, PO_4, Cr, Na, K, Citrate, pH)

[10] For cohorts 1 and 2: outpatient laboratory testing on days -14 to -10 before admission include: blood Cr, Ca, Alb, Mg, PO_4, 25-OH Vitamin D, Hematology (RBC, Hgb, Hct, RBC indices, WBC)

[11] Interval lab tests at outpatient laboratory will be done in those for whom the screening visit is >21 days prior to Period 2.

[12] After the last dose of CLTX-305 (encaleret), for participants continuing to Period 3, dispense supply of CLTX-305 (encaleret) before discharge.

[13] ET and EoT - a final FU call should occur within 30 ±7 days from the date of the last dose of CLTX-305 (encaleret) in Period 2.

[14] ECG assessments: Day 1, 3 and 5 each at 3 hrs ± 30 min post dose (AM)

Table C Period 3 Schedule of Activities

Period 3 - After discharge in Period 2 (Day 6)								FU outpatient labs[2] 2 to 3 ± 2days	FU outpatient labs[2] 7 ± 2 days	FU- after last dose 30 ± 7 days	Un-scheduled visit[3]
Study Dosing Period											
Weeks	**1, 2, 3, 4**	**6**	**NIH CC 8**	**12**	**NIH CC 16**	**20**	**NIH CC EoT/ET[1] 24**				
Days (windows)	**± 2**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**				
Telephone Contact (NIH PI/Study Staff)	X	X		X		X	X	X	X	X	X
AEs and SAEs, Con meds	X	X	X	X	X	X	X			X	X
Review compliance[4]/Titration	X	X	X	X	X	X	X				
Outpatient laboratory[5]	X	X		X		X		X	X	X	
NIH CC visit			X		X		X				
Renal ultrasound, DXA scan							X				
Dispense study drug			X		X		X[15]				
Height[6] and weight			X		X		X				
Vital signs[7]			X		X		X				
Physical examination[8]			X		X		X				
Safety Laboratory [9]			X		X		X				
Blood β-HCG pregnancy test (WOCBP only)			X		X		X				
ECG, 12-lead			X		X		X				
Study drug administration[10]			X		X		X				
PD blood collection[11]			X		X		X				
PK blood collection[12]							X				
Timed Interval & 24-hour Urine[13,14]			X		X	X[14]	X			X[14]	

Abbreviations: Adverse Event = AE; Albumin = Alb; Alanine aminotransferase = ALT; Blood urea nitrogen = BUN; Aspartate aminotransferase = AST; Alkaline Phosphatase = Alk Phos; Electrocardiogram = ECG; BID = Twice daily; Blood Pressure = BP; Calcium = Ca; Calcium Sensing Receptor = CaSR; Chloride = Cl; Concomitant medication = Con. meds; Creatinine = Cr; C-telopeptide = CTX; Dual-energy X-ray Absorptiometry = DXA; Early Termination = (ET); End of Treatment = EoT; Follow-up = FU; Follicle-Stimulating Hormone = FSH; Glucose = Glu; Heart Rate = HR; Hematocrit = Hct; Hemoglobin = Hgb; Lactate Dehydrogenase = LDH; Intact Parathyroid Hormone = iPTH; Magnesium = Mg; National Institute of Health Clinical Center = NIH CC; Parathyroid Hormone = PTH; Phosphate = PO_4; Phosphorus = P; Potassium = K; Pharmacodynamic =

PD; Pharmacokinetic = PK; Procollagen type 1 N-propeptide = P1NP; Prothrombin Time/ Prothrombin Time = PT/INR; Red Blood Cell Count = RBC; Thromboplastin Time = PTT; Serious Adverse Event = SAE; QD = Once daily; Total Bilirubin = Tbili; Triglycerides = TGL; White Blood Count = WBC; Women Of Child Bearing Potential = WOCBP

[1] If participant discontinues from the study early (ET) or withdraws from taking CLTX-305 (encaleret) (EoT), before completing Period 3 per protocol, participant will be asked to return to the NIH CC as soon as possible for the ET/EoT visit assessments and return the unused CLTX-305 (encaleret). Participant should revert to their outpatient regimen of oral calcium and active vitamin D. Participants will go through FU activities as stated in table and footnote 2, and then will have a safety FU call 30 day ± 7 days.

[2] Participants who withdraw from taking CLTX-305 (encaleret) (EoT) before completing Period 3 per protocol or who elect not to continue into the LTE will obtain the following outpatient laboratory assessments after the last dose of CLTX-305 (encaleret) and after re-starting their prior regimen of oral calcium and active vitamin D: blood Cr, Ca, Alb, Mg, PO4. Follow-up (FU) call should occur within 3-5 days to review the lab results and receive guidance on clinical management of their ADH1 as they transition to their prior clinical care providers.

[3] Unscheduled visits: For laboratory evaluation following dose adjustment or assessment or follow-up of an AE, in which clinically indicated procedures will be performed.

[4] Document current CLTX-305 (encaleret) dose and calcium dosing regimen, any modifications, and reason for modifications.

[5] Outpatient laboratory testing: Blood samples for clinical laboratory panels (Na, Cl, bicarbonate, K, BUN, Cr and including Alb, Ca, Mg, PO_4, iPTH, CTX and P1NP).

[6] Height measured only at ET visit.

[7] Vital signs include supine or sitting blood pressure (BP) by automated cuff, heart rate (HR), and respiratory rate.

[8] Focused Physical exams: weight measurement at all visits.

[9] Safety Labs collected at the NIH CC visits– Chemistry (Na, K, Cl, bicarbonate, Glu, BUN, Cr, Alb, total protein, Ca, Mg, PO_4, 25-OH Vitamin D, Cholesterol, TG, AST, ALT, Tbili, Alk phos, LDH, amylase, lipase, uric acid), Hematology (RBC, Hgb, Hct, RBC indices, WBC, diff), Coagulation (PT/PTT/INR).

[10] CLTX-305 (encaleret) administered and recorded during the NIH CC visit/in-house PK/PD collection days.

[11] See Table E : Non-intensive Sampling Days for PD measures and timepoints and Table L : Research Sample Collection.

[12] See Table E : Use Non-intensive Sampling Days schedule for PK timepoints.

[13] See Table E : see time intervals for urine collections for calculation of fractional excretion rates and 24-hour total excretion of urine Ca, Mg, PO_4, Cr, cAMP, citrate, Na, K, pH during the NIH CC visits

[14] Outpatient 24-hr urine Ca, Mg, PO_4, Cr, Na, K, citrate, pH at 20 weeks. Participants who withdraw from taking CLTX-305 (encaleret) (EoT) before completing Period 3 per protocol or chose not to continue into the LTE will obtain 24-hr urine at 30 ± 7 days follow-up.

[15] Week 24 drug dispensing is only for participants who continue into the LTE; If a participant is not immediately continuing into the LTE, no drug will be dispensed.

Table D Long-term Extension Schedule of Activities

LTE - After last day in week 24 in Period 3										FU outpatient labs[2,14] 2 to 3 ± 2 days	FU outpatient labs[2,14] 7 ± 2 days	FU- after last dose[12,14] 30 ± 7 days	Un-scheduled visit[3]
Study Dosing Period													
Months [14]	**NIH CC**		**NIH CC**		**NIH CC**		**NIH CC**		**NIH CC EoT/ET[1]**				
	0[13]	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**				
Days (windows)		**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**+30**				
Reconsent[13]	X												
Telephone Contact (NIH PI/Study Staff)		X		X		X		X		X	X	X	X
AEs and SAEs, Con meds	X	←----------							----------→	X	X	X	X
Review compliance[4]/dose adjustment as needed		X	X	X	X	X	X	X	X				
Outpatient laboratory[5]		X		X		X		X		X	X	X	
NIH CC visit			X		X		X		X				
Renal ultrasound, DXA scan					X				X[15]				
Dispense study drug	X		X		X		X						
Height[6] and weight			X		X		X		X				
Vital signs[7]			X		X		X		X				
Physical examination			X		X		X		X				
Safety and Drug Monitoring Laboratory[8]	X[13]		X		X		X		X				
Blood β-HCG pregnancy test (WOCBP only)[9]			X		X		X		X				
ECG, 12-lead			X		X		X		X				
Study drug administration[10]	X	←----------							----------→				
24-hour Urine[11]		X	X	X	X	X	X	X	X			X[12]	

Abbreviations: Adverse Event = AE; Albumin = Alb; Alanine aminotransferase = ALT; Blood urea nitrogen = BUN; Aspartate aminotransferase = AST; Alkaline Phosphatase = Alk Phos; Electrocardiogram = ECG; BID = Twice daily; Blood Pressure = BP; Calcium = Ca; Calcium Sensing Receptor = CaSR; Chloride = Cl; Concomitant medication = Con. meds; Creatine Kinase = CK; Creatinine = Cr; C-telopeptide = CTX; Dual-energy X-ray Absorptiometry = DXA; Early Termination = (ET); End of Treatment = EoT; Follow-up = FU; Follicle-Stimulating Hormone = FSH; Glucose = Glu; Heart Rate = HR; Hematocrit = Hct; Hemoglobin = Hgb; Lactate Dehydrogenase = LDH; Intact

Parathyroid Hormone = iPTH; Magnesium = Mg; National Institute of Health Clinical Center = NIH CC; Parathyroid Hormone = PTH; Phosphate = PO_4; Phosphorus = P; Potassium = K; Pharmacodynamic = PD; Pharmacokinetic = PK; Procollagen type 1 N-propeptide = P1NP; Prothrombin Time/ Prothrombin Time = PT/INR; Red Blood Cell Count = RBC; Thromboplastin Time = PTT; Serious Adverse Event = SAE; QD = Once daily; Total Bilirubin = Tbili; Triglycerides = TGL; White Blood Count = WBC; Women Of Child Bearing Potential = WOCBP

[1] If participant discontinues from the study early (ET) or withdraws from taking CLTX-305 (encaleret) (EoT), before completing LTE per protocol, participant will be asked to return to the NIH CC within 30 days following the last dose for the ET/EoT visit assessments and return the unused CLTX-305 (encaleret). Participant should resume oral calcium and active vitamin D under the supervision of the study team while the encaleret is being safely discontinued. Follow-up labs should beperformed per this Schedule of Assessments.

[2] Participants who withdraw from taking CLTX-305 (encaleret) (EoT) before transitioning to the CLTX-305-302/CALIBRATE LTE per protocol will obtain the following outpatient laboratory assessments after the last dose of CLTX-305 (encaleret) and after re-starting their prior regimen of oral calcium and active vitamin D: blood Cr, Ca, Alb, Mg, iPTH, PO4. Follow-up (FU) call should occur within 3-5 days to review the lab results and receive guidance on clinical management of their ADH1 as participants transition to prior standard of care.

[3] Unscheduled visits: For laboratory evaluation following dose adjustment or assessment or follow-up of an AE, in which clinically indicated procedures will be performed

[4] Document current CLTX-305 (encaleret) dose and calcium dosing regimen, any modifications, and reason for modifications

[5] Outpatient laboratory testing: Blood samples for clinical laboratory panels (Na, Cl, bicarbonate, K, BUN, Cr and including Alb, Ca, Mg, PO_4, iPTH, CTX, and P1NP).

[6] Height measured only at month 24/final visit or ET visit

[7] Vital signs include supine or sitting blood pressure (BP) by automated cuff, heart rate (HR), and respiratory rate.

[8] Safety and Drug Monitoring Labs collected at the NIH CC visits approximately 4 hours after the morning encaleret dose – Chemistry (Na, K, Cl, bicarbonate, Glu, BUN, Cr, Alb, total protein, Ca, Mg, PO4, iPTH, 25-OH Vitamin D, CTX, P1NP, Cholesterol, TG, AST, ALT, Tbili, Alk phos, LDH, amylase, lipase, uric acid, CK), Hematology (RBC, Hgb, Hct, RBC indices, WBC, diff), Coagulation (PT/PTT/INR), Research labs (FGF23 and mid-molecule PTH). HIV, viral hepatitis panel should be repeated within 3 months prior to transition to CLTX-305-302/CALIBRATE.

[9] Blood β-HCG pregnancy test can be performed at the NIH CC on the day of transition to CLTX-305-302/CALIBRATE Phase 3 LTE, and an aliquot will also be sent to the central lab for the CLTX-305-302/CALIBRATE Phase 3 LTE.

[10] CLTX-305 (encaleret) administered and recorded during the NIH CC visit/in-house days.

[11] Outpatient 24-hr urine collection for Ca, Mg, PO4, Cr, Na, K, citrate, pH

[12] A final follow-up safety telephone call and outpatient labs will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret).

[13] If a participant is not able to enter the LTE immediately following Period 3, then participant will be reconsented to and may restart CLTX-305 (encaleret) at the previous therapeutic dose determined in Period 3. Safety and Drug Monitoring Laboratory tests should be done while participant is at the NIH CC.

[14] When participant transitions to CLTX-305-302/CALIBRATE Phase 3 LTE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 LTE study.

[15] If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the renal ultrasound and DXA scan will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE.

1.3.1 Pharmacokinetic, Pharmacodynamic, and Urine Sampling Times

Table E Non-intensive BID Sampling Days

Period 1: Day 4 (BID Dosing)

Period 3: PK/PD sampling days

	Timepoint ± 20 min. (relative to AM dose)
Blood Assays	
PK[1] samples	-15 min, +30 min, 2, 4, 8, 11, 13 hrs
Intact PTH	-15 min, +30 min*, 2, 4, 8, 11, 13, 17 hrs
Serum bone markers: CTX, P1NP	-15 min, 13 hrs
1, 25-$(OH)_2$ Vitamin D, cAMP	-15 min, 4, 8, 13,17, 24 hrs[2]
Ca, PO_4, Mg, Cr, albumin	-15 min, +30 min*, 2, 4, 8, 11, 13, 17, 24 hrs[2]
K, CK	-15 min, 13 hrs
Urine Assays:	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, cAMP, pH	-15 min 0-4 h, 4-8 h, 8-13 h, 13-17 h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Na, K, Citrate, pH	0, 24 hrs (Start collection after first morning void and end 24 hours later)

[1] PK in Period 3 only collected at 24 weeks;

[2] 24 hour timepoint only collected in Period 3

* +30 min timepoint only collected in Period 3 at 24 weeks

Table F Non-intensive BID Sampling Days - (if CLTX-305 (encaleret) dose is ≤ 180 mg BID)

Period 2: Days 1, 2, 3 & 4

	Timepoint ± 20 min. (relative to AM dose)
Blood Assays	
PK samples	-15 min, 2, 4 hrs
Intact PTH	-15 min, +30 min, 2, 4, 8, 11, 13, 17 hrs
1, 25-$(OH)_2$ Vitamin D	-15 min, 4, 8, hrs
Ca, PO_4, Mg, Cr, albumin	-15 min, +30 min, 2, 4, 8, 11, 13, 17 hrs
K, CK	-15 min, 13 hrs
Urine Assays:	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, pH	-15 min[1], 0-4 h, 4-8 h, 8-13 h, 13-17 h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Na, K, Citrate, pH	0, 24 hrs (Start collection after first morning void and end 24 hours later)

[1] -15 min urine is done on Period 2 (Day 1) only

Table G Non-intensive BID Sampling Days - (if CLTX-305 (encaleret) dose is > 180 mg BID)

Period 2: Days 2, 3 & 4

	Timepoint ± 20 min. (relative to AM dose)
Blood Assays	
PK samples	15 min, +30 min, 2, 4, 8, 11, 13 hrs
Intact PTH	-15 min, +30 min, 2, 4, 8, 11, 13, 17 hrs
1, 25-$(OH)_2$ Vitamin D	-15 min, 4, 8,
Ca, PO_4, Mg, Cr, albumin	-15 min, +30 min, 2, 4, 8, 11, 13, 17 hrs
K, CK	-15 min, 13 hrs
Urine Assays:	
Timed Interval Urine Collections: Ca, Mg, P, Cr, pH	0-4 h, 4-8 h, 8-13 h, 13-17 h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Na, K, Citrate, pH	0, 24 hrs (Start collection after first morning void and end 24 hours later)

Table H Intensive Sampling Days for QD dosing

Period 1: Days 1, 2, 3

	Timepoint ± 10 min (relative to AM dose)
Blood Assays:	
PK samples	-15 min, +30 min, 1, 1.5, 2, 3, 4, 6, 8, 13 hrs
Intact PTH	-15 min, +30 min, 1, 1.5, 2, 3, 4, 6, 8, 13, 17 hrs
Serum bone markers: CTX, P1NP	-15 min, 13 hrs
1, 25-$(OH)_2$ Vitamin D, cAMP	-15 min, 4, 8, 13, 17 hrs
Ca, PO_4, Mg, Cr, albumin	-15 min, +30 min, 1, 2, 3, 4, 6, 8, 13, 17 hrs
K, CK	-15 min, 13 hrs
Urine Assays	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, cAMP, pH	-15 min[1], 0-4 h, 4-8h, 8-13h, 13-17h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Citrate, Na, K, pH	0, 24 hrs (Start collection after first morning void and end 24 hours later)

[1] -15 min urine is done on Period 1 (Day 1) only

Table I Intensive Sampling Days for BID dosing

Period 1: Day 5

	Timepoints ± 10 min (relative to AM & PM doses)
Blood Assays	
PK samples	TRT AM Dose: -15 min, +30 min, 1, 1.5, 2, 3, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1, 1.5, 2, 3, 4, 6, 15 hrs
Intact PTH	TRT AM Dose: -15 min, +30 min, 1, 1.5, 2, 3, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1, 1.5, 2, 3, 4, 6, 8, 15 hrs
Serum bone markers: CTX, P1NP	TRT AM Dose: -15 min, 8 hrs
1, 25-$(OH)_2$ Vitamin D, cAMP	TRT AM Dose: -15 min, 4, 8 hrs
	TRT PM Dose: 4, 8, 15 hrs
Ca, P, Mg, Cr, albumin	TRT AM Dose: -15 min, +30 min, 1, 1.5, 2, 3, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1, 1.5, 2, 3, 4, 6, 8, 15 hrs
K, CK	TRT AM Dose: -15 min, 8 hrs
Urine Assays	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, cAMP, pH	0-4 h, 4-8h, 8-13h, 13-17h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Citrate, Na, K, pH	0-24 hrs (Start collection after first morning void and end 24 hours later)

Abbreviation: Time Relative To = TRT

Table J Intensive Sampling Days for BID dosing - (if CLTX-305 (encaleret) dose is > 180 mg BID)

Period 2: Day 5

	Timepoints ± 10 min (relative to AM & PM doses)
Blood Assays	
PK samples	TRT AM Dose: -15 min, +30 min, 1.5, 2, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1.5, 2, 4, 6, 15 hrs
Intact PTH	TRT AM Dose: -15 min, +30 min, 1.5, 2, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1.5, 2, 4, 6, 8, 15 hrs
Ca, PO_4, Mg, Cr, albumin	TRT AM Dose: -15 min, +30 min, 1.5, 2, 4, 6, 8 hrs
	TRT PM Dose: +30 min, 1.5, 2, 4, 6, 8, 15 hrs
K, CK	TRT AM Dose: -15 min, 8 hrs
Urine Assays	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, pH	0-4 h, 4-8h, 8-13h, 13-17h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Citrate, Na, K, pH	0-24 h (Start collection after first morning void and end 24 hours later)

Abbreviation: Time Relative To = TRT

Table K Intensive Sampling Days for BID dosing- (if CLTX-305 (encaleret) dose is ≤ 180 mg BID)

Period 2: Day 5

	Timepoints ± 10 min (relative to AM & PM doses)
Blood Assays	
PK samples	TRT AM Dose: -15 min, 1.5, 4 h
	TRT PM Dose: +30 min, 1.5, 4, 15 h
Intact PTH	TRT AM Dose: -15 min, 1.5, 4, 8 hrs
	TRT PM Dose: +30 min, 1.5, 4, 8, 15 hrs.
Serum bone markers: CTX, P1NP	TRT AM Dose: -15 min 8 hrs.
1, 25-$(OH)_2$ Vitamin D, cAMP	TRT AM Dose: -15 min 4, 8 hrs.
	TRT PM Dose: 4, 8, 15 hrs.
Ca, PO_4, Mg, Cr, albumin	TRT AM Dose: -15 min, 1.5, 4, 8 hrs.
	TRT PM Dose: +30 min, 1.5, 4, 8, 15 hrs.
K, CK	TRT AM Dose: -15 min, 8 hrs.
Urine Assays	
Timed Interval Urine Collections: Ca, Mg, PO_4, Cr, cAMP, pH	0-4 h, 4-8h, 8-13h, 13-17h, 17-24 h
24-Hour urine: Ca, Mg, PO_4, Cr, Citrate, Na, K, pH	0-24 h (Start collection after first morning void and end 24 hours later)

Abbreviation: Time Relative To = TRT

Table L Research Sample Collection Timepoints in Periods 1 and 3

Period 1: Day 1 and Day 4

Period 3: Weeks 8, 16, and 24

	Timepoint ± 10 min (relative to AM dose)
Research Specimens:	
Including FGF23 and mid-molecule PTH	-15 min, +30 min, 2, 4, 8, 11, 13 hrs

2 INTRODUCTION

2.1 Study Rationale

The rationale for developing CLTX-305 (encaleret) as a potential treatment for hypocalcemia in patients with ADH1 is based on both preclinical and clinical data. CLTX-305 (encaleret) is a CaSR antagonist (calcilytic). CLTX-305 (encaleret) interfered with the effect of extracellular calcium to suppress PTH secretion from isolated bovine parathyroid cells at physiological calcium concentrations and shifted the IC_{50} of the calcium-PTH curve rightward (See Investigator Brochure). Calcilytics in general have been shown, in both in vitro and vivo models, to shift the aberrant CaSR "set-point" back towards a normal IC_{50} for calcium, resulting in increased PTH secretion and elevation of blood calcium concentrations in cellular and animal models of ADH1 (Dong et al, 2015; Hannan et al, 2015).

Preliminary clinical data also support potential utility of calcilytics to treat humans with ADH1. Intravenous administration of a structurally related small molecule calcilytic, NPSP795, in five patients with ADH1, was associated with dose-related increased plasma PTH levels and decreased urinary fractional calcium excretion, although without a clear increase in cCa (Roberts et al, 2019). This small proof-of-concept study utilized a very rapid-acting but short-lived calcilytic agent and was further limited in the dose range tested. However, taken together with in vitro and in vivo data, the study is supportive of further testing of calcilytics in ADH1. Of note, the systemic exposures achieved in the ADH1 participants across 3 doses tested, were comparable to doses that caused hypercalcemia in healthy volunteers with presumed normal CaSR function during a separate single ascending-dose study. This suggests that patients with ADH1 may require larger doses of a calcilytic, compared to euparathyroid individuals, to achieve similar increases in calcium levels.

CLTX-305 (encaleret) can cause hypercalcemia acutely, in healthy volunteers and postmenopausal women, at doses of 30 mg, with some additional effect at doses of 50 and 100 mg. At doses higher than 30 mg, the primary effect was to increase the duration of PTH and calcium elevation. Chronically, CLTX-305 (encaleret) doses of 7.5, 10 and 15 mg were associated with an increased propensity for hypercalcemia. Taken together these data from euparathyroid participants suggest that the steep portion of the dose-response curve for CLTX-305 (encaleret) effects on calcium concentrations occurs over approximately a one log range (10–100 mg) with a definitive efficacy to raise calcium acutely at 30 mg (for review of CLTX-305 (encaleret) dose-response for PTH, calcium and calcium-related hormones see Investigator Brochure).

Rationale for Periods 1, 2 and 3 (dose exploration, dose consolidation, and dose stabilization)

Given the lack of any prior data on the safety and dose-response to CLTX-305 (encaleret) in ADH1 patients, this initial part of the study is designed as a Phase 2b, safety, tolerability and dose-ranging exercise that will be conducted in 3 steps. The initial Period 1 is to be conducted entirely on an inpatient basis, exploring the safety and efficacy-related dose-response to CLTX-305 (encaleret) administered as escalating doses given once or twice daily

over 5 days. All participants will be instructed to stop taking calcitriol on Day -1, the day of admission, but continue their oral calcium supplement regimen until admitted. Magnesium supplements and potassium citrate will be discontinued starting the morning of Day 1. Calcium supplements will be discontinued or decreased starting on Day 1, based on the estimated dietary calcium intake, targeting a combined calcium intake of >1000 mg/day. Following Period 1 participants will resume oral calcium, calcitriol, and other held supplements, upon discharge from the study center.

Following an interval of sufficient duration (NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009)) to ensure that participants have adequately recovered the Hgb levels following the intensive blood sampling of Period 1, they will return to the study center for Period 2, which will also be conducted entirely on an inpatient basis. By initiating Period 2 dosing with CLTX-305 (encaleret) at a well-tolerated dose already studied in Period 1, further adjustments can be made at steady-state over the 5-day duration of Period 2 ("dose consolidation"). A second group of individuals with ADH1 (Cohort 2) who are naïve to CLTX-305 (encaleret) will be invited to join the study beginning with Period 2, drawing on the experience with starting doses and dose adjustment in the participants in Period 1 and their initial experience in Period 2.

Following the completion of Period 2, eligible participants will be discharged from the NIH CC and enter into Period 3 where they will receive CLTX-305 (encaleret) as an outpatient with close safety and laboratory monitoring for a period up to 24 weeks. Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit. Following the outpatient treatment in Period 3, participants may continue into a Long-term Extension.

