Encaleret (CLTX-305) Normalizes Mineral Homeostasis Parameters in Patients with Autosomal Dominant Hypocalcemia Type 1 over 24 months in a Phase 2 Study (NCT04581629)

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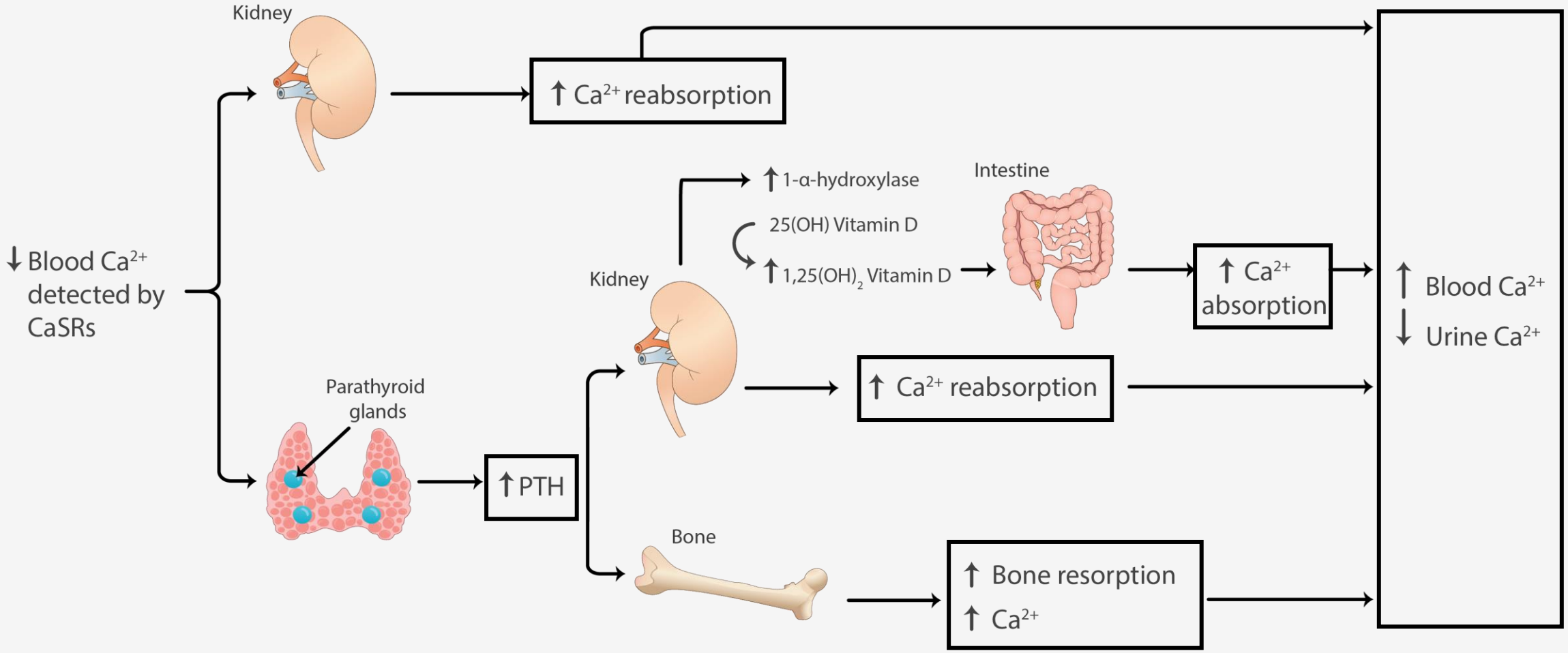
Disclosures

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.

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

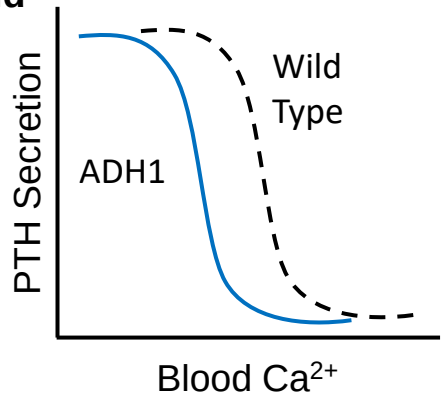


Ca^{2+} = ionized calcium; PTH = parathyroid hormone; CaSR = calcium-sensing receptor

