Encaleret (CLTX-305) Normalizes Mineral Homeostasis Parameters in Patients with Autosomal Dominant Hypocalcemia Type 1 in a 6-month Phase 2 Study [NCT04581629]

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National Institute of Dental and Craniofacial Research

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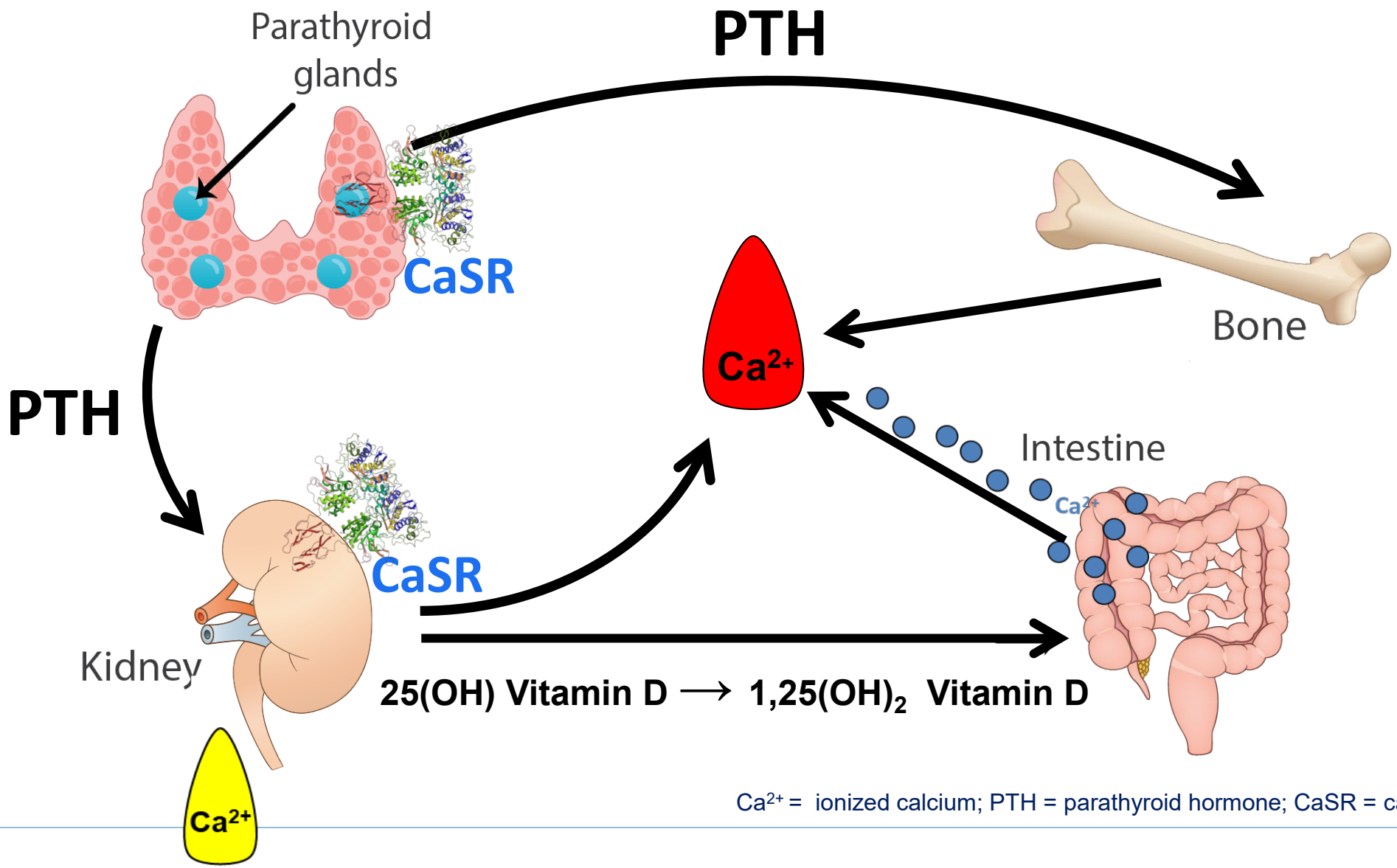
Disclosures

- This study was supported by a public/private partnership between the NIDCR Intramural Research Program and BridgeBio affiliate Calcilytix Therapeutics, Inc.
- Encaleret is currently under clinical development, and its safety and efficacy have not been evaluated by any regulatory authority.

