Sustained Normalization of Mineral Homeostasis in Autosomal Dominant Hypocalcemia Type 1: Results from a Phase 2 Study Over 42 Months of Encaleret (CLTX-305) Treatment (NCT04581629)

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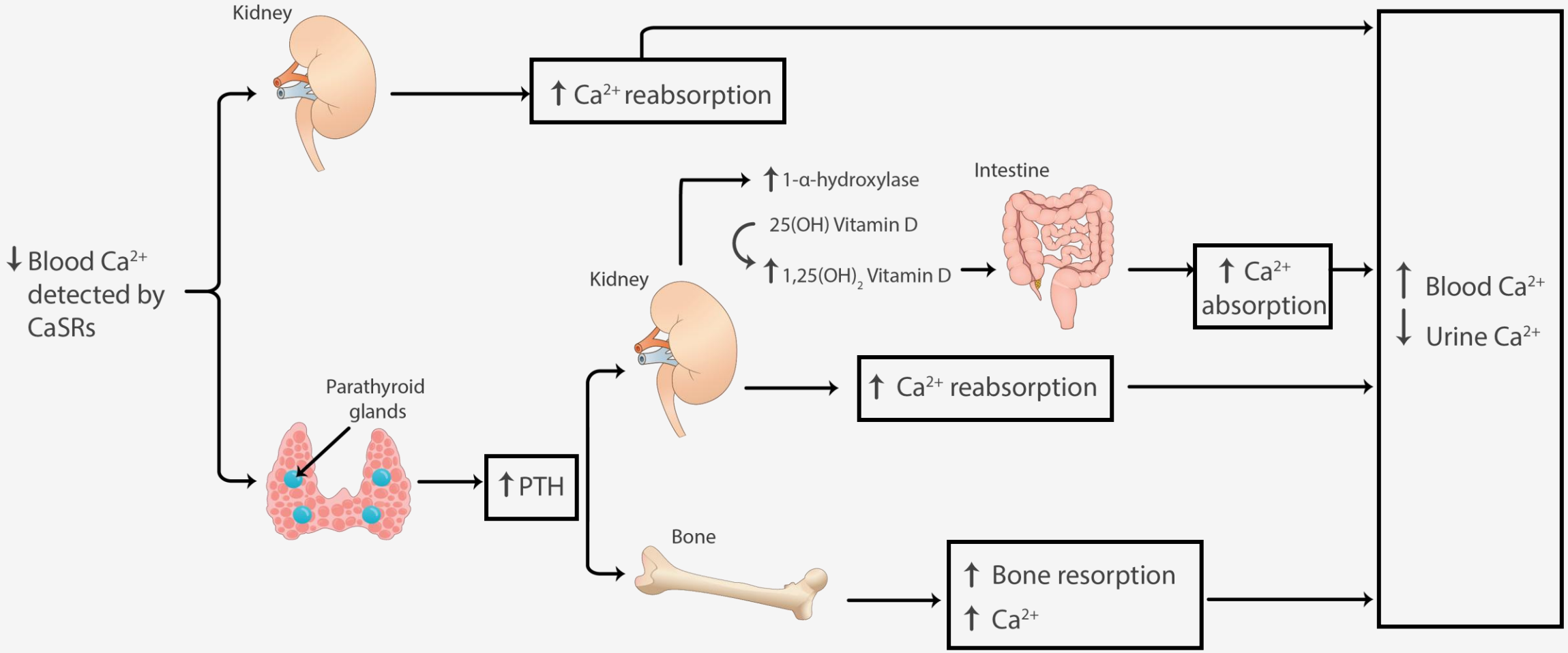
Disclosures

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.

The views expressed in this educational program are those of the faculty and do not necessarily represent the views of the Endocrine Society

Blood calcium is maintained by four organs regulated by the CaSR and PTH

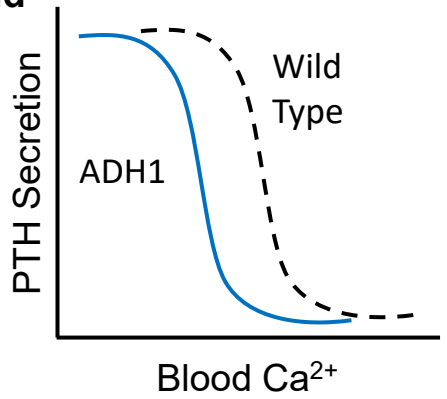


Ca^{2+} = ionized calcium; PTH = parathyroid hormone; CaSR = calcium-sensing receptor

