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Encaleret (CLTX-305) Phase 2B Results in ADH1

June 2022

Encaleret is an investigational drug. Its safety and efficacy have not been fully evaluated by any regulatory authority.

Alexis and Jackson
Living with ADH1

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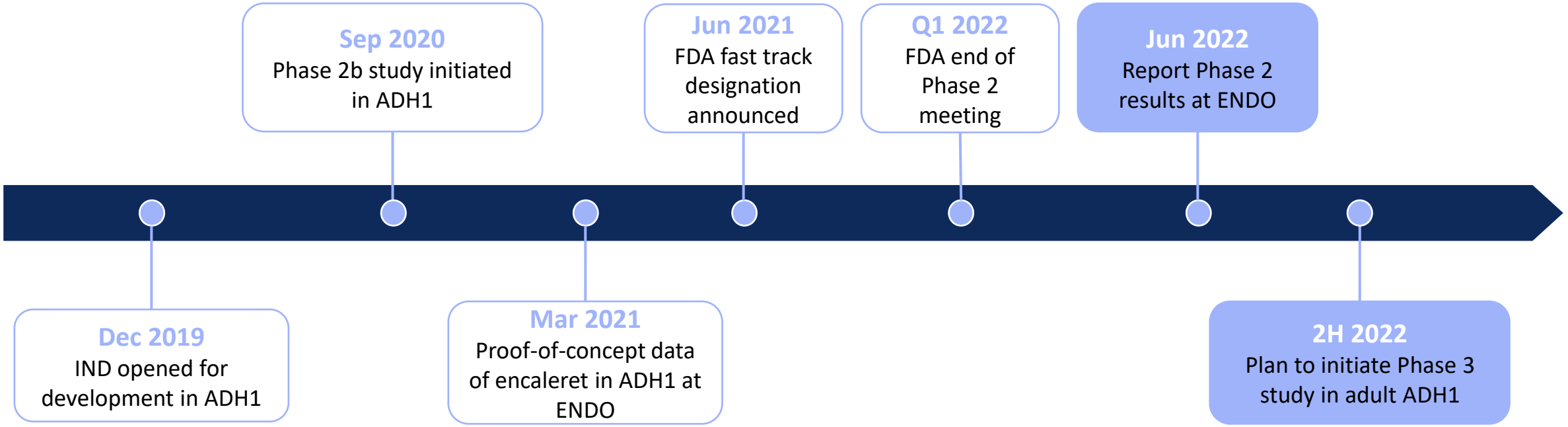
Encaleret Development Program

Neil Kumar, Ph.D.

Founder and CEO

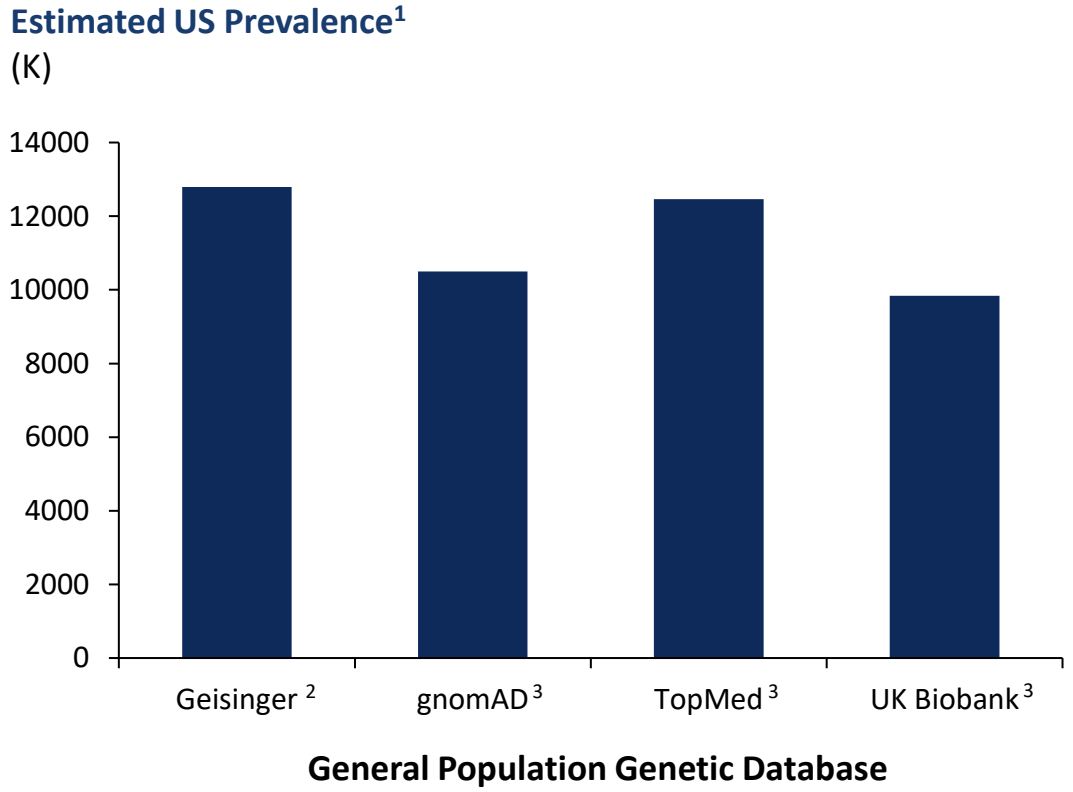
Encaleret program history: From IND to Phase 3-ready program in less than 3 years



- Encaleret rapidly progressed from IND to Phase 2 results in less than 3 years
- Phase 2 assessed safety, tolerability, and durability of encaleret treatment in ADH1 for 24 weeks

ADH1 is a serious condition for which treatable patient numbers may grow meaningfully as diagnosis rates increase

~12k carriers of ADH1 causing variants in the US



Analogous ADH1 market includes XLH

	XLH	ADH1
Prevalence (US)	12K[4]	12K
Disease burden	Hypophosphatemia	Acute hypocalcemia risk, long-term hypercalciuria risk
Standard of care	Vitamin D, daily phosphate	Vitamin D, daily calcium
Registrational endpoint	Serum phosphate	Blood and urine calcium
Projected consensus peak year sales	>$2bn[5]	~$700m

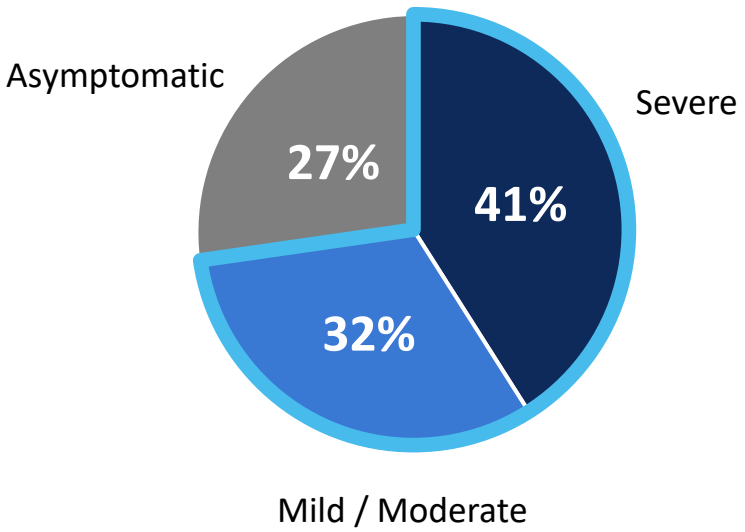
[1]US population estimated as 328M. [2]Dershem, et al. Amer Jour of Hum Genetics 2020. [3]Data obtained from the gnomAD, TopMed, and UK Biobank databases as of 2022. [4]Ultragenyx public materials. [5]Evaluate.
XLH = x-linked hypophosphatemia.