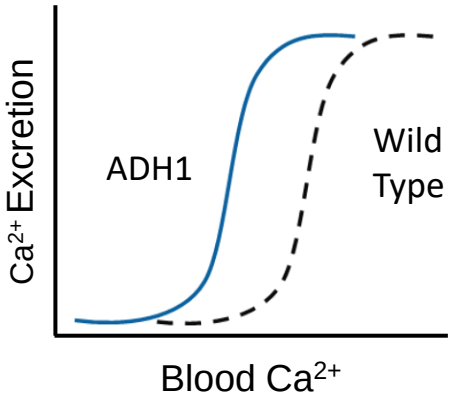
Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia Type 1 (ADH1)

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

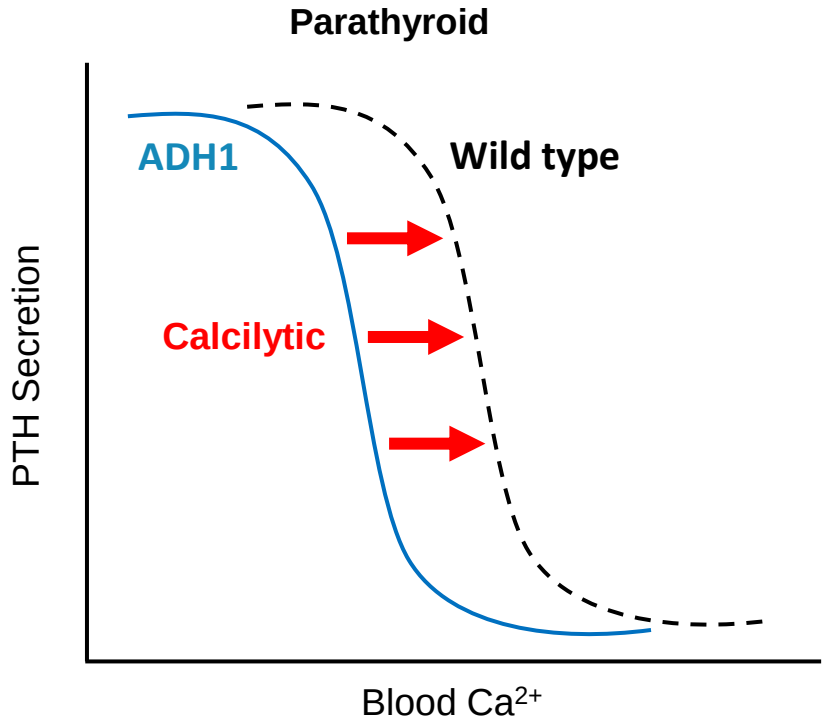
Chronic Kidney Disease

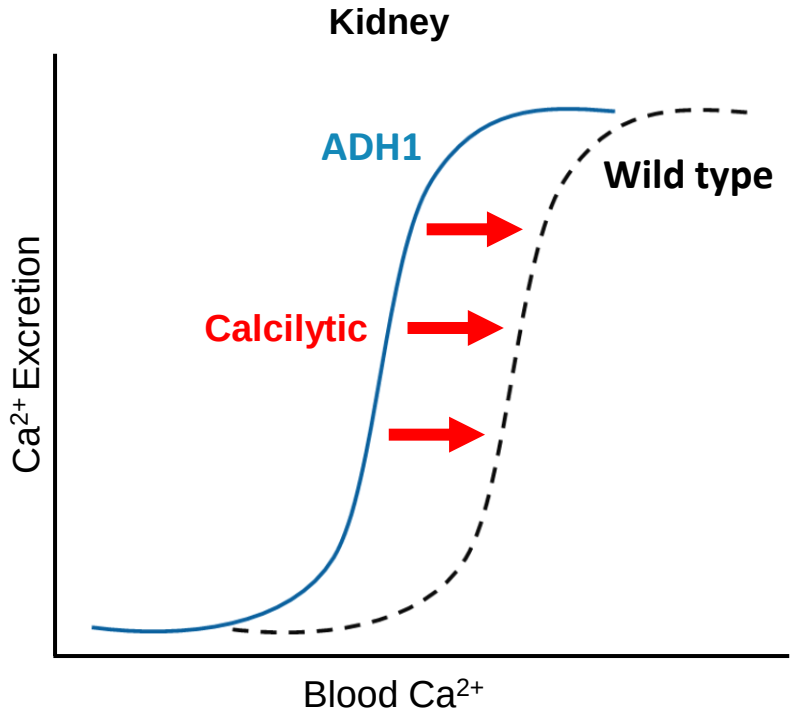
Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

Roszko, et al. Front. Physiol. 2016.