Rationale for the Long-term Extension (LTE)

Participants who have completed Period 3 and continue to meet study eligibility criteria may continue in a Long-term Extension (LTE) for continuous safety evaluation of CLTX-305 (encaleret). The primary objective of LTE is to assess the longer-term safety and tolerability of CLTX-305 (encaleret) in ADH1 participants. The secondary objective will be to obtain long-term efficacy (durability) data of CLTX-305 (encaleret) treatment with respect to mineral homeostasis and related measures.

The LTE is designed to obtain additional safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first.

At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments should be completed per Schedule of Assessments (see Section 1.3 Table D).

2.2 Background

CLTX-305 (encaleret) (known previously as JTT-305 or MK-5442), is an oral calcium-sensing receptor (CaSR) antagonist (calcilytic), originally developed for the treatment of osteoporosis, that is now being evaluated as a potential treatment for autosomal dominant hypocalcemia type 1 (ADH1) in this dose finding proof-of-concept trial.

Previously, CLTX-305 (encaleret) was 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-participant program of which 1,280 were exposed to CLTX-305 (encaleret) in eight phase 1 and four phase 2 studies including exposures up to 52 weeks. 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.

Hypercalcemia was identified as an on-target but dose-limiting side effect in the osteoporosis program as reviewed below. Hypercalcemia was a safety issue in the osteoporosis program, whereas it is considered a marker for efficacy in the ADH1 program. The goal of the current program is to develop CLTX-305 (encaleret) as a targeted therapy to treat hypocalcemia and disturbed calcium homeostasis in patients with chronic hypocalcemia due to activating mutations in the calcium sensing receptor (CaSR).

2.2.1 Pharmacokinetics and Product Metabolism

CLTX-305 (Nonproprietary name: encaleret, molecular formula $(C_{29}H_{33}ClFNO_4)_2 \cdot H_2SO_4 \cdot H_2O$, molecular weight 1144.15) is formulated as 5, 10, 30 and 60 mg white film coated tablets for the current clinical trial. The 10 and 30 mg dosage strengths are round tablet presentations; the 60 mg dosage strength can be round or a modified oval tablet presentation. The active agent inhibits the CaSR, via allosteric modulation, with an IC_{50} 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 (IC_{50} > 3000 nM) is inactive and M3 (IC_{50} 67.3 + 6.6 nM) is active.

CLTX-305 (encaleret) is rapidly absorbed in humans (t_{max} median 1.5 hr. (range 0.75–3 h at most single doses or at steady-state). The elimination half-life (t1/2) is approximately 11-14 hours at steady state (14 days). Dose-proportional increases in plasma CLTX-305 (encaleret) concentrations were documented over the dose range (5, 15, 30, 50 and 100 mg) in the fasted state without significant food effect. CLTX-305 (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 CLTX-305 (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 t_{max} approximately 2 hr. and M3 median t_{max} 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 participants) were observed in CLTX-305 (encaleret) pharmacokinetics. AUC and C_{max} 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 C_{max} and approximately 2x increase in AUC_{0-24} with slightly less effect on M1 and M3.

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

2.2.2 Efficacy of CLTX-305 (encaleret) in Prior Clinical Trials

During the prior development program in osteoporosis, dose-related increases of endogenous serum parathyroid hormone (PTH) and calcium (Ca) were observed in participants with presumed normal CaSR function (i.e., healthy volunteers and postmenopausal women with osteoporosis). In healthy postmenopausal women, repeat CLTX-305 (encaleret) doses of 15 or 20 mg resulted in consistent elevations in intact PTH (iPTH) over 3-4 hours post single daily dosing. The stimulatory effect on iPTH was consistent, without evidence for tachyphylaxis, after 6 and 12 months of once daily administration. CLTX-305 (encaleret) dosing in phase 2 studies was limited to 15 mg once daily (QD) to minimize hypercalcemia.

With chronic once-daily dosing up to 15 mg, albumin-corrected blood calcium (cCa) levels reached a plateau with up to 30% of participants 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). Such hypercalcemia was asymptomatic, modifiable by decreasing calcium/vitamin D supplementation, and/or resolved after stopping CLTX-305 (encaleret) dosing. No serious adverse events (SAEs) related to either hyper- or hypocalcemia were observed in the CLTX-305 (encaleret) program for osteoporosis in postmenopausal women (See IB Section 5.2).

In summary, extensive data from the prior osteoporosis development program demonstrated that CLTX-305 (encaleret) is associated with dose-proportional increases in peak serum iPTH levels in participants presumably expressing wild-type *CaSR*, with iPTH elevations lasting less than 8-12 hours but associated with elevations in cCa at chronic daily oral doses of 15 mg or above.

2.2.3 Autosomal Dominant Hypocalcemia, Type 1

ADH1 is a rare disorder of systemic calcium homeostasis caused by activating mutations of the CaSR gene leading to hypocalcemia (Hannan 2012, Hofer 2003). The CaSR plays the dominant role in regulating systemic calcium homeostasis by controlling PTH secretion and urinary calcium excretion in response to variations in blood calcium levels (Hofer 2003,

Gunn 2004). Negative allosteric modulators of the CaSR, (so-called calcilytic agents) may represent a potential targeted therapy for ADH1.

The prevalence of ADH1 is uncertain (Lienhardt A, 2001) and has previously been estimated to occur in 1 in 70,000 (Gunn 2004); however, the disease is recognized as rare by the National Institutes of Health (NIH) Office of Rare Disease Research (Genetic and Rare Disease (GARD) Number: 2877) and Orphanet (Orpha Number: 428).

ADH1 is characterized by variable degrees of hypocalcemia with abnormally low levels of parathyroid hormone (PTH), hyperphosphatemia and low magnesium levels usually with persistent hypercalciuria (Roszko 2016). Symptoms of hypocalcemia most commonly include paresthesia, muscle spasms, cramps, tetany, circumoral numbness, and can be of variable intensity including inducing seizures. Hypocalcemia can also present with laryngospasm, neuromuscular irritability, cognitive impairment, personality disturbances, prolonged QT intervals, electrocardiographic changes that mimic myocardial infarction, or heart failure.

In patients with ADH1, hypocalcemia occurs primarily due to increased sensitivity of the CaSR to extracellular ionized calcium which suppresses iPTH-secretion and leads to lower levels of endogenous 1,25-$(OH)_2$ Vitamin D (decreasing calcium absorption from the gut) and lower levels of calcium reabsorption in the kidney (leading to hypercalciuria). Hypercalciuria is therefore worse in patients with ADH1 compared with other forms of hypoparathyroidism because of two mechanisms contributing to decreased renal calcium reabsorption: 1. reduced PTH-mediated reabsorption of calcium from the primary renal filtrate, 2. the presence of hyperactive CaSRs in the distal renal tubules preventing appropriate calcium reabsorption. Furthermore, standard treatment with oral calcium and calcitriol supplementation tends to worsen hypercalciuria which is associated with long-term morbidity such as nephrolithiasis, nephrocalcinosis and chronic kidney disease that can progress to renal failure (Khan 2018, Li 2018).

For this reason, the consensus approach to management of ADH1 is to balance oral supplementation of calcium and calcitriol with the known high risk for renal calcifications, kidney stones and kidney failure (Roszko et al, 2016). This means the healthcare provider must help the patient find a regimen that can maintain the lowest serum calcium concentrations compatible with symptom relief to minimize hypercalciuria. Thiazide diuretics are sometimes added for their modest urinary calcium lowering effects.

Experimental treatment with PTH(1-34) in ADH1 participants was able to correct serum calcium but did not abrogate hypercalciuria (Winer 2012, Winer 2014, Gafni 2015). Exogenous PTH(1-84) is approved for the orphan indication of hypoparathyroidism but the clinical study in patients with established hypoparathyroidism that supported approval excluded patients with hypoparathyroidism due to calcium sensing receptor mutations (Mannstadt, 2013).

CLTX-305 (encaleret) may prove to be a therapy uniquely targeted to the underlying pathogenesis of altered calcium homeostasis in patients with ADH1 where resetting the CaSR “set-point” might normalize serum calcium and lower requirements for oral

supplementation with calcium and active vitamin D and without increasing the risk of iatrogenic chronic hypercalciuria.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

CLTX-305 (encaleret) has been generally well tolerated in humans during chronic treatment up to and beyond 12 months. In a prior osteoporosis development program, CLTX-305 (encaleret) was administered to over 1280 healthy men and post-menopausal women; no specific safety issues or signals were seen with acute dosing 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 CLTX-305 (encaleret), except for its known, on-target pharmacological effect to stimulate endogenous PTH hormone release and dose-related hypercalcemia (in euparathyroid participants) as described above. Details for all previous non-clinical and clinical studies with CLTX-305 (encaleret) can be found in the CLTX-305 (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 CLTX-305 (encaleret) and placebo or comparator arms (other than differences in calcium levels).

A thorough QT study in healthy participants showed no clinically meaningful QTc prolongation following a single oral dose of up to 100 mg CLTX-305 (encaleret) at any of the examined timepoints.

In preclinical safety and toxicology studies the dose-limiting effects of CLTX-305 (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 CLTX-305 (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 CLTX-305 (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 t_{max} ~2 hr. and M3 median t_{max} ~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). CLTX-305 (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, CLTX-305 (encaleret) co-administration with ketoconazole, a potent CYP3A4 inhibitor, resulted in ~1.67x increase in C_{max} and ~2x increase in AUC_{0-24} 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).

It is not known if CLTX-305 (encaleret) could have an effect on pregnancy or breastfeeding in humans. CLTX-305 (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 child-Bearing 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.

There are currently no approved alternative therapies for people with ADH1 to maintain blood calcium levels in the normal or low-normal range other than oral calcium and active vitamin D supplementation. The activating mutation in the CaSR leads to an insufficient iPTH response to low blood levels of calcium such that these patients are hypocalcemic without therapy. The goal of therapy is to raise blood calcium concentrations sufficiently to improve/abrogate symptoms and improve function and well-being. Current therapy with oral supplements presents challenges due to the frequency and pill-burden of using calcium and active vitamin D as well as the iatrogenic complication related to hypercalciuria which results from increasing the overall calcium load. These complications of current therapy often include nephrocalcinosis, progressive renal dysfunction and can result in renal failure. Treatment with CLTX-305 (encaleret) is being explored as a potential alternative or adjunctive treatment to maintain blood calcium levels while minimizing hypercalciuria.

In the dose-escalating and dose-finding components of Periods 1, 2 and 3, participants may experience fluctuations in their blood calcium and phosphate levels including the potential for hypocalcemia, hypercalcemia, and/or hypophosphatemia. The long-term risk of such fluctuations with CLTX-305 (encaleret) are not expected to be larger than the risk of current therapy however such fluctuations may be more frequent during the initial dose-escalating/dose finding portions of the clinical study. The clinical study is designed to minimize the risk of untoward fluctuations in blood calcium, phosphate and related serum chemistries: During the dose-finding Periods 1 and 2, participants will be supervised with frequent monitoring of blood calcium and phosphate levels multiple times per day and may receive treatment for hypocalcemia, hypercalcemia, or hypophosphatemia as required while effective doses of CLTX-305 (encaleret) are being identified. Each participant is assessed for evidence of an individualized effective dose of CLTX-305 (encaleret) during the in-house periods before entering outpatient Period 3. During Period 3 participants continue a combination of their oral calcium supplements and individualized starting dose of CLTX-305 (encaleret) and will undergo at least weekly re-assessment and dose-titration based on

outpatient laboratory monitoring results and telephone contact visits with the investigative site staff. The outpatient approach to dose and regimen modification is similar to the current practice for optimizing conventional treatment with oral calcium and active vitamin D.

Additional risks and potential discomforts related to the frequent blood and urine sampling procedures in the supervised setting of the in-house stays during Periods 1 and Periods 2 are addressed in the Informed Consent Document and include evaluations of medical history, physical examination, renal ultrasound and EKG. 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 during Periods 1 and 2 to reduce participant burden during intensive sampling requirements. Adjustments in sampling may be necessary to reduce the burden of sampling if blood losses from either central or peripheral catheters breach 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 ADH1 will closely evaluate dose-related effects on calcium and phosphate homeostasis and otherwise employ routine safety monitoring (For details on CLTX-305 (encaleret) safety data, see IB Section 5.3).

2.3.2 Known Potential Benefits

There are no definitive currently known benefits of CLTX-305 (encaleret) in the target population of patients with hypocalcemia due to ADH1. In vitro and in vivo studies, including preclinical data in mouse models suggest that calcilytic agents including CLTX-305 (encaleret) may shift the sensitivity of the ADH1-mutated CaSR back towards “normal” resulting in normalization of blood calcium levels. In a pilot study in humans with ADH1, an investigational calcilytic was shown to dose-dependently stimulate PTH acutely associated with transient suppression of urinary calcium excretion although the doses and times tested may have been insufficient to demonstrate definitive changes in serum calcium levels (Roberts et al 2019).

2.3.3 Assessment of Potential Risks and Benefits

Taken together, both preclinical and available clinical data support further clinical development of CLTX-305 (encaleret) as a potential therapy targeted to the molecular defects in ADH1. Current standard of care, which includes oral calcium and active vitamin D supplementation, is complicated by the increased sensitivity of the CaSR to exogenous calcium which leads to an exaggerated urinary calcium excretion in response to small increases in blood calcium. This augmented urinary calcium excretion occurs both because iPTH levels are sub-optimal due to the altered CaSR function in the parathyroid glands, and due to the over-stimulation of the CaSR in the distal renal tubules, both of which contribute to enhanced urinary calcium loss and are associated with chronic complications of renal

function. CLTX-305 (encaleret), as a calcilytic agent, may dampen the CaSR to facilitate achievement and maintenance of the therapeutic targets of normalized blood calcium concentrations while also avoiding or minimizing hypercalciuria.

One challenge to clinical development of CLTX-305 (encaleret) is that the doses of CLTX-305 (encaleret) that will be effective in patients with ADH1 may be higher than the doses previously identified as raising blood calcium in extensive clinical experience in euparathyroid participants (postmenopausal women in the prior osteoporosis program). Effective doses of CLTX-305 (encaleret) for patients with ADH1 cannot be determined without execution of a specifically designed clinical trial. The current proposed clinical trial is designed to utilize conventional early drug development approaches, including single and multiple-ascending doses, while leveraging prior safety exposure data, to address the important questions of dose-response, acute safety and tolerability, and definitive proof-of-concept regarding the extent to which CLTX-305 (encaleret) can act to normalize blood calcium in participants with ADH1.

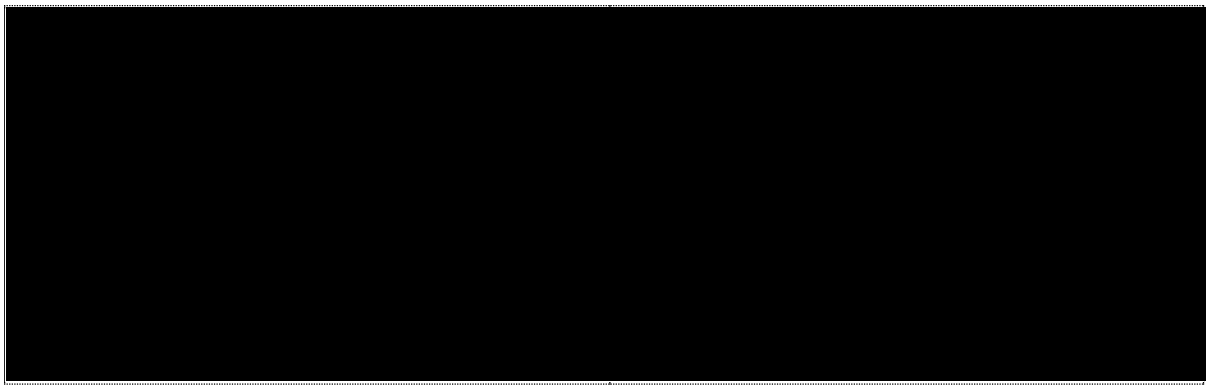
The study is designed to minimize known potential risks (as described above) while maximizing the range of doses studied to increase the probability of establishing a definitive proof-of-concept of the potential utility of CLTX-305 (encaleret) as a treatment for hypocalcemia in patients with ADH1.

Patients with renal impairment due to ADH1 have been described but there are no dedicated studies addressing all aspects of this disease complication and its progression over time. In patients with post-surgical hypoparathyroidism who have no detectable PTH or low normal residual iPTH, there are case series that show that renal impairment with a decrease of $\geq$ 25% eGFR and chronic kidney disease impairment have been described. The dose of calcium supplementation was significantly related to the decrease in renal function in these reports (Ponce de León-Ballesteros G., *et al*, 2020). Based on this important implication, participants with evidence of renal impairment, eGFR $\geq$ 25 mL/minute/1.73 m^2 using CKD-EPI (for participants < 18 years old the Schwartz equation will be calculated) may be enrolled.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Periods 1 and 2 • Evaluate the safety and tolerability of single and multiple doses of CLTX-305 (encaleret) in participants with ADH1 Period 3: • Evaluate the safety, tolerability and efficacy of CLTX-305 (encaleret) in participants with ADH1 for 24 weeks LTE: • Evaluate the longer-term safety and tolerability of CLTX-305 (encaleret) in ADH1 participants from Period 3 for approximately 25 months (approximately 2 years)	Periods 1, 2, and 3: • Adverse events (AEs), clinical safety laboratory tests, vital signs, and electrocardiograms (ECGs) Period 3: • Albumin-corrected blood calcium concentrations (cCa) and 24-hr urinary calcium excretion after treatment with CLTX-305 (encaleret) for 24 weeks LTE: • Adverse events (AEs), clinical safety laboratory tests, vital signs for approximately 25 months (approximately 2 years)
Secondary	
Periods 1 and 2: • Evaluate the effect of CLTX-305 (encaleret) to increase serum iPTH levels after both single and multiple doses across a dose range in participants with ADH1	Periods 1 and 2: • iPTH blood concentrations profiles (24-hours) over time after single and multiple doses of CLTX-305 (encaleret)
Periods 1, 2, and 3: • Evaluate the pharmacodynamic (PD) effects of CLTX-305 (encaleret) on blood calcium concentrations • Evaluate the PD effects of CLTX-305 (encaleret) on associated measures of calcium homeostasis including 1,25-$(OH)_2$ Vitamin D levels and urinary calcium excretion • Evaluate the PD effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP)	Periods 1, 2, and 3: Pharmacodynamic endpoints measured over time up to 24 weeks (final visit): • Blood calcium - Absolute levels and change from baseline in cCa • Urinary calcium clearance (fractional excretion and 24-hour total excretion) • Renal function (eGFR) • Serum levels of 1,25-$(OH)_2$ Vitamin D • Blood samples for magnesium, phosphate, creatinine • Urine samples for pH, magnesium, phosphate, sodium, potassium, creatinine, cAMP, citrate

	• Bone resorption markers collagen cross-linked C-telopeptide (CTx) • Bone formation markers – blood procollagen type 1 N-propeptide (P1NP)
• Evaluate the PK of both single and multiple ascending doses of CLTX-305 (encaleret) in participants with ADH1.	• PK parameters: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), area under the concentration-time curve (AUC) from time 0 to the last measurable time point ($AUC_{(0-t)}$), AUC from time 0 to 24 hours ($AUC_{(0-24)}$), AUC extrapolated to infinity ($AUC_{(0-inf)}$) following single-doses. • Determination of the steady state PK parameters: C_{max}, trough concentration (C_{trough}), and AUC over the dosing interval $AUC_{(0-tau)}$
<u>LTE:</u> • Obtain long-term data on efficacy (durability) of CLTX-305 (encaleret) on blood calcium concentrations • Evaluate the long-term PD effects of CLTX-305 (encaleret) on associated measures of mineral homeostasis including, iPTH, 1,25-$(OH)_2$ Vitamin D levels and urinary calcium excretion • Evaluate the long-term PD effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP)	<u>LTE:</u> • Blood calcium - Absolute levels and change from baseline in cCa • Urinary calcium clearance (fractional excretion and 24-hour total excretion) • Blood levels of iPTH • Renal function (eGFR) • Serum levels of 1,25-$(OH)_2$ Vitamin D • Blood samples for magnesium, phosphate, creatinine • Urine samples for pH, magnesium, phosphate, sodium, potassium, creatinine, cAMP, citrate • Bone resorption markers collagen cross-linked C-telopeptide (CTx) • Bone formation markers – blood procollagen type 1 N-propeptide (P1NP)
[redacted]	



4 STUDY DESIGN

4.1 Overall Design

This will be a single-site, open-label, dose-ranging and dose maintenance study to evaluate the safety, tolerability and efficacy of CLTX-305 (encaleret) to maintain normal albumin-corrected blood calcium (cCa) in participants with hypocalcemia due to ADH1. It will consist of two inpatient periods of dose initiation, escalation and steady-state adjustment (Periods 1 and 2), an outpatient dose stabilization and maintenance period including NIH clinical visits (Period 3), and a long-term extension (LTE).

The LTE is designed to obtain additional safety data and evaluate durability of efficacy for CLTX-305 (encaleret). The LTE also allows for continued treatment of enrolled participants with CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first.

Two principal cohorts are planned:

- **Cohort 1**: up to 8 participants (minimum of 5) will initially be enrolled into Period 1 (inpatient), after which they may return to participate in Period 2 (inpatient, after at least an 8-week interval). Participants who complete Period 2 will be eligible to enter Period 3 (outpatient) for up to 24 weeks of dosing with CLTX-305 (encaleret).
- **Cohort 2**: up to 10 additional participants (minimum of 5) will enroll directly into Period 2 (inpatient). The initiation of Cohort 2 will be based on evaluation of accumulated data from Cohort 1. Cohort 2 participants who complete Period 2 will be eligible to enter Period 3 (outpatient) to receive up to 24 weeks of CLTX-305 (encaleret).

Participants from both cohorts who complete Period 2 will be eligible to enter Period 3. Outpatient dosing with CLTX-305 (encaleret) will be determined from review of individual dose-response data from Periods 1 and/or 2 based on identifying well-tolerated BID doses with preliminary evidence for efficacy. During the initial outpatient period (Period 3), participants will undergo additional individualized dose titration as necessary in response to safety data and the results of key efficacy measures. Participants who complete Period 3 (up to Week 24) and who elect to continue in the LTE will receive CLTX-305 (encaleret) for additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first.