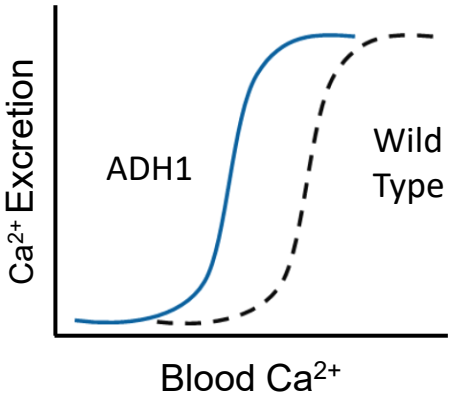
Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia Type 1 (ADH1)

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

Parathyroid



Kidney



Hypersensitive CaSR causes dysregulation of Ca homeostasis

- 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

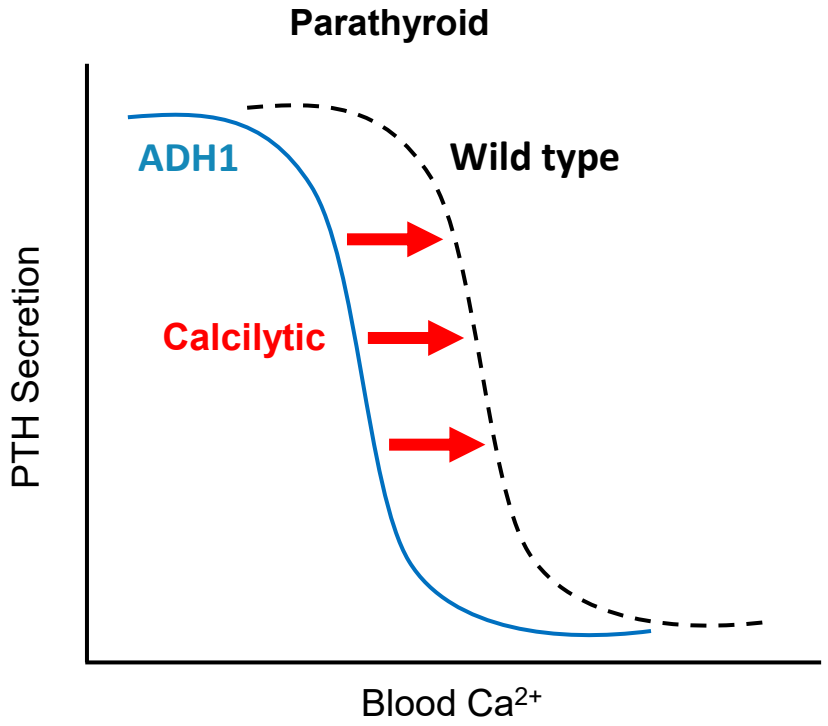
Chronic Kidney Disease

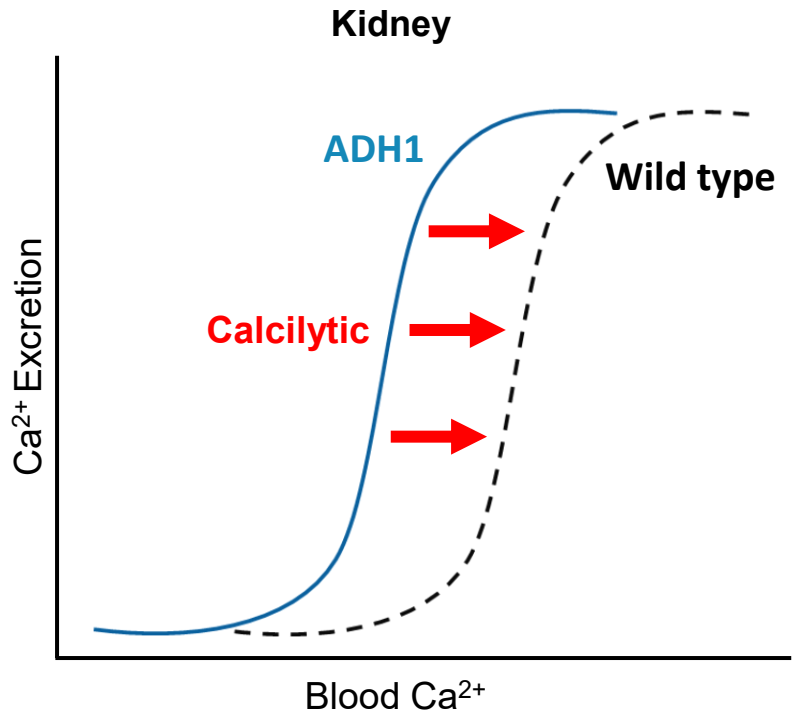
Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

Roszko, et al. Front. Physiol. 2016.