ADH1 unmet need is large with significant disease burden and no interventions specifically approved

>70% of ADH1 cases exhibit symptoms of hypocalcemia[1]

ADH1 cases (n=192)

%

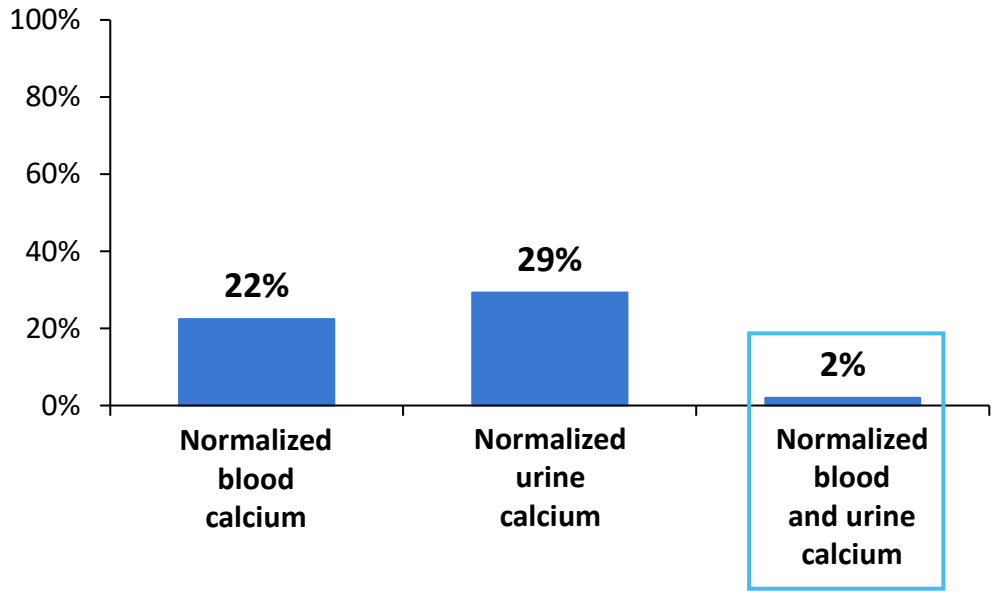


Median age of diagnosis[1]: 25 years
Range: 0 – 77 years

Current treatments inadequately address symptom burden[1]

Individuals receiving calcium and/or active vitamin D (n=58)

%



[1]Roszko, et al., ASBMR Annual Meeting, 2021.

Phase 2 Results

Rachel Gafni, M.D.

Senior Research Physician and Head of the Mineral Homeostasis Studies Group

National Institute of Dental and Craniofacial Research of the National Institutes of Health (NIH)

Encaleret is an investigational drug. Its safety and efficacy have not been fully evaluated by any regulatory authority.

Encaleret (CLTX-305) Restored Mineral Homeostasis in a Phase 2 Study in Autosomal Dominant Hypocalcemia Type 1 (ADH1) [NCT04581629]

RI Gafni, IR Hartley, KL Roszko, EF Nemeth, KA Pozo, R Sani-Grosso, AS Mathew, AV Sridhar, MS Roberts, JC Fox, MT Collins

Prepared for presentation at the ENDO 2022 Annual Meeting

NIH National Institute of Dental and Craniofacial Research

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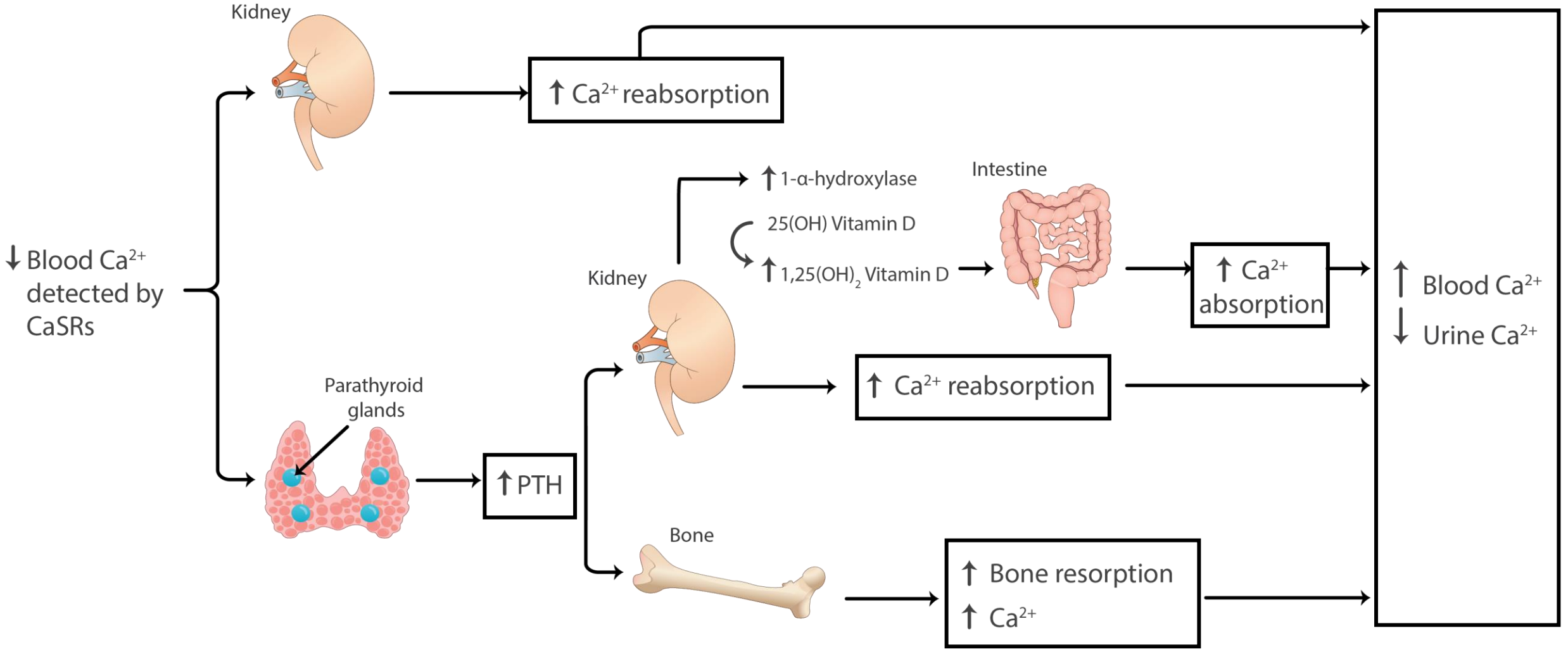
Blood calcium is maintained by four organs regulated by the calcium-sensing receptor (CaSR) and parathyroid hormone (PTH)

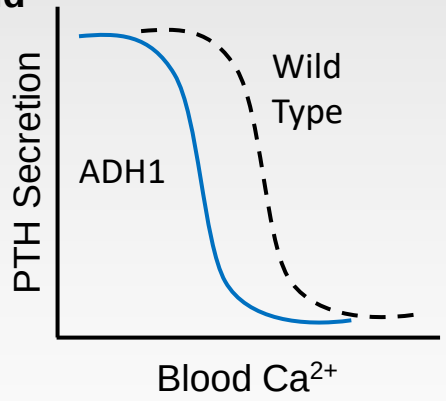


Ca2+ = ionized calcium; PTH = parathyroid hormone; CaSR = calcium-sensing receptor