Figure A Study Overview Schematic

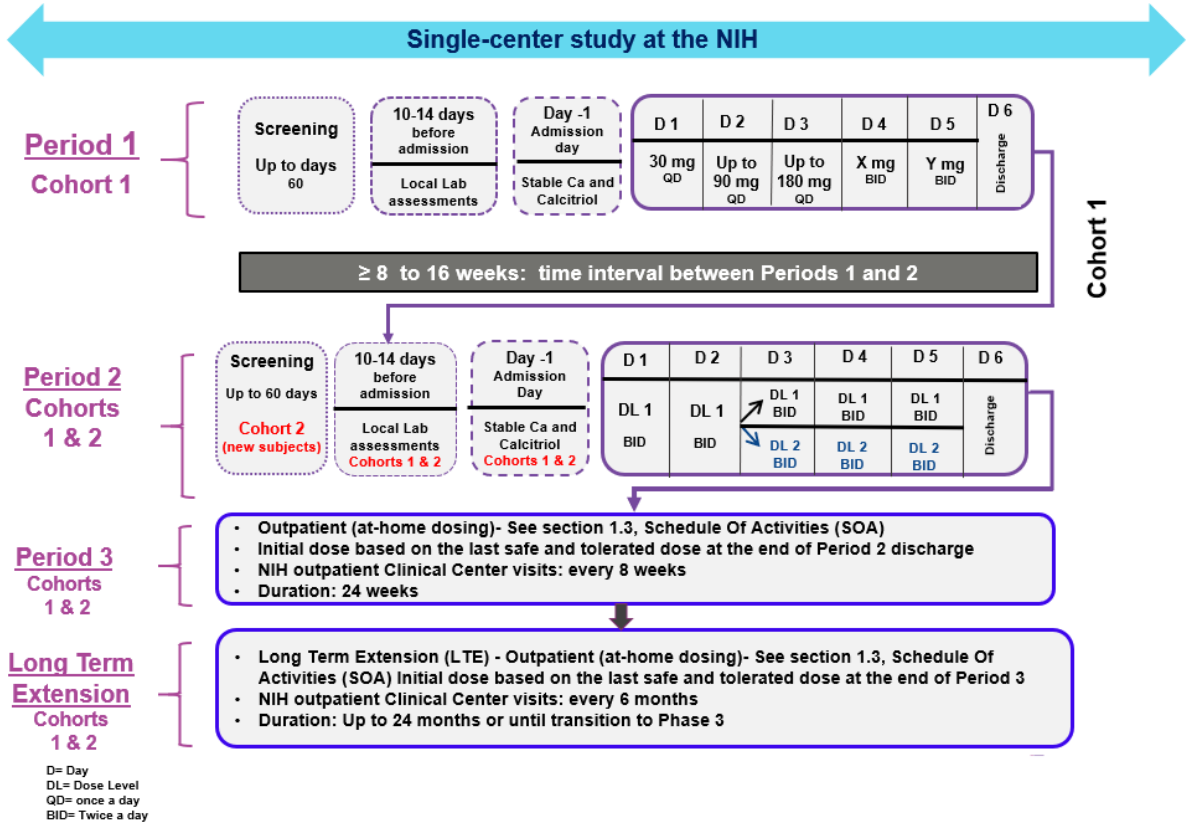
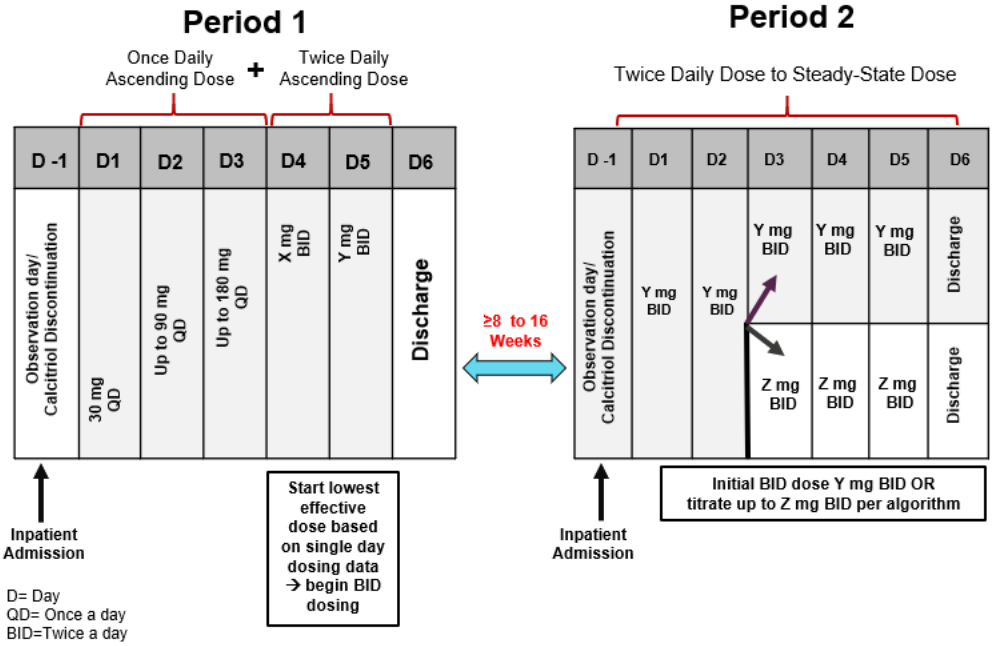
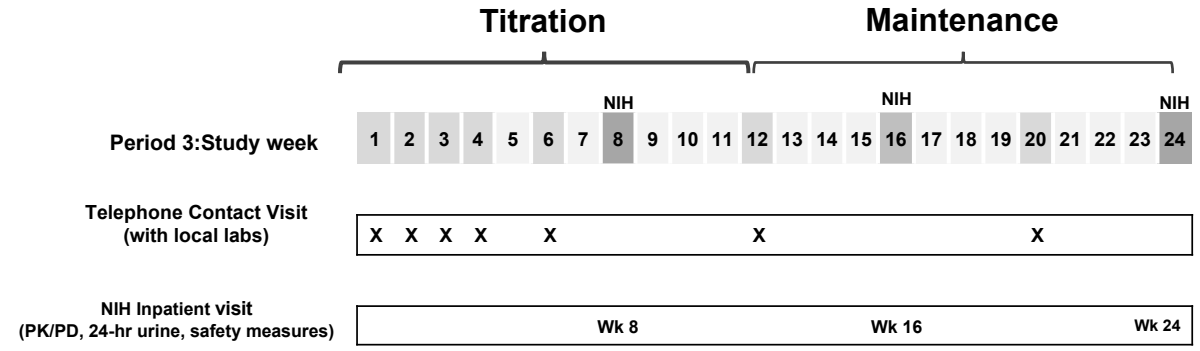


Figure B Detailed Schematic for Periods 1 and 2 (Single and Multiple Ascending Dose Testing)



A schematic of Period 3 is shown in Figure C.

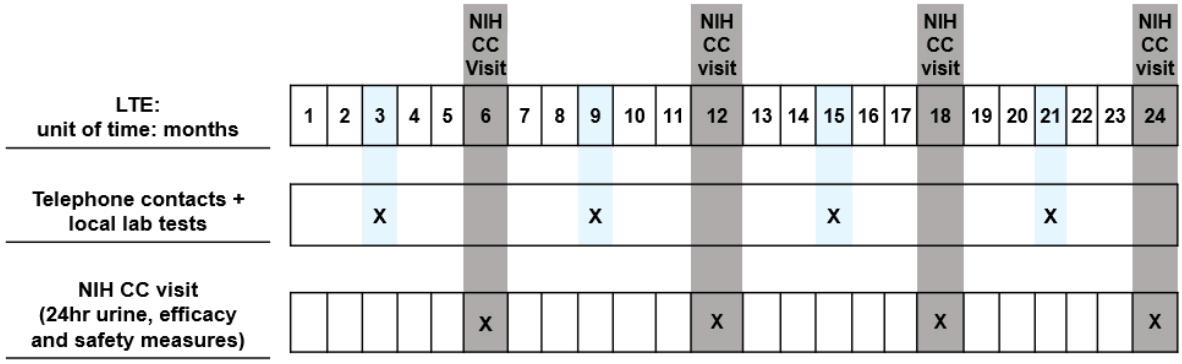
Figure C Detailed Schematic for Period 3



Wk= Week

Shading to help visualization - Dark Grey (NIH visit), Light Grey (Telephone contact), as indicated

Figure D Detailed Schematic for Long-term Extension (LTE)



Shading to help visualization - Dark Grey (NIH CC visit)

- **Period 1** - Is an inpatient stay that consists of 5 dosing days during which participants will undergo a once-daily (QD) dose escalation for 3 days followed by 2 days of twice daily (BID) dosing at an individualized test dose of CLTX-305 (encaleret).
- **Period 2** - Is an inpatient stay that consists of 5 dosing days during which participants will receive BID doses of CLTX-305 (encaleret) based on individual responses from Period 1 (for participants who complete Period 1) or review of aggregate data from Period 1 (for participants in Cohort 2 entering Period 2 without prior exposure to CLTX-305 (encaleret)). The initial dose, dose level 1 (DL1) will be administered for approximately 2 days (48 hours) with cCa monitoring. Participants will undergo encaleret dose up- or down-titration depending on cCa levels, with a potential

increase in dose if cCa remains below the lower limit of normal and potential decrease in dose if cCa is greater than or equal to the upper limit of normal. A final test day (Day 5) will include frequent blood and urine sampling to collect 24-hour PK/PD profiles.

- **Period 3** - Is an outpatient dosing period that consists of administration of CLTX-305 (encaleret) for up to 24 weeks. Participants completing Period 2 will continue to self-administer CLTX-305 (encaleret) at an initial BID dose based on their tolerance and response to BID dosing during Period 2. Initial titration will be based on each participant's need for symptom control and ongoing monitoring of efficacy endpoints (primarily cCa and urine calcium excretion) with a goal to optimize cCa in the normal range while minimizing hypercalciuria. Participants will not take calcitriol but may take calcium supplementation as needed to ensure a minimum daily dietary intake of 1000 mg. Participants may receive oral calcium supplements as directed by the investigative site if they are not able to achieve a minimum of 1000 mg per day of dietary calcium intake. Guidance on overall outpatient titration is discussed in Section 6.1.5 and in Section 8.2.3. The need for additional dose adjustments may depend on factors potentially related to the time course of changes in parathyroid gland function, intestinal calcium absorption, bone resorption, and kidney function, all of which will be monitored. Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit.

Long-term Extension (LTE) - Outpatient dosing with CLTX-305 (encaleret) will continue for an additional period of time, up to 25 months (approximately 2 years), or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever comes first, after completion of the Week 24 visit in Period 3. Participants completing Period 3 will continue to receive clinical supplies of CLTX-305 (encaleret) at the same BID dose based on their tolerance and response to BID dosing during CLTX-305 (encaleret) dosing in Period 3**.** Participants will not take calcitriol but may take calcium supplementation as needed to achieve a minimum daily intake of 1000 mg. Participants may receive oral calcium supplements as directed by the investigative site if they are not able to achieve a minimum of 1000 mg per day of dietary calcium intake. A final follow-up safety visit in the LTE will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret) is taken as part of this protocol for participants who withdraw from the study or CLTX-305 (encaleret) before transitioning to the CLTX-305-302/CALIBRATE Phase 3 LTE.

At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments should be completed per Schedule of Assessments (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) should be returned to the investigative site.

4.2 Scientific Rationale for Study Design

For detailed background on the study rationale see Section 2.1 (Study Rationale). The current Add clinical trial is designed to test CLTX-305 (encaleret) across a range of doses administered both once and twice daily to determine the ability of a calcilytic to raise blood calcium in patients with ADH1.

The current study is designed to confirm the utility of the calcilytic agent, CLTX-305 (encaleret), to treat hypocalcemia due to ADH1 through allosteric antagonism of the mutated CaSR in these patients. The study is designed to identify minimally effective doses, steady state pharmacokinetic/pharmacodynamic (PK/PD) relationships, and/or maximally tolerated doses in the target population of people with confirmed ADH1. Such data will be established during in-house periods 1 & 2 resulting in individualized dosing that will inform starting doses for outpatient exposure during Period 3. Initial outpatient dosing may be further titrated, along with oral calcium supplements, with the goal of optimizing blood calcium without the need for calcitriol while minimizing urinary Ca excretion.

Due to the orphan nature of ADH1, and the rarity of available participants for participation in this clinical trial, the Sponsor believes it is reasonable to anticipate extending the study into an outpatient Period 3 based on the expectation that Periods 1 and 2 will identify both individualized and rational average effective doses across both Cohorts 1 and 2.

4.3 Justification for Dose

The current study proposes to initiate first-in-patient dosing in the new target population of participants with ADH1, at 30 mg of CLTX-305 (encaleret). This dose has been shown previously to be safe and well tolerated in non-ADH1 participants (i.e., people not harboring pathogenic, gain-of-function variants that drive ADH1) and was unequivocally associated with increased plasma iPTH and elevation of cCa. It is expected that this may be an ineffective or minimally effective dose in ADH1 and therefore represents a logical starting dose upon which to base dose-escalation and dose-finding. For details of the PK/PD relationship of CLTX-305 (encaleret) in euparathyroid participants with presumed normal CaSR function, See the Investigator's Brochure.

Using both single ascending and multiple-ascending dose paradigms, the proposed study will explore the PK-PD relationship of CLTX-305 (encaleret) in participants with ADH1. Because ADH1 is an orphan disease with few identified potential participants, and because of the well characterized safety data available from the prior development program, we propose to conduct individualized dose escalation in a cohort of approximately 16 participants. It is not possible to predict what dose of CLTX-305 (encaleret), on average, will result in elevated calcium in ADH1 but it is anticipated that dosing may need to proceed from 30 mg through at least a log increase. The supervised in-house testing during Periods 1 and 2 will allow dosing to proceed based on safety and tolerability with close monitoring for evidence of efficacy based on changes in iPTH and cCa for each participant. Doses that elevate cCa, for example > 1mg/dL, within 1-5 days, would establish a definitive proof-of-concept for CLTX-305 (encaleret) as a potential treatment for ADH1. Doses that are associated with hypercalcemia would establish an upper bound or maximally tolerated dose.

Given that Periods 1 and 2 are designed to identify individually effective doses of CLTX-305 (encaleret), as well as potential upper bounds, these results should facilitate the choice of outpatient starting doses, likely at lower doses, as well as inform the initial approach to outpatient dose adjustment and optimization during Period 3.

Period 3 is designed to identify individualized chronic doses. Due to the different timeframes for PTH action (relatively immediately limiting calcium loss in the urine, followed by increasing endogenous 1,25-(OH)2 Vitamin D effects on GI absorption, and eventually mobilizing bone calcium), chronic outpatient doses may be lower than doses shown to be acutely effective. The dose-response curves for both iPTH stimulation and cCa elevation from Periods 1 and 2 may also inform updated PK-PD models which are currently based on non-ADH1 participants (Cabal 2013, Shrestha 2010). Taken together, individualized participant data and the ongoing accrual of data on all participants should facilitate rational outpatient dosing and titration.

The LTE is designed to obtain additional safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first. Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE.

At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional. Follow-up assessments are to be completed per Schedule of Assessments (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) should be returned to the investigative site.

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 or assent form, which must be obtained prior to initiation of study procedures.
2. Age ≥ 16 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 an activating mutation of the CaSR gene
6. 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 CLTX-

305 (encaleret) and during the study treatment period. When the thiazide is being used as an antihypertensive, alternative therapy will be offered.

7. Participants being treated with strong CYP3A4 inhibitors (including clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) should ideally, if clinically appropriate, discontinue these medications during the screening period for at least 5 half-lives prior to initiation of CLTX-305 (encaleret). Participants who must remain on strong CYP3A4 inhibitors may still enroll if they are able to remain on their medications at stable doses throughout the trial.
8. Participants being treated with magnesium or potassium citrate supplements should discontinue such treatment starting on Day -1 during Period 1 and Period 2 and may be asked to discontinue treatment during Period 3 if the blood magnesium and urine citrate are within the normal ranges during Period 1 and Period 2.

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 PTH 1-84 or 1-34 within the previous 3 months
2. History of hypocalcemic seizure within the past 3 months
3. Blood 25-OH Vitamin D level < 25 ng/mL
    a. If participant 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 participant will be eligible to continue to the treatment phase of the study.
4. Participants with hemoglobin (Hgb) < 13 g/dL for men and < 12 g/dL for women
    a. If participant has a low Hgb at the screening visit due to iron, B12, or folate deficiency, they will be prescribed supplementation. Once the Hgb level is > 13 in men or > 12 in women, the participants will be eligible to continue to the treatment phase of the study.
5. Abnormal laboratory values which in the opinion of the investigator, would make the participant not suitable for participation in the study
6. Estimated glomerular filtration rate (eGFR) < 25 mL/minute/1.73 m^2 using CKD-EPI (for participants < 18 years old the Schwartz equation will be calculated)
7. 12-lead resting electrocardiogram (ECG) with clinically significant abnormalities
8. Participants with positive hepatitis B surface antigen (HBsAg), Hepatitis A immunoglobulin M (IgM), or human immunodeficiency virus (HIV) viral serology test results 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.

9. 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
10. 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 participant). 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 participant.
    - Combination of the following (a+b or 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 methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
11. Sexually active male participants who are unwilling to use a condom during vaginal intercourse while taking the CLTX-305 (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 CLTX-305 (encaleret) dose in Period 1, Period 2 (for Cohort 2) until the end of study participation. Condoms are not required if the participant is vasectomized or if the participant's partner is not a woman of child-bearing potential.
12. Hypersensitivity to any active substance or excipient of CLTX-305 (encaleret)
13. History of drug or alcohol dependency within 12 months preceding the Screening Visit
14. History of thyroid or parathyroid surgery
15. Current participation in other investigational drug studies
16. Unwillingness to refrain from blood donation within 12 weeks prior to screening visit from the start of the study enrollment through one year after the last dose of the study drug

5.3 Inclusion of Vulnerable Participants

Participants between 16 and 18 years of age may be enrolled in this study. Older adolescents have the capacity to provide adequate assent in an intensive Phase 2a study for which benefit in this disorder remains uncertain. Younger children are excluded because of the intensity of the procedures with uncertain clinical benefit.

5.4 Lifestyle Considerations

Not applicable.

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. 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). Due to the ultra-orphan nature of ADH1, all data derived from participants during screening will be entered into the clinical trial database regardless of whether an individual participant is included or excluded from the active treatment periods.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a failing to meet criteria outlined in Section 5 may be rescreened once. The PI will discuss with Sponsor if additional screening attempts are warranted so that a joint decision can be made and recorded if necessary for a specific participant. Rescreened participants should be assigned the same participant number as for the initial screening.

5.6 Strategies for Recruitment and Retention

ADH1 is a rare disease with varying estimates on the order of 1500 patient prevalence in the United States. ADH1 is designated as an orphan disease consistent with this ultra-rare prevalence. A number of participants are identified and known to NIH investigators, some of whom have participated in prior clinical evaluations at the NIH in a prior pilot study utilizing a related calcilytic compound, NPSP795 (Roberts et al 2019). Initial recruitment will include contacting known potential participants with ADH1. Additional recruitment may proceed through referrals from worldwide clinical and research experts involved in this specialized area of mineral metabolism. Finally, outreach through patient advocacy organizations worldwide will also be pursued.

While most established ADH1 patients aged $\geq$ 16 years old will likely be eligible to participate according to protocol inclusion/exclusion criterion, it is estimated that up to 20 potential participants may be enrolled to support up to 16 participants entering the treatment phase of the study.

Potential participants will undergo the informed consent/assent process and be screened during an admission to 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 first in-house admission and throughout the clinical trial to encourage and enhance retention.

5.6.1 Costs

Compensation (see below) for participation in the trial will be per NIH guidelines as described in the Informed Consent and related attachments. Participants will not be billed by NIH and the Sponsor for any research or related clinical care that participants will receive at the NIH Clinical Center for this study. The NIH Clinical Center will provide short-term medical care for any injury resulting from participation in this clinical trial. Costs for local medical care related to the clinical trial but not otherwise covered by participant's own insurance may be compensated by the Sponsor.

5.6.2 Compensation

Participants will be compensated for participation in this clinical trial via check or direct deposit to the adult or minor participant. If the minor does not have a bank account or is unable to deposit checks, an alternative arrangement will be made with the participant and parent/guardian.

Maximum compensation will be $2550, paid in $850 installments at the completion of the first three study periods. Participants will not be compensated for participation in the LTE.

If participant 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 participant to book his/her own travel. For minor participants, travel and Children's Inn/hotel accommodation will also be provided for 1 parent or legal guardian. 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. Participant 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

During **Period 1** participants from Cohort 1 will receive CLTX-305 (encaleret) QD and BID per protocol with water as described in Section 8.2.1.

During **Period 2** participants from both Cohort 1 and Cohort 2 will receive CLTX-305 (encaleret) BID with water as described in Section 8.2.2

During **Period 3** participants from both Cohort 1 and Cohort 2 who enter Period 3 will be discharged home to continue taking CLTX-305 (encaleret) BID with water as described in Section 8.2.3.

During LTE participants who have completed Period 3 will continue taking CLTX-305 (encaleret) BID with water as an outpatient as described in Section 8.2.4.

6.1.1 Study Intervention Description

The investigational medicinal product (IMP), CLTX-305 (encaleret), will be provided as white film-coated tablets containing encaleret sulfate drug substance (active ingredient encaleret) and may be provided in 5, 10, 30 and 60 mg doses in bottles. If the 5mg tablet is not available for use, then the 10 mg tablets may be split according to the related specifications indicated in the Pharmacy manual provided by the Sponsor. No other dose strength may be split.

If the 10 mg tablet needs to be split, the participant should cut one 10 mg encaleret tablet each day and take half of the tablet in the morning and the other half of the split tablet in the evening, assuring that the participant receives a full 10 mg dose per day. Participant should follow the manufacturer instructions for use included with the pill cutter. In the event that half of the split 10 mg tablet is lost, the participant should cut a new tablet in half for the evening dose and discard the remaining half. The participant should start with a new 10 mg tablet the following morning.

Full details regarding CLTX-305 (encaleret) packaging are provided in the Pharmacy Manual.

6.1.2 Dosing and Administration

For details on Dosing of CLTX-305 (encaleret) see Section 8.2.

For additional background on Dose Justification see Section 4.3.

Dosing of CLTX-305 (encaleret) in participants with ADH1 is informed by prior experience of both acute and chronic dosing of CLTX-305 (encaleret) in the osteoporosis program that included exposures up to 1 year primarily in postmenopausal women with presumed normal CaSR function. The proposed starting dose is 30 mg in ADH1 because this is a dose proven to result in acute elevations in cCa in euparathyroid participants without an ADH1 mutations.

Based on peer-reviewed data from a pilot human study of a related calcilytic agent, NPSP795 (Roberts et al 2019), which also studied a top dose known to cause a rise in calcium in euparathyroid participants but not in ADH1 participants, we anticipate that the starting dose of 30 mg may be ineffective or minimally effective but represents a rational initial dose that has been demonstrated as safe and well tolerated previously.

Because a comprehensive safety database exists from the prior osteoporosis development program, including 12 months or more duration of safety exposure, the current first-in-ADH1 study will include repeat dosing, dose-escalation and dose individualization over time in individual ADH1 participants. Similar to cross-over designs, conducting dose-escalation within participants should reduce variability and increase the precision of dose/response modeling compared to an approach that might use separate parallel or sequential cohorts. Up to 16 participants studied should be feasible and allow characterization of individual and group mean dose-exposure-response profiles as well as proof-of-concept on elevation of cCa. Our approach is preferable since the ultra-orphan nature of the disease makes conventional parallel group dose finding not feasible.

CLTX-305 (encaleret) will be tested both as a single daily dose and as a twice daily dose. In the prior osteoporosis program CLTX-305 (encaleret) was administered once daily and this was seen to stimulate a transient increase (spike) in iPTH levels secretion within 2 hours and a second lower plateau level of iPTH (still elevated compared to baseline) for up to 12 hours at doses of 30 mg and above. Despite both PK (drug exposure) and PD (increased iPTH levels) lasting less than 24 hours, some evidence for increased trough cCa (measured 24 hours after last dose) suggests that once daily dosing and once-daily dose escalation should be tested in ADH1 participants.

CLTX-305 (encaleret) may be administered within 30 minutes prior to meals. Administration with meals was shown in prior Phase 1 trials to be associated with adequate systemic absorption, prompt increases in plasma levels of iPTH but with a slightly blunted PTH C_{max} compared to administration while fasted (See Investigator's Brochure for details and results of Phase I trials). Recommendation for administration within 30 minutes prior to meals was chosen as the paradigm for ADH1 dosing because, unlike in the osteoporosis program, the goal in ADH1 patients is not to maximize PTH C_{max} but to facilitate increased iPTH levels above baseline throughout the day, adequate to raise blood cCa levels into the normal range. It is anticipated, however, that twice daily dosing may result in lower iPTH levels C_{max} and more stable iPTH level over the course of 24 hours versus single daily dosing. The protocol is designed to test this hypothesis by conducting both once-daily and twice daily dose escalation in Period 1 and twice-daily dose escalations in Period 2.

An overview and general description of the study strategy for intervention CLTX-305 (encaleret) administration is presented below. Additional detail on doses, regimens and titration algorithm/guidance for each Period can be found under the appropriate sub-section of Section 8.2, including flowcharts for dosing in Period 1 (Figure E) and Period 2 (Figure F).

6.1.3 Period 1 (Single Ascending Dose Escalation and BID PK/PD profile) – Cohort 1

In Period 1, eligible Cohort 1 participants are admitted to the NIH CC after completing screening tests. On days 1-3 of admission, Cohort 1 participants will undergo single daily dosing and protocol-specified dose-escalation of CLTX-305 (encaleret) from the initial dose of 30 mg on Day 1, increasing to a maximum dose of 180 mg on Day 3. Based on the individualized responses to QD dose escalation an individualized dose of CLTX-305 (encaleret) will be chosen for BID administration on Days 4 and 5.

Days 1, 2 and 3 (QD Dose Escalations): Up to 8 participants (minimum of 5) will undergo a single-dose, dose-escalation over the first 3 days of admission in Period 1. Morning doses will be administered on Days 1, 2 and 3, respectively, accompanied by frequent blood and urine sampling for 24-hours for PK/PD measures. CLTX-305 (encaleret) will be administered in the morning within 30 minutes prior to breakfast. If dose escalation is limited due to tolerability or hypercalcemia, then the investigator, in consultation with the Sponsor, may choose to interrupt the pre-specified dose escalation (for example see Section 6.1.7 and Section 8.2.1). In this case, the investigator, in consultation with sponsor, may choose to repeat the last well-tolerated dose on Days 2 and 3, or titrate down as appropriate.

Dose-escalation will take place sequentially on Days 1, 2 and 3 without interim wash-out because prior extensive PK-PD data supports minimal drug accumulation over 24 hours when dosed once daily (for details see the Investigator's Brochure). Similarly, it is expected that iPTH levels will not remain elevated for 24 hours after dosing when CLTX-305 (encaleret) is administered once-daily. However, any carryover effects that may occur should not confound the objective of demonstrating an acutely efficacious dose of CLTX-305 (encaleret). For any given participant, cCa values > 10.5 mg/dL, during a dosing interval, will indicate that a top dose of CLTX-305 (encaleret) has been reached for that individual and further dose escalation will not be necessary. In this scenario, the investigator, in consultation with the Sponsor, may choose to repeat the last well-tolerated dose on the remaining QD testing days (e.g., Days 2 and 3), as appropriate. Detailed examples of dose and titration modifications based on the cCa response are shown in Figure E in Section 8.2.

Days 4 and 5 (BID Dose Escalation): Based on each participant's individual PD responses to QD dose-escalation, an individualized dose of CLTX-305 (encaleret) will be chosen for BID dosing on Days 4 and 5. CLTX-305 (encaleret) will be administered once in the morning and once in the evening, within 30 minutes prior to breakfast and dinner. The dose selected should be based on each participant's response in cCa and/or PTH levels during the prior QD dosing (Days 1-3). A guidance algorithm for BID dosing, based on the individual response to QD dosing in Period 1, is presented in Figure E in Section 8.2.