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

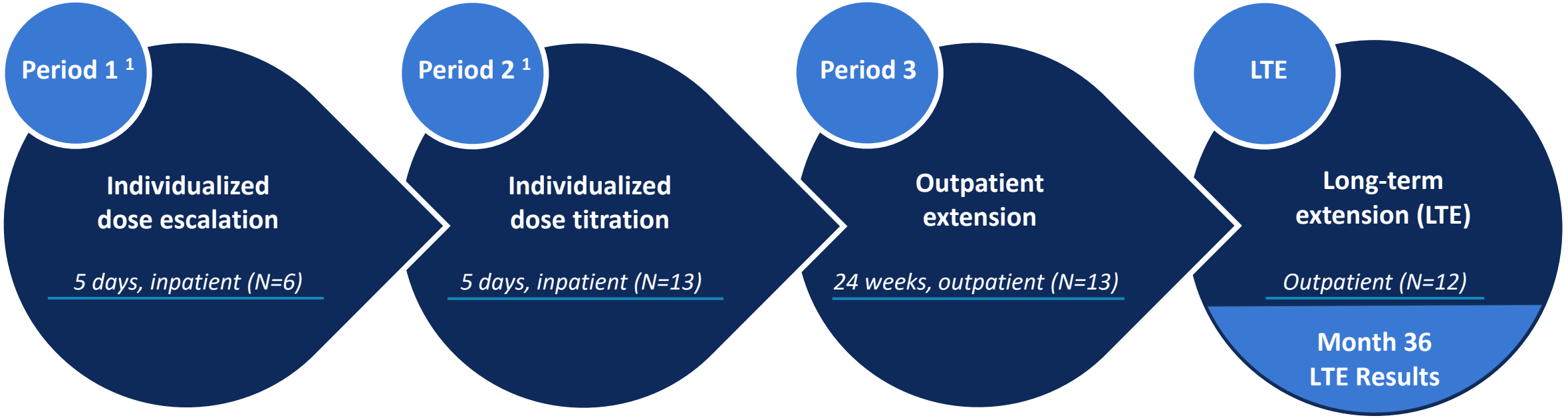
- Encaleret is an investigational negative allosteric modulator of the CaSR that can decrease CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1





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)

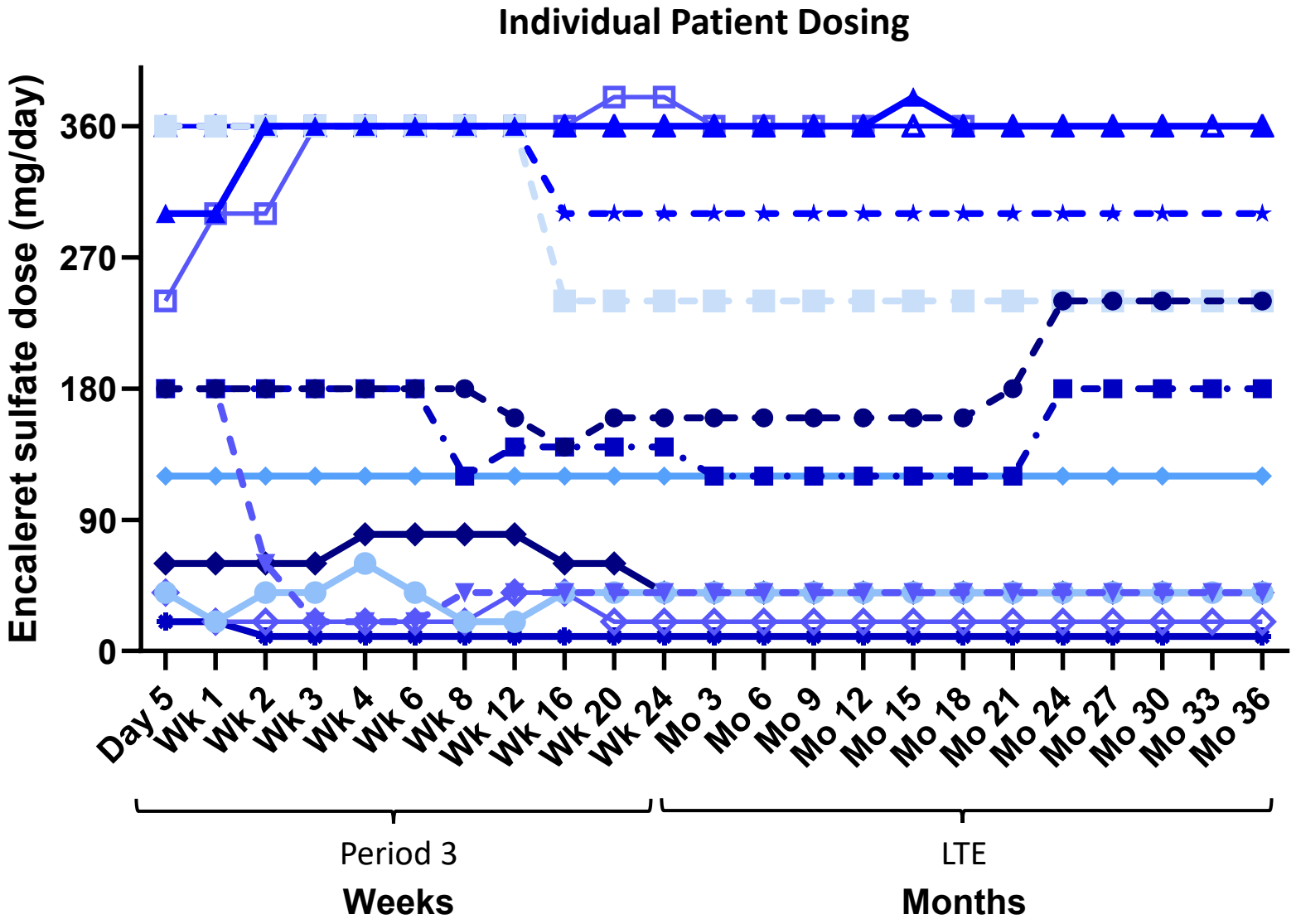
1. Standard of care (calcium and active vitamin D) was discontinued prior to the first encaleret dose.