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

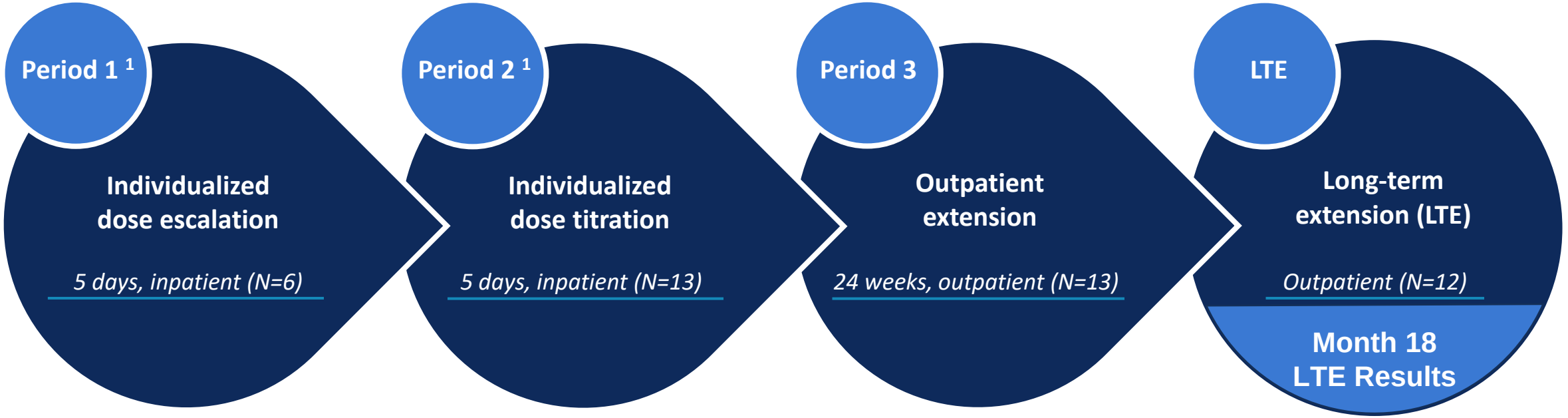
- Encaleret is an investigational negative allosteric modulator of the CaSR that can decrease CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1





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)

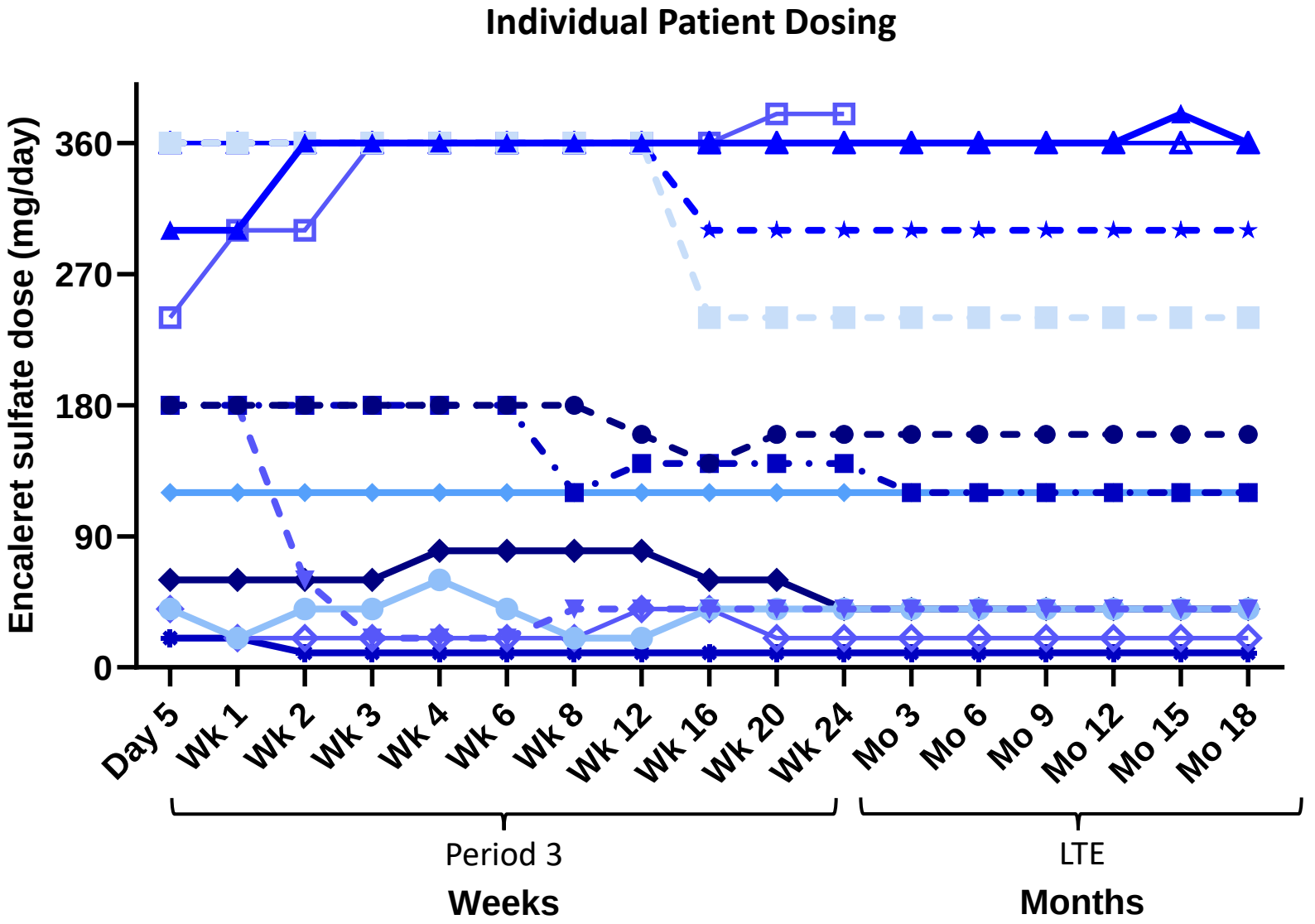
1. Standard of care (calcium and active vitamin D) was discontinued prior to the first encaleret dose.