6.1.4 Period 2 (BID Dosing) – Cohorts 1 and 2

In Period 2, eligible Cohort 1 participants, who have completed Period 1, may return after at least 8 weeks for admission to NIH for Period 2. After all Cohort 1 participants have finished Period 1 and the data analyzed, the Sponsor will open enrolment for Cohort 2 participants. Eligible Cohort 2 participants may enroll directly into Period 2, after completing the consent

and screening process per protocol. In Period 2 all participants will initiate CLTX-305 (encaleret) BID dosing given within 30 minutes prior to breakfast and dinner on Days 1 and 2. cCa concentrations will be monitored frequently throughout Period 2, and CLTX-305 (encaleret) doses will be up- or down-titrated as needed to target normal cCa concentrations. Assessment of the 24-hour PK/PD profile of CLTX-305 (encaleret) with BID dosing will be conducted on Day 5. A guidance algorithm for initiating and titrating BID dosing during Period 2 is presented in Section 8.2.2, and in the algorithm/guidance in Figure F.

6.1.5 Period 3 (Cohort 1 and Cohort 2) – Outpatient Dosing

In Period 3, the initial outpatient dose of CLTX-305 (encaleret) will be individualized based on the results from inpatient Periods 1 and/or 2 as described in greater detail in Section 8.2.3. Period 3 will include a titration phase of approximately 12 weeks and a maintenance phase of approximately 12 weeks for a total outpatient exposure to CLTX-305 (encaleret) of 24 weeks. Titration will be conducted by the NIH investigators at scheduled or unscheduled telephone contact visits based on review of outpatient chemistry results for cCa, Mg, phosphorous at NIH CC visits (approximately every 8 weeks) based on assessment of both blood and urine calcium results as described, with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. Oral calcium supplementation may be used as needed on top of a minimum daily dietary intake of at least 1000 mg.

6.1.6 Long-term Extension (Cohort 1 and Cohort 2) – Outpatient Dosing

In the Long-term Extension (LTE), participants will continue CLTX-305 (encaleret) per the dosing regimen established in the maintenance phase of Period 3. Telephone contacts along with outpatient laboratory assessments will be performed every 6 months starting at Month 3 with NIH CC visits occurring every 6 months starting at Month 6. CLTX-305 (encaleret) doses may be titrated as needed based on assessment of both blood and urine results as described, with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. Oral calcium supplementation may be used as needed on top of a minimum daily dietary intake of at least 1000 mg.

6.1.7 Dose Limiting Toxicity

The goal of the current study in participants with ADH1, is to elevate cCa concentrations, including identifying doses capable of raising cCa beyond the normal range. It is important to establish if an allosteric modulator of the CaSR is capable of causing hypercalcemia at all, in patients with activating mutations of the CaSR. The study is designed to monitor for cCa elevations in a closely supervised and expert setting familiar with acute treatment and intervention, if necessary. In the prior osteoporosis program, hypercalcemia, identified by laboratory testing, was confirmed as a dose-limiting effect in presumed euthyroid participants without *CaSR* mutations, however, of note, laboratory hypercalcemia was not clearly associated with hypercalcemic symptoms; the events were detected in routine laboratory

monitoring and were managed by withholding or lowering the dose of CLTX-305 (encaleret).

Another inherent study objective is assessment of safety and tolerability across different doses and regimens including characterizing dose-limiting adverse events, determining maximum doses associated with acceptable safety risk, as well as determining doses that can effectively raise or maintain stable normal cCa concentrations.

Based on experience accumulated in human clinical testing, from the prior osteoporosis program, no specific safety signal or adverse event profile was identified with acute or chronic dosing with CLTX-305 (encaleret). Dose-limiting hypercalcemia was the only signal that required chronic doses to be limited to 15 mg QD in an otherwise healthy population of postmenopausal women treated for up to 12 months.

Since there is no specifically expected adverse event profile or anticipated dose-limiting toxicity in humans, safety monitoring for CLTX-305 (encaleret) will be based on established approaches and principles. Protocol-specified safety measures based on adverse event monitoring, safety laboratories, vital signs, physical exam, and EKGs will be assessed during the NIH visits. For any individual participant, the experience of an adverse event will be evaluated and recorded according to the guidance given in Section 8.5.3, and appropriate action with respect to study drug administration will be made according to the judgment and assessment of the investigator.

It is expected that higher doses of CLTX-305 (encaleret) will be necessary to see comparable changes in cCa in participants with ADH1 compared to previously tested participants with normal CaSR function and therefore the current protocol stipulates potential dose escalation higher than 100 mg including doses possibly > 400 mg acutely in order to identify effective doses in the new target population of participants with abnormal CaSR function where cCa elevations would represent efficacy and not a safety side-effect.

The proposed starting dose for participants with ADH1 is 30 mg, which was well tolerated, in healthy normal volunteers, without a specific safety signal, but was also rapidly effective in raising cCa. It is expected that this dose will not be effective or may be minimally effective in raising cCa in ADH1 participants. Therefore, based on known safety and efficacy on cCa, CLTX-305 (encaleret) 30 mg represents a rational initial dose for this first-in-ADH1 trial. Moreover, CLTX-305 (encaleret) was acutely safe and well tolerated across a range from 5-100 mg in non-ADH1 participants (approximately 10-fold range). Original Phase 1, single-escalating dose trials in healthy humans with presumed normal CaSR function, were designed to escalate up to 400 mg CLTX-305 (encaleret); however, a top dose of 100 mg was identified based on rising cCa concentrations. The top dose in people with presumed normal CaSR function was chosen as 100 mg, to avoid excessive cCa elevations, and was used safely as the top dose in a Phase I thorough QTc study.

Of note, although people with ADH1 may show a right-shifted dose-response compared to healthy non-ADH1 people, there is no biological reason to expect the dose-response trajectory to be significantly steeper in participants with ADH1. Therefore, it is important to plan for appropriate dose-escalation in this first-in-ADH1 trial, to focus on proof-of-calcium-

raising effect. The planned dose range for QD exploration in ADH1 participants includes a range from 30 to 180 mg (approximately 6-fold range). If higher doses are required to confirm efficacy on cCa, dose escalation will continue but switch to BID regimens as specified in greater detail in the algorithm/guidance in Section 8.2.

In the prior osteoporosis program, hypercalcemia adverse events were not symptomatic and were identified based on scheduled periodic laboratory assessments. Dose-limiting thresholds for post- CLTX-305 (encaleret) cCa levels are specified as part of the dosing and titration algorithms in Section 8.2. In Summary, participants who achieve a post-dose cCa > 10-10.5 mg/dL (in Period 1) and cCa > 10 mg/dL (in Period 2) during the dose escalation will not proceed to higher CLTX-305 (encaleret) doses. Participants with cCa values between 10-10.5 mg/dL during dose escalation in Period 1, will have their doses increased by 30 mg only. Participants who achieve cCa > 10-10.5 mg/dL in Period 1 and >10 mg/dL in Period 2 will have their dose maintained or reduced and undergo final frequent sampling as appropriate.

6.1.8 Dose Modifications

See above for general principles of dosing and titration limitations based on toxicity or hypercalcemia. See Section 8.2 for details of the dosing guidance algorithm for each Period.

Dose modifications should be made according to the protocol-specified guidance/algorithm described in Section 8.2 based on cCa thresholds of > 10-10.5 mg/dL in Period 1 and > 10 mg/dL in Period 2. Similarly, titration in outpatient Period 3 and the LTE will be based primarily on periodic assessment of cCa and where cCa > 10 mg/dL would also require dose modification.

For participants who develop clinical laboratory abnormalities unrelated to the dosing algorithm parameters (e.g., corrected calcium) indicating that further conduct of per protocol clinical assessments/procedures may put the participant at risk may have their CLTX-305 (encaleret) dosing interrupted at the discretion of the principal investigator and should be captured as adverse events. Because of the intensive sampling required during the conduct of the in-hospital assessments, procedures related to the collection of blood in terms of sampling technique or frequency of sampling and/or blood volume may have their scheduled dosing interrupted so as to allow the patient to recover and continue the study treatment at a later date (re-initiation). The time interval separating the day of the interrupted dose and the day to re-initiate dosing will be less than or equal to 56 days. The participant with an interrupted dose may be re-initiated at the next protocol-specified dose level of CLTX-305 (encaleret) at the discretion of the principal investigator. A participant with a dose interruption shall continue to meet eligibility criteria for the study.

6.1.9 Drug Administration

During Period 1 and Period 2 inpatient NIH CC stays, on days CLTX-305 (encaleret) is given once a day, participants will receive one dose in the morning that may be administrated within 30 minutes prior to breakfast with about 8 ounces of water. On days CLTX-305 (encaleret) is given twice a day, participants will receive one dose in the morning and the

second dose in the evening and can be administered within 30 minutes prior to breakfast and dinner with about 8 ounces of water.

During Period 3 and the LTE, participants will be instructed by the investigator/designee to take one dose of CLTX-305 (encaleret) in the morning and the second dose in the evening. Taking the dose within 30 minutes of breakfast and dinner is suggested but not required.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

The site research pharmacist or delegated personnel will maintain an accurate record of the receipt of the CLTX-305 (encaleret) shipped by the Sponsor, including the date and quantity received. In addition, an accurate drug disposition record will be kept that specifies the amount to be administered to each participant, the date of dispensation, and any amount returned. This inventory record must be available for inspection at any time, and copies of this record will be provided to the Sponsor at the conclusion of the study. At the completion of the study, the site research pharmacist or delegated personnel will provide the Sponsor with a complete record of CLTX-305 (encaleret) accountability.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The CLTX-305 (encaleret) will be provided as white film-coated tablets containing the active ingredient CLTX-305 (encaleret) provided in 5, 10, 30 and 60 mg doses.

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

The Sponsor will provide the study center with drug supplies. The CLTX-305 (encaleret) is to be stored at controlled room temperature between 20°C and 25°C with excursions permitted between 15°C and 30°C in the Sponsor provided bottles.

In Periods 1 and 2, all participants will receive CLTX-305 (encaleret) only as dispensed and administered by investigative site staff at the NIH CC. All unused CLTX-305 (encaleret) must be returned to the Sponsor or destroyed on-site with approval by the Sponsor, after a final CLTX-305 (encaleret) accountability has been completed. If unused CLTX-305 (encaleret) is not returned to the Sponsor, proof of destruction must be provided to the Sponsor.

In Period 3 and LTE participants will be given CLTX-305 (encaleret) to allow outpatient BID self-administration at an individualized starting dose with overage to allow for dose up-titration at the discretion of the investigator, between NIH CC visits. If needed, additional CLTX-305 (encaleret) may be mailed to the participant by the NIH CC pharmacy per standard NIH CC pharmacy procedures. Participants will return unused CLTX-305 (encaleret) at each designated NIH CC visit which will be reviewed for accountability and an

estimate of compliance. Participants must return unused CLTX-305 (encaleret) to the NIH CC at their next visit. CLTX-305 (encaleret) accountability will be performed by the NIH pharmacist or delegated personnel. After a final CLTX-305 (encaleret) accountability is completed any unused CLTX-305 (encaleret) must be returned to the Sponsor or destroyed on-site with approval by the Sponsor and in accordance with procedure at NIH. If unused CLTX-305 (encaleret) is not returned to the Sponsor, proof of destruction must be provided to the Sponsor.

6.2.4 Preparation

Not applicable.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label study.

6.4 Study Intervention Compliance

For inpatient Periods 1 and 2, CLTX-305 (encaleret) will be administered by site staff and recorded. The time of CLTX-305 (encaleret) administration will be documented in the appropriate 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. During outpatient Period 3 and LTE, participants will self-administer CLTX-305 (encaleret) and should be giving instruction on dosing. In respect to CLTX-305 (encaleret) administration refer to section: “Drug Administration.” At each study visit and during telephone contacts, site staff will review and record compliance (e.g., document missed doses) and review and record any dose changes.

6.5 Concomitant Therapy

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

All participants will be instructed to stop taking calcitriol on Day -1, the day of admission, but continue their oral calcium supplement regimen. Participants will receive at least 1,000 mg total daily calcium derived from diet and supplementation throughout the treatment period.

Participants being treated with thiazide diuretics may be enrolled if they are willing and able to discontinue thiazides 5 half-lives prior to initiation of CLTX-305 (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), if clinically appropriate, should

discontinue these medications during the screening period at least 5 half-lives prior to initiation of CLTX-305 (encaleret) and during the study treatment period. Otherwise, participants being treated with strong CYP3A4 inhibitors should remain on stable doses throughout the trial.

Participants being treated with nirmatrelvir/ritonavir for COVID-19 may decrease the encaleret dosing to once daily during the 5-day treatment course given that ritonavir is a strong CYP3A4 inhibitor. Participants may take calcium supplementation as needed if they experience symptoms of hypocalcemia during this time. After completion of the 5-day nirmatrelvir/ritonavir treatment course, participants may resume twice daily encaleret.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An early termination (premature discontinuation) will occur if a participant who signs the informed consent/assent form (ICF) and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures. Participants can be early terminated from the study for any of the reasons to include the following:

- AEs
- Protocol violation
- If it is discovered that the participants did not meet protocol entry criteria, and continued participation would present unacceptable risk to participant's health
- Non-compliance with administration of the investigational medicinal product CLTX-305 (encaleret/IMP).
- Withdrawal of consent: study participants may withdraw consent at any time for any reason without prejudice to future treatment. In the event of study withdrawal, the participant will be encouraged to undergo ET procedures as a final visit.
- Lost to follow-up (site should attempt at least 3 documented phone calls, followed by a registered letter to the participant's last known mailing address)
- Pregnancy at any time after signing the ICF. CLTX-305 (encaleret) should be discontinued immediately, and pregnancy reported (Section 8.5.8)
- Participant transitions to the CLTX-305-302/CALIBRATE Phase 3 LTE
- Study terminated by the Sponsor
- Site closed by the Sponsor/designee
- PI's decision based on participants' safety

7.2 Participant Discontinuation/Withdrawal from the Study

During Periods 1 and 2, if participants discontinue participation or are terminated early from the study, they should have all safety assessments for Early Termination (ET) as listed in the Schedule of Activities. When participants are discontinued from study medication, as described above in Section 7.1, they should be converted back to their outpatient regimen of oral calcium and active Vitamin D. Participants will be instructed to undergo outpatient laboratory testing of their blood calcium within 1-3 days 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 calcium results and advise on optimizing their outpatient clinical management.

During Period 3 and LTE, participants receive CLTX-305 (encaleret) to self-administer in the outpatient setting. A process for returning and reconciling CLTX-305 (encaleret) will be followed. When a participant discontinues the study or withdraws from taking study medication, they will revert to their prior outpatient regimen of oral calcium and active Vitamin D to address their underlying ADH1 and maintain cCa blood concentrations as they return to their prior clinical care providers. Participants will be instructed to undergo outpatient laboratory testing of their blood calcium within 1–3 days of discontinuing study medication and to have those results sent to NIH investigators for review. Study investigator should contact the participant to review the blood calcium results and advise on optimizing their outpatient clinical management. Arrangements will be made to return study medication to the study site for proper reconciliation and disposal.

Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE Phase 3 LTE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 LTE study.

All participants who received CLTX-305 (encaleret) and terminate early from the study, regardless of cause, with exception of transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, should undergo follow-up procedures according to Section 1.3 Table D SOA. The reason for early termination from the study will be reflected in the CRF. If a participant terminates early from the study because of an AE, the PI/study staff must record the AE as the reason for discontinuation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she missed at least 3 documented phone calls, followed by no response after a registered letter to the participant's last known mailing address is received.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- 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

All participants must sign the Informed Consent Form (ICF) prior to any study-related procedures. Screening must be completed within 60 days prior to admission to the NIH CC (See Table A and Table B for Period 1 and Period 2 Schedule of Activities and Section 1.3 for details on Screening Assessments).

The first screening visit will be conducted at the NIH CC to determine participant eligibility, document current metabolic status, assess dietary calcium intake, and perform genotyping to confirm the type of ADH gene mutation (if specific information is not available; See Section 8.3.4). 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 the start of Period 1 or Period 2, Day -1. Each participant'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. The total blood volume collected during the screening visit for each participant will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). NIH investigators may recommend adjustments to a participant'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 to Period 1 or Period 2 per protocol.

After completing screening assessments, any AE/SAE reported by a study participant, whether or not CLTX-305 (encaleret) 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."

8.2 Treatment Period

8.2.1 Period 1 (Single Ascending Dose Escalation and BID PK/PD profile) – Cohort 1

For participants whose screening visit is > 21 days before initiation of study drug, outpatient laboratory testing will be performed 10-14 days prior to admission for blood and urine chemistry to be reviewed by the NIH investigators.

All participants will be instructed to stop taking calcitriol on Day -1, the day of admission, but continue their oral calcium supplement regimen until admitted.

Day -1 (Admission): Eligible participants in Cohort 1 will be admitted to the NIH CC the day prior to dosing in Period 1.

Days 1, 2 and 3 (QD Dose Escalations): Up to 8 participants (minimum of 5) will undergo a single-dose, dose-escalation over the first 3 days of admission. Morning doses with a starting dose of 30 mg will be administered on Days 1, 2 and 3, respectively, accompanied by frequent blood and urine sampling for 24-hours for PK/PD measures (For details of PK/PD assays and timepoints see Section 1.3.1, including Table E, Table H, Table I, and Table L. CLTX-305 (encaleret) will be administered in the morning, with water, within 30 minutes prior to breakfast. If dose escalation is limited due to tolerability or hypercalcemia (Also see Section 6.1.3), the investigator, in consultation with the Sponsor, may choose to repeat the last well-tolerated dose on Days 2 and 3, or down-titrate, as appropriate (See below for dosing guidance algorithm).

Days 4 and 5 (BID Dose Escalation): Based on each participant's individual PD responses to QD dose-escalation, an individualized dose of CLTX-305 (encaleret) will be chosen for BID dosing on Days 4 and 5. CLTX-305 (encaleret) will be administered once in the morning and once in the evening, within 30 minutes prior to breakfast and dinner. The dose selected should be based on each participant's response in cCa and/or PTH levels during the prior QD dosing (Days 1–3). The investigator, in consultation with the Sponsor, will likely choose either 90 or 180 mg administered BID (for total daily doses of 180 and 360 mg, respectively) but will decide according to the following criteria for each participant:

> The lowest dose that resulted in an increase in cCa by ≥ 1 mg/dL during the dosing interval, or the lowest dose that maintained cCa in the normal range without exceeding the upper limit of the reference range over the dosing interval

AND / OR:

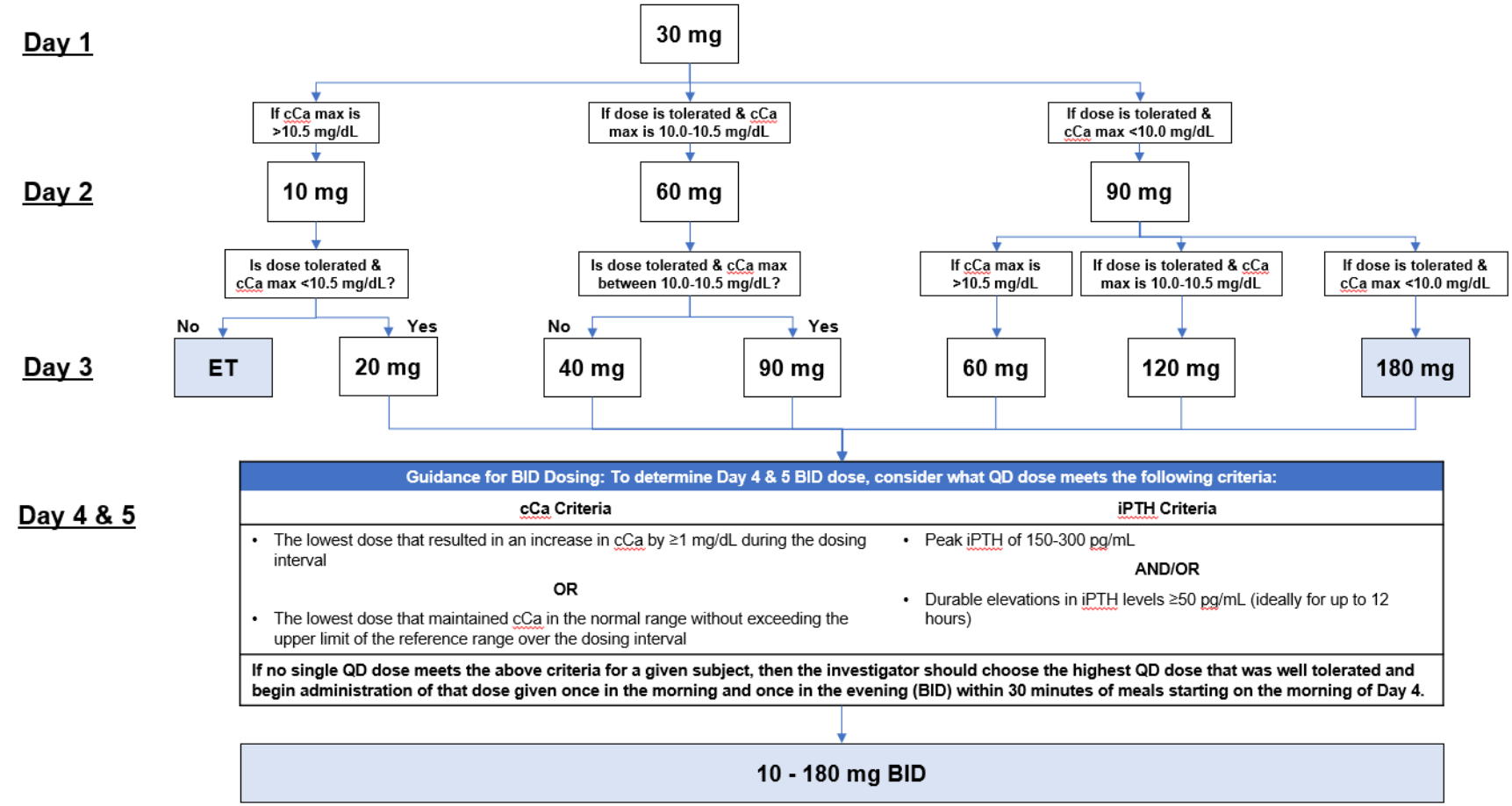
> Peak iPTH 150–300 pg/mL and/or
>
> Sustained elevations in iPTH levels ≥ 50 pg/ml (ideally for up to 12 hours)

If no single QD dose meets the above criteria for a given participant, then the investigator should choose the highest QD dose that was well tolerated and begin administration of that dose given once in the morning and once in the evening recommended within 30 minutes prior to meals (BID) starting on the morning of Day 4.

Monitoring of cCa and iPTH will occur during BID dosing on Days 4 and 5 with frequent blood and urine sampling for PK/PD. For details on the timepoints and assays for PK/PD samples on Day 5 see Section 1.3.1 and specifically Table I. The total blood volume collected during Period 1 for each participant will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). If a participant has a low body weight (<50 kg for adults or <55 kg for adolescents), the blood volume taken will be reduced to remain within the NIH guidelines of 10.5mL/kg/8w (adult) and 9.5 mL/kg/8w (pediatric). The last dose of study medication will occur in the evening of Day 5.

A schematic of dose modifications based on the guidance described above is shown below in Figure E:

Figure E Dosing Guidance Algorithm for Period 1



Day 6 (Discharge): After the PK/PD blood sampling is collected on the morning of Day 6 all participants will resume their prior conventional treatment regimen. During Day 6, cCa levels will be monitored throughout the day. This period can be extended if additional monitoring or treatment (e.g., to stabilize calcium) is needed prior to discharge.

Outpatient testing done in Period 1 on day 7-8 (~ 24-48 hours after expected discharge from the NIH clinical center) will ideally be collected at the NIH CC. If this is not practical, with the participant's permission, contact information for the participant will be provided to a sponsor-contracted healthcare service to schedule a mutually agreeable time for sample collection in the home. Blood samples collected will be evaluated for CLTX-305 (encaleret) concentrations as well as for blood creatinine, albumin, calcium, magnesium, phosphate, and PTH. This will allow both an evaluation of calcium homeostasis as well as a final PK sample while CLTX-305 (encaleret) concentrations are washing-out after Period 1. Given that the half-life of CLTX-305 (encaleret) at steady state is ~ 10-14 hours, the PK sample will represent a timepoint between 40-70 hours after the last dose of CLTX-305 (encaleret) (administered in the evening of Day 5). A telephone contact will be conducted on day 9-11 or once the calcium results are available to be reviewed with investigative site staff.

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 available at the NIH Clinical Center investigative site and can be measured either in the event of severe hypocalcemia or if there is any question about the accuracy of the cCa measure. Collection of ionized calcium will occur at the discretion of the expert investigators based on the clinical scenario on a case-by-case basis.

8.2.2 Period 2 (BID Dosing) - Cohorts 1 and 2

For cohort 1, 10-14 days before admission to the NIH CC, participants will undergo outpatient laboratory testing for blood and urine chemistry (Table B). For cohort 2 participants whose screening visit is > 21 days before initiation of study drug, outpatient laboratory testing will be performed 10-14 days prior to admission for blood and urine chemistry.

Results will be reviewed by the NIH investigators.

Participants who complete the screening visit midweek have the option to stay overnight at NIH CC during the intervening days prior to the start of Period 2, Day -1.

All participants will be instructed to stop taking calcitriol on Day -1, the day of admission, but continue their oral calcium supplement regimen until admitted. Magnesium supplements and potassium citrate will be discontinued starting the morning of Day 1. Calcium supplements will be discontinued or decreased starting on Day 1, based on the estimate dietary calcium intake, targeting a combined calcium intake of > 1000 mg/day.