Baseline Characteristics

Characteristic	Study Population (N = 13)	*Normal Range*
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
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.

Phase 2B Oral Encaleret Dosing Summary



Period 3 (n=13)

Optimized dose adjustments

Week 24 Mean+SD: **172±140 mg/day**

LTE (n=12)

Maintenance dose

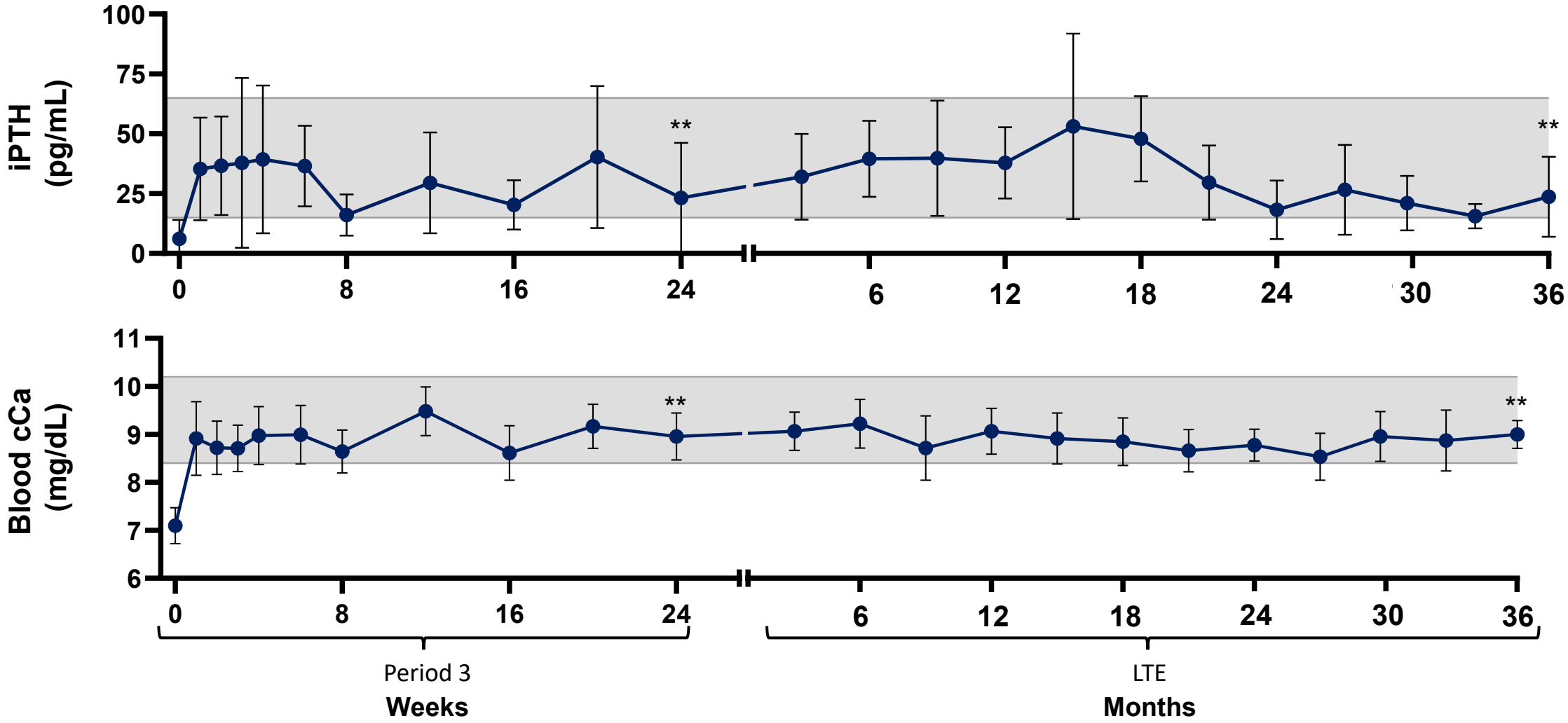
Month 36 Mean+SD: **151±133 mg/day**

Encaleret was overall well-tolerated

	Periods 2 and 3 N=13	LTE N=13
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**	**2 (15%)**
Post-operative right shoulder pain		1
Chest pain		1