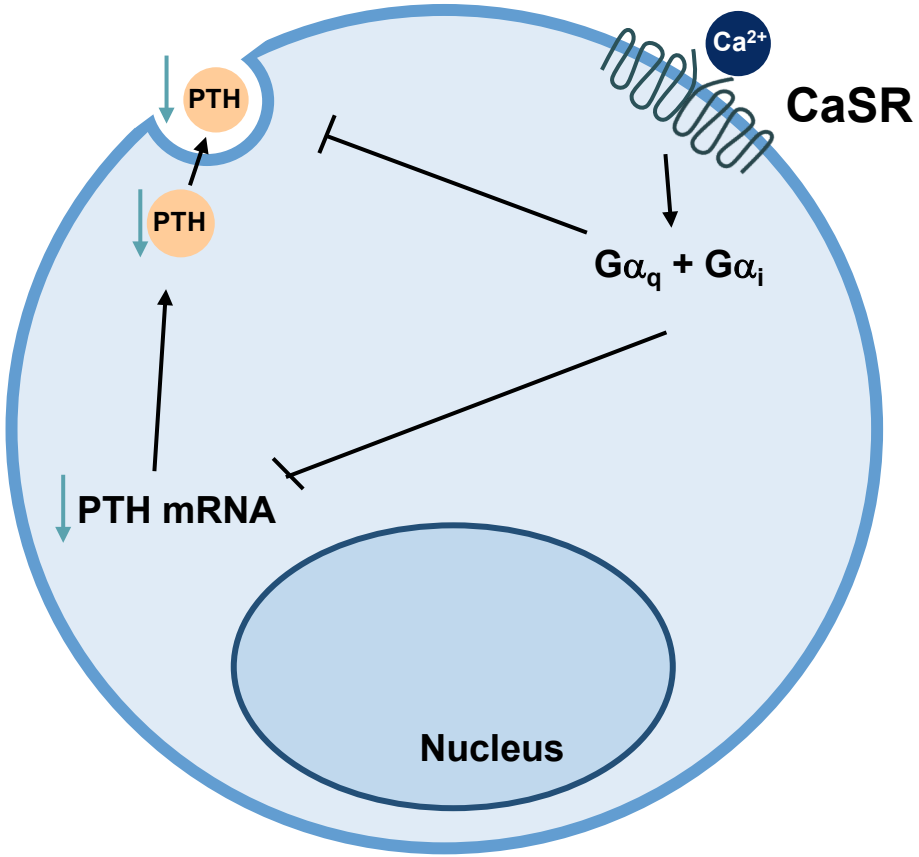
Blood calcium is regulated by PTH and the CaSR



Ca^{2+} = ionized calcium; PTH = parathyroid hormone; CaSR = calcium-sensing receptor

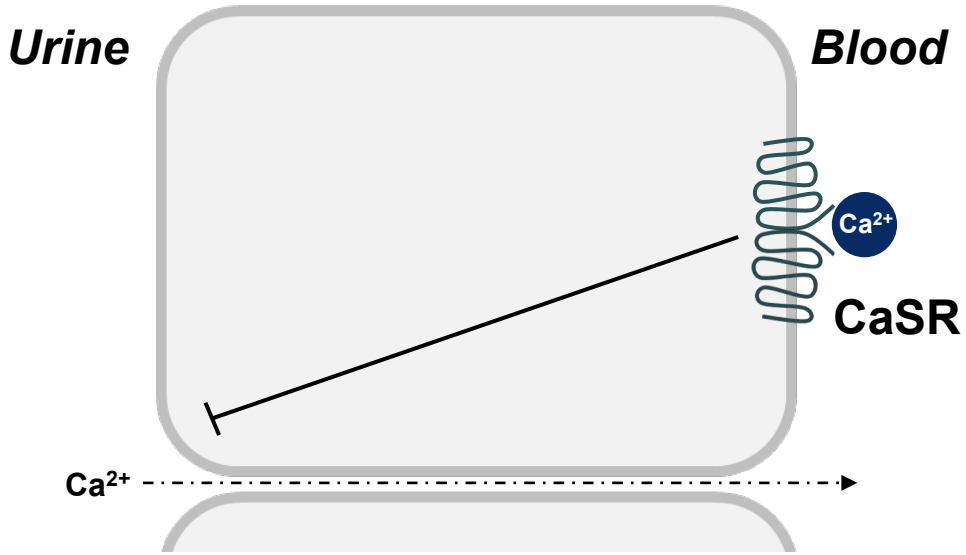
CaSR maintains blood calcium through action at the parathyroid gland and renal tubule

Parathyroid cell



CaSR decreases PTH synthesis and secretion in response to ↑ blood Ca^{2+}

Renal Tubule

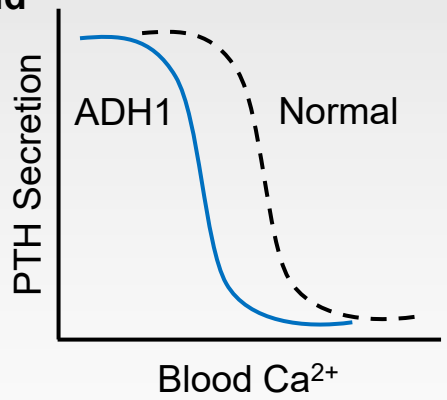


CaSR decreases renal tubular Ca^{2+} reabsorption in response to ↑ blood Ca^{2+}

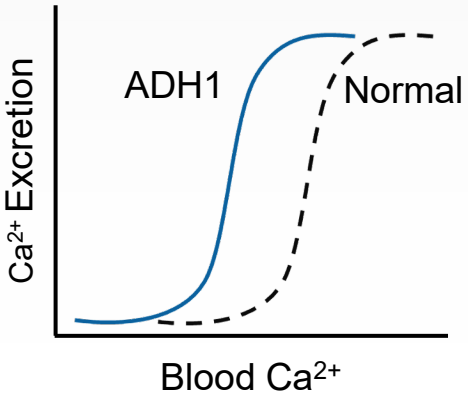
CASR activating variants cause Autosomal Dominant Hypocalcemia (ADH1)