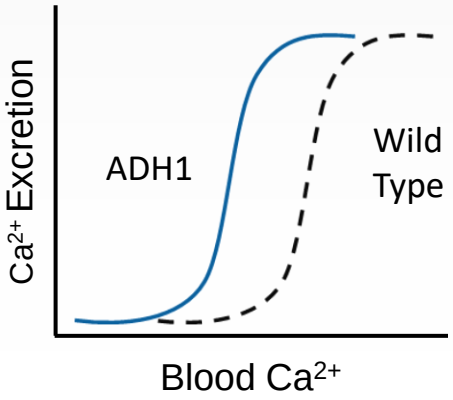
Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia Type 1 (ADH1)

Activating variants in the *CASR* increase tissue sensitivity to Ca^{2+}

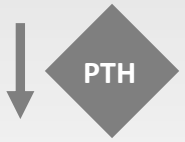
Parathyroid



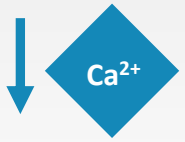
Kidney



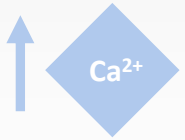
Hyperactive CaSR causes dysregulation of Ca homeostasis



Decreased parathyroid hormone (PTH) secretion



Decreased blood calcium



Increased urinary calcium

Clinical Manifestations

Acute symptoms

Hypocalcemic seizures

Paresthesia

Tetany

Muscle cramps

Long-term complications

Nephrolithiasis

Nephrocalcinosis

Chronic Kidney Disease

Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

Roszko, et al. Front. Physiol. 2016.

Encaleret, an investigational oral calcilytic, may be a potential treatment for ADH1

- Calcilytics are negative allosteric modulators of the CaSR that decrease CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1

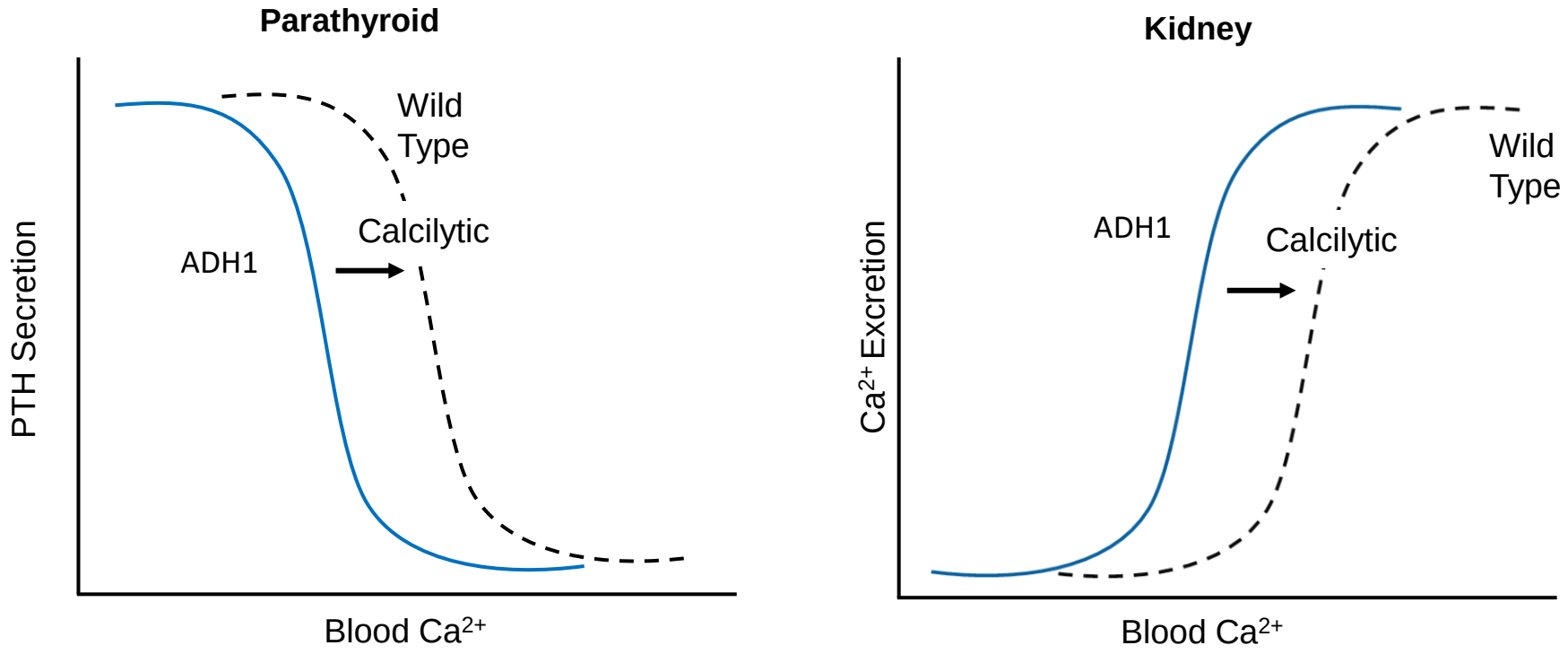
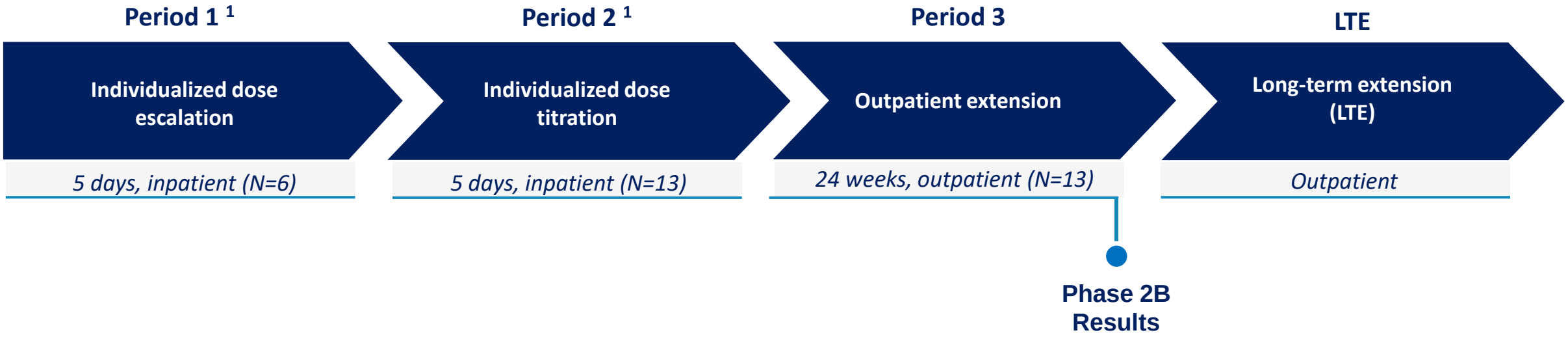


Figure adapted from Tfelt-Hansen J, et al. Curr Med Chem. 2002.

Encaleret Phase 2B Study Design – CLTX-305-201



Key study objectives:

- Safety and tolerability
- Blood calcium concentration
- Urine calcium concentration
- Intact parathyroid hormone concentration

Additional measures:

- Blood 1,25-$(OH)_2$-vitamin D, magnesium, and phosphate
- Urine creatinine, cAMP, citrate, phosphate, sodium, magnesium
- Bone turnover markers (serum collagen C-telopeptide, serum procollagen Type 1 N-propeptide)

[1]Standard of care (calcium and active vitamin D) was discontinued prior to the first encaleret dose.