Number of subjects experiencing any Treatment-Emergent Adverse Event (TEAE)	**13 (100%)**	**13 (100%)**
Mild	13 (100%)	13 (100%)
Moderate	2 (15%)	8 (62%)
Severe	0	1 (8%)
Number of TEAEs Reported	**81**	**153**
Mild	79 (98%)	121 (79%)
Moderate	2 (2%)	31 (20%)
Severe	0	1 (1%)
Treatment-related TEAEs[1]	**16 (20%)**	**2 (1%)**
Hypophosphatemia	10 (63%)	0
Hypercalcemia	6 (37%)	2 (100%)

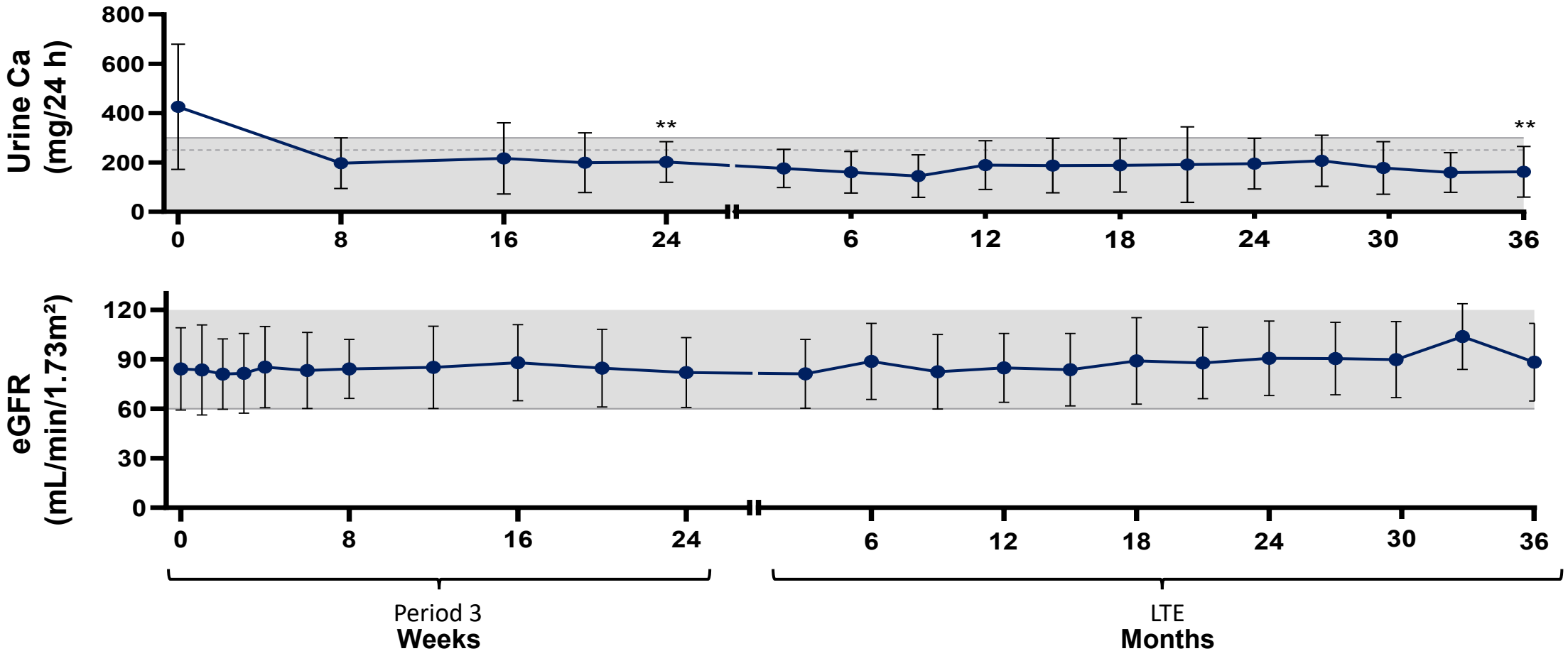
Data as of Mar 3, 2025. 1. Treatment-related TEAEs were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related TEAEs were counted as the number of events per period and are presented as a percentage of the total number of TEAEs.