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

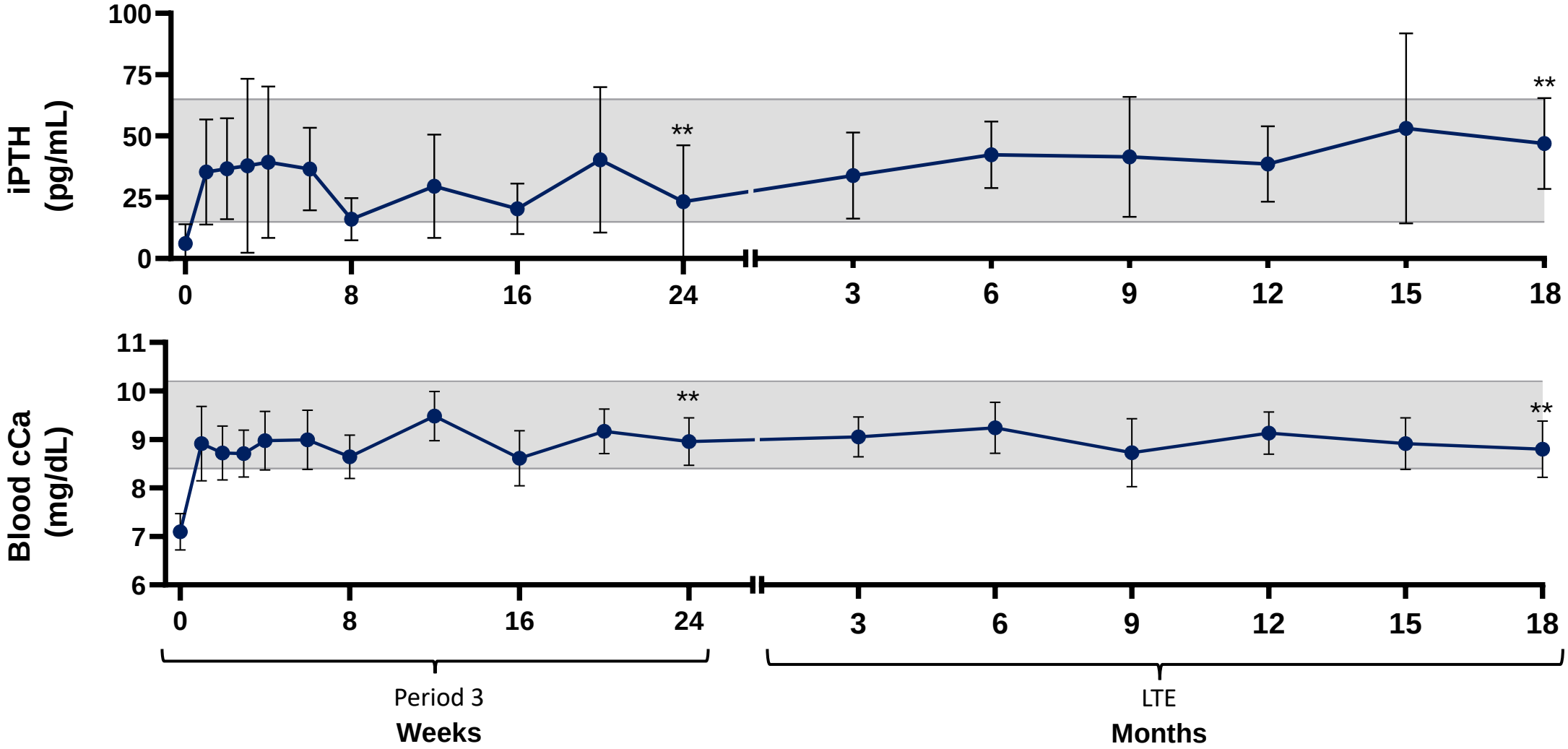
Month 18 Mean+SD: **151±133 mg/day**

Encaleret was well-tolerated with no serious adverse events reported

	Periods 2 and 3 N=13	LTE N=13
Number of subjects experiencing any Serious Adverse Event	**0 (0%)**	**0 (0%)**
Number of subjects experiencing any Treatment-Emergent Adverse Event (TEAE)	**13 (100%)**	**12 (92%)**
Mild	13 (100%)	12 (92%)
Moderate	2 (15%)	7 (54%)
Severe	0	0
Number of TEAEs Reported	**81**	**78**
Mild	79 (98%)	65 (83%)