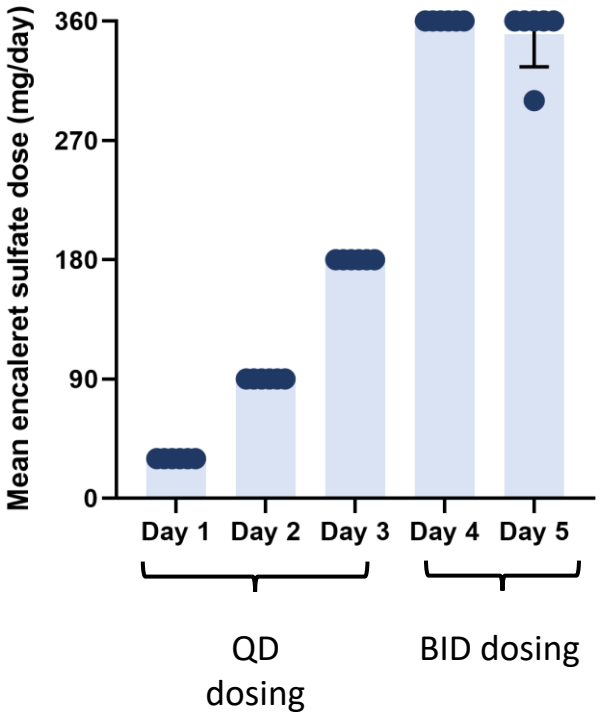
Baseline Characteristics

Characteristic	Study Population (N = 13)	*Normal Range*
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Nephrocalcinosis/Nephrolithiasis, n (%)	10 (77%)	
eGFR (mL/min/1.73 m^2)	84 ± 25	>60
Calcium[1,2] (mg/dL)	7.1 ± 0.4	8.4 –10.2
Intact PTH[2] (pg/mL)	6.3 ± 7.8	15 – 65
Phosphate[2] (mg/dL)	4.5 ± 1.1	2.3 – 4.7
Magnesium[2] (mg/dL)	1.7 ± 0.2	1.6 – 2.6
24h Urine Calcium (mg/24h)	384 ± 221	< 250 - 300
Supplements		
Elemental Calcium (mg/day) [mean (range)]	2120 (750-4800)	
Calcitriol (µg/day) [mean (range)]	0.7 (0.2-2.0)	
***CASR* Variants**	C131Y (2), P221L (2), E604K (1), A840V (3), F788C (1), T151M (1), Q245R (1), I692F (1), E228K (1)	

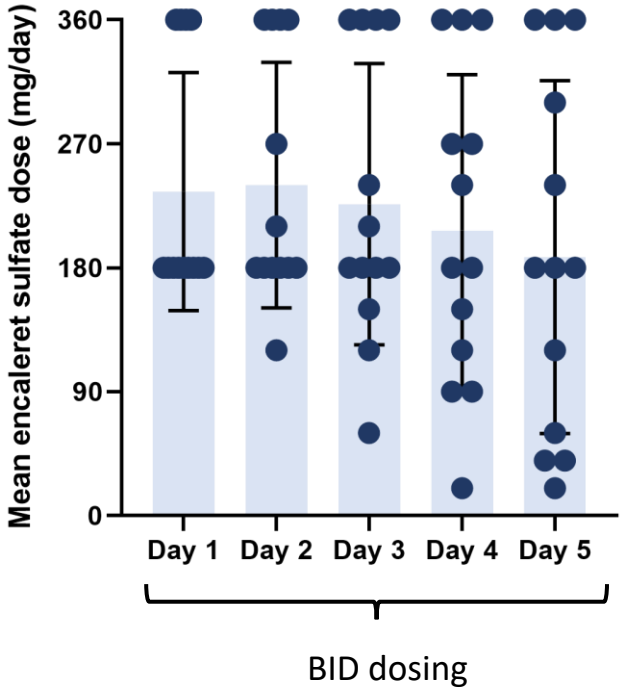
Data reported as mean±SD. GFR = estimated glomerular filtration rate calculated by the CKD-EPI equation. The encaleret starting dose was either 180mg BID or 90mg BID in Period 2.
[1]Albumin-corrected calcium. [2]Measurements taken pre-dose Day 1, Period 2.

Phase 2B Oral Encaleret Dosing Summary

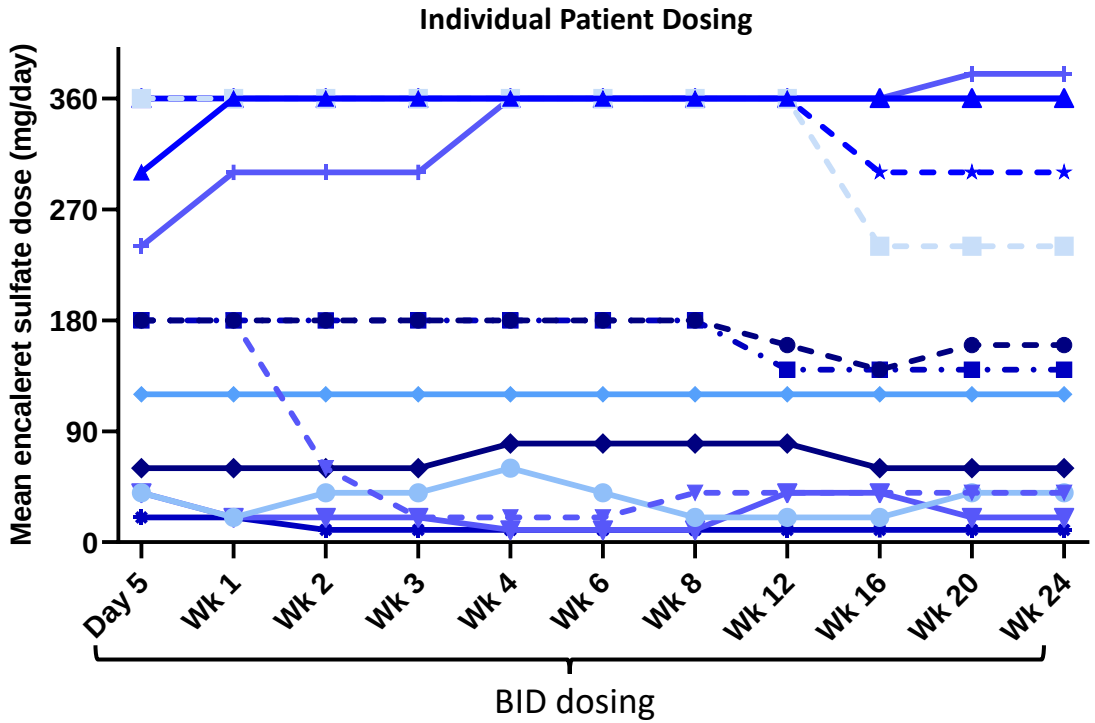
Period 1 Dosing
Defined dose escalation
Day 5 Mean: 350.0±22.4 mg/day



Period 2 Dosing
Individualized dose titration
Day 5 Mean: 178.3±123.7 mg/day



Period 3 Dosing
Optimized dose adjustments
Wk 24 Mean: 172.0±140 mg/day



Periods 1 and 2 data reported as mean±SD.