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

Parathyroid



Kidney



Hyperactive CaSR causes

- PTH ↓ — **Decreased PTH secretion**
- Ca^{2+} ↓ — **Decreased blood calcium**
- Ca^{2+} ↑ — **Increased urinary calcium**

Clinical Manifestations

Acute symptoms

Hypocalcemic seizures

Paresthesia

Tetany

Muscle cramps

Long-term complications

Nephrolithiasis

Nephrocalcinosis

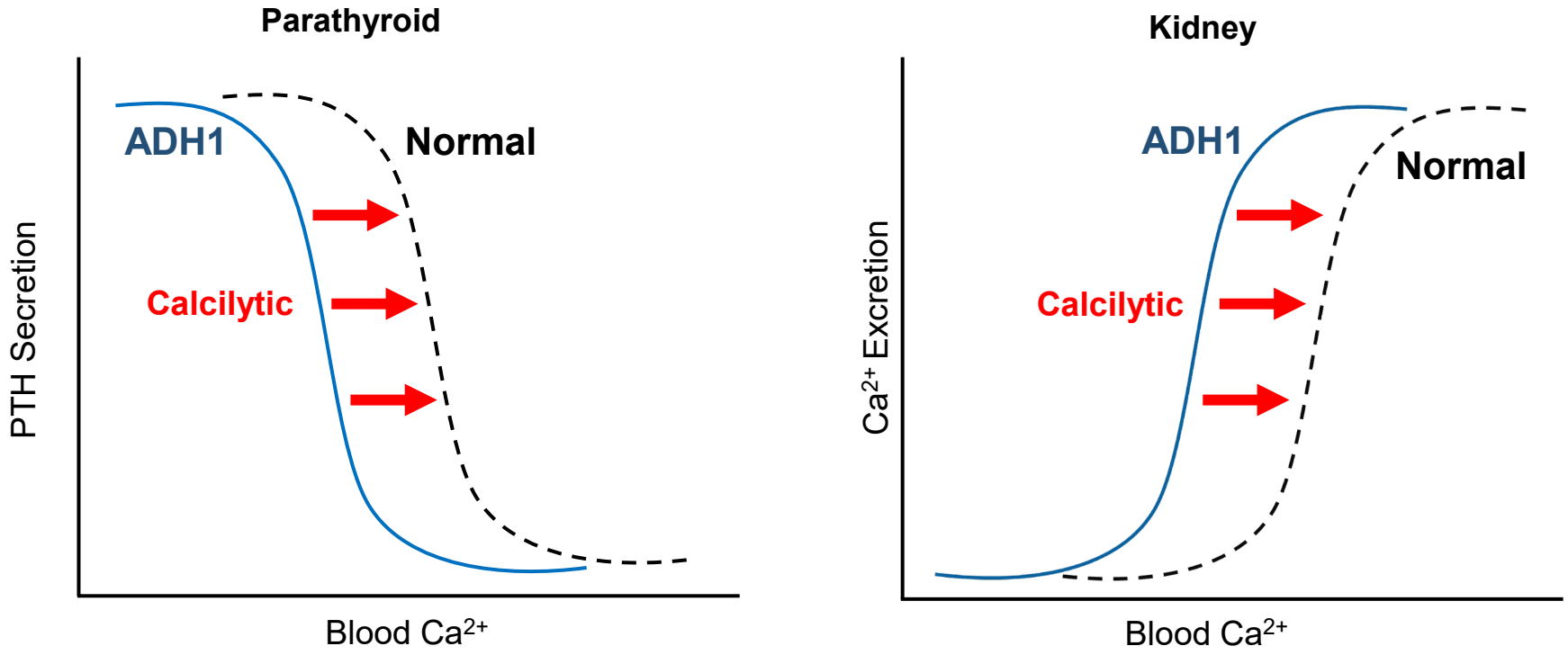
Chronic Kidney Disease

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

Roszko, et al. Front. Physiol. 2016.

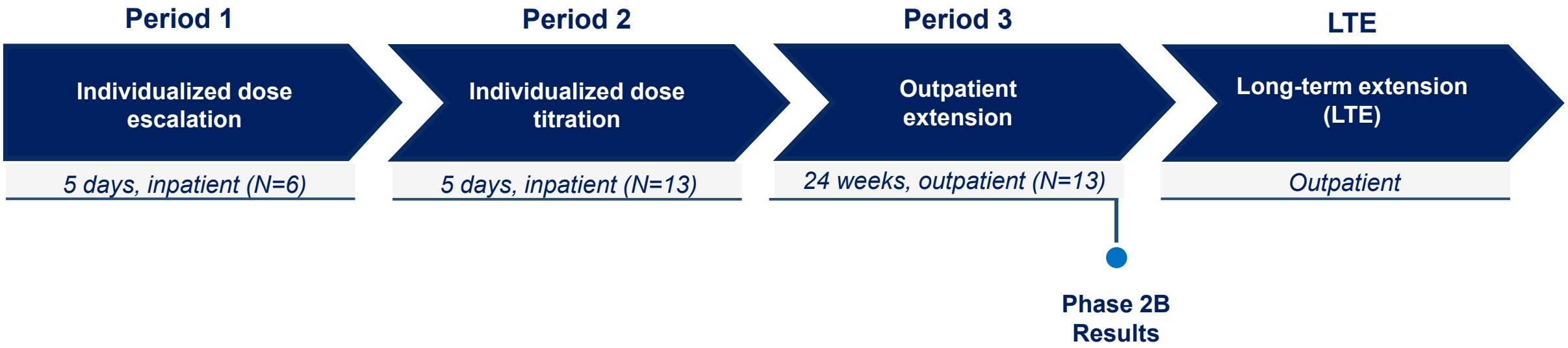
Encaleret, an investigational oral calcilytic, may be a potential treatment for ADH1