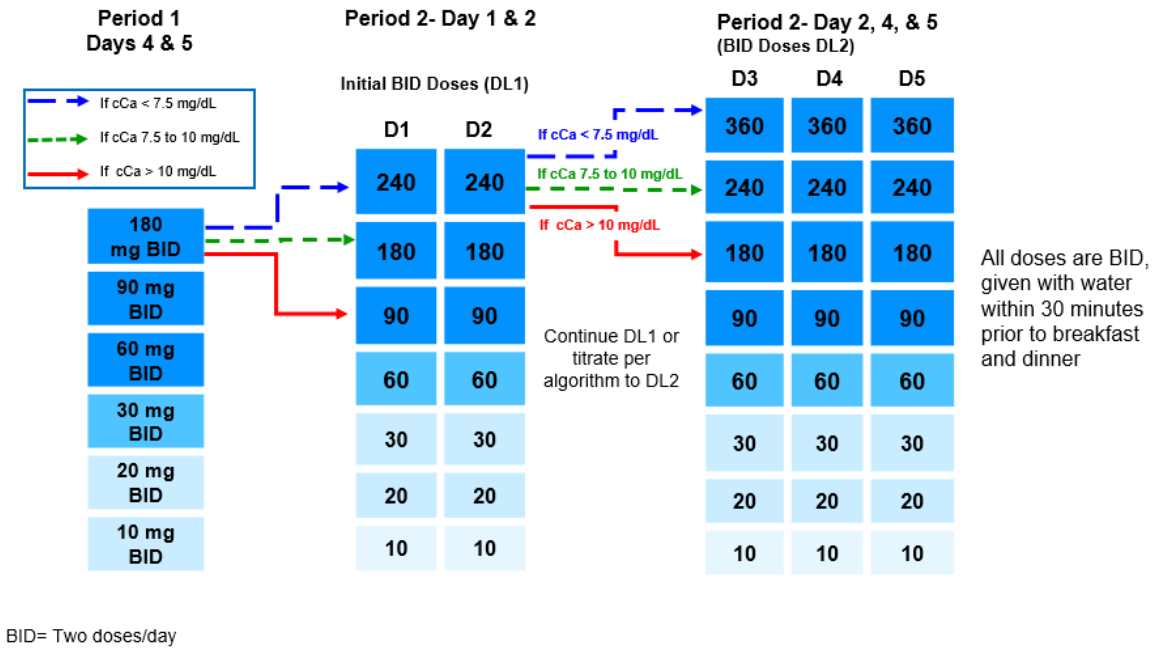
Day -1 (Admission): Eligible participants will be admitted to the NIH Clinical Center the day prior to dosing.

Cohort 1- Participants in Cohort 1 who complete Period 1 will be scheduled to return for Period 2 after at least 8 weeks and up to 16 weeks (minimum of 8 weeks between Period 1 and 2 for participant participating in both Periods to recover blood volume and hematocrit levels). BID dosing will be individualized based on each participant's prior responses to CLTX-305 (encaleret) during Period 1.

The first 7 participants who have completed CLTX-305-201 Period 2 and entered into Period 3 have had a wide range of CLTX-305 (encaleret) dose requirements from 10 mg once daily to 180 mg BID suggesting that CLTX-305 (encaleret) dosing is highly individualized. As a result, all remaining participants in Period 2 will receive an initial CLTX-305 (encaleret) 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The CLTX-305 (encaleret) dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 5, 10, 30, or 60 mg increments based on the available CLTX-305 (encaleret) tablet strengths. A frequent sampling test day with additional serial blood and urine sampling to assess 24-hour PK/PD profiles will be performed on Day 5. For details on the PK/PD timepoints during frequent sampling on Day 5 see Section 1.3.1 specifically Table J and Table K.

The total blood volume collected during Period 2 for Cohort 1 participants will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). These volumes include the cumulative potential collection over an 8-week period: -10-14-day labs, Day -1 safety labs, Period 2 inpatient week, and 4 weeks of outpatient labs in Period 3. If a participant has a low body weight (<43 kg for adults or <48 kg for adolescents), the blood volume taken will be reduced to remain within the NIH guidelines of 10.5mL/kg/8w (adult) and 9.5 mL/kg/8w (pediatric). If, at any time, the CLTX-305 (encaleret) dose is associated with a cCa > 10 mg/dL, then the dose should be reduced to a lower dose level. An example of how CLTX-305 (encaleret) dosing may be adjusted is provided in Figure F below.

Figure F Dosing Guidance Algorithm for Period 2 – Cohort 1



Cohort 2 – Cohort 2 will commence after Cohort 1 has completed Period 1 and the PD dose responses and safety have been reviewed. Participants will receive an initial CLTX-305 (encaleret) 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The CLTX-305 (encaleret) dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 5, 10, 30, or 60 mg increments based on the available CLTX-305 (encaleret) tablet strengths. The total blood volume collected during Period 2 for Cohort 2 participants will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). These volumes include the cumulative potential collection over an 8-week period: screening visit labs, -10-14 day labs, Day -1 safety labs, Period 2 inpatient week, and 4 weeks of outpatient labs in Period 3.

Participants will take the final dose of study medication in the evening of Day 5. After the final serial PK/PD blood sampling on the morning of Day 6, all participants completing Period 2 will be eligible for participation in Period 3 to receive CLTX-305 (encaleret) at the same BID dose (or lower) in an outpatient setting. Participants entering Period 3 will be discharged from NIH Clinical Center on the dose determined by the investigators to be effective and tolerated for each individual during Period 2.

If a participant does not participate in Period 3, the participant will resume their prior conventional outpatient treatment regimen on Day 6 prior to discharge.

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 available at the NIH Clinical Center investigative site and can be measured either in the event of severe hypocalcemia or if there is any question about the accuracy of the cCa measure. Collection of ionized calcium will occur at the discretion of the expert investigators based on the clinical scenario on a case-by-case basis.

8.2.3 Period 3 (Cohort 1 and Cohort 2) - Outpatient Dosing

Period 3 will include a titration phase of approximately 12 weeks and a maintenance phase of approximately 12 weeks for a total outpatient exposure to CLTX-305 (encaleret) of approximately 24 weeks. In Period 3, the initial outpatient dose of CLTX-305 (encaleret) will be based on the results from inpatient Periods 1 and 2. Outpatient titration will be conducted by the NIH investigators with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations while minimizing the need for calcium supplements, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. If blood cCa levels are > 10.5 mg/dL, the NIH investigators can consider holding the CLTX-305 (encaleret) dose and restarting CLTX-305 (encaleret) at a lower dose after blood cCa has decreased to < 10 mg/dL. Oral calcium supplementation may be used as needed on top of a minimum dietary intake of at least 1000 mg daily. Participants previously treated with magnesium and potassium citrate supplements when not on CLTX-305 (encaleret) may not be restarted on treatment during Period 3, if the blood magnesium and urine citrate are within the normal ranges during Period 2.

For participants who require CLTX-305 (encaleret) doses < 10 mg BID to achieve the treatment goals described above, and the 5 mg tablets are not available, the 10 mg tablets may be split according to the related specifications indicated in the Pharmacy manual provided by the Sponsor in order to receive 5 mg BID dosing. Of note, no other dose strength besides the 10 mg tablet may be split. If the 10 mg tablet needs to be split, the participant should cut one 10 mg encaleret tablet each day and take half of the tablet in the morning and the other half of the split tablet in the evening, assuring that the participant receives a full 10 mg dose per day. Participant should follow the manufacturer instructions for use included with the pill cutter. In the event that half of the split 10 mg tablet is lost, the participant should cut a new tablet in half for the evening dose and discard the remaining half. The participant should start with a new 10 mg tablet the following morning.

Study visits include inpatient NIH Clinical Center visits every 8 weeks. PK assessments will be done at week 24 only; PD assessment will be done at weeks 8, 16 and 24 for evaluation of safety. AEs and concomitant medications will be recorded during these visits. Participants will be contacted by telephone per protocol at intervals during titration and maintenance, to

review the results of outpatient laboratory blood and urine assessments, confirm adequacy of the current regimen of study medication (including supplements), inquire about hypo/hypercalcemia symptoms, and assess for AEs. Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit.

For details on the visit schedule and assessments in Period 3 see Section 1.3.

The total blood volume collected over 24 weeks during Period 3 for each participant will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). This includes the 3 inpatient NIH visits.

If a participant reaches week 24 prior to the LTE being in place, the participant can discontinue CLTX-305 (encaleret) and restart calcitriol and/or calcium supplements until the LTE is implemented. Upon entry into the LTE, the participant will be reconsented to and may restart CLTX-305 (encaleret) at the previous therapeutic dose determined in Period 3.

8.2.4 Long-term Extension (LTE)

LTE will include continuation of outpatient treatment with CLTX-305 (encaleret) at the dose established in the maintenance phase of Period 3. CLTX-305 (encaleret) doses may be titrated as needed during LTE based on assessment of both blood and urine calcium results as described, with the goal maintaining optimal CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. Oral calcium supplementation may be used as needed on top of a minimum daily dietary intake of at least 1000 mg. Participants previously treated with magnesium and potassium citrate supplements when not on CLTX-305 (encaleret) may not be restarted on treatment during LTE, if the blood magnesium and urine citrate are within the normal ranges during Period 3.

Study visits include inpatient or outpatient NIH CC visits every 6 months starting at Month 6 and telephone contacts along with outpatient laboratory assessments every 6 months starting at Month 3. Laboratory assessments will be performed every 3 months for evaluation of efficacy and safety. Laboratory assessments at the NIH CC will be collected approximately 4-hours post-AM CLTX-305 (encaleret) dose. AEs and concomitant medications will be recorded during these visits. Participants will be contacted by telephone per protocol at intervals during LTE to review the results of outpatient laboratory blood and urine assessments, confirm adequacy of the current regimen of study medication (including supplements), inquire about hypo/hypercalcemia symptoms, and assess for AEs. The LTE is designed to obtain additional long-term safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first.

For details on the visit schedule and activities in LTE see Section 1.3.

The total blood volume collected over approximately 25 months during LTE for each participant will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). This includes the 4 inpatient or outpatient NIH CC visits.

Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit. If a participant ends involvement in the study before completing the Period 3 activities, steps outlined in Schedule of Activities will be followed, see Section 1.3 Table C.

At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments are to be completed (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) needs to be returned to the investigative site.

8.2.5 Follow-up and Early Termination

Participants will receive a follow-up call 30 ± 7 days after their last dose of the study medication for assessment of AEs.

If participants discontinue from taking part in the study or are terminated early from the study, they should have all safety assessments for Early Termination (ET) as listed in the Schedule of Activities (Section 1.3).

When a participant discontinues or withdraws from taking study medication, they will revert to their prior outpatient regimen of oral calcium and active Vitamin D to address their underlying ADH1 and maintain cCa blood concentrations as they return to their prior clinical care providers. Participants will be instructed to undergo outpatient laboratory testing of their blood calcium within 1–3 days of discontinuing study medication and to have those results sent to NIH investigators for review. Study investigator should contact the participants to review the blood calcium results and advise on optimizing their outpatient clinical management.

Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE Phase 3 LTE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 LTE study.

Transition to CLTX-305-302/CALIBRATE Phase 3 Long Term Extension

Participants from CLTX-305-201 who meet the study screening eligibility criteria of the CLTX-305-302/CALIBRATE Phase 3 study will enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE. If assessments for 25-OH Vitamin D, eGFR, 12-lead resting ECG, viral hepatits panel and HIV have been completed either at the NIH CC or via outpatient lab within the 3 months prior to transitioning into the CLTX-305-302/CALIBRATE LTE, they do not need to be repeated for eligibility purposes. Other assessments performed during the final CLTX-305-201 ET/EoT study visit will be acceptable for assessment of CLTX-305-302/CALIBRATE eligibility criteria. Blood β-HCG pregnancy test can be performed at the NIH CC on the day of transition to CLTX-305-

302/CALIBRATE Phase 3 LTE, and an aliquot will also be sent to the central lab for the CLTX-305-302/CALIBRATE Phase 3 LTE.

If a participant discontinued encaleret during the CLTX-305-201 LTE for family planning purposes, the participant may enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE once family planning is complete if he/she meets the study eligibility criteria per the CLTX-305-302/CALIBRATE protocol and the CLTX-305-302/CALIBRATE Encaleret Resumption Criteria. Participants will resume encaleret as described in the CLTX-305-302/CALIBRATE protocol.

Assessments in the CLTX-305-302/CALIBRATE Phase 3 LTE will be conducted approximately every 3 months as described in CLTX-305-302/CALIBRATE protocol's Schedule of Assessments. Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will receive encaleret for an additional period of approximately 48 months or until participant has access to commercial encaleret, or the Sponsor decides to end the study, whichever occurs first.

8.3 Efficacy Assessments

8.3.1 Pharmacokinetic and Pharmacodynamic Blood Sampling

All PK blood samples will be analyzed by the CRO contracted by the Sponsor. All PD blood samples will be managed by the NIH laboratory. Details for sample processing and handling are provided in the Study Procedures Manual. The times for collection of these samples are detailed in the Schedule of Activities in Section 1.3.1.

The efficacy assessments include evaluations of serum cCa concentrations over time and urinary excretion of calcium over time.

For a tabular listing of PK/PD and safety analytes in Blood and Urine, See Section 1.3.1.

8.3.2 Timed Interval and 24-hour urine

The times for collection of these samples are detailed in the Schedule of Activities in Section 1.3 and in a tabular listing of PK/PD and safety analytes in Blood and Urine Section 1.3.1.

8.3.3 Clinical Evaluations

Not applicable.

8.3.4 Samples for Genetic/Genomic Analysis

8.3.5 Description of the Scope of Genetic/Genomic Analysis

For participants with no prior documented activating mutation in the CaSR or an affected first-degree relative (with associated documentation collected and filed in participant's study binder), the diagnosis of ADH1 will be confirmed by genetic testing at screening.

If a participant's CaSR mutation has not been confirmed at Screening, blood samples will be collected for somatic analysis of the CaSR gene.

If no pathogenic variant in the CaSR is identified, additional testing for other genetic forms of hypoparathyroidism may be offered to the participant.

No additional genetic testing is required as part of this protocol.

8.3.6 Description of how Privacy and Confidentiality of Medical Information/Biological Specimens will be Maximized

CaSR gene mutation analyses will be conducted according to a somatic analysis assay performed at a certified genetics lab. Participant samples will be anonymized using a designated participant number and initials.

Since all participant data in this clinical trial will be anonymized using the same system, each participant's identity will remain anonymous in the clinical trial database.

The clinical trial database, which may be shared with appropriate regulatory agencies, in addition to access from the Sponsor and investigators, will contain clinical/demographic data on participant's age, ethnicity, sex, diagnosis, treatment, response to treatment, adverse events as per the standards of human clinical research, however, all the data will be anonymized without any link to individual identifying information.

8.3.7 Management of Results

The anonymized results of a participant's CaSR mutational analysis will be kept in a secured manner at the NIH. Participants who wish to receive the results of their CaSR gene mutation analysis may do so. This is a research-related test.

Genetic counseling will be made available. Most participants eligible to participate will already be aware of their CaSR mutational status and aware of the diagnosis of ADH1. Consent for mutational analysis including receipt of information on the results will take place under the auspices of an experimental clinical research study filed with the FDA under an Investigational New Drug submission.

If no pathogenic variant in the CaSR is identified, additional testing for other genetic forms of hypoparathyroidism may be offered to the participant.

8.3.8 Genetic counseling

For participants who have not already had confirmation of their specific genetic mutation and who therefore submit to genetic mutation analysis, discussion of the results will be conducted by the expert investigators at the NIH and may also be conducted in conjunction with professional genetic counseling by associated staff with appropriate expertise to provide participants with sufficient interpretive information.

8.4 Safety and Other Assessments

8.4.1 Physical Examinations

At the times detailed in the Schedule of Activities in Section 1.3, 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 as described in Section 8.5.1.

8.4.2 Vital Signs

Vital signs will be assessed in accordance to times and details indicated in the Schedule of Activities tables in Section 1.3. 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 as described in Section 8.5.1.

8.4.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the times detailed in the Schedule of Activities (Section 1.3). 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 participant. All laboratory tests (PD and safety) during the Dosing Periods 1 and 2 will be measured at the NIH Clinical Center.

Outpatient testing done in Period 1 on day 7–8 (~ 24–48 hours after expected discharge from the NIH clinical center) will ideally be collected at the NIH CC. If this is not practical, with the participant's permission, contact information for the participant will be provided to a sponsor-contracted healthcare service to schedule a mutually agreeable time for sample collection in the home. Blood samples collected will be evaluated for CLTX-305 (encaleret) concentrations as well as for blood creatinine, albumin, calcium, magnesium, phosphate, and PTH. This will allow both an evaluation of calcium homeostasis as well as a final PK parameter while CLTX-305 (encaleret) concentrations are washing-out after Period 1. Given that the half-life of CLTX-305 (encaleret) at steady state is ~ 10–14 hours, the PK sample will represent a timepoint between 40-70 hours after the last dose of CLTX-305 (encaleret) (administered in the evening of Day 5). A telephone contact will be conducted on day 9-11 or once the calcium results are available to be reviewed with investigative site staff.

Laboratory testing during outpatient Period 3 and LTE will include outpatient laboratory collection of blood and urine for calcium and calcium-related analytes including safety laboratory tests.

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 as described in Section 8.5.5.

8.4.4 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 as described in Section 8.5.5.

8.4.5 Dual-energy X-Ray Absorptiometry (DXA)

Bone densitometry of the spine, hip, distal radius, and total body will be performed by DXA at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during the LTE (see Schedule of Activities tables in Section 1.3). If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the DXA scan will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE.

Radiation exposure. This research study involves exposure to radiation from four DXA scans performed at the screening visit, Week 24 during Period 3, and Months 12 and 24 during the LTE. This radiation exposure is not necessary for medical care and is for research purposes only. The amount of radiation participants will receive in this study is well below the dose guidelines established by the NIH Radiation Safety Committee for child (less than 500 mrem per year) or adult (less than 5000 mrem per year) research participants. The effective dose that participants will receive from participation in this research study is less than four millirem. This protocol has been approved by the Radiation Safety Committee.

8.4.6 Renal Ultrasound

Renal ultrasound will be performed at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during LTE (see Schedule of Activities tables in Section 1.3). If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the renal ultrasound will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE.

8.5 Adverse Events and Serious Adverse Events

8.5.1 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)).

8.5.2 Definition of Serious Adverse Events (SAE)

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

- Results in death
- Is life threatening; i.e., in the opinion of the investigator, the AE places the study participant at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Results in study participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on 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.

8.5.3 Classification of an Adverse Event

8.5.3.1 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 participant's CRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a participant 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 participant.

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

8.5.3.2 Relationship to Study Intervention

The investigator must assess the relationship of the event to the study drug. The causal relationship of the AE is assessed using a binary system, and AEs are classified as either 'related' or 'unrelated' as defined below.

- **Related**: The available evidence suggests the adverse event is most likely due to the study drug. For example, a temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the study participant's clinical state, concurrent disease or concomitant therapies.
- **Not related**: The available evidence suggests the adverse event is most likely related to factors other than the administration of the study drug. Such other factors may include the underlying disease state, comorbidities, an intercurrent illness, concomitant medication(s) or procedures.
- The investigator may change the causality assessment at any time based on new accumulated information.
- An AE with causal relationship not initially determined will require follow-up to assign causality.

8.5.3.3 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 for the study intervention.

8.5.4 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.

8.5.5 Adverse Event Reporting

Any untoward event that is reported from the time that the study participant signs the ICF until 30 ± 7 days after the last dose of CLTX-305 (encaleret) 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 participant's CRF.

All AEs and SAEs reported by the participant (or participant's legal 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 participant (or participant's legal representative) occurring outside a defined study visit (from the time the participant signs the ICF to 30 ± 7 days after the last dose of CLTX-305 (encaleret) must be documented.

All AEs must be recorded on the appropriate AE reporting page of the participant's CRF whether or not they are considered causally related to the CLTX-305 (encaleret).

For every AE, the investigator must:

- Provide an assessment of the severity, causal relationship to CLTX-305 (encaleret), and seriousness of the event (i.e., whether it is a SAE)
- Document all actions taken with regard to CLTX-305 (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.

8.5.6 Serious Adverse Event Reporting

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor or its designated representative must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to the Sponsor/designee on the SAE Form. The Sponsor's Medical Monitor may also be notified by telephone.

In addition, SAEs that are assessed by the investigator as related to study drug(s) and occurring after 30 days post the last dose of CLTX-305 (encaleret) will also be reported to the Sponsor/designee within 24 hours of when the site becomes aware of the event.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center staff must transmit the SAE Form to the Sponsor/designee. Even if an initial report is made by telephone, the study center staff must still complete the SAE Form with all available details and send the form within 24 hours of knowledge of the event.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The investigator is expected to take all therapeutic measures necessary to treat and promote resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the participant's CRF. The study center staff must follow all SAEs until resolution or until the SAE is deemed stable. The Sponsor/designee may contact the study center to solicit additional information or follow-up on the event.

Email all relevant SAE or pregnancy report forms to the Sponsor/designee at the following email address:

Email for SAEs and pregnancy:
CLTX-305-201@prahs.com

Contact information for the Sponsor's Medical Monitor is as follows:

[redacted]
Email: [redacted]
Telephone: [redacted]
Calcilytix Therapeutics, Inc.
1800 Owens Street, Suite C-1200
San Francisco, CA 94158

Backup contact:

[redacted]
Email: [redacted]
Telephone: [redacted]
Calcilytix Therapeutics, Inc.
1800 Owens Street, Suite C-1200
San Francisco, CA 94158

All SAEs (except deaths due to progressive disease) will be reported to the NIDCR Office of the Clinical Director no later than 7 days after the PI first learns of the event.

8.5.7 Events of Special Interest

Hypocalcemia in ADH1

The main goal of CLTX-305 (encaleret) treatment in participants with ADH1 is to raise serum calcium levels. Hypocalcemia is not an expected side-effect of treatment with CLTX-305 (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 dose-finding with the CLTX-305 (encaleret) and potentially establishing clinical proof-of-concept. Under these circumstances there is a risk that participants could experience symptoms of hypocalcemia prior to achieving an effective dose of CLTX-305 (encaleret). In order to mitigate this risk, the study design emphasizes safety foremost. All changes to oral maintenance medications in conjunction with CLTX-305 (encaleret) dosing will be conducted with participants in residence at the NIH Clinical Center in the first two periods, with multiple daily measurements of blood calcium and close supervision by health professionals with experience caring for individuals with ADH1. 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.

Assessment of Blood Calcium Concentrations

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 available at the NIH Clinical Center investigative site and can be measured either in the event of severe hypocalcemia or if there is any question about the accuracy of the cCa measure. Collection of ionized calcium will occur at the discretion of the expert investigators based on the clinical scenario on a case-by-case basis.

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 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. 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 safety and proof-of-concept trial at the NIH is that the expert investigators have significant experience in managing these patients as well as specific

historical knowledge about the clinical course and management of many members of the expected cohort to be studied. 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, an initial and follow-up ECG as appropriate based on clinical assessment (bradycardia e.g.) and/or if cCa is < 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 below) for mild-moderate events. In the case on 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 below).

Addition of Oral Calcium Supplements and/or Calcitriol

Since all participants will be attempting to consume at least 1000 mg dietary calcium per day throughout the trial, additional supplemental oral calcium in the range of 1,000–2,000 mg additional supplement may be given as required with close follow-up of cCa. Transient requirements for calcium supplementation and/or 1-2 doses of calcitriol (at doses based on each participant's prior known sensitivity and dosing of outpatient calcitriol, if known, e.g., likely in the range of 0.5-2 mcg) resulting in stabilized calcium levels, need not interfere with per protocol dose escalation, particularly if required on Days 1 and 2 before CLTX-305 (encaleret) effective doses may have been achieved. More severe or prolonged hypocalcemia unresponsive to oral supplementation may require early termination from the study period at the judgement of the investigator. If calcium levels are not stable and if evidence of clinically significant hypocalcemia precludes further dosing in the study period, CLTX-305 (encaleret) dosing will be stopped and participants may be re-started on their prior outpatient regimen of oral calcium and calcitriol and discharged when stable, with close follow-up. Such participants may be eligible to return for either a repeat of the study period or to the next per protocol study period, at the discretion of the investigator and the Sponsor.

Intravenous Calcium supplementation:

In the event of severe hypocalcemia, the NIH Clinical Center has the facilities to conduct advanced supportive care including intravenous fluid replacement, supplemental oxygen, continuous ECG monitoring, and bedside ionized calcium monitoring if required. Intravenous calcium may be given as clinically indicated.

8.5.8 Reporting of Pregnancy

Study center personnel must report every pregnancy from the time study participant signs the ICF until 30 ± 7 days after the last dose of CLTX-305 (encaleret). Within 24 hours of

learning of the pregnancy, study center personnel must report the event to the Sponsor or its designated representative on the Clinical Trial Pregnancy Form, even if no AE has occurred.

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 participant is hospitalized for hemorrhage), a separate SAE Form must be completed (in addition to the Pregnancy Form) as described in Section 8.5.5 and Section 8.5.6, with the appropriate serious criterion (e.g., hospitalization) indicated.

In the event that a participant becomes pregnant, the investigator is required to contact the Sponsor Medical Monitor/designee within 24 hours of awareness.