Encaleret was well-tolerated with no serious adverse events reported

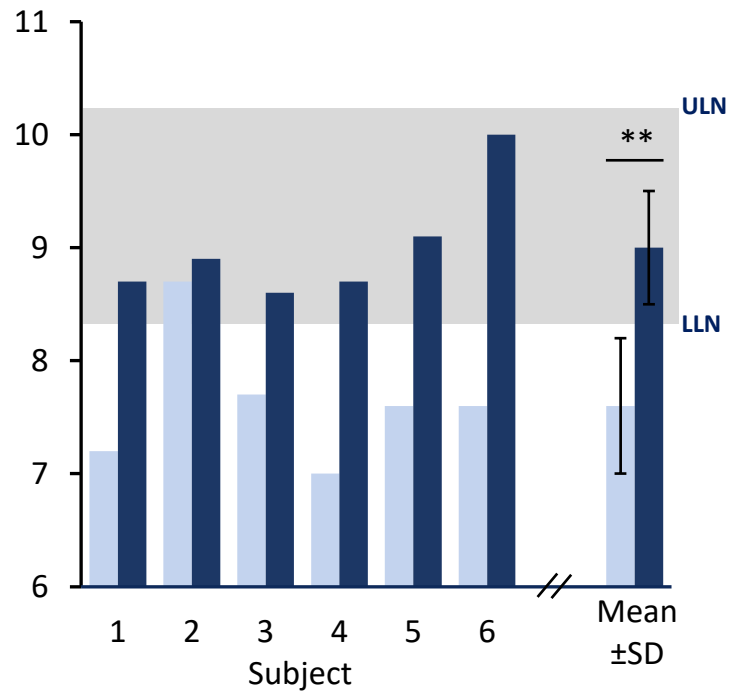
	Period 1 N=6	Periods 2 and 3 N=13
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**	**0 (0%)**
Number of subjects experiencing any Adverse Event	**6 (100%)**	**13 (100%)**
Mild	6 (100%)	13 (100%)
Moderate	0	2 (15%)
Severe	0	0
Number of Adverse Events Reported	**8**	**78**
Mild	8 (100%)	76 (97%)
Moderate	0	2 (3%)
Severe	0	0
Treatment-related Adverse Events[1]	**2 (33%)**	**16 (21%)**
Hypophosphatemia	2 (100%)	10 (63%)
Hypercalcemia	0 (0%)	6 (37%)

Data as of Mar 8, 2022. [1]Treatment-related adverse events were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs.

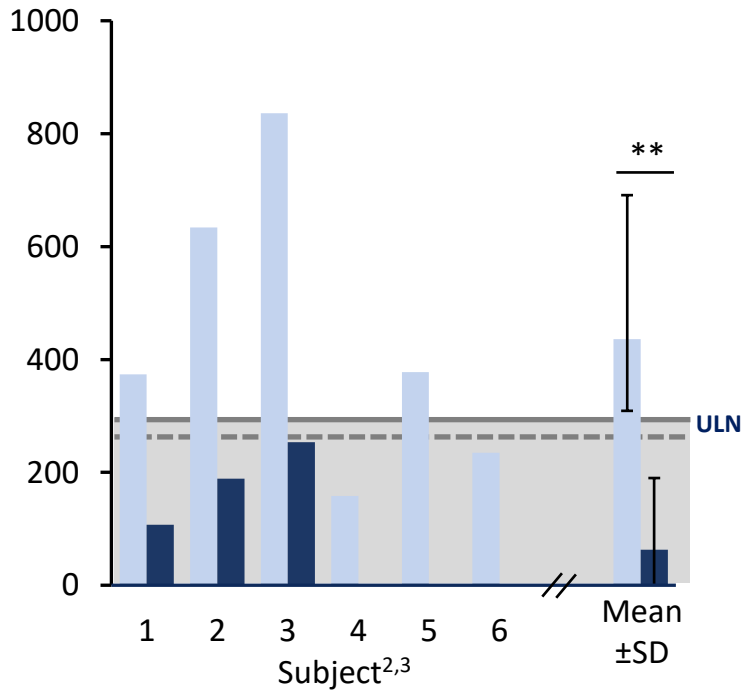
Period 1 Results (n=6): Encaleret increased PTH secretion and normalized blood and urine calcium

Baseline Value (Day 1)
Mean Value (Day 5) on encaleret 180 mg BID[1]