- 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



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
- Urine calcium
- Intact parathyroid hormone

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)

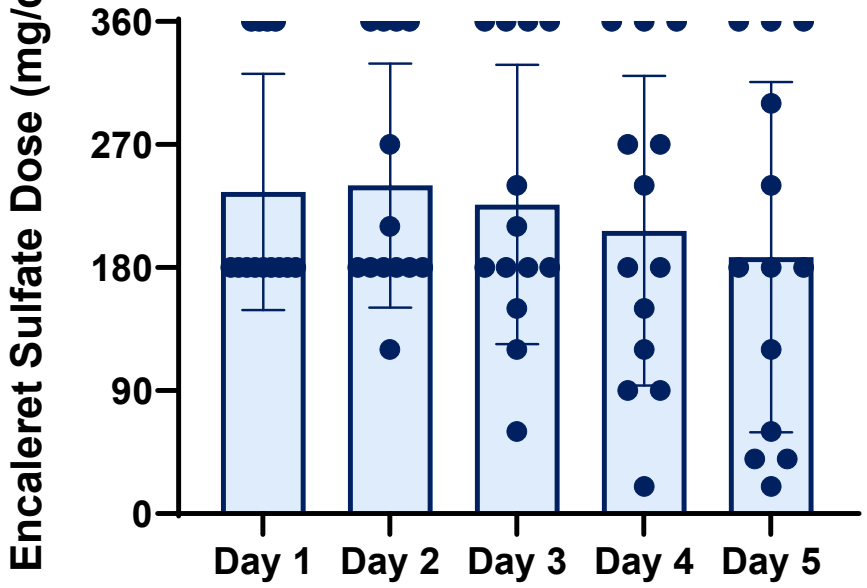
Baseline Characteristics

Characteristic	Study Population (N = 13)	*Normal Range*
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Corrected Calcium[1,2] (mg/dL)	7.1 ± 0.4	8.4 –10.2
Intact PTH (pg/mL)	6.3 ± 7.8	15 – 65
Phosphate (mg/dL)	4.5 ± 1.1	2.3 – 4.7
Magnesium (mg/dL)	1.7 ± 0.2	1.6 – 2.6
24h Urine Calcium (mg/24h)	384 ± 221	< 250 - 300
Nephrocalcinosis/Nephrolithiasis, n (%)	10 (77%)	
eGFR (mL/min/1.73 m^2)	84 ± 25	>60
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)	

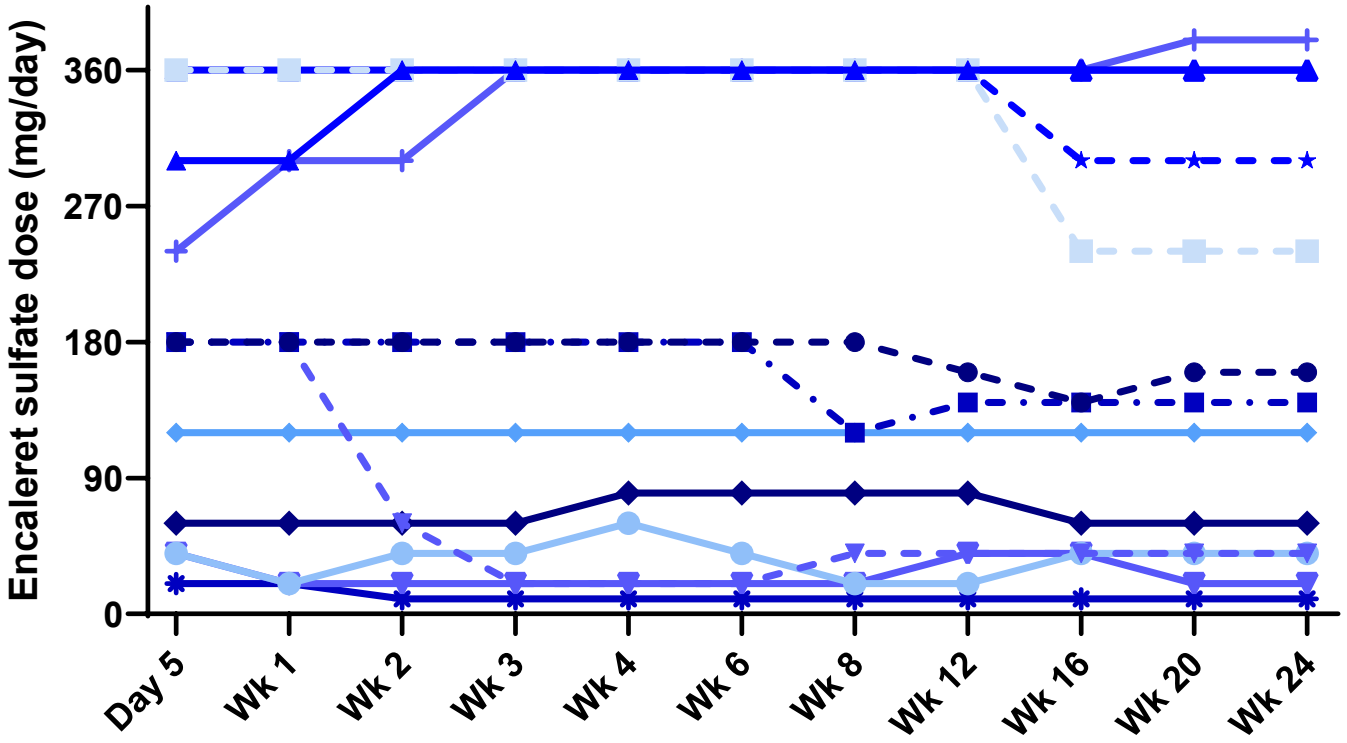
Data reported as mean±SD. eGFR = estimated glomerular filtration rate calculated by the CKD-EPI equation.
1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1, Period 2.