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

If the partner of a male participant becomes pregnant after initiation of CLTX-305 (encaleret) and within 30 ± 7 days of the last dose, the study team will inform the Sponsor Medical Monitor/designee. If the partner agrees, the study team will amend the protocol to allow for follow-up of the pregnancy.

8.6 Unanticipated Problems

8.6.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** 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.

8.6.2 Unanticipated Problem Reporting

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

8.6.3 NIH Intramural IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NIH Intramural IRB.

9 STATISTICAL CONSIDERATIONS

All analysis details will be provided in a formal statistical analysis plan (SAP).

9.1 Statistical Hypothesis

All data will be descriptively analyzed with no hypothesis testing.

9.2 Sample Size Determination

The sample size of up to 8 participants in Period 1 (Cohort 1) and up to 10 additional participants in Period 2 (Cohort 2), is consistent with conventional first-in-human single and multiple ascending studies (SAD and MAD) that generally enroll between 8–10 participants per dose arm with escalation being based on safety and tolerability.

The sample size for the current study is not based on statistical testing of a formal powered hypothesis. The proposed clinical trial represents a re-purposing of CLTX-305 (encaleret), leveraging extensive exposure and safety data from the prior osteoporosis program, to conduct a modified single and multiple-ascending dose study in a new target population of patients with ADH1. However, a recent publication of a different experimental calcilytic agent, NPSP795 (Roberts 2019), reported preliminary evidence for a dose-response on iPTH in participants with ADH1 with a sample size of 5 study participants. The authors speculated that despite testing doses known to raise iPTH robustly in non-ADH1 study participants, larger doses would have been required to stimulate iPTH in ADH1 participants sufficiently to also see elevations in cCa. The current protocol is designed to explore a broad potential dose range for safety and tolerability, however, the proposed sample size of approximately 16 participants may be sufficient to confirm a definitive proof-of-concept on either iPTH and/or cCa if effective doses are achieved.

9.3 Populations for Analyses

Safety Population: All study participants who received at least one dose of study drug CLTX-305 (encaleret)

PK Population: All participants who received at least one dose of study drug CLTX-305 (encaleret) and who have sufficient PK samples drawn to enable the calculation of PK parameters for CLTX-305 (encaleret).

PD Population: All study participants with PD data.

9.4 Statistical Analyses

All analysis details will be provided in a formal statistical analysis plan (SAP).

9.5 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment.

9.6 Safety Analyses

Safety and tolerability parameters will be summarized using descriptive statistics, where appropriate. All safety data will be provided in data listings.

AEs will be coded using the MedDRA dictionary. The incidence of each treatment-emergent AE (TEAE) will be summarized by system organ class, preferred term and treatment assignment. Multiple AEs mapped to the same preferred term will be counted once per participant. Concomitant medications will be coded using the WHO Drug Dictionary with generic term and Anatomical Therapeutic Chemical (ATC) code and summarized by ATC code, WHO Drug generic name, and treatment. Reasons for early termination will be summarized by treatment group assignment. Safety laboratory findings, vital signs, and 12-lead ECGs will be summarized descriptively and listed by treatment assignment and visit. Values and changes from baseline at scheduled time points will be summarized. Laboratory data will be listed and values and changes from baseline at each visit will be summarized. An additional listing of treatment-emergent laboratory abnormalities will be provided.

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it was not present before the first dose of CLTX-305 (encaleret) or if it was present before the first dose of CLTX-305 (encaleret) but increased in severity during the treatment period. If more than 1 AE is reported before the first dose of CLTX-305 (encaleret) and is coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs that were also coded to that preferred term and that occurred during the period. An AE that occurs more than 30 ± 7 days after the last dose of CLTX-305 (encaleret) will not be counted as a TEAE.

9.7 Pharmacokinetic Analyses

PK parameters will be calculated for each participant and summarized by treatment. Only participants with sufficient data to calculate each PK parameter will be included in the summary of each PK endpoint.

9.8 Pharmacodynamic Analyses

PD parameters will be calculated for each participant and summarized by treatment. Only participants with sufficient data to calculate each PD parameter will be included in the analysis.

9.9 Interim Analysis

Due to the open-label study design and quantitative laboratory analytes used to derive PK and PD endpoints, both the Sponsor and NIH investigator will be able to conduct joint periodic data reviews on an ongoing basis throughout the study.

Review of safety, tolerability, and effects on iPTH and cCa will be conducted on Period 1 single-dose and multiple-dose (QD and BID) responses prior to commencement of Period 2.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 Informed Consent Process

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administrating study intervention. Study ICF will be submitted with this protocol as appropriate.

The informed consent document will be provided as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomfort 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 any research activities taking place.

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 participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/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 the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required.

Note: When required, the witness signature will be obtained similarly as described for the investigator and participant below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below.

For electronic consent:

The study team will confirm with the subject 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, subjects/LARs and investigators will view the same approved consent document simultaneously in their respective locations. The identity of the subject will be determined by verifying a

government issued identification card via the telehealth platform, prior to obtaining the signature.

iMED consent 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.

If a participant reaches week 24 of Period 3 prior to the LTE being in place, upon entry into the LTE, the participant will be reconsented to and may restart CLTX-305 (encaleret) at the previous therapeutic dose determined in Period 3.

10.1.1 Consent/Assent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. Participants who are 16 or 17 at the time of enrollment will use the same consent form and be asked to sign in the assent section of the signature page, in addition to having a parent/Legally Authorized Representative (LAR) sign. If a participant becomes an adult (18 years of age) while participating in the study, the participant will be re-consented at their next NIH CC visit.

If a participant does not read and write in English, the short-form ICF in the participant's preferred language will be utilized per NIH policies.

The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source

document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this 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, the Investigational New Drug (IND) the Sponsor and regulatory authorities as appropriate. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and the Sponsor (as appropriate) 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.

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/or Food and Drug Administration (FDA).

10.3 Confidentiality and Privacy

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

Participant confidentiality and privacy is strictly held in trust by the participating investigators, study staff, and sponsor/and designee. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All participants' records will only be identified by participant initials and participant number. Participants' names are not to be transmitted to the Sponsor. The investigator will keep a master participant list on which the participant number and the full name, address, and telephone number of each participant are listed. The study participant'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. The study authorized representatives of the Sponsor, representatives of the Institutional Review Board (IRB), 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 NIH Clinical Center will permit access to such records.

In addition to periodic monitoring occurring within the system by the Sponsor personnel and/or authorized Sponsor representatives, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study center and answered electronically by NIH Clinical Center. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the investigator's approval of all changes performed on his or her participants' data, will be collected.

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 participant 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. All study records must be available for inspection by the Sponsor, its authorized representatives, and regulatory officials.

The investigator must retain a copy of all records that support CRFs for this study (e.g., ICFs, clinical laboratory reports, source documents, CLTX-305 (encaleret) 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 or otherwise notified in writing by the Sponsor.

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. The Sponsor must be notified in writing of the name and address of the new custodian before such transfer is made.

No study records shall be destroyed without notifying the Sponsor and giving the Sponsor the opportunity to arrange long-term storage for such study records or to authorize in writing the destruction of records after the required retention period.

10.4 Future Use of Stored Specimens and Data

A unique participant code, as opposed to personal identifiers, will be used on the CRFs, and in the study database. A participant 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 participant code log that is maintained in secure research files at the NIH. Samples received for PK analysis by Calcilytix/or designee from participants consented to this protocol, may be destroyed or unused samples sent back to the NIH for additional research purposes. 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 ADH1, its complications and other conditions for which individuals with ADH1 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.

10.5 Safety Oversight

Safety monitoring for this study will be the responsibility of the investigator along with the NIDCR Clinical Director and the Calcilytix (the Sponsor) Medical Monitor with support from the Sponsor's designee (contract-research organization (CRO) Medical Monitor and safety/pharmacovigilance groups). Serious adverse events will be reported directly to the Sponsor/designee (CRO) and reviewed by the Calcilytix Medical Monitor.

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. The investigator will review aggregate data reports quarterly to review enrollment progress and AEs. Trends will be discussed with the NIH and Calcilytix study teams to ensure participant safety; study compliance and recruitment goals are met.

This study will have a Data and Safety Monitoring Committee (DSMC), that is monitored by the NIDCR Division of Intramural Research. The DSMC will operate in accordance with the approved charter.

Serious adverse event monitoring will be supported by the Sponsor's designee (CRO safety and pharmacovigilance group), the Calcilytix Medical Monitor and Calcilytix/designee site study monitor. The investigator will review the SAE report, request additional information about the event if necessary and provide a medical monitor assessment within 2 business days of receipt of the SAE report. The investigator and the Sponsor/designee Medical Monitor may discuss specific events or trends if noted. The investigator will determine the appropriate clinical action for the participant.

Because the study is an open-label, dose finding, proof-of-concept trial, data review will be performed on an ongoing basis as each participant proceeds throughout all Periods of the study with respect to identifying individualized effective doses of CLTX-305 (encaleret). Dosing decisions based on blood corrected calcium concentrations will be the responsibility of the NIH investigators in consultation with the Sponsor on an ongoing basis guided by the dosing algorithm described in the protocol. The Sponsor and NIH investigators will conduct a review of available data from Cohort 1 once at least 5 participants have completed Period 1 and as required thereafter, prior to opening enrolment of Cohort 2. These reviews will be documented and will include determinations of accumulated risk/benefit, tolerability and efficacy on normalizing blood corrected calcium concentrations as they inform potential starting doses for participants in Cohort 2 entering Period 2.

Additional details of the process and procedures for safety monitoring will be documented in the Safety Monitoring Plan prepared in collaboration with the Sponsor's designated CRO.

10.6 Clinical Monitoring

Before the first participant is dosed in the study, the Sponsor/designee (CRO) will meet with the investigator and the investigator's staff to review the procedures for conducting the study and to train the staff on recording the data on the eCRF. The Sponsor/designee (CRO) will routinely monitor the progress of the study by conducting on-site or virtual/remote visits thereafter. The Sponsor/designee (CRO) 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 Sponsor/designee (CRO) 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 Sponsor/designee (CRO) via the system, providing missing or corrected data, approving all changes performed on the data, and endorsing the participants data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and a password that together will represent a traditional handwritten signature.

Additional details of the process and procedures for Clinical study research site monitoring will be documented in the Clinical Monitoring Plan prepared in collaboration with the Sponsor's designated CRO.

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, and data are generated, and biological specimens are

collected, documented (recorded), and reported in compliance with the protocol, International Council on 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.

The Sponsor/designee will conduct site audits as stipulated in study-related plan(s). The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

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 serial test worksheets will be provided for use as source document worksheets for recording data for each participant 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 Medidata RAVE, a 21 CFR Part 11-compliant data capture system provided by the CRO. 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 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 on 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, or as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

10.8.3 LTE Electronic Data Capture

For administrative purposes, LTE data for participants may be housed in the eCRF for CLTX-305-201 and in the eCRF for CLTX-305-302/CALIBRATE. When the NIH site is activated in CLTX-305-302/CALIBRATE, the database for CLTX-305-201 will be cleaned and closed. LTE participants will be able to consent to the LTE portion of the CLTX-305-302/CALIBRATE study for the purpose of data capture to support the LTE summary of the CLTX-305-201 CSR. LTE data captured in CLTX-305-201 and CLTX-305-302/CALIBRATE for these participants will be summarized in the CSR for CLTX-305-201. The CSR for CLTX-305-302/CALIBRATE will not include data from the subjects originating from CLTX-305-201.

10.9 Protocol Deviations

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801. Deviations must be addressed in study source documents and reported to the Sponsor. The investigator is responsible for knowing and adhering to the reviewing IRB requirements. Additional details on the process and procedures of identifying and managing protocol deviations will be available in the Sponsor/designee (CRO) data monitoring plan.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any change, 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 participant, 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:

This study is sponsored by Calcilytix Therapeutic Inc., and publications of data from this study will be in alignment with the NIH and Calcilytix Therapeutics Inc. Cooperative Research and Development Agreement (CRADA).

National Institutes of Health (NIH) Public Access Policy ensures that the public has access to the published results. NIH funded research requires that NIH scientists 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 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. Results from this trial will be made available 12 months after the primary study completion date. Calcilytix will consider requests from qualified researchers for access to Calcilytix clinical Data.

10.10.2 Genomic Data Sharing Plan

Not applicable. See Section 10.3 (Confidentiality and Privacy)

10.10.3 Agreement Type

The NIDCR investigator(s) and Calcilytix will sign the protocol and Cooperative Research and Development Agreement, (CRADA) to confirm agreement. The investigator(s) will not implement any amendment (deviation or changes of the protocol) without agreement by the Calcilytix (the Sponsor) and IRB approval, except where necessary to eliminate immediate hazard(s) to study participants, or when change(s) involve only logistical or administrative aspects of the study. Any logistical or administrative changes will be done in agreement with Calcilytix and documented within 30 days on implementation.

10.11 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 at sponsor/and designee in conjunction with the NIH 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.

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Appendix 1 Summary of Changes

SUMMARY OF CHANGES

Section No./Title	Changes	Rationale
Original Protocol Vs. Amendment 1		
Cover page	1. Update cover page and Protocol version. 2. Added IND number. 3. Changes in Key Sponsor Contact information 4. Updated list of abbreviation.	Administrative change
1.1 Synopsis	Updated for consistency with 3 Objectives and Endpoints	Administrative change and/or typographical
1.2 Schema; 1.3/Tables A & B: SOAs	Change footnote numbering to reflect update tables.	Administrative change and/or typographical
1.3 Tables A & B: SOAs; Schema	"Baseline" replaced with "Admission" Arrow moved to between Period 1 Period 2 Boxes	Changes for clarification only
1.3 Tables A, B and C: SOAs	Update footnotes and tables: 1. Table: A, B, C: Added treatment discontinuation rules. 2. Table A: Added local labs and PK sample collection on Day 7 or 8 after discharge from the NIH CC in Period 1. 3. Table A: Added telephone contact during Day 9 to 11 to review labs results with PI and to review AEs/Con meds. 30 ± 7 days after discharge. 4. Tables A & B: Added DXA scan. 5. Table: A, B &, C: added reference to PK/PD blood sample collection Tables in footnotes. 6. Tables A & B: Added clarification related to the frequency for height measurement. 7. Tables A, B & C: Added clarification about vital signs assessment.	Changes in response to Agency advice and for clarification

Section No./Title	Changes	Rationale
	8. Tables A, B, & C**:** footnote referring to table D, E and F: Changed 24-hour urine interval lab sample collection added Na and K.	
1.3.1 Table D, E & F	1. Table D: Removed PK Samples timepoint at 17hrs. 2. Tables D, E & F: Removed parenthesis related to calculations related information for Timed Interval Urine collection and 24-hour urine. 3. Tables D, E & F: Added Na, and K to 24-hour urine collection list of tests. 4. Table D and E: Timed Interval Urine collection: Added -15 min. timepoint and related footnotes. Modified 9hrs. to 8hrs. timepoints 5. Table F: Addition of -15 min. timepoint sample collection for PM dose for: PK, Intact PTH, 1, 25-(OH)2 Vitamin D, cAMP and Ca, P, Mg, Cr, albumin.	Reassessment and revision of timepoints and testing
1.3.1 Table G	Added new table for Research Sample collection & associated timepoint during Periods 1,2, and 3.	Additional sample collection for research testing
2.2.3 Background-Autosomal Dominant Hypocalcemia, Type 1	Refined the description of Hypercalciuria is in patients with ADH1.	Addition of language for clarification
5.1 Inclusion criteria	Added inclusion criteria 6 and 7: - Criteria 6: Instruction related to use of Thiazide - Criteria 7: Instruction related to use of CYP3A4 inhibitors	Changes in response to Agency advice
5.2 Exclusion criteria 3a	Outlined cholecalciferol or ergocalciferol supplementation for a blood 25-OH Vitamin D level < 25 ng/mL at the screening visit.	Addition of language for clarification

Section No./Title	Changes	Rationale
6.5 Concomitant Therapy	Added new text providing instructions and clarifications for concomitant medications use and/or discontinuation of thiazide and strong CYP3A4 inhibitors.	Change in response to Agency advice
7.1, 7.2 & 8.2.4 Participant Discontinuation/Withdrawal from the Study & Follow-up and Early Termination	For clarity, information related to participant discontinuation in the study were moved from Section 7.1 to Section 7.2. Added instructions regarding safety follow- up, resuming prior medication in case of discontinuation from CLTX-305 (encaleret), withdrawal or early termination from the study.	Change in response to Agency advice and clarification
8.2.1, 8.2.2, and 8.4.3 Periods 1 and 2; Cohorts 1 and 2 and, Clinical Laboratory Determinations	Added clarifying language to indicate that for participants with screening visit > 21 days before initiation of study drug, outpatient laboratory testing will be performed 10-14 days prior to admission for blood and urine chemistry. Added Day 7-8 post discharge laboratory testing to allow evaluation of calcium homeostasis as well as a final PK considering the half-life of CLTX-305 (encaleret) is about 10 to 14 hours to represent a timepoint between 40 to 70 hours after the last dose of CLTX-305 (encaleret) on the evening of Day 5. Added information to clarify how both pre-study calcemic status as well as changes associated with experimental interventions will be measured and calculated in accordance with the specification of the NIH Clinical Center laboratory	Change in response to Agency advice and additional testing measurement clarification
8.3.4.1 & 8.3.4.3 Description and Scope of Genetic Analysis & Management of Results	Clarified ADH1 genetic testing at screening. Added- If no pathogenic variant in the *CaSR* is identified, testing for other genetic forms of hypoparathyroidism may be offered to the participant.	Clarification and allowance of testing for other genetic forms of hypoparathyroidism

Section No./Title	Changes	Rationale
8.4.5 Dual Energy X-Ray Absorptiometry (DXA)	Added DXA at Screening for bone mineral density measurement.	Change in response to Agency advice
8.5.7 Events of Special Interest	Added description of hypocalcemia due to ADH1 and algorithm to discriminate normal versus abnormal blood calcium levels. Clinical symptoms, evaluation and treatment hypocalcemia are added.	Change in response to Agency advice
8.5.8 Reporting of pregnancy	Added information related partner pregnancy reporting.	Addition of language for clarification
10.4 Future use of Stored Specimens and Data	Added clarification regarding sample storage.	Addition of language for clarification
10.10.1 Human Data Sharing Plan	Added clarification regarding availability of results.	Addition of language for clarification
Section No./Title	**Amendment 2- Date 10 June 2020** (Pre-IRB review changes)	**Rationale**
5.3 Inclusion of vulnerable participants	Added rational for including 16- and 17-years old participants and not younger due to their capacity to provide assent.	Addition of language for clarification
5.6.2 Compensation	Details added related to NIH Policy, amount, mode of payment, and travel arrangement.	Addition of information
10.1.1 Consent/Assent Procedures and Documentation	Added information related to use of the same consent and signature process for 16- and 17-years old participants and parent/Legally Authorized Representative (LAR).	Addition of information for clarification
Section No./Title	**Amendment 3: Date 24 June 2020** (response to IRB review)	**Rationale**
8 Study Assessments and Procedures- subsections: 8.1, 8.2.1, 8.2.2 and 8.2.3	Added details related to amount of blood volume to be collected during screening, Period 1, Period 2, and Period 3.	Change in response to IRB feedback

Section No./Title	Changes	Rationale
10.1.1 Consent/Assent Procedures and Documentation	Added re-consenting process language for participants who reach 18 years of age during participation in the study.	Change in response to IRB feedback
Section No./Title	**Amendment 4: Date 24 August 2020** (response to DSMC review)	**Rationale**
Sponsor Signature Page	Incorporated as part of the document	Administrative change
1.2 Schema: Periods 1,2, 3 and 3	Modified to clarify Period 1, Day 1 and Day 2 doses could be up to 90 mg QD and up to 180 mg QD, respectively.	Modified for Clarification
1.3 Schedule of Assessment –Tables A, B, C- Footnotes Section 8.2.1 Period 1 (single Ascending Dose Escalation and BID PK/PD profile)-Cohort 1	1. Table A, B, and C- clarified safety lab tests 2. Table A, and C, section 8.2.1, and 8.4.3- list outpatient laboratory testing specifically. 3. Table A- clarified outpatient lab testing on day -14 to -10 and removed PTH. 4. Table A- clarified on Days 1, 2, 3 participants will receive BID doses based on Days 1 -3.	Modified for Clarification
1.3.1 Pharmacokinetic, Pharmacodynamic, and Urine Sampling Times, Table F	Timepoints modified: - Eliminated all -15 min TRT PM blood draw. - Modified timed interval Urine collections to 4-8 h, and 8-13.	Clarifications in consideration to IP dosing time
4 Study Design, 4.1 Overall Design- Figure A and B	Modified to indicate in Period 1, Days 2 and 3 up to 90 mg QD, and 180 mg QD dose of the CLTX-305 (encaleret) may be administered.	Change per NIDCR DSMC recommendation
5 Study population 5.2 Exclusion Criteria 7, subsection a	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.	Change per NIDCR DSMC recommendation
6.1.2.1, Period 1 (Single Ascending Dose Escalation and BID PK/PD profile) Cohort 1	Clarification added to indicate dose adjustment increasing CLTX-305 (encaleret)to a maximum of 180 mg on Day 3 may occur.	Change per NIDCR DSMC recommendation

Section No./Title	Changes	Rationale
6.1.2.4 Dose Limiting Toxicity 6.1.2.5 Dose Modification	Change the cCA threshold to 10 to 10.5 mg/dL in Periods 1 and 2 and consideration related to dose escalation and/or adjustment accordingly.	Change per NIDCR DSMC recommendation
8 Treatment Period Figure D	Modified Figure D and change the cCA from 11 mg/dL to 10.5 mg/dL and consideration related to dose escalation by 30 mg.	Change per NIDCR DSMC recommendation
8.2.1- Period 1 (Single Ascending Dose Escalation and BID PK/PD profile) – Cohort 1	Clarified that on Days 1, 2, and 3 (QD dose Escalations: The starting dose on Day 1 is 30 mg.	Addition of language for clarification
8.2.1 - Figure D - Dosing Guidance Algorithm for Period 1	Dosing Algorithm modified in consideration to changes in cCa threshold and dose adjustment.	Change per NIDCR DSMC recommendation
10.5 Safety Oversight	Include the language outlining involvement of DSMC that is established by NIDCR.	Addition of language for clarification
8.4.3 Clinical Laboratory determination	For outpatient labs, added creatinine and albumin	Modification for clarification
Section No./Title	**Amendment 5: Date 01 February 2021**	**Rationale**
Key Sponsor Contact: 8.5.9 Serious Adverse Event Reporting	- New Contact and related information added: [redacted] - Updated: Phone number for second contact	- Contact information added, and updated
Section 1.1 – Synopsis-Objectives and Endpoints Section 3- Objectives and Endpoints	- Moved evaluation of safety and tolerability for Period 3 from Secondary to the Primary Objectives and Endpoint. - Added Periods 2 and 3 to the first Primary safety Endpoint - Added 24-hour urinary calcium excretion to primary endpoint for Period 3 - Added: Renal function (eGFR) to secondary endpoint for Periods 1, 2 and 3	- Clarification added, and modified the order of the Objectives and Endpoints - Added renal function measure to secondary endpoint for all study Periods

Section No./Title	Changes	Rationale
1.2 – Schema-Schematic for Periods 1, 2, and 3 4.1 Overall Design Figures A, B, and C 8.2.2 – Period 2 (BID) – Cohorts 1 and 2	- Time interval between Period 1 and Period 2 for participants in Cohort 1 changed from 8 to 12 to ≥ 8 to 16 weeks. - Period 3 and figure: added asterisk to indicate PK at week 24	- Clarification and update on minimum and maximum time intervals between Periods 1 and 2 - Clarification of study visit week for PK measurement
1.3 – Schedule of Activities Table B- Period 2 8.1 Screening Procedures 8.2.2 – Period 2 (BID Dosing) – Cohorts 1 and 2 Section 8.2.2 – Figure E Dosing Guidance Algorithm for Period 2-Cohort 1	- Table B- Added ECG measurement to Day 1, Day 3 and Day 5 - Table B- Footnote 1- Added clarification for screening visit that may include inpatient overnight stay as well as option for additional overnight stay at NIH CC if participant is to start the study midweek. - Table B- Footnote 4- added iron panel to be done if clinically indicated - Footnote 10-assessments apply to Cohort 1 and 2 and added, Hematology (RBC, Hgb, Hct, RBC indices, WBC) - Added clarification to stop taking calcitriol on Day -1 until admitted - Added instruction for discontinuation of magnesium, potassium citrate on Day 1 and calcium based on estimate dietary calcium intake targeting a combined calcium intake of > 1000 mg/day - Update the limit of cCa from >10.5 to >10.0 for dose reduction - Update total blood volumes to be collected - Figure E – outlined normal rage to 7.5 to 10 mg/dL, and changed cCa from >10.5 to >10.0 for dose reduction	- Additional ECG for QTC - - analysis - Allowing flexibility in consideration to screening assessments and COVID-19 pandemic travel limitations - Added as additional safety measure and clarification - Added supplement intake management on Day 1 - Clarification, and correction of the cCa for dose reduction in text and related figure
1.3- Schedule of Activities- Table C- Period 3	- Added ECG measures during Period 3 NIH CC visits. - Table column and Footnote 2, 5 and 14 updated: Follow-up (FU) days for outpatient labs after last dose of CLTX-305 (encaleret)	- Additional ECG measures for QTC analysis - Harmonization with section 8.4.4 of the protocol