Moderate	2 (2%)	13 (17%)
Severe	0	0
Treatment-related TEAEs[1]	**16 (20%)**	**1 (1%)**
Hypophosphatemia	10 (63%)	0
Hypercalcemia	6 (37%)	1 (100%)

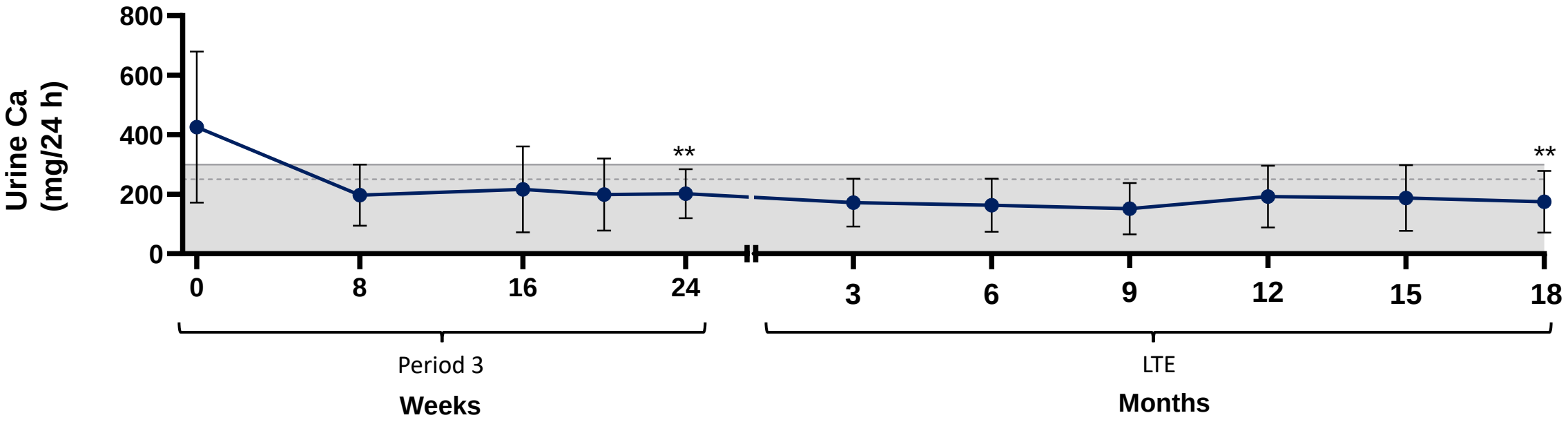
Data as of Dec 12, 2023. 1. Treatment-related TEAEs were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related TEAEs were counted as the number of events per period and are presented as a percentage of the total number of TEAEs.

Encaleret normalized mean iPTH and blood calcium over an 24-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 18 compared to Baseline.