Encaleret Dosing

Period 2 Dosing*



Period 3 Dosing*



*Administered in two divided doses per day

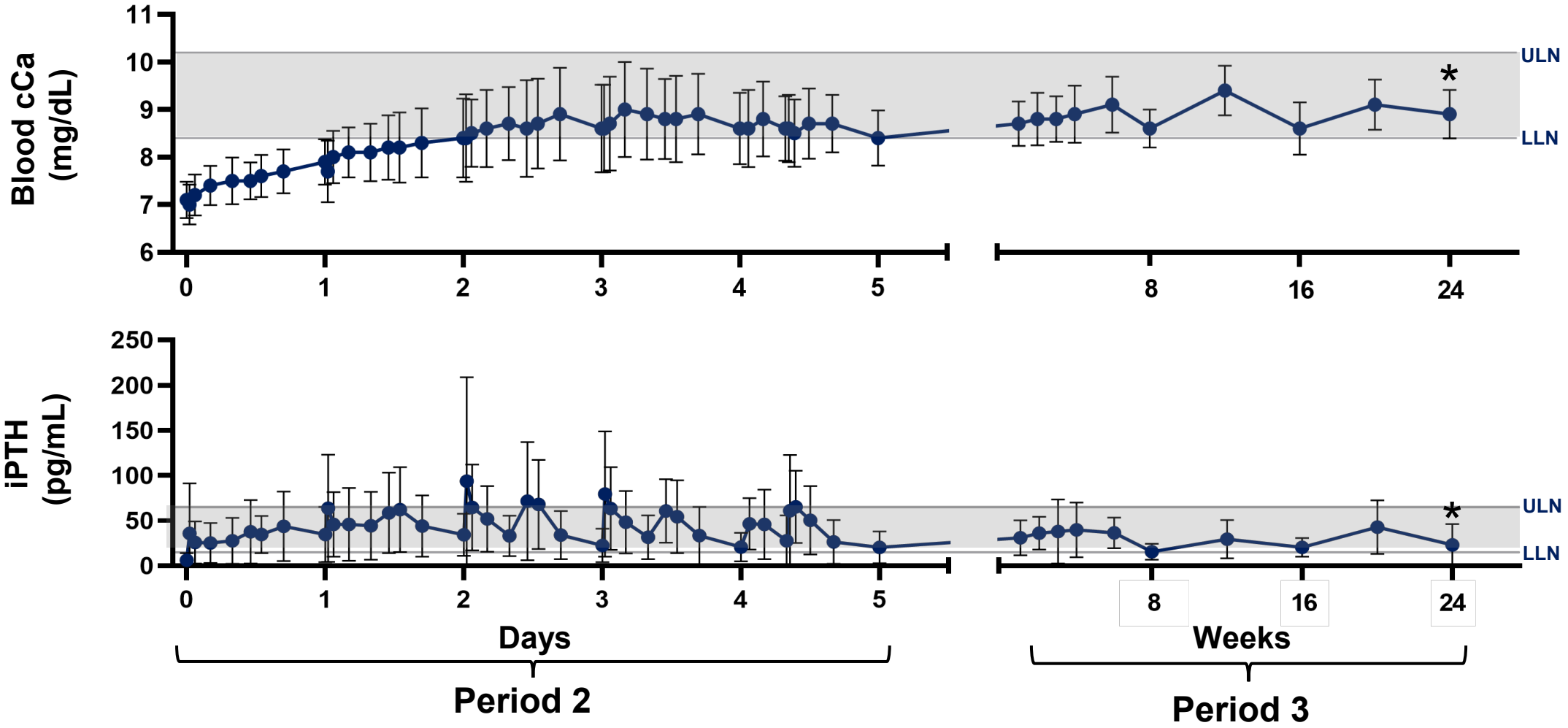
Period 2 dosing reported as mean±SD. One patient temporarily was administered once daily dosing until a lower dosage was available.