Section No./Title	Changes	Rationale
	- changed FU days to 2 to 3 ± 2 days - added FU days of 7 ± 2 days - added Na, K, Cl, Ca, Mg, PO_4, Cr, pH and 24-hour urine assessments to the 30 ± 7 days safety FU - Footnote 13: Clarification that related assessment to be done at the NIH CC	- Addition of laboratory safety assessment and clarification related to assessments during the NIH CC visit
2.3. Risk/Benefit Assessment 2.3.1 Known Potential Risks 2.3.2 Known Potential Benefits	- Added preclinical metabolism and excretion information and citation related to eGFR threshold change consideration - Citation- Reference added to Section 11 - Addition of risk for venous thrombosis procedure - Addition of blood collection method: central catheter	- Providing rational in support of change in exclusion criteria related to eGFR - Addition of option for blood collection
1.3.1 Pharmacokinetic, Pharmacodynamic, and Urine Sampling Times	- Added tables to this section to modify timepoints and assessments– These changes are for Period 2 and 3	- Changes in consideration to amount of blood volume collected
5.1 Inclusion Criteria 8.2.2 Period 2 (BID Dosing) – Cohorts 1 and 2 8.2.3 Period 3 (Cohort 1 and Cohort 2) – Outpatient Dosing	- New criteria # 8- instruction for discontinuation of magnesium, potassium citrate on Day 1 and calcium based on estimate dietary calcium intake targeting a combined calcium intake of > 1000 mg/day during and Period 2 and possible discontinuation of these supplement during Period 3 if blood Mg and urine citrate are within the normal range during previous Periods. - Updated Total volume of blood collected during Period 2	- New inclusion criteria - To collect safety lab assessments and 24-hour urine information - Updated after recalculation of total blood volume collection
5.2 Exclusion Criteria 4, 6, 11 and 16	- Criteria # 4 – Hemoglobin (Hgb) criteria for Male and Female included in for the study - Criteria # 6 – Added information related to rationale for eGFR threshold change. Citation- Reference added to section 11. Estimated glomerular filtration rate (eGFR) < 25 mL/minute/1.73 m^2. - Criteria # 11 – Condoms are not required if the participant has a female partner who is not of child-bearing potential.	- Hemoglobin criteria 4 and 16 related to participations' safety - Expanded threshold for eGFR in the related exclusion criteria and added rationale

Section No./Title	Changes	Rationale
	- Criteria # 16 – exclusion of participants who donate blood during the study	for this change in Risk/Benefit section - Revised to further clarify requirements for contraception
4.1 Overall Study Design 9.2 Sample size	Change the maximum number of participants in Period 2 from up to 8 additional participants to up to 10 participants	Increase the maximum number of participants in Period 2
6.1.7 Dose Modifications	Added guidance language for dose interruption and dose resumption	Information added related to dose interruption and continuation
8.4.3 Clinical Laboratory Determinations	Information added on reporting of laboratory AEs resulting in clinical intervention	Clarification related to reporting laboratory AEs
8.4.4 Electrocardiograms	added additional ECG measurement during Period 2	Added additional ECG measures for safety
10.6 Clinical Monitoring 10.8.1 Data Collection and Management Responsibilities	Option for virtual/remote monitoring visits added	Flexibility for onsite or virtual study monitoring visits in consideration to COVID-19 pandemic limitations
Section No./Title	**Amendment 6: Date 03 June 2021**	**Rationale**
All sections of the protocol	Replaced: references of study subjects to study participants throughout the documents	General Administrative change: Consistency of terms used throughout the protocol
All sections of the protocol	Replaced: CLTX-305 with CLTX-305 (encaleret)	General Administrative change: Consistency of terms used throughout the protocol
Protocol Cover page	Calcilytix address has changed, new address is inserted as: 1800 Owens Street, Suite C-1200 San Francisco, CA 94158	Updated- Sponsor change of address
Protocol Cover page The Sponsor Signature page	Contact Information for the new Sponsor [redacted] added:	Updated pertinent sections of the protocol to reflect name and

Section No./Title	Changes	Rationale
8 Study assessment and procedure 8.5 Adverse Events and Serious Adverse Events	[redacted] Telephone: [redacted] Calcilytix Therapeutics, Inc. 1800 Owens Street, Suite C-1200 San Francisco, CA 94158	contact information for the [redacted]
1 Protocol Summary 1.1 Protocol Summary Synopsis 3 Objectives and Endpoints	Primary Objective added (new texts): LTE: - Evaluate the longer-term (25 months or about 2 years) safety and tolerability of CLTX-305 (encaleret) Primary Endpoint for Period 3 reworded to: - Albumin-corrected blood calcium concentrations (cCa) and 24-hr urinary calcium excretion after treatment with CLTX-305 (encaleret) for 25 weeks Primary Endpoint added: LTE: - Adverse events (AEs), clinical safety laboratory tests, vital signs Secondary Objective added: Periods 1,2, and 3: - Evaluate the PD effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP) LTE: - Obtain long-term data on efficacy (durability) of CLTX-305 (encaleret) on blood calcium concentrations - Evaluate the long-term PD effects of CLTX-305 (encaleret) on associated measures of mineral homeostasis	For addition of the LTE to the protocol to support participants' continuation of dosing with CLTX-305 (encaleret) based on data to date and avoid interruption of IP if participants are benefiting from taking CLTX-305 (encaleret) and if elect to stay on the study. Added- Long-term safety and efficacy data will be collected during the LTE. Added- Related primary and secondary objective and endpoint assessments are outlined.

Section No./Title	Changes	Rationale
	including iPTH, 1,25-$(OH)_2$ Vitamin D levels and urinary calcium excretion - Evaluate the long-term effects of CLTX-305 (encaleret) on bone turnover markers including C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP) Secondary Endpoints updated: - Secondary Endpoints rearranged to clarify that PK assessments are only for Periods 1, 2, and 3, and PD assessments are for Periods 1, 2, 3, and LTE [redacted]	

Section No./Title	Changes	Rationale
1 Protocol Summary 1.1 Synopsis- Study duration and Participant Duration	Changed: Total duration of the study from approximately 24 months to approximately 41 months Added: Participants that continue to meet study eligibility criteria after Period 3 may continue in the Long-term Extension (LTE) for approximately 25 additional months.	Added total duration of study and duration of participants involvement in the study related to the addition of the LTE to the protocol
1 Protocol Summary 1.2 Schema 4.1 Overall Design Figure C	Period 3 schema correction- removed asterisk at 24-hour urine and week 24 (present in Amend. 5) as 24-hour urines are collected at all visits noted in schema Added the schema for LTE	Correction for Period 3 schema to align 24-hour urine collection at all visits noted. Addition of the LTE to the list of schemata
1 Protocol Summary 1.3 Table C	Added DXA scan for Week 24 NIH CC visit. Included the definition to the list of abbreviation under the table Table C: Added missing definition for C-telopeptide (CTx) and procollagen type 1 N-propeptide (P1NP) in the list of abbreviation under the table. Added telephone contact (NIH PI/Study Staff) under the FU outpatient labs 7±2 days column and associated Footnote 2: follow-up visits and instructions for testing changed added for participants who opt to leave the study after Period 3 and not continue participate in the LTE portion of the study. Table C Footnote 3: added unscheduled visits for laboratory evaluation following dose adjustment Table C Footnote 14: added 24-hr urine to be collected 30 days after CLTX-305 (encaleret) withdrawal if ET prior to Period 3 completion or chose not to enter LTE Table C footnote 15: Week 24 study drug dispensing is only for participants who continue into the LTE; If a participant is	Added DXA to the list of assessments to be done at week 24, for continued safety monitoring. Added FU telephone contact and safety labs on days 7± 2 after week 24 assessment visits and assessment for participants who opt not to continue in LTE after Period 3. Added steps in consideration to study drug dispensation for those participants who do not elect to go into LTE or unable to move to LTE immediately. Added laboratory evaluation following dose adjustment to the unscheduled visits

Section No./Title	Changes	Rationale
	not immediately continuing into the LTE, no drug will be dispensed.	
1.3 Table D	Added Schedule of Activities (SOA) for LTE; relabeled previous tables D1 thru G to E thru L	Added SOA for addition of the LTE to the protocol and relabeled other tables to provide further clarity
1 Protocol Summary 1.3.1 Pharmacokinetic and Pharmacodynamic -Table E	Footnote number 1: removed superscript 1 corresponding to table footnote 1, in the row for Timed Interval Urine Collection,	Correction
2 Introduction- 2.1 Study Rationale	Added rationale for Periods 1, 2, 3 in this section in addition to the information in section 4.2 Added rationale for the LTE	Addition of rationale for the Periods 1 through 3 in this pertinent section Added the rationale for addition of LTE to the protocol
2 Introduction 2.2.1 Pharmacokinetics and Product Metabolism	Added information on CLTX-305 (encaleret) dosing tablets: The 10 and 30 mg dosage strengths are round tablet presentations; the 60 mg dosage strength can be round or a modified oval tablet presentation. Updated information related to CLTX-305 (encaleret) half-life to provide clarity: The elimination half-life (t1/2) is approximately 11-14 hours at steady state (14 days).	Updated information to provide clarity
4 Study Design 4.1 Overall Design	Added the following language as last sentence to Period 3: Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit. Added the following language to include LTE: It will consist of two inpatient periods of dose initiation, escalation and steady-state adjustment (Periods 1 and 2), an	Clarification regarding participant status if participant elects not to participate in LTE Clarification, and addition of language/instructions related to the LTE in the protocol

Section No./Title	Changes	Rationale
	outpatient dose stabilization and maintenance period including NIH clinical visits (Period 3), and a Long-term Extension (LTE). The LTE is designed to obtain additional safety data and evaluate durability of efficacy for CLTX-305 (encaleret). The LTE also allows for continued treatment of enrolled participants with CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first. During the initial outpatient period (Period 3), participants will undergo additional individualized dose titration as necessary in response to safety data and the results of key efficacy measures. Participants who complete Period 3 (up to Week 24) and who elect to continue in the LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first.	
4 Study Design 4.1 Overall Design, Figure A and Figure D	Figure A: added LTE after Period 3 Figure D: Added a separate schema for the LTE Updated Period 2 dosing as follows: The initial dose, dose level 1 (DL1) will be administered for approximately 2 days (48 hours) with cCa monitoring. Participants will undergo CLTX-305 (encaleret) dose up- or down-titration depending on cCa levels, with a potential increase in dose if cCa remains below the lower limit of	For addition of the LTE to the protocol and to the Overall Study Design Schema and a separate schema for LTE. Clarification to Period 2 CLTX-305 (encaleret) dosing. Clarification of calcium supplementation in Period 3

Section No./Title	Changes	Rationale
	normal and potential decrease in dose if cCa is greater than or equal to the upper limit of normal. Period 3 language on oral calcium supplements updated: Participants may receive oral calcium supplements as directed by the investigative site if they are not able to achieve a minimum of 1000 mg per day of dietary calcium intake. Added the following language as last sentence for Period 3: Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit. Added Long-term Extension (LTE) description related to dose determination, instructions related to the supplement intake, and end of LTE planning if prescription encaleret is not available is added as two separate paragraphs at the end of this section	Clarification regarding participant status if participant elects not to participate in LTE
4 Study Design 4.3 Justification for Dose	Language related to the LTE is added as the last two paragraphs in this section	For addition of the LTE to the protocol
5 Study Population 5.2 Exclusion Criteria	Exclusion criteria #11 updated from condum use until the end of Period 3 to the end of study participation	Updated to account for continued condum use if participating in LTE
5 Study Population 5.6 Strategies for Recruitment and Retention	Updated information related to the number of participants identified to date (at the time of the protocol Amendment 6) Compensation update related to the LTE portion of the study	For addition of the LTE to the protocol

Section No./Title	Changes	Rationale
5 Study Population 5.6.2 Compensation	Updated reference to NIH policy from "NIH Policy OHSRP SOP13, Appendix A" to "NIH HRPP policy 3014-302 Subject Recruitment and Compensation"	Updated to reference current NIH HRPP policy
6 Study Intervention 6.1 Study Intervention(s) Administration	Added language related to LTE: During LTE participants who have completed Period 3 will continue taking CLTX-305 (encaleret) BID with water as an outpatient as described in Section 8.2.4	For addition of the LTE to the protocol
6 Study Intervention 6.1.2 Dosing and Administration 6.1.9 Drug administration	Updated the language in both sections to indicate the timing of the meals in association with the CLTX-305 (encaleret) administration is a recommendation rather than a requirement.	Updated to allow flexibility for mealtime in association with the CLTX-305 (encaleret) administration
6 Study Intervention 6.1.4 Period 2 (BID Dosing) – Cohorts 1 and 2 6.1.5 Period 3 (Cohort 1 and Cohort 2) – Outpatient Dosing 6.1.6 Long-term Extension (Cohort 1 and Cohort 2)- Outpatient Dosing	Updated Period 2 dosing as follows: In Period 2 all participants will initiate CLTX-305 (encaleret) BID dosing given within 30 minutes prior to breakfast and dinner on Days 1 and 2. cCa concentrations will be monitored frequently throughout Period 2, and CLTX-305 (encaleret) doses will be up- or down-titrated as needed to target normal cCa concentrations. Updated Period 3 Outpatient Dosing, last two sentence to: Titration will be conducted by the NIH investigators at scheduled or unscheduled telephone contact visits based on review of outpatient chemistry results for cCa, Mg, phosphorous at NIH CC visits (approximately every 8 weeks) based on assessment of both blood and urine calcium results as described, with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations, avoiding symptoms of hypo- or	Clarification on Period 2 and Period 3 CLTX-305 (encaleret) dosing and addition of the LTE to the protocol

Section No./Title	Changes	Rationale
	hypercalcemia, and minimizing the extent of hypercalciuria. Oral calcium supplementation may be used as needed on top of a minimum daily intake of at least 1000 mg. Added new paragraph with related LTE: In the Long-term Extension (LTE), participants will continue CLTX-305 (encaleret) per the dosing regimen established in the maintenance phase of Period 3. Telephone contacts along with outpatient laboratory assessments will be performed every 6 months starting at Month 3 with NIH CC visits occurring every 6 months starting at Month 6. CLTX-305 (encaleret) doses may be titrated as needed based on assessment of both blood and urine calcium results as described, with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting low normal cCa concentrations, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. Oral calcium supplementation may be used as needed on top of a minimum daily intake of at least 1000 mg.	
6 Study Intervention 6.1.7 Dose Limiting Toxicity	Updated to reflect Periods 1 and 2 CLTX-305 (encaleret) dose adjustments in the setting of cCa > 10 mg/dL: In Summary, participants who achieve a post-dose cCa > 10-10.5 mg/dL (in Period 1) and cCa > 10 mg/dL (in Period 2) during the dose escalation will not proceed to higher CLTX-305 (encaleret) doses. Participants with cCa values between 10-10.5 mg/dL during dose escalation in Period 1, will have their doses increased by 30 mg only. Participants who achieve cCa > 10-10.5 mg/dL in Period 1 and >10 mg/dL in Period 2	Updated to reflect CLTX-305 (encaleret) dose adjustments in the setting of increased cCa levels

Section No./Title	Changes	Rationale
	will have their dose maintained or reduced and undergo final frequent sampling as appropriate.	
8 Study Assessments and Procedures 8.2.2 Period 2 (BID Dosing) – Cohorts 1 and 2	Cohort 1 dosing language updated to reflect dosing experience from Periods 2 and 3: The first 7 participants who have completed CLTX-305-201 Period 2 and entered into Period 3 have had a wide range of CLTX-305 (encaleret) dose requirements from 10 mg once daily to 180 mg BID suggesting that encaleret dosing is highly individualized. As a result, all remaining participants in Period 2 will receive an initial encaleret 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The encaleret dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 10, 30, or 60 mg increments based on the available encaleret tablet strengths. A frequent sampling test day with additional serial blood and urine sampling to assess 24-hour PK/PD profiles will be performed on Day 5. If, at any time, the CLTX-305 (encaleret) dose is associated with a cCa > 10 mg/dL, then the dose should be reduced to a lower dose level. Clarified that Figure F is considered an example of how encaleret dosing may be adjusted. Cohort 2 dosing language updated to reflect dosing experience from Periods 2 and 3:	CLTX-305 (encaleret) dosing updated to reflect experience from participants who have completed Period 2 and continue into Period 3

Section No./Title	Changes	Rationale
	Cohort 2 will commence after Cohort 1 has completed Period 1 and the PD dose responses and safety have been reviewed. Participants will receive an initial encaleret 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The encaleret dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 10, 30, or 60 mg increments based on the available encaleret tablet strengths.	
8 Study Assessments and Procedures 8.2.3 Period 3 (Cohort 1 and Cohort 2) – Outpatient Dosing	Added phosphorus to the following sentence: Outpatient titration will be conducted by the NIH investigators with the goal of optimizing the CLTX-305 (encaleret) dose without calcitriol, targeting normal cCa and phosphorus concentrations while minimizing the need for calcium supplements, avoiding symptoms of hypo- or hypercalcemia, and minimizing the extent of hypercalciuria. Added sentence regarding CLTX-305 (encaleret) dosing consideration if blood cCa is > 10.5 mg/dL: If blood cCa levels are > 10.5 mg/dL, the NIH investigators can consider holding the CLTX-305 (encaleret) dose and restarting CLTX-305 (encaleret) at a lower dose after blood cCa has decreased to < 10 mg/dL. Added the following language to second paragraph, last sentence:	Adding phosphorus keeps sentence consistent with section 6.1.5 For addition of guidance on CLTX-305 (encaleret) dosing should blood cCa be > 10.5 mg/dL; Clarification regarding participant status if participant elects not to participate in LTE Addition of guidance if participants complete week 24 prior to LTE being in place

Section No./Title	Changes	Rationale
	Participants are considered to have completed the study once they complete 24 weeks of Period 3 and the safety follow-up visit. Added guidance language for participants should they reach week 24 prior to LTE being in place: If a participant reaches week 24 prior to the LTE being in place, the participant can discontinue CLTX-305 (encaleret) and restart calcitriol and/or calcium supplements until the LTE is implemented. Upon entry into the LTE, the participant will be reconsented to and may restart encaleret at the previous therapeutic dose determined in Period 3.	
8 Study Assessments and Procedures 8.2.4 Long-term Extension	Paragraph added related to language for the LTE: Describing visit timing, visit procedures	For addition of the LTE to the protocol and the related visit timing and procedures
8 Study Assessment and Procedures 8.3.1 Pharmacokinetic and Pharmacodynamic Blood Sampling	Clarifying text added to indicate PK analysis is done by the Sponsor contracted CRO/service provider	Clarification related to contracting responsibility and management for the CRO/service provider performing the PK analysis
8 Study Assessment and Procedures 8.4.5 Dual-energy X-Ray Absorptiometry (DXA) 8.4.6 Renal Ultrasound	Added/updated/corrected procedure for Period 3 and LTE via the first paragraph of this section Period 3: -Bone densitometry of the spine, hip, distal radius, and total body will be performed by DXA at Screening per the Schedule of Activities Section 1.3, at Week 24 during Period 3, at Month 12 during LTE, and the last NIH CC visit.	Added, updated and corrected this section to clarify and include Period 3 DXA and add this assessment to the LTE. Added a separate procedure section related to the Renal Ultrasound

Section No./Title	Changes	Rationale
	-Added the amount of effective dose as 4 millirem 8.4.6- added a paragraph related to the timing or Renal Ultrasound procedure and exposure information	
8 Study Assessment and Procedures 8.5.6 Serious Adverse Events 8.5.7 Events of Special Interest	Sentence added: All SAEs (except deaths due to progressive disease) will be reported to the NIDCR Office of the Clinical Director no later than 7 days after the PI first learns of the event. In "Clinical Evaluation and Treatment of Hypocalcemia", corrected "EKG" to "ECG"	Added NIH process requirement Missed correction in previous revision
8 Study Assessment and Procedures 8.6.2 Unanticipated Problem Reporting (UPs)	Added 'the Sponsor' to the end of the first paragraph for reporting of (UPs)- missed during the previous protocol revisions	Clarification- Adding Sponsor to receive reports related to UPs as the IND holder accountable for FDA reporting as required and applicable
9 Statistical Considerations 9.6 Safety Analyses	Corrected last sentence to: An AE that occurs more than 30 ± 7 days after the last dose of CLTX-305 (encaleret) will not be counted as a TEAE.	Missed correction in previous revision
10 Regulatory and Operational Considerations	Added clarifying language for reporting to the [redacted] Clarifying Calcilytix's responsibilities and regulatory accountabilities as the Sponsor.	Clarifying roles within the Sponsor whom to receive report and responsible and accountable for on the Sponsor side for the study

Section No./Title	Changes	Rationale
10.1 Informed Consent Process	Added guidance language for informed consent process should participant reach week 24 prior to LTE being in place: If a participant reaches week 24 of Period 3 prior to the LTE being in place, upon entry into the LTE, the participant will be reconsented to and may restart CLTX-305 (encaleret) at the previous therapeutic dose determined in Period 3.	Addition of consenting guidance if participants complete week 24 prior to LTE being in place
Section No./Title	**Amendment 7: Date 12 November 2021**	**Rationale**
SPONSOR AGREEMENT-page	Edited language: Added: approval, to indicate Sponsor's related language for Medical Director's approval of the protocol is reflected Removed: I agree to comply with the International Council on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.	Adjustment of text to clarify Sponor's role in protocol approval and documentation of the approval
1 Protocol Summary 1.2 Schema, Overall Design	Added: Cohort 1 to Cohort 2 before the arrow for LTE to reflect that Cohort 1& 2 can participate in LTE Removed- Ph3 related text from the LTE text box	Corrections on the overall study schema
1 Protocol Summary 1.3 Schedule of Activities, Table D Long-term Extension Schedule of Activities	Removed – "Timed Interval" for urine collection. Added – "Creatine Kinase = CK" to the Abbreviations in the footnotes and to list of Safety and Drug Monitoring Labs in footnote 8	Clarifications of urine and blood collections during LTE.