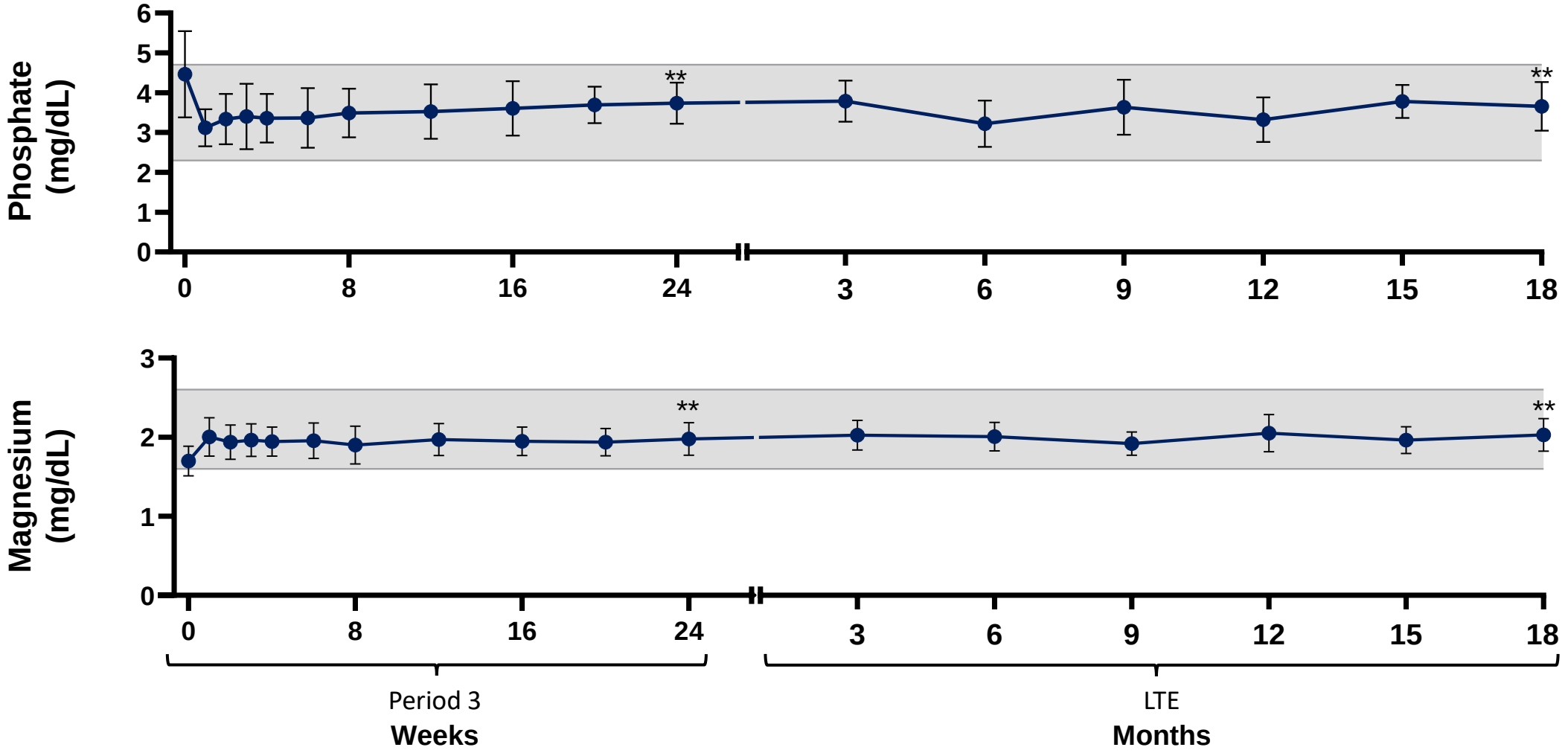
Encaleret decreased mean urine calcium into the normal range