Encaleret normalized mean iPTH and blood calcium over a 42-month period



Data reported as mean+SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range. Values shown for weeks 0, 8, 16, and 24 are pre-encaleret.
** p-value < 0.01 Week 24 and LTE Month 36 compared to Baseline.

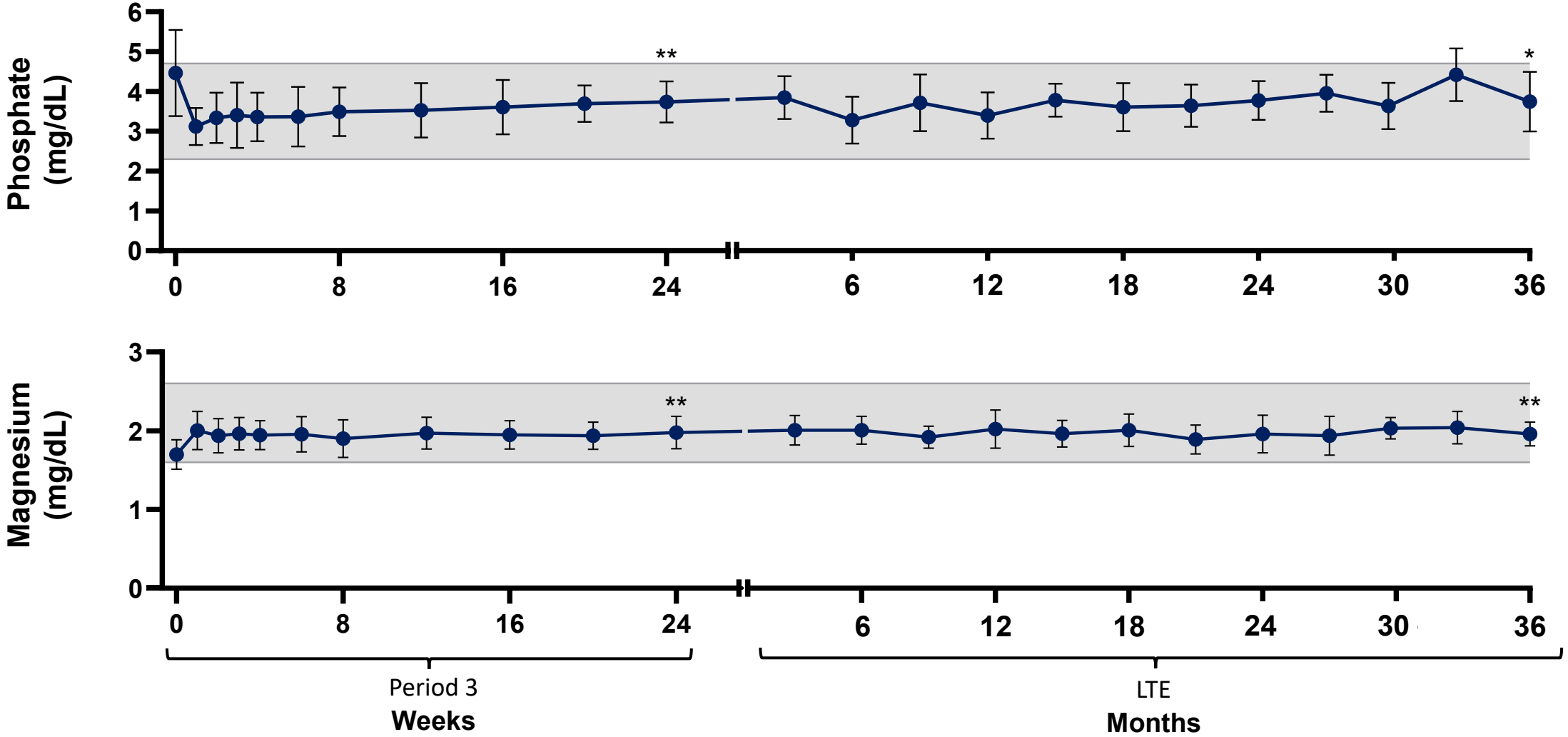
Encaleret decreased mean urine calcium into the normal range with no change in eGFR over 42 months



No progression of renal calcifications on ultrasound observed at Period 3 Week 24, LTE Month 12, 24, or 36

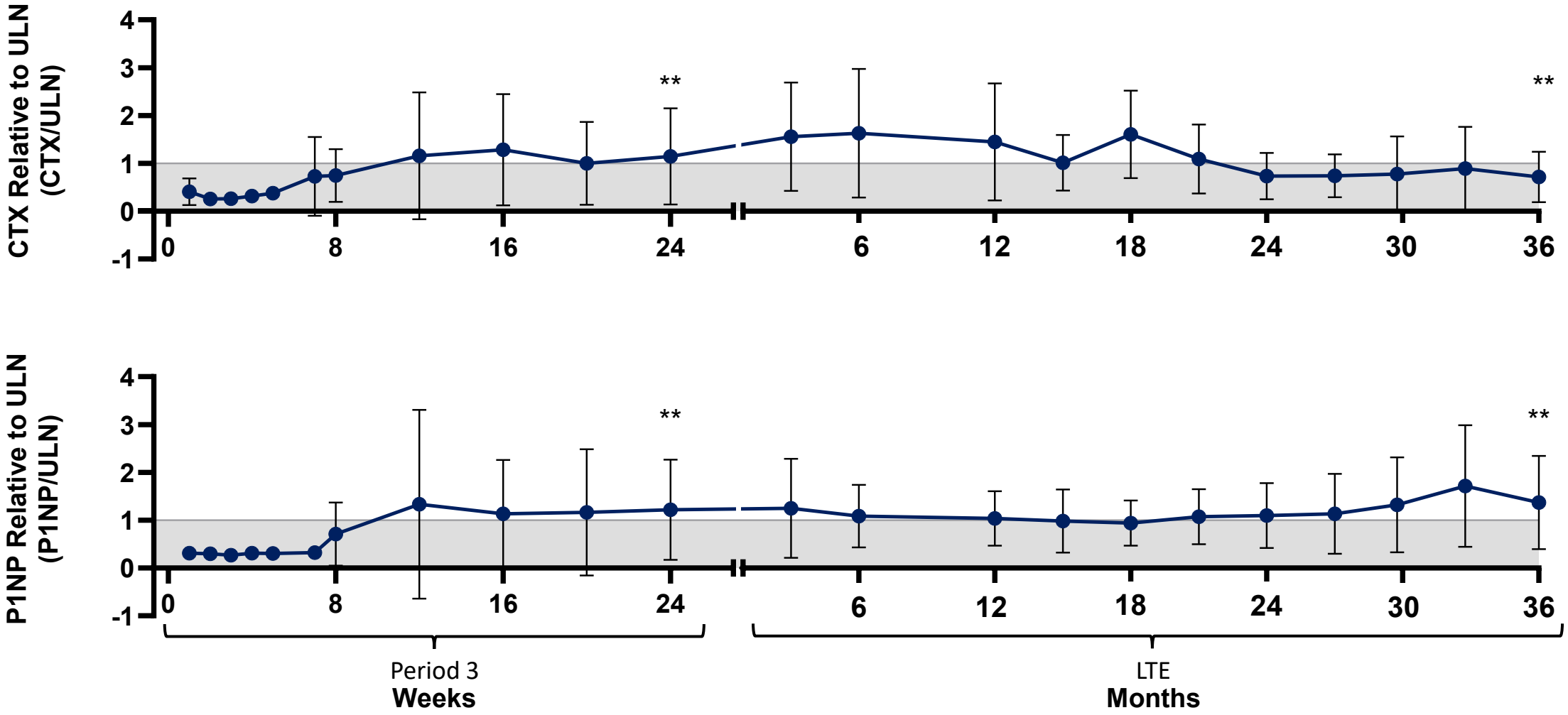
Data reported as mean+SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. ** p-value < 0.01 Week 24 and LTE Month 36 compared to Baseline.

Encaleret decreased mean blood phosphate and increased mean blood magnesium



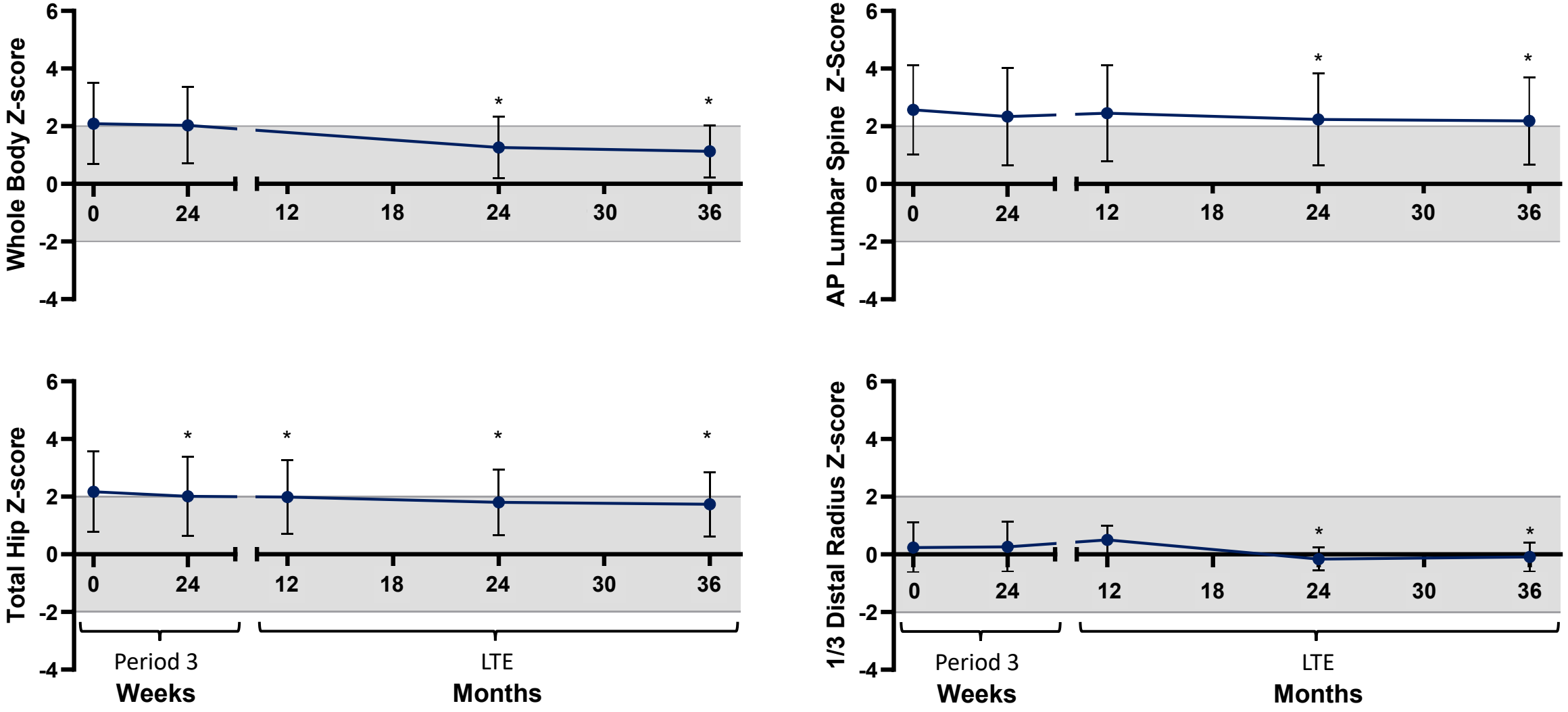
Data reported as mean+SD. Gray shading reflects normal range. The measures shown for weeks 0, 8, 16, and 24 are pre-encaleret. * p-value < 0.05, ** p-value < 0.01 Week 24 and LTE Month 36 mean compared to Baseline.

Encaleret increased bone turnover markers



Data reported as mean+SD after correcting for sex and menopausal status in individual participants. Gray shading reflects normal range. ** p-value < 0.01 Week 24 and LTE Month 36 mean compared to Baseline. Measures shown for weeks 8, 16, and 24 are pre-encaleret dose.

On encaleret, DXA Z-scores decreased from baseline at all sites at Month 24 but stabilized at Month 36



n=10-11. DXA data not available on 2 participants due to surgical hardware. * p< 0.05 compared with Baseline.

Summary

- In patients with ADH1, encaleret administered twice daily rapidly corrects and maintains mineral homeostasis within the normal range, as demonstrated by:
  - ✓ Increase in PTH
  - ✓ Correction of hypocalcemia
  - ✓ Normalization of mean 24-hr urine calcium
  - ✓ Reduction in mean blood phosphate
  - ✓ Increase in mean blood magnesium
- Bone turnover markers increased with some participants above the normal range
- BMD Z-scores decreased at 24 months but remained stable at 36 months
- Encaleret was well-tolerated over 42 months
- Participants continue on long-term encaleret treatment in the LTE of the Phase 3 [CLTX-305-302] CALIBRATE study
- CALIBRATE Phase 3 study topline data are anticipated in the second half of 2025

Acknowledgements

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