Encaleret was well-tolerated with no serious adverse events (AEs)

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

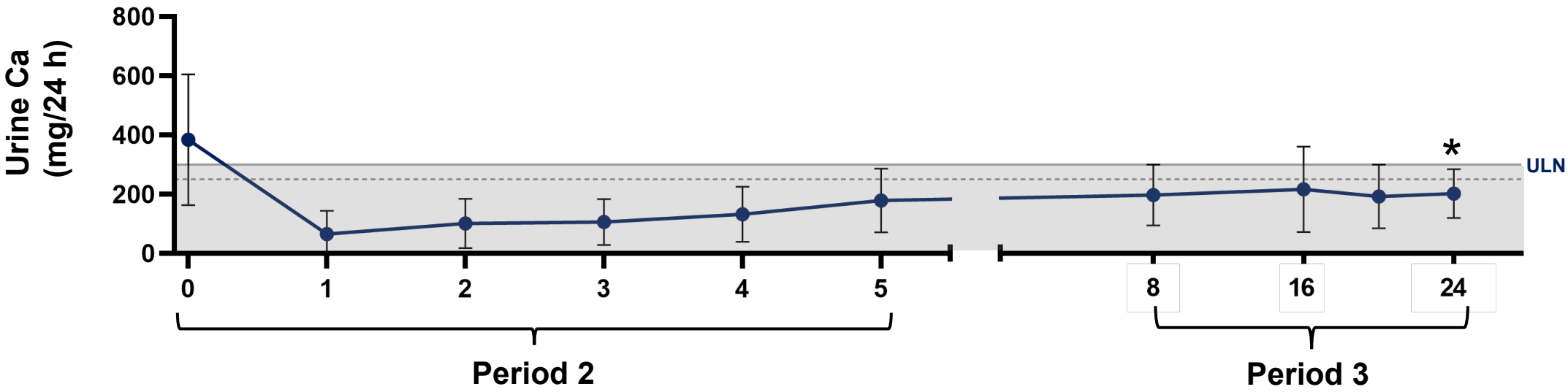
Data as of Mar 8, 2022. 1. Treatment-related adverse events were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs.

Encaleret increased mean blood calcium and mean iPTH



*p-value < 0.01 Week 24 mean compared to Baseline. 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. cCa values shown for weeks 8, 16, and 24 are pre-dose levels.

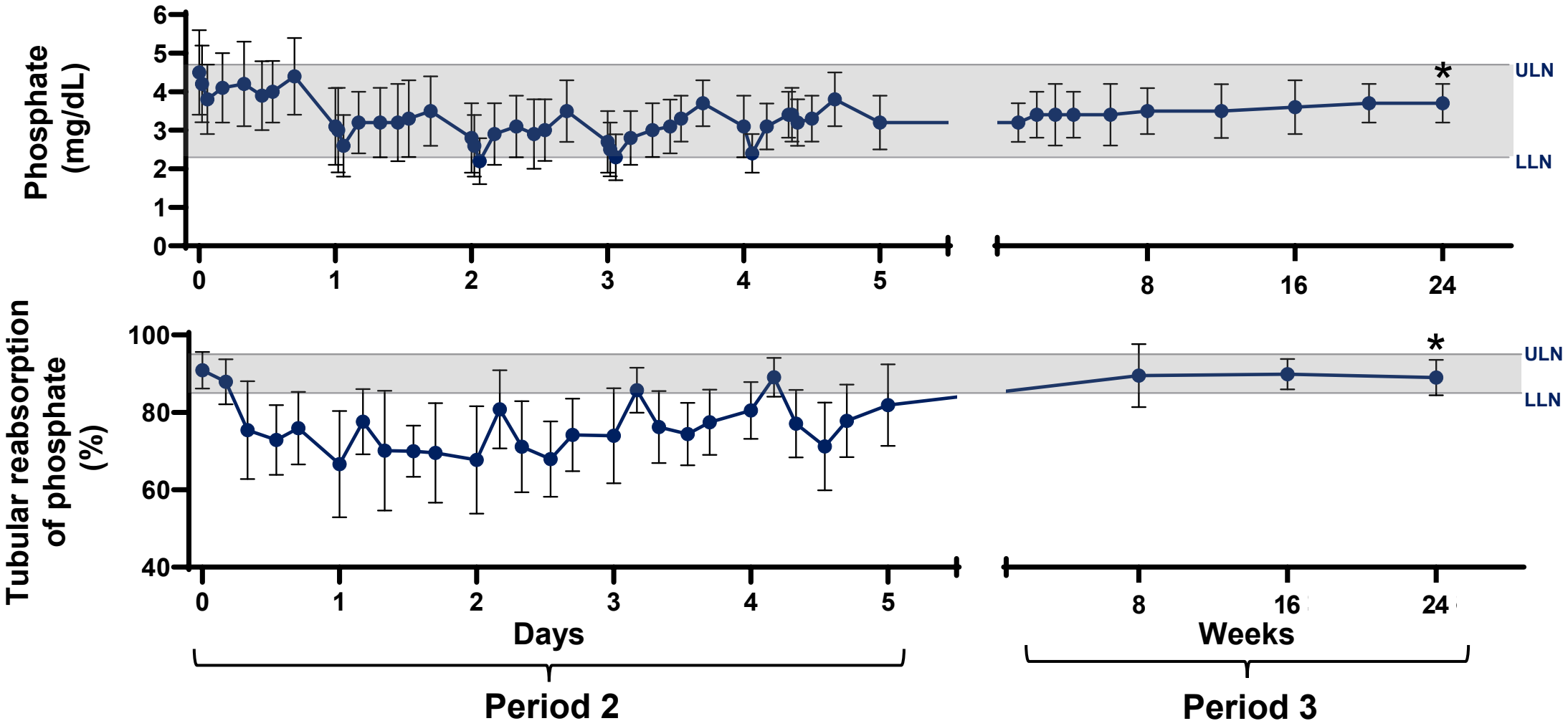
Encaleret decreased mean urine calcium into the normal range