Section No./Title	Changes	Rationale
1 Protocol Summary 1.3.1 Pharmacokinetic, Pharmacodynamic, and Urine Sampling Times Table E	Added: Footnote 2 under table "24 hour timepoint only collected in Period 3"	Further clarifies timepoint for 24 hour sample collection
6 Study Information 6.1 Study Intervention(s) Administration 6.1.1 Study Intervention Description 8 Study Assessments and Procedures 8.2.3 Period 3 (Cohort 1 and Cohort 2)-Outpatient dosing	Updated study intervention description to match current IB, and adding 5mg dosage Added- If the 5mg tablet is not available for use, then the 10 mg tablets may be split according to the related specifications indicated in the Pharmacy manual provided by the Sponsor. No other dose strength may be split. Added- If the 10 mg tablet needs to be split, the participant should cut one 10 mg encaleret tablet each day and take half of the tablet in the morning and the other half of the split tablet in the evening, assuring that the participant receives a full 10 mg dose per day. Participant should follow the manufacturer instructions for use included with the pill cutter. In the event that half of the split 10 mg tablet is lost, the participant should cut a new tablet in half for the evening dose and discard the remaining half. The participant should start with a new 10 mg tablet the following morning.	Allowance for splitting 10 mg tablets only to provide provisions for 5 mg dosing with instructions for administration and related timing

Section No./Title	Changes	Rationale
6 Study Information 6.1.5 Period 3 (Cohort 1 and Cohort 2)-Outpatient Dosing 6.1.6 Long-term extension (Cohort 1 and Cohort 2)-Outpatient Dosing 8 Study Assessments and Procedures 8.2.3 Period 3 (Cohort 1 and Cohort 2)- Outpatient Dosing 8.2.4 Long-term Extension (LTE) 8.5.7 Events of Special Interest Addition of Oral Calcium Supplements and/or Calcitriol	Added 'dietary' to following statements in multiple sections of the protocol: Oral calcium supplementation may be used as needed on top of a minimum dietary intake of at least 1000 mg daily. Since all participants will be receiving at least 1000 mg dietary calcium per day throughout the trial, additional supplemental oral calcium in the range of 1,000–2,000 mg additional supplement may be given as required with close follow-up of cCa.	Clarification related to use of dietary calcium
Section No./Title	**Amendment 8: 16 August 2022**	**Rationale**
Title Page Key Sponsor Contacts	Removed [redacted]	Personnel has departed from Calcilytix
1 Protocol Summary 1.1 Synopsis	Changed "Study Duration" to "Primary Study Duration" Changed paragraph: "Estimated time from when the study opens to enrollment until completion or data analysis is approximately 41 months" To: "Estimated time from when the study opens to enrollment until completion of Period 3 is approximately 16 months."	Differentiate the core study from the Long-term extension and include the transition to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	Changed paragraph: "Total duration of study participation, including Periods 1, 2, and 3, will be approximately 12 months for each participant, including up to 60 days between the screening visit and study drug initiation. Participants that continue to meet study eligibility criteria after Period 3 may continue in the Long-term Extension (LTE) for approximately 25 additional months" To: "Total maximum duration of study participation, including Periods 1, 2, and 3, will be approximately 16 months for each participant, which includes up to 60 days between the screening visit and study drug initiation and up to 16 weeks between Periods 1 and 2. Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first."	
1 Protocol Summary 1.2 Synopsis: Overall Study Design	Changed the LTE box from "(24 months or until encaleret approval)" to "(Up to 24 months, or until transition to Phase 3)"	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension
1.3 Schedule of Activities (SOA) Table D Long-term Extension Schedule of Activities	Changed Days (windows) of NIH CC EoT/ET from "± 7" to "+30"; Edited footnote 1 from: "If participant discontinues from the study early (ET) or withdraws from taking CLTX-305 (encaleret) (EoT), before completing LTE per protocol, participant will be asked to return to the NIH CC as soon as possible for the ET/EoT visit assessments and return the unused CLTX-305 (encaleret).	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	Participant should revert to their outpatient regimen of oral calcium and active vitamin D." To: "If participant discontinues from the study early (ET) or withdraws from taking CLTX-305 (encaleret) (EoT), before completing LTE per protocol, participant will be asked to return to the NIH CC within 30 days following the last dose for the ET/EoT visit assessments and return the unused CLTX-305 (encaleret). Participant should resume oral calcium and active vitamin D under the supervision of the study team while the encaleret is being safely discontinued. Follow-up labs should be performed per this Schedule of Assessments." Edited footnote 2 from: "Participants who complete the LTE or withdraw from taking CLTX-305 (encaleret) (EoT) before completing LTE per protocol will obtain the following outpatient laboratory assessments after the last dose of CLTX-305 (encaleret) and after re-starting their prior regimen of oral calcium and active vitamin D: blood Cr, Ca, Alb, Mg, iPTH, PO4. Follow-up (FU) call should occur within 3-5 days to review the lab results and receive guidance on clinical management of their ADH1 as participants transition to prior standard of care." To: "Participants who withdraw from taking CLTX-305 (encaleret) (EoT) before transitioning to the CLTX-305-302/CALIBRATE LTE per protocol will obtain the following outpatient laboratory assessments after the last dose of CLTX-305 (encaleret) and after re-starting their prior regimen of oral calcium and active vitamin D: blood Cr, Ca, Alb, Mg, iPTH, PO4. Follow-up (FU) call should occur within 3-5 days to review the lab results and receive guidance on clinical	

Section No./Title	Changes	Rationale
	management of their ADH1 as participants transition to prior standard of care." Added "HIV, viral hepatitis panel should be repeated within 3 months prior to transition to CLTX-305-302/CALIBRATE." To footnote 8. Added new footnote 13: "When participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed."	
2 Introduction 2.1 Study Rationale	Changed paragraphs: "The LTE is designed to obtain additional safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first. If at the end of the LTE (duration of about 25 months, or approximately 2 years) prescription encaleret is not available, participants will be placed back on the conventional therapy after the follow-up assessments are completed (see Section 1.3 Table D)." To: "The LTE is designed to obtain additional safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first. At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments should be completed per Schedule of Assessments (see Section 1.3 Table D)."	
2.3.1 Known Potential Risks	Added Paragraph: "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)." Changed Paragraph: "In the dose-escalating and dose-finding components of Periods 1, 2 and 3, participants may experience fluctuations in their blood calcium levels including the potential for hypocalcemia and/or hypercalcemia. The long-term risk of such fluctuations with CLTX-305 (encaleret) are not expected to be larger than the risk of current therapy however such fluctuations may be more frequent during the initial dose-escalating/dose finding portions of the clinical study. The clinical study is designed to minimize the risk of untoward fluctuations in blood calcium and related serum chemistries: During the dose-finding Periods 1 and 2, participants will be	Adding phototoxicity and hypophosphatemia as a potential known risks

Section No./Title	Changes	Rationale
	supervised with frequent monitoring of blood calcium levels multiple times per day and may receive treatment for hypocalcemia or hypercalcemia as required while effective doses of CLTX-305 (encaleret) are being identified. Each participant is assessed for evidence of an individualized effective dose of CLTX-305 (encaleret) during the in-house periods before entering outpatient Period 3. During Period 3 participants continue a combination of their oral calcium supplements and individualized starting dose of CLTX-305 (encaleret) and will undergo at least weekly re-assessment and dose-titration based on outpatient laboratory monitoring results and telephone contact visits with the investigative site staff. The outpatient approach to dose and regimen modification is similar to the current practice for optimizing conventional treatment with oral calcium and active vitamin D." To: "In the dose-escalating and dose-finding components of Periods 1, 2 and 3, participants may experience fluctuations in their blood calcium and phosphate levels including the potential for hypocalcemia, hypercalcemia, and/or hypophosphatemia. The long-term risk of such fluctuations with CLTX-305 (encaleret) are not expected to be larger than the risk of current therapy however such fluctuations may be more frequent during the initial dose-escalating/dose finding portions of the clinical study. The clinical study is designed to minimize the risk of untoward fluctuations in blood calcium, phosphate and related serum chemistries: During the dose-finding Periods 1 and 2, participants will be supervised with frequent monitoring of blood calcium and phosphate levels multiple times per day and may receive treatment for hypocalcemia, hypercalcemia, or hypophosphatemia as	

Section No./Title	Changes	Rationale
	required while effective doses of CLTX-305 (encaleret) are being identified. Each participant is assessed for evidence of an individualized effective dose of CLTX-305 (encaleret) during the in-house periods before entering outpatient Period 3. During Period 3 participants continue a combination of their oral calcium supplements and individualized starting dose of CLTX-305 (encaleret) and will undergo at least weekly re-assessment and dose-titration based on outpatient laboratory monitoring results and telephone contact visits with the investigative site staff. The outpatient approach to dose and regimen modification is similar to the current practice for optimizing conventional treatment with oral calcium and active vitamin D." Changed paragraph: "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 ADH1 will closely evaluate dose-related effects on calcium homeostasis and otherwise employ routine safety monitoring (For details on CLTX-305 (encaleret) safety data, see IB Section 5.3)." To: "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 ADH1 will closely evaluate dose-related effects on calcium and phosphate homeostasis and otherwise employ routine safety monitoring (For details on CLTX-305 (encaleret) safety data, see IB Section 5.3)."	

Section No./Title	Changes	Rationale
4 Study Design 4.1 Overall Design	Changed paragraph: "The LTE is designed to obtain additional safety data and evaluate durability of efficacy for CLTX-305 (encaleret). The LTE also allows for continued treatment of enrolled participants with CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first." To: "The LTE is designed to obtain additional safety data and evaluate durability of efficacy for CLTX-305 (encaleret). The LTE also allows for continued treatment of enrolled participants with CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first." Changed paragraph: "Participants from both cohorts who complete Period 2 will be eligible to enter Period 3. Outpatient dosing with CLTX-305 (encaleret) will be determined from review of individual dose-response data from Periods 1 and/or 2 based on identifying well-tolerated BID doses with preliminary evidence for efficacy. During the initial outpatient period (Period 3), participants will undergo additional individualized dose titration as necessary in response to safety data and the results of key efficacy measures. Participants who complete Period 3 (up to Week 24) and who elect to continue in the LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	they have access to CLTX-305 (encaleret) via prescription, whichever occurs first." To: "Participants from both cohorts who complete Period 2 will be eligible to enter Period 3. Outpatient dosing with CLTX-305 (encaleret) will be determined from review of individual dose-response data from Periods 1 and/or 2 based on identifying well-tolerated BID doses with preliminary evidence for efficacy. During the initial outpatient period (Period 3), participants will undergo additional individualized dose titration as necessary in response to safety data and the results of key efficacy measures. Participants who complete Period 3 (up to Week 24) and who elect to continue in the LTE will receive CLTX-305 (encaleret) for additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first." **Figure A Study Overview Schematic** Changed "Long Term Extension" box "Duration" from "24 months" to "Up to 24 months or until transition to Phase 3" Changed paragraphs: **Long-term Extension (LTE)** - Outpatient dosing with CLTX-305 (encaleret) will continue for approximately 25 months (approximately 2 years) after completion of the Week 24 visit in Period 3. Participants completing Period 3 will continue to receive clinical supplies of CLTX-305 (encaleret) at the same BID dose based on their tolerance and response to BID dosing during CLTX-305 (encaleret) dosing in Period 3. Participants will not take calcitriol but may take calcium supplementation as needed to achieve a minimum daily intake	

Section No./Title	Changes	Rationale
	of 1000 mg. Participants may receive oral calcium supplements as directed by the investigative site if they are not able to achieve a minimum of 1000 mg per day of dietary calcium intake. A final follow-up safety visit in the LTE will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret) is taken as part of this protocol. If at the end of the LTE (duration of about 25 months, or approximately 2 years) prescription encaleret is not available, participants will be placed back on the conventional therapy after the follow-up assessments are completed (see Section 1.3, Table D). To: "**Long-term Extension (LTE)** - Outpatient dosing with CLTX-305 (encaleret) will continue for an additional period of time, up to 25 months (approximately 2 years), or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever comes first, after completion of the Week 24 visit in Period 3. Participants completing Period 3 will continue to receive clinical supplies of CLTX-305 (encaleret) at the same BID dose based on their tolerance and response to BID dosing during CLTX-305 (encaleret) dosing in Period 3. Participants will not take calcitriol but may take calcium supplementation as needed to achieve a minimum daily intake of 1000 mg. Participants may receive oral calcium supplements as directed by the investigative site if they are not able to achieve a minimum of 1000 mg per day of dietary calcium intake. A final follow-up safety visit in the LTE will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret) is taken as part of this protocol.	

Section No./Title	Changes	Rationale
	At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments should be completed per Schedule of Assessment (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) should be returned to the investigative site."	
4.3 Justification for Dose	Changed paragraphs: "Participants who complete Period 3 (completing up to 25 weeks) may enter LTE of this study and receive CLTX-305 (encaleret) doses for an additional of approximately 25 months (approximately 2 years). The LTE is designed to obtain additional safety data and to continue to provide enrolled participants with CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first. If at the end of the LTE (duration of about 25 months, or approximately 2 years) prescription encaleret is not available, participants will be placed back on the conventional therapy after the follow-up assessments are completed (see Section 1.3 Table D)." To: "The LTE is designed to obtain additional safety data for CLTX-305 (encaleret). Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first. Participants who transfer	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional. Follow-up assessments are to be completed per Schedule of Assessments (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) should be returned to the investigative site."	
6 Study Intervention 6.1.8 Dose Modifications	Corrected third paragraph first sentence from: "For participants who develop clinical laboratory assessments unrelated to the dosing algorithm parameters (e.g., corrected calcium) indicating that further conduct of per protocol clinical assessments/procedures may put the participant at risk may have their CLTX-305 (encaleret) dosing interrupted at the discretion of the principal investigator." To: "For participants who develop clinical laboratory abnormalities unrelated to the dosing algorithm parameters (e.g., corrected calcium) indicating that further conduct of per protocol clinical assessments/procedures may put the participant at risk may have their CLTX-305 (encaleret) dosing interrupted at the discretion of the principal investigator and should be captured as adverse events."	Correction of incorrect word ("laboratory assessment" to "laboratory abnormalities"; clarification to capture abnormalities as adverse events
6.2.2 Formulation, Appearance, Packaging, and Labeling	Updated first paragraph to: "The CLTX-305 (encaleret) will be provided as white film-coated tablets containing the active ingredient CLTX-305 (encaleret) provided in 5, 10, 30 and 60 mg doses."	Included 5mg tablet size

Section No./Title	Changes	Rationale
6.5 Concomitant Therapy	Added paragraph: "Participants being treated with nirmatrelvir/ritonavir for COVID-19 may decrease the encaleret dosing to once daily during the 5-day treatment course given that ritonavir is a strong CYP3A4 inhibitor. Participants may take calcium supplementation as needed if they experience symptoms of hypocalcemia during this time. After completion of the 5-day nirmatrelvir/ritonavir treatment course, participants may resume twice daily encaleret."	Clarify how to manage CLTX-305 dosing when nirmatrelvir/ritonavir may be used for COVID-19 treatment in participants.
7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal 7.1 Discontinuation of Study Intervention	Added "Participant transitions to the CLTX-305-302/CALIBRATE Phase 3 LTE" to list of reasons	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension
7.2 Participant Discontinuation/Withdrawl from the Study	Added paragraph: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed." Changed paragraph: "All participants who received CLTX-305 (encaleret) and terminate early from the study, regardless of cause, should undergo a 30-day (± 7 days) follow-up telephone call after the last dose of CLTX-305 (encaleret). The reason for early	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	termination from the study will be reflected in the CRF. If a participant terminates early from the study because of an AE, the PI/study staff must record the AE as the reason for discontinuation." To: "All participants who received CLTX-305 (encaleret) and terminate early from the study, regardless of cause, with exception of transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, should undergo follow-up procedures according to Section 1.3 Table D SOA. The reason for early termination from the study will be reflected in the CRF. If a participant terminates early from the study because of an AE, the PI/study staff must record the AE as the reason for discontinuation."	
8 Study Assessments and Procedures 8.2.2 Period 2 (BID Dosing) – Cohorts 1 and 2	Updated seventh paragraph to: "The first 7 participants who have completed CLTX-305-201 Period 2 and entered into Period 3 have had a wide range of CLTX-305 (encaleret) dose requirements from 10 mg once daily to 180 mg BID suggesting that CLTX-305 (encaleret) dosing is highly individualized. As a result, all remaining participants in Period 2 will receive an initial CLTX-305 (encaleret) 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The CLTX-305 (encaleret) dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 5, 10, 30, or 60 mg increments based on the available CLTX-305 (encaleret) tablet strengths. A frequent sampling test day with additional serial blood and urine sampling to assess 24-hour PK/PD profiles will be performed on Day 5. For details on the PK/PD	Included 5mg tablet size

Section No./Title	Changes	Rationale
	timepoints during frequent sampling on Day 5 see Section 1.3.1 specifically Table J and Table K." Updated ninth paragraph to: "**Cohort 2** – Cohort 2 will commence after Cohort 1 has completed Period 1 and the PD dose responses and safety have been reviewed. Participants will receive an initial CLTX-305 (encaleret) 90 mg BID dose for at least 3-4 doses for evaluation of safety, tolerability and the ability to modulate cCa levels. The CLTX-305 (encaleret) dose will be up- or down-titrated as needed to maintain cCa levels below 10 mg/dL and blood phosphorus levels above the lower limit of normal. Dosing will be adjusted in 5, 10, 30, or 60 mg increments based on the available CLTX-305 (encaleret) tablet strengths. The total blood volume collected during Period 2 for Cohort 2 participants will be less than the blood volume limits per participant as per NIH Guidelines for Blood Draw Limits for Research Purposes (M95-9, June 2009). These volumes include the cumulative potential collection over an 8-week period: screening visit labs, -10-14 day labs, Day -1 safety labs, Period 2 inpatient week, and 4 weeks of outpatient labs in Period 3."	
8.2.4 Long-term Extension (LTE)	Changed second paragraph, last sentence from: "Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of approximately 25 months (approximately 2 years) or until they have access to CLTX-305 (encaleret) via prescription, whichever occurs first." To: "Participants who elect to continue in LTE will receive CLTX-305 (encaleret) for an additional period of time, up to 25 months (approximately 2 years) or until they transition to	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	the CLTX-305-302/CALIBRATE Phase 3 LTE, whichever occurs first." Deleted paragraph: "If at the end of the LTE (duration of about 25 months, or approximately 2 years) prescription encaleret is not available, participants will be placed back on the conventional therapy after the follow-up assessments are completed (see Section 1.3 Table D)." And replaced with: "At any point during the LTE, and before transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, participants can choose to stop participation and be placed back on the conventional therapy. Follow-up assessments are to be completed (see Section 1.3 Table D) and clinical supply of CLTX-305 (encaleret) needs to be returned to the investigative site."	
8.2.5 Follow-up and Early Termination	Added paragraphs: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed. **Transition to CLTX-305-302/CALIBRATE Phase 3 Long Term Extension**	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension

Section No./Title	Changes	Rationale
	Participants from CLTX-305-201 who meet the study screening eligibility criteria of the CLTX-305-302/CALIBRATE Phase 3 study will enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE. If assessments for 25-OH Vitamin D, eGFR, 12-lead resting ECG, viral hepatits panel and HIV have been completed either at the NIH CC or via outpatient lab within the 3 months prior to transitioning into the CLTX-305-302/CALIBRATE LTE, they do not need to be repeated for eligibility purposes. Other assessments performed during the CLTX-305-201 ET/EoT visit will be acceptable for assessment of CLTX-305-302/CALIBRATE eligibility criteria. If a participant discontinued encaleret during the CLTX-305-201 LTE for family planning purposes, the participant may enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE once family planning is complete if he/she meets the study eligibility criteria per the CLTX-305-302/CALIBRATE protocol and the CLTX-305-302/CALIBRATE Encaleret Resumption Criteria. Participants will resume encaleret as described in the CLTX-305-302/CALIBRATE protocol. Assessments in the CLTX-305-302/CALIBRATE Phase 3 LTE will be conducted approximately every 3 months as described in CLTX-305-302/CALIBRATE protocol's Schedule of Assessments. Participants who transfer to the CLTX-305-302/CALIBRATE LTE will receive encaleret for an additional period of approximately 48 months or until participant has access to commercial encaleret, or the Sponsor decides to end the study, whichever occurs first."	
10 Regulatory and Operational Considerations	Added paragraphs:	For studies conducted at NIH CC, HMID (Health Information

Section No./Title	Changes	Rationale
10.1 Informed Consent Process	The informed consent document will be provided as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomfort 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 any research activities taking place. 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 participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/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 the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document on screens at their respective locations; the same screen may be used when both the investigator and the participant are co-located but this is not required.	Management Division) wants all CC protocols to include the current iMED language as all consent forms are to be transitioned to the iMED system.

Section No./Title	Changes	Rationale
	Note: When required, the witness signature will be obtained similarly as described for the investigator and participant below. Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below. **For electronic consent:** The study team will confirm with the subject 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, subjects/LARs and investigators will view the same approved consent document simultaneously in their respective locations. The identity of the subject will be determined by verifying a government issued identification card via the telehealth platform, prior to obtaining the signature. iMED consent 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	

Section No./Title	Changes	Rationale
	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.	
10.4 Future Use of Stored Specimens and Data	Changed paragraph: "All stored samples are coded and do not have personal identifiers. The codes for identifiers are contained in a participant code log that is maintained in secure research files at the NIH. Samples received for PK analysis by Calcilytix/or designee from participants consented to this protocol, will be destroyed after use. 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." To: "All stored samples are coded and do not have personal identifiers. The codes for identifiers are contained in a participant code log that is maintained in secure research files	Clarifying sample usage for future use at NIH

Section No./Title	Changes	Rationale
	at the NIH. Samples received for PK analysis by Calcilytix/or designee from participants consented to this protocol, may be destroyed or unused samples sent back to the NIH for additional research purposes. 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.participants' consent."	
10.8.3 LTE Electronic Data Capture	Added new section 10.8.3 LTE Electronic Data Capture	Capture the transition planning to the CLTX-305-302/CALIBRATE Phase 3 Long-term extension
Section No./Title	**Amendment 9: 25 April 2023**	**Rationale**
1 PROTOCOL SUMMARY 1.3 Schedule of Activities (SOA) Table D Long-term Extension Schedule of Activities	Footnote 13 changed from: "When participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed." To: "When participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 study."	Reduction of assessment and testing required to transfer to Phase 3 study
4.1 Overall Design	Long-term Extension (LTE): First paragraph, last sentence changed from: "A final follow-up safety visit in the LTE will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret) is taken as part of this protocol."	Clarify final follow-up safety visit for participants not transitioning to the Phase 3 study.

Section No./Title	Changes	Rationale
	To: "A final follow-up safety visit in the LTE will occur 30 ± 7 days after the last dose of CLTX-305 (encaleret) is taken as part of this protocol for participants who withdraw from the study or CLTX-305 (encaleret) before transitioning to the CLTX-305-302/CALIBRATE LTE."	
7.2 Participant Discontinuation/Withdrawal from the Study	Changed third paragraph from: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed." To: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 study."	Reduction of assessment and testing required to transfer to Phase 3 study in order to minimize duplicative testing for participants
8.2.5 Follow-up and Early Termination	Changed fourth paragraph from: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant	Reduction of assessment and testing required to transfer to Phase 3 study in order to minimize duplicative testing for participants

Section No./Title	Changes	Rationale
	transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to complete the ET/EoT visit assessments, return the unused CLTX-305 (encaleret), and complete the screening assessments for the CLTX-305-302/CALIBRATE Phase 3 study. Follow-up labs will not be needed." To: "Participants who transfer to the CLTX-305-302/CALIBRATE Phase 3 LTE will continue encaleret dosing at their prescribed dose until enrolled into the CLTX-305-302/CALIBRATE Phase 3 LTE. When a participant transitions to CLTX-305-302/CALIBRATE, participant will be asked to return to the NIH CC to return the unused CLTX-305 (encaleret), and complete any remaining eligibility assessments for the CLTX-305-302/CALIBRATE Phase 3 study."	
8.2.5 Follow-up and Early Termination	Transition to CLTX-305-302/CALIBRATE Phase 3 Long Term Extension: Change first paragraph from: "Participants from CLTX-305-201 who meet the study screening eligibility criteria of the CLTX-305-302/CALIBRATE Phase 3 study will enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE. If assessments for 25-OH Vitamin D, eGFR, 12-lead resting ECG, viral hepatits panel and HIV have been completed either at the NIH CC or via outpatient lab within the 3 months prior to transitioning into the CLTX-305-302/CALIBRATE LTE, they do not need to be repeated for eligibility purposes. Other assessments performed during the CLTX-305-201 ET/EoT visit will be acceptable for assessment of CLTX-305-302/CALIBRATE eligibility criteria." To:	Reduction of assessment and testing required to transfer to Phase 3 study in order to minimize duplicative testing for participants

Section No./Title	Changes	Rationale
	"Participants from CLTX-305-201 who meet the study screening eligibility criteria of the CLTX-305-302/CALIBRATE Phase 3 study will enroll directly into the CLTX-305-302/CALIBRATE Phase 3 LTE. If assessments for 25-OH Vitamin D, eGFR, 12-lead resting ECG, viral hepatits panel and HIV have been completed either at the NIH CC or via outpatient lab within the 3 months prior to transitioning into the CLTX-305-302/CALIBRATE LTE, they do not need to be repeated for eligibility purposes. Other assessments performed during the final CLTX-305-201 ET/EoT study visit will be acceptable for assessment of CLTX-305-302/CALIBRATE eligibility criteria. Blood β-HCG pregnancy test can be performed at the NIH CC on the day of transition to CLTX-305-302/CALIBRATE Phase 3 LTE, and an aliquot will also be sent to the central lab for the CLTX-305-302/CALIBRATE Phase 3 LTE."	
8.4.5 Dual-energy X-Ray Absorptiometry (DXA)	Changed first paragraph from: "Bone densitometry of the spine, hip, distal radius, and total body will be performed by DXA at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during the LTE (see Schedule of Activities tables in Section 1.3)." To: "Bone densitometry of the spine, hip, distal radius, and total body will be performed by DXA at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during the LTE (see Schedule of Activities tables in Section 1.3). If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the DXA will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE."	Reduction of assessment and testing required to transfer to Phase 3 study

Section No./Title	Changes	Rationale
8.4.6 Renal Ultrasound	Changed the paragraph from: "Renal ultrasound will be performed at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during LTE (see Schedule of Activities tables in Section 1.3)." To: "Renal ultrasound will be performed at Screening during Periods 1 and 2, at Week 24 during Period 3, and at Month 12 and Month 24 during LTE (see Schedule of Activities tables in Section 1.3). If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the renal ultrasound will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE."	Reduction of assessment and testing required to transfer to Phase 3 study
8.5.6 Backup Contact	Changed from [redacted] to [redacted]	Change in personnel at Calcilytix
Section No./Title	**Amendment 10: 18 May 2023**	**Rationale**
Throughout the document	Corrected formatting errors and made minor updates to enhance readability	Fix formatting errors and minor updates for clarity
Sponsor's Agreement Page	Changed Sponsor Approver from [redacted] to [redacted]	Administrative change
1 PROTOCOL SUMMARY 1.1 Synopsis	Corrected the Primary Endpoints, Period 3 duration to 24 weeks	Typographical error
1 PROTOCOL SUMMARY 1.3 Schedule of Activities (SOA) Table D: Long-term Extension SOA: Footnote #9	Added footnote #9, "Blood β-HCG pregnancy test can be performed at the NIH CC on the day of transition to CLTX-305-302/CALIBRATE Phase 3 LTE, and an aliquot will also be sent to the central lab for the CLTX-305-302/CALIBRATE Phase 3 LTE" Updated subsequent footnote numbers to reflect the change	To align with Section 8.2.5

Section No./Title	Changes	Rationale
1 PROTOCOL SUMMARY 1.3 Schedule of Activities (SOA) Table D: Long-term Extension SOA: Footnote #14 7.2 Participant Discontinuation/ Withdrawal from the Study 8.2.5 Follow-up and Early Termination	Revised text in Table D footnote #14, Section 4.1, Section 7.2 and Section 8.2.5 to add "Phase 3 LTE"	For clarity and consistency only
1 PROTOCOL SUMMARY 1.3 Schedule of Activities (SOA) Table D: Long-term Extension SOA: Footnote #15	Added footnote #15: "If the Month 24 visit aligns with the transition to the CLTX-305-302/CALIBRATE Phase 3 LTE, then the renal ultrasound and DXA scan will be performed once as part of the CLTX-305-302/CALIBRATE Phase 3 LTE"	To align with Section 8.4.5 and Section 8.4.6.