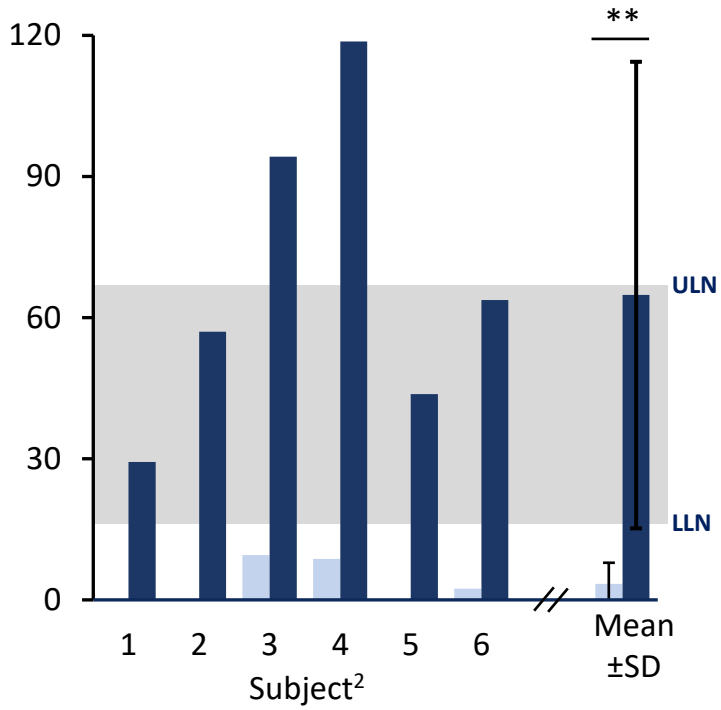
Albumin-corrected blood calcium
mg/dL



Urine calcium
mg/day

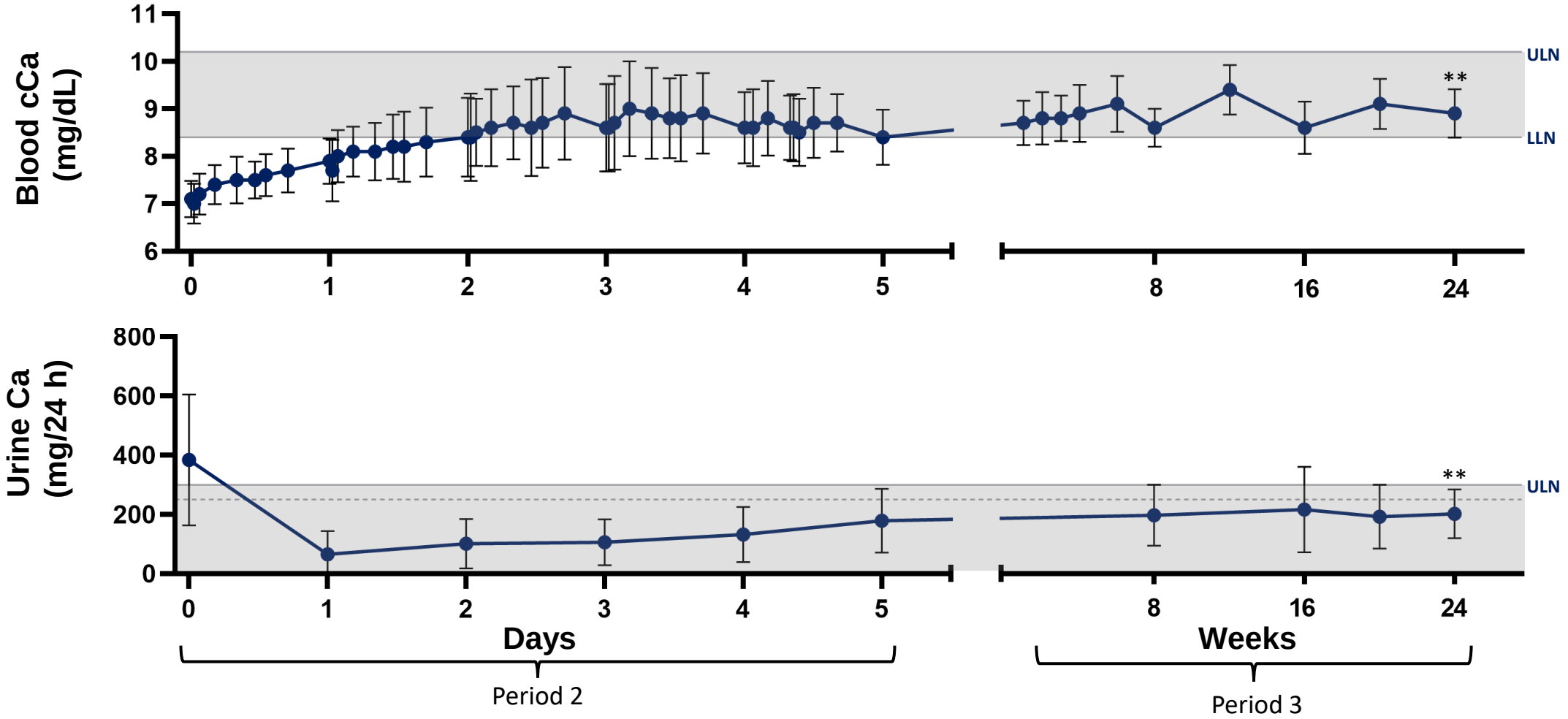


Intact parathyroid hormone
pg/mL



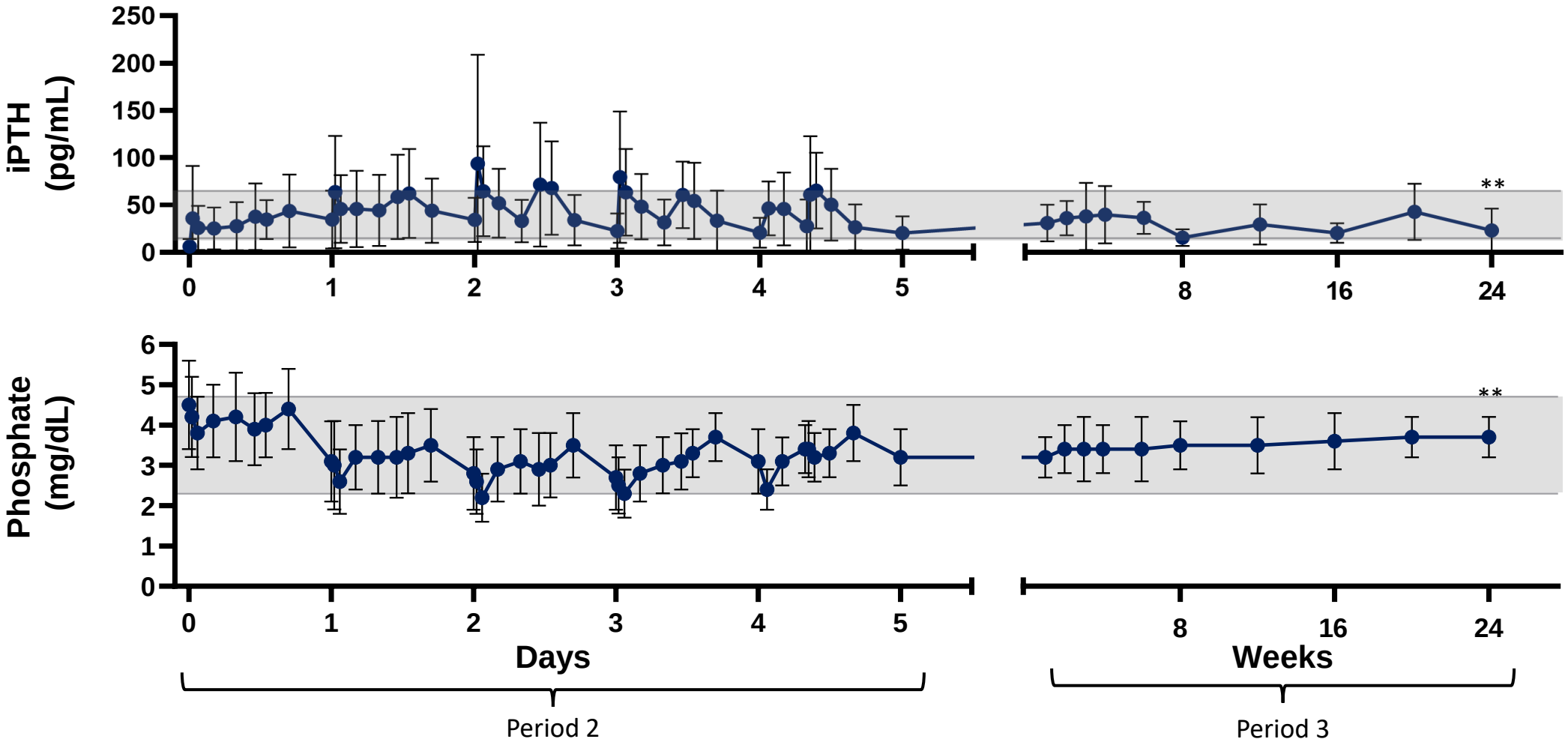
[1]Encaleret dose adjusted to 180/120 in 1 subject on Day 5. [2]Values below limit of assay quantitation recorded as "0". [3]Day 4 values used in two subjects given Day 5 values unavailable. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. ** p-value < 0.01.

Periods 2 and 3 Results (n=13): BID encaleret restored and maintained mean blood and urine calcium in the normal range over a 24-week period



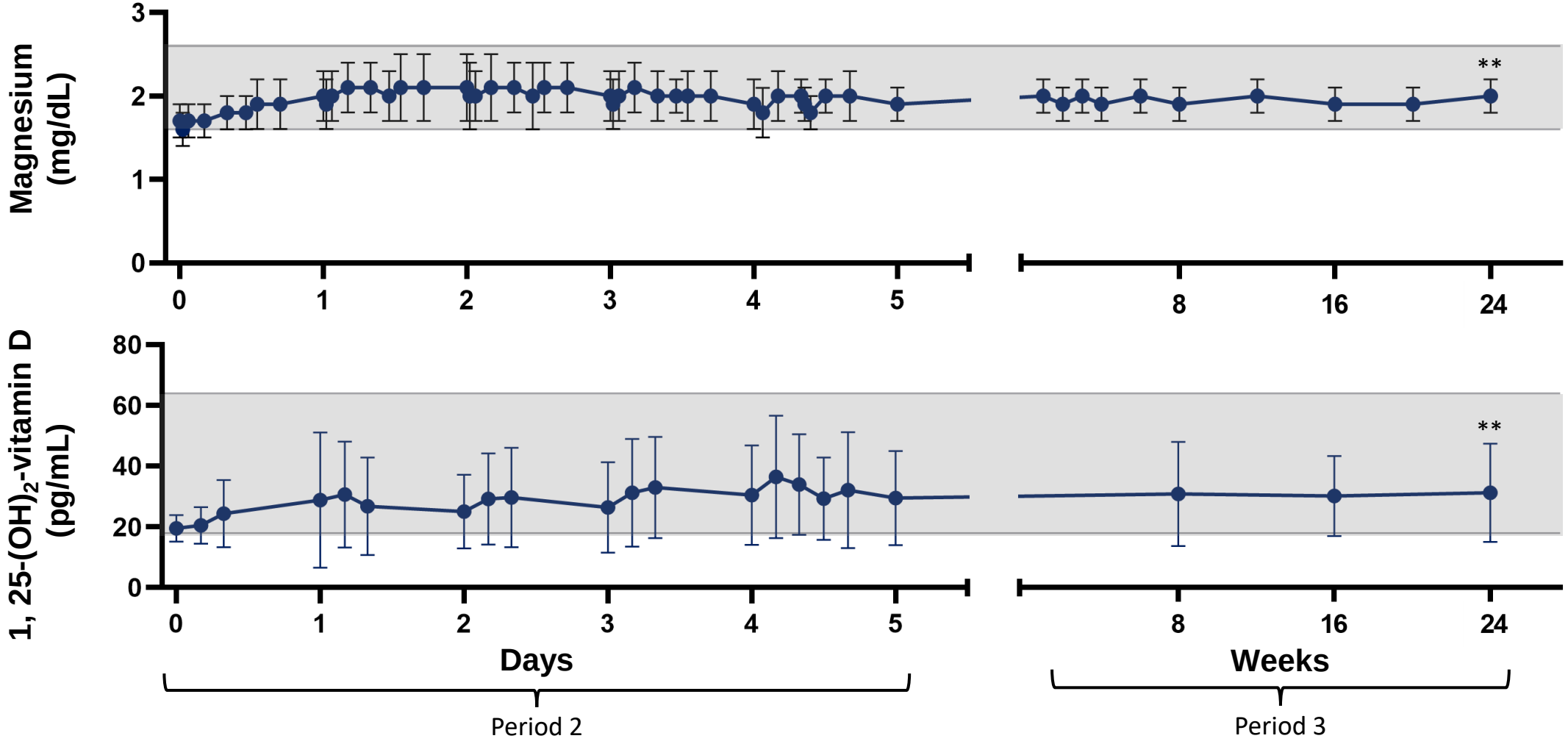
Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. cCa values shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.