No progression of renal calcifications on ultrasound at Week 24

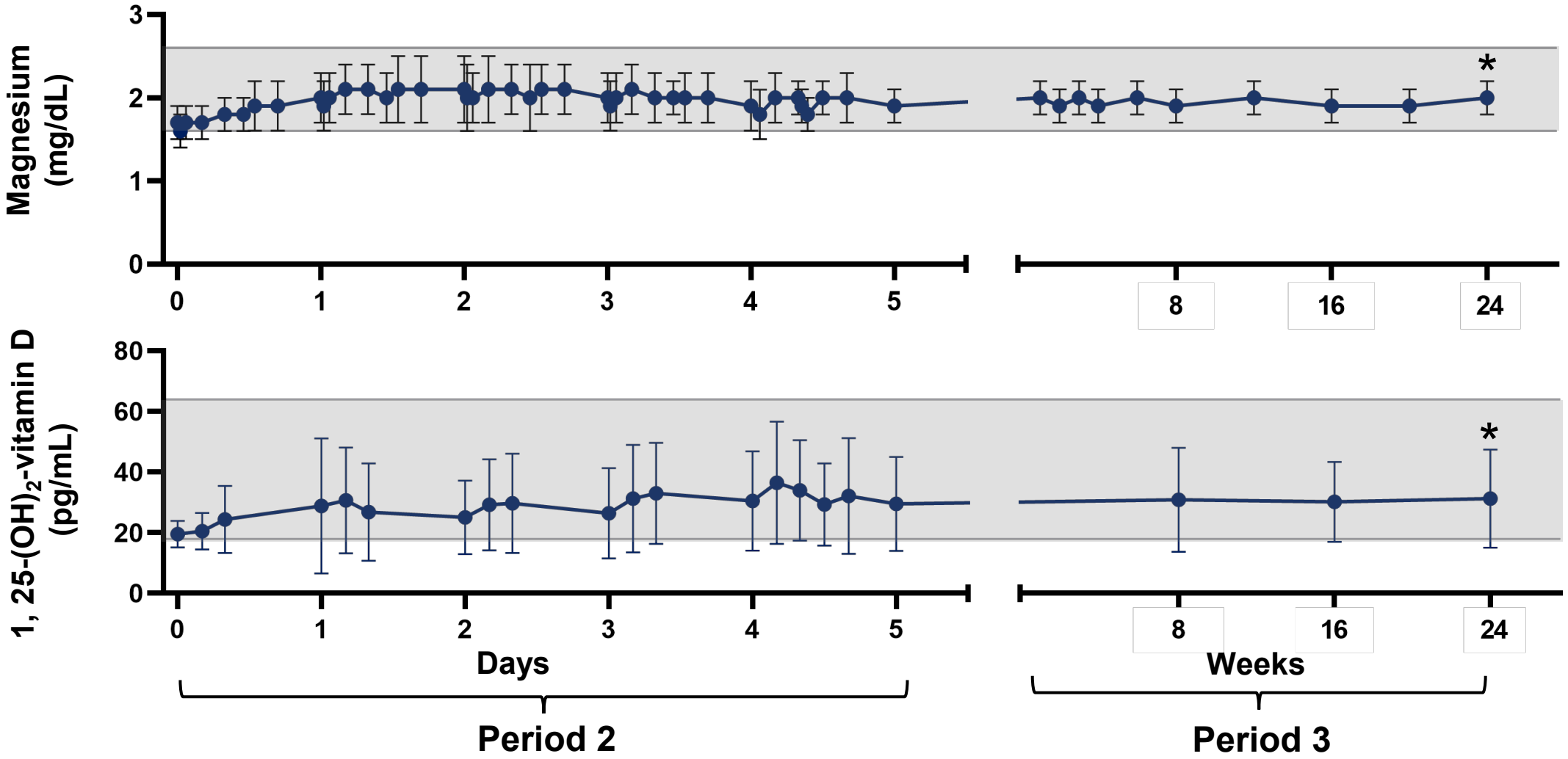
*p-value < 0.01 Week 24 mean compared to Baseline. Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. Solid line = male ULN; dashed line = female ULN.