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

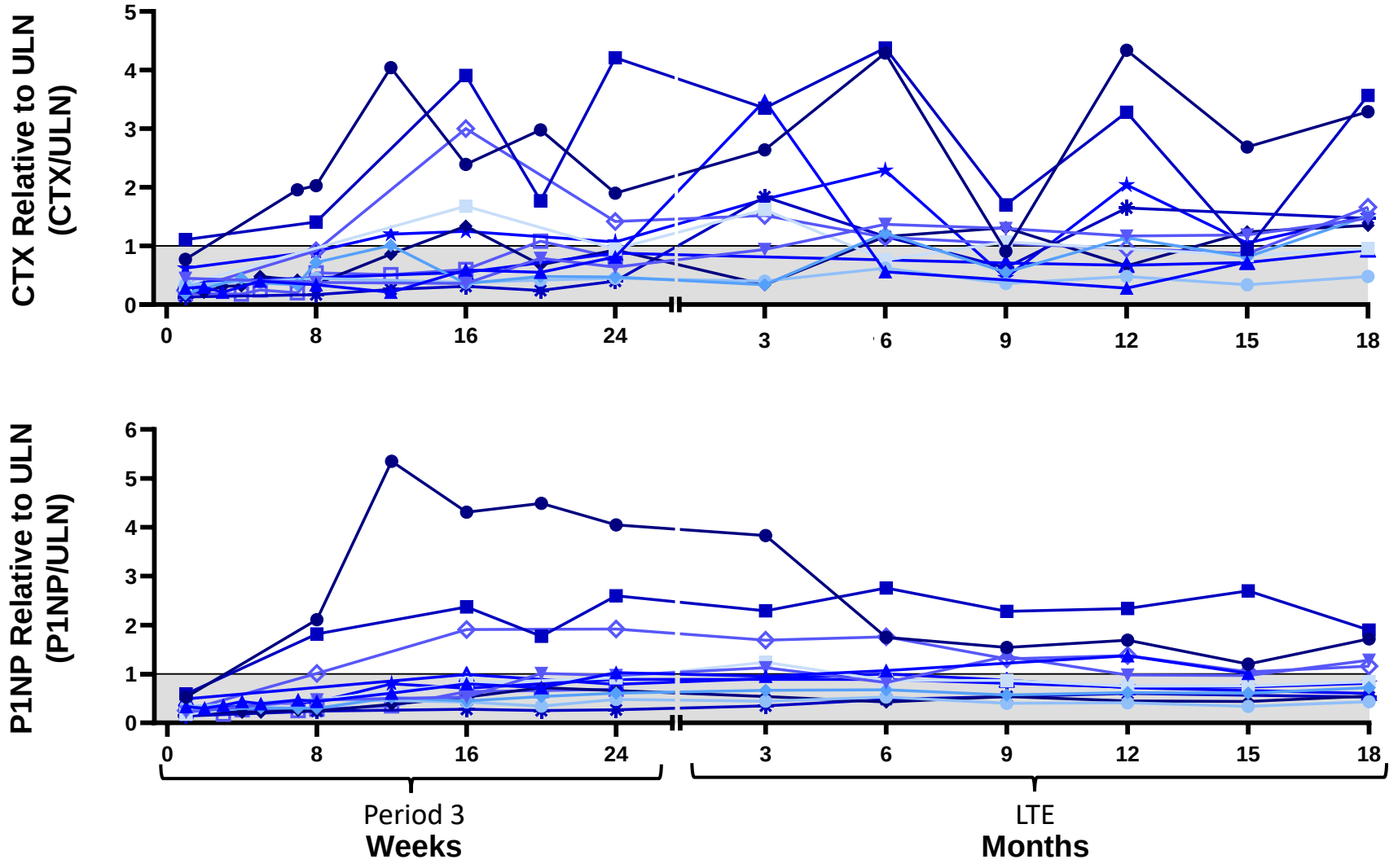
Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. ** p-value < 0.01 Week 24 and LTE Month 18 compared to Baseline.

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 < 0.01 Week 24 and LTE Month 18 mean compared to Baseline.

Encaleret increased bone turnover markers



8/12 participants >1 at LTE Month 18

5/12 participants >1 at LTE Month 18

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.

Encaleret had minimal short-term effects on bone density

DXA Anatomical Site n = 11	Screening Z-score Mean ± SD (n = 11)	Period 3, Week 24 Z-score Mean ± SD (n = 11)	LTE, Month 12 Z-score Mean ± SD (n = 10)
Total Body	2.1 ± 1.4	2.0 ± 1.3	N/A
AP Lumbar Spine	2.6 ± 1.5	2.3 ± 1.7	2.5 ± 1.7
Total Hip	2.2 ± 1.4	2.0 ± 1.4*	2.0 ± 1.3*
1/3 Distal Radius	0.2 ± 0.9	0.3 ± 0.9	0.5 ± 0.5

DXA data not available on 2 participants due to surgical hardware. * p< 0.05 compared with screening

