# Sustained Normalization of Mineral Homeostasis in Autosomal Dominant Hypocalcemia Type 1: Results from a Phase 2 Study Over 18 Months of Encaleret (CLTX-305) Treatment (NCT04581629)

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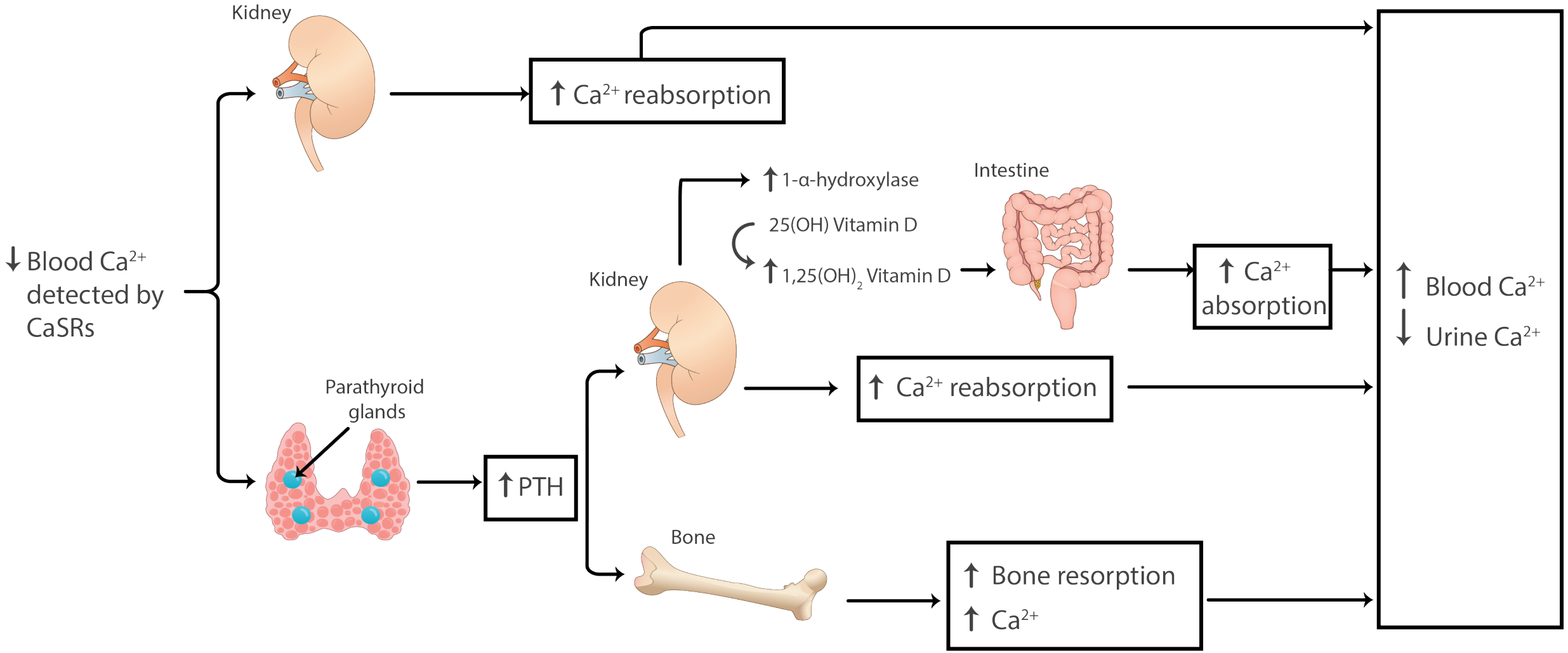
# Disclosures

- 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.

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

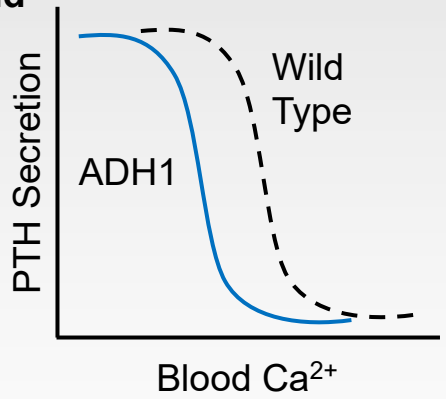



$Ca^{2+}$ = ionized calcium; PTH = parathyroid hormone; CaSR = calcium-sensing receptor

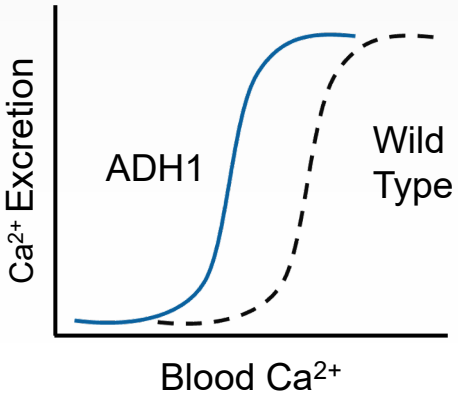
# Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia (ADH1)

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

**Parathyroid**




**Kidney**




## Hyperactive CaSR causes dysregulation of Ca homeostasis

- ↓ PTH — **Decreased parathyroid hormone (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