Encaleret decreased mean blood phosphate and acutely lowered mean TRP



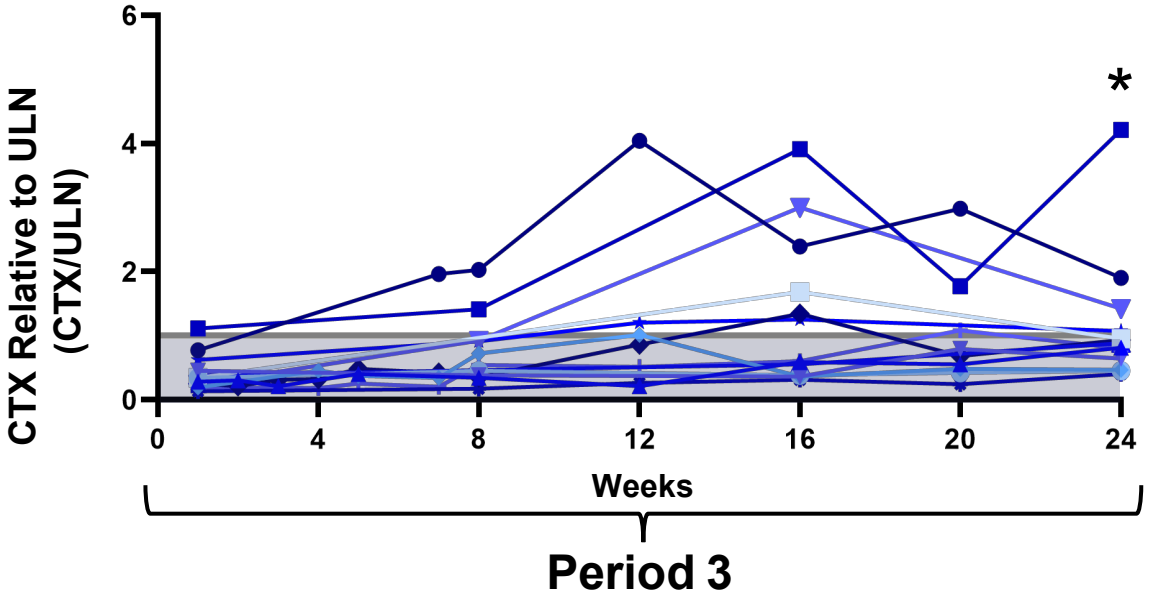
* p-value < 0.01. Week 24 mean compared to Baseline. Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. The measures shown for weeks 8, 16, and 24 are pre-dose levels.

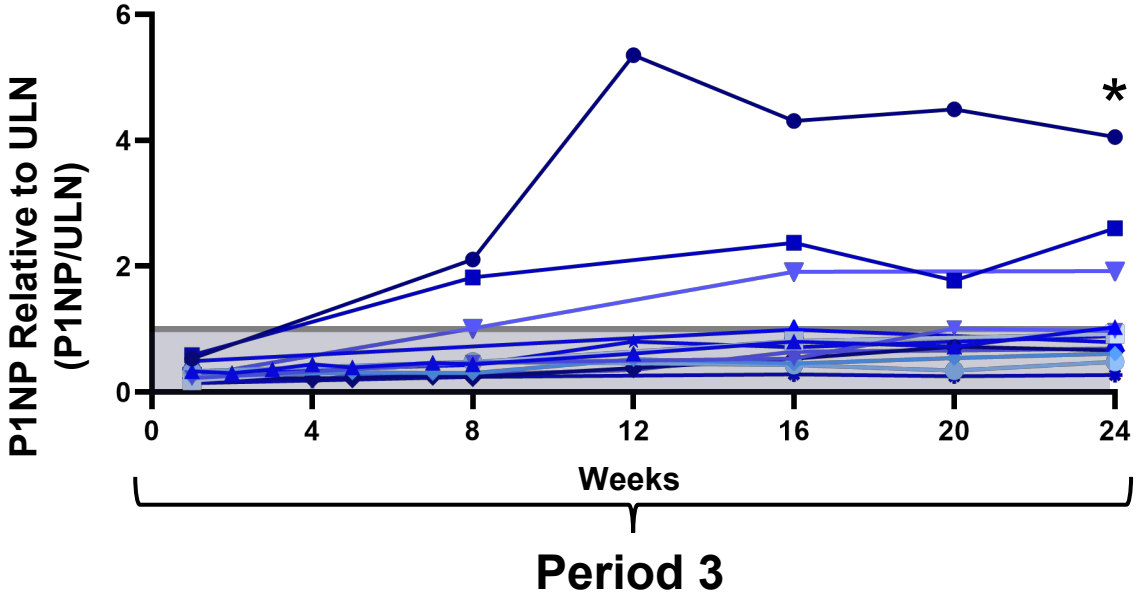
Encaleret increased mean blood magnesium and mean 1,25-$(OH)_2$-vitamin D



*p-value < 0.01 Week 24 mean compared to Baseline. 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-dose levels.

Encaleret increased bone turnover markers





*p<0.01, mean change from baseline vs 24 weeks, Data as of Mar 8, 2022. CTX and P1NP corrected for sex and menopausal status. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-dose levels.

Encaleret had minimal short-term effects on bone density

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

* $p < 0.05$. Data as of Mar 8, 2022. DXA data not available on 2 participants due to surgical hardware.

Summary

- Encaleret restored mineral homeostasis in 13 individuals with ADH1, as demonstrated by:
  - Normalization of the following mean values:
    - iPTH
    - Blood calcium
    - 24-hr urine calcium
    - Blood phosphate
    - Blood magnesium
    - $1,25(OH)_2$-vitamin D
  - Increase in bone turnover (within normal range in 10/13 participants)
- Encaleret was well-tolerated over 24 weeks, with no serious adverse events reported
- Long-term extension is ongoing
- Phase 3 study planned for initiation in late 2022

Acknowledgements

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NIH National Institute of Dental and Craniofacial Research