Summary

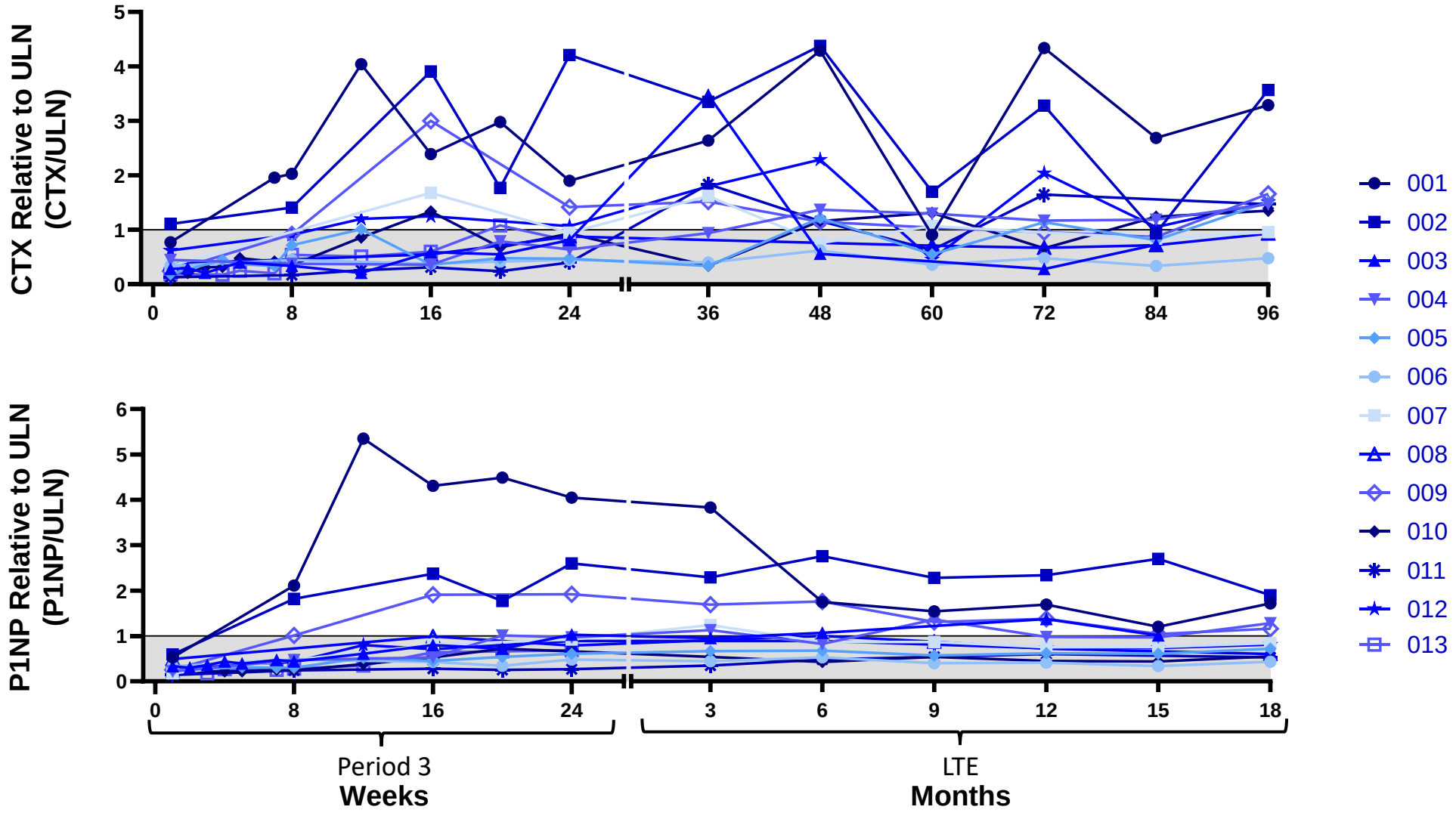
- In patients with ADH1, encaleret administered twice daily rapidly corrects and maintains mineral homeostasis within the normal range, as demonstrated by:
  - ✓ Increase in PTH
  - ✓ Correction of hypocalcemia
  - ✓ Normalization of mean 24-hr urine calcium
  - ✓ Reduction in mean blood phosphate
  - ✓ Increase in mean blood magnesium
- Bone turnover markers increased with some participants above the normal range
- BMD Z-scores were stable except for minimal decrease in the total hip
- Encaleret was well-tolerated over 24 months, with no serious adverse events reported
- This study is now closed as all patients have transitioned to the LTE of the Phase 3 [CLTX-305-302] CALIBRATE study
- Topline data from the CALIBRATE Phase 3 study are anticipated in 2025

Acknowledgements

Thanks to the patients, referring physicians, and the support staff at the National Institutes of Health

Back-up Slide

Period 3 and LTE bone turnover markers



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