Period 2 and 3 Results (n=13): BID encaleret increased mean PTH and decreased mean blood phosphate into the normal range



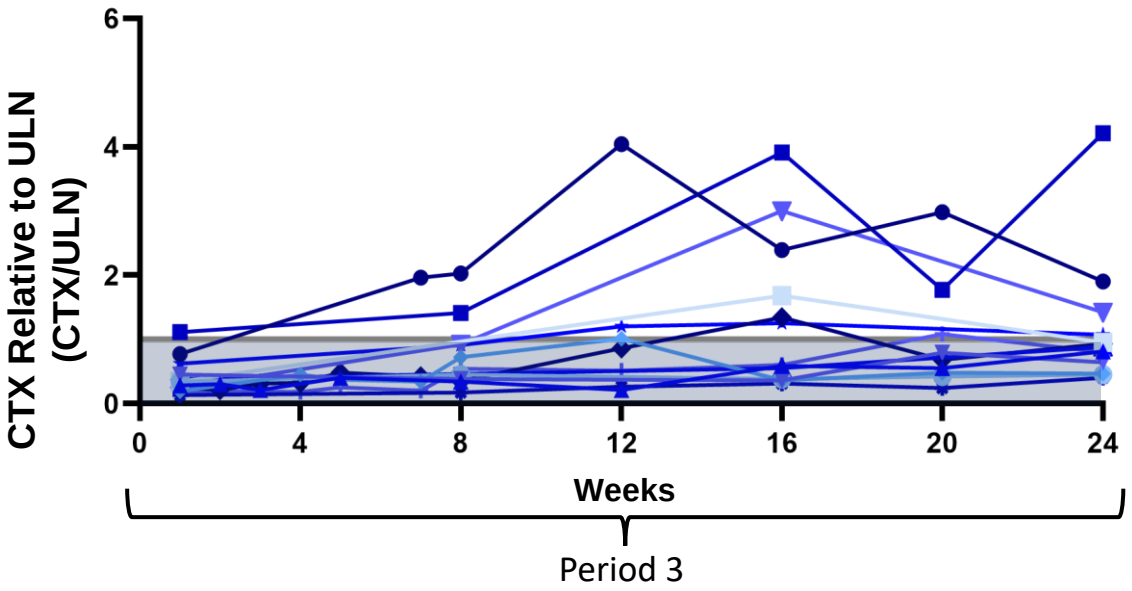
Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range. The measures shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.

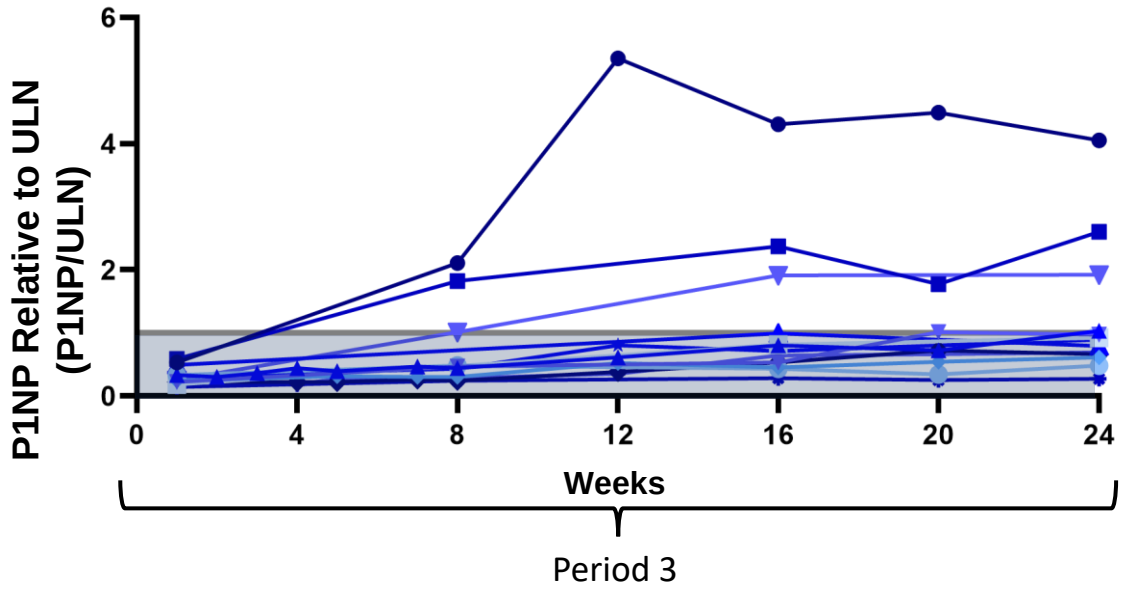
Period 2 and 3 Results (n=13): BID encaleret increased mean blood magnesium and mean 1,25-$(OH)_2$-vitamin D



Data as of Mar 8, 2022 reported as mean+SD. Gray shading reflects normal range. The measures shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.

Period 3 Results: BID encaleret increased bone turnover markers (n=13) and had minimal short-term effects on bone density (n=11)





DXA Anatomical Site n = 11	Screening Z-score Mean ± SD	Period 3, Week 24 Z-score Mean ± SD
Total Body	2.1 ± 1.4	2.0 ± 1.3
AP Lumbar Spine	2.6 ± 1.5	2.3 ± 1.7
Total Hip	2.2 ± 1.4	2.0 ± 1.4*
1/3 Distal Radius	0.2 ± 0.9	0.3 ± 0.9

Data as of Mar 8, 2022. CTX and P1NP reported as individual participant data and were corrected for sex and menopausal status. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-encaleret. DXA data not available on 2 participants due to surgical hardware. * p-value < 0.05 Week 24 mean compared to Screening. Mean change in bone turnover markers at 24 Weeks was significant (p-value <0.01)

Summary

- In 13 individuals with ADH1, encaleret administered twice daily for 24 weeks restored mineral homeostasis as demonstrated by:
  - Increase in PTH
  - Correction of hypocalcemia
  - Normalization of mean 24-hr urine calcium
  - Reduction in blood phosphate
  - Increase in mean magnesium and 1,25-$(OH)_2$-vitamin D
  - Increase in bone turnover while remaining in the normal range in most participants
- Encaleret was well-tolerated over 24 weeks, with no serious adverse events reported
- Outpatient evaluation of encaleret in the Phase 2b long-term extension is ongoing
- Phase 3 study is planned for initiation in 2022

Phase 3 Registrational Study Design

Mary Scott Roberts, M.D.

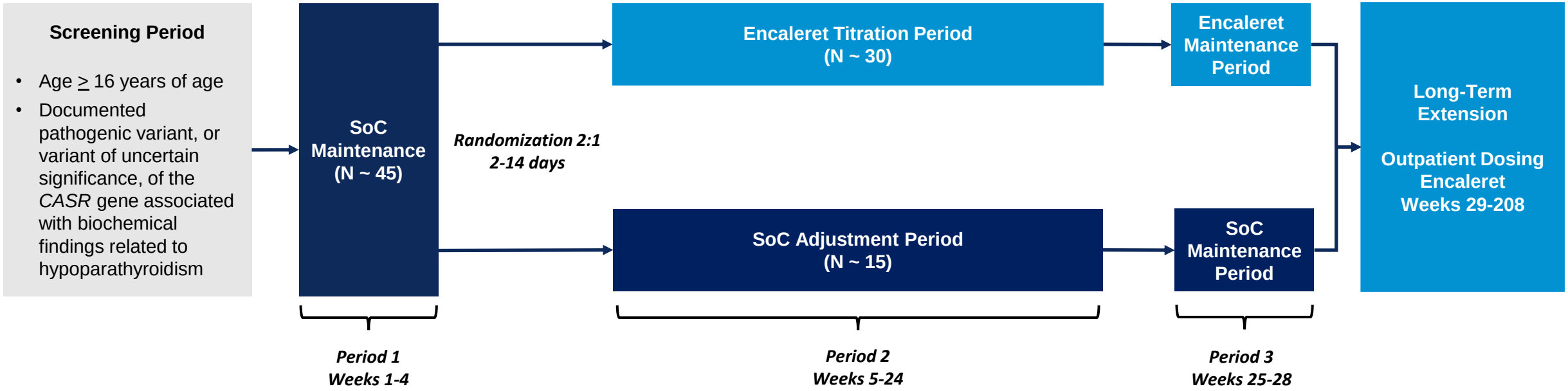
Sr. Director, Clinical Development, Cardiorenal

Encaleret is an investigational drug. Its safety and efficacy have not been fully evaluated by any regulatory authority.

Phase 3 Registrational Study Design

CALIBRATE

CLTX-305-302: global, multi-center, randomized, open-label, two-arm study



Primary Composite Endpoint:

- Proportion of participants achieving:
  - Blood Ca within the target range **AND**
  - 24-hour urine Ca within the reference range or ≥ 50% reduction from baseline

Select Secondary Endpoints:

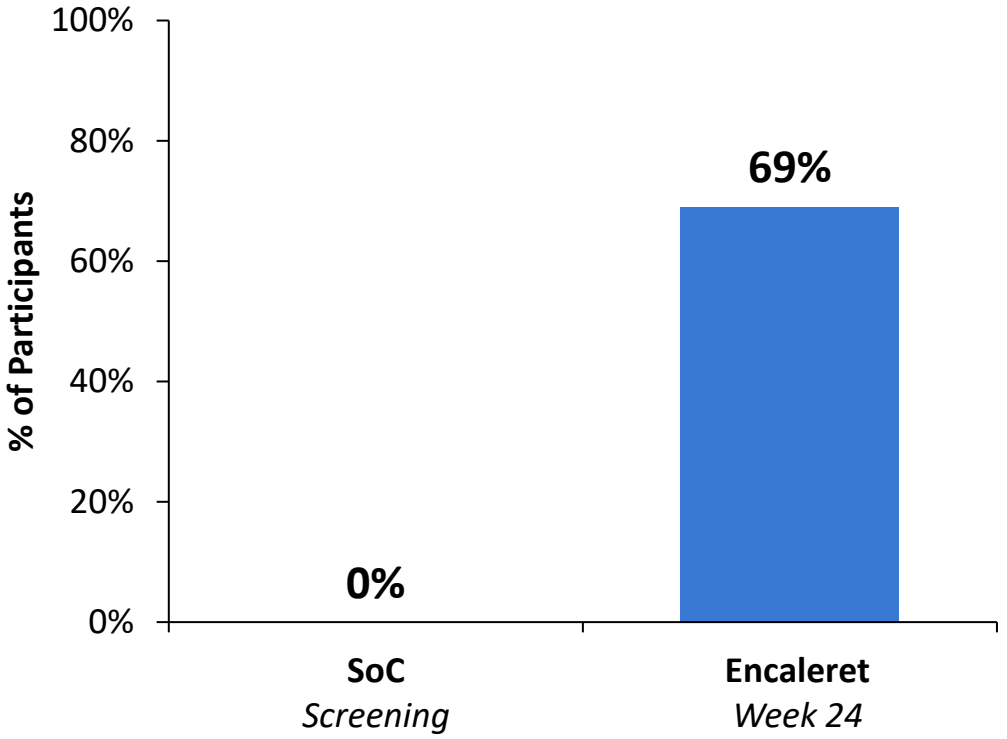
- Blood iPTH, 1,25-$(OH)_2$ Vitamin D, magnesium, and phosphate
- Urine magnesium and phosphate
- Bone turnover markers
- Renal ultrasound and renal function
- ER/urgent care visits and/or hospitalizations
- Quality of life (SF-36)

SoC = standard of care; a combination of oral activated Vitamin D and/or calcium supplements. CASR = calcium sensing receptor gene. Ca = calcium. iPTH = intact parathyroid hormone.

Based on Phase 2 results, 69% of participants responded to encaleret as intended by the planned Phase 3 primary composite endpoint

Individuals achieving both blood Ca and urine Ca in the target range

SoC vs Encaleret (n=13)



Ca = calcium; SoC = standard of care (calcium and active vitamin D)

Summary of encaleret Phase 2 data and next steps

Phase 2 Data

- ✓ Encaleret maintained normalized mean corrected blood calcium and 24-hour urine calcium excretion for 24 weeks
- ✓ Mean PTH increased and phosphate decreased into the normal range and were maintained for 24 weeks
- ✓ Encaleret was well-tolerated when administered twice daily over 24 weeks, with no serious adverse events reported
- ✓ Consistent improvements in mineral homeostasis suggest encaleret may become an effective treatment for ADH1

Anticipated Next steps

- ☐ **2H 2022**: Initiate Phase 3 CALIBRATE registrational study
- ☐ **2023:** Expect complete enrollment in CALIBRATE study
- ☐ **2023**: Announce top line Phase 3 data
- ☐ **2023+**: Continued updates from Phase 2 long-term extension

2019
- IND Opened

2020
- Phase 2 study initiated
- US ODD granted[1]

2021
- Ph2 PoC data reported
- FTD granted
- EU ODD granted[1]

2022
- Global regulatory authority interactions on registration approach
- Phase 2 data reported
- Plan to initiate Phase 3 study

2023+
- Announce Phase 3 topline data
- Initiate clinical studies in pediatric ADH1
- Evaluate encaleret in non-genetic hypoparathyroidism

[1]Orphan designation includes 7 years of market exclusivity in the US and 10 years in EU. PoC = Proof of Concept. FTD = Fast Track Designation. ODD = Orphan Drug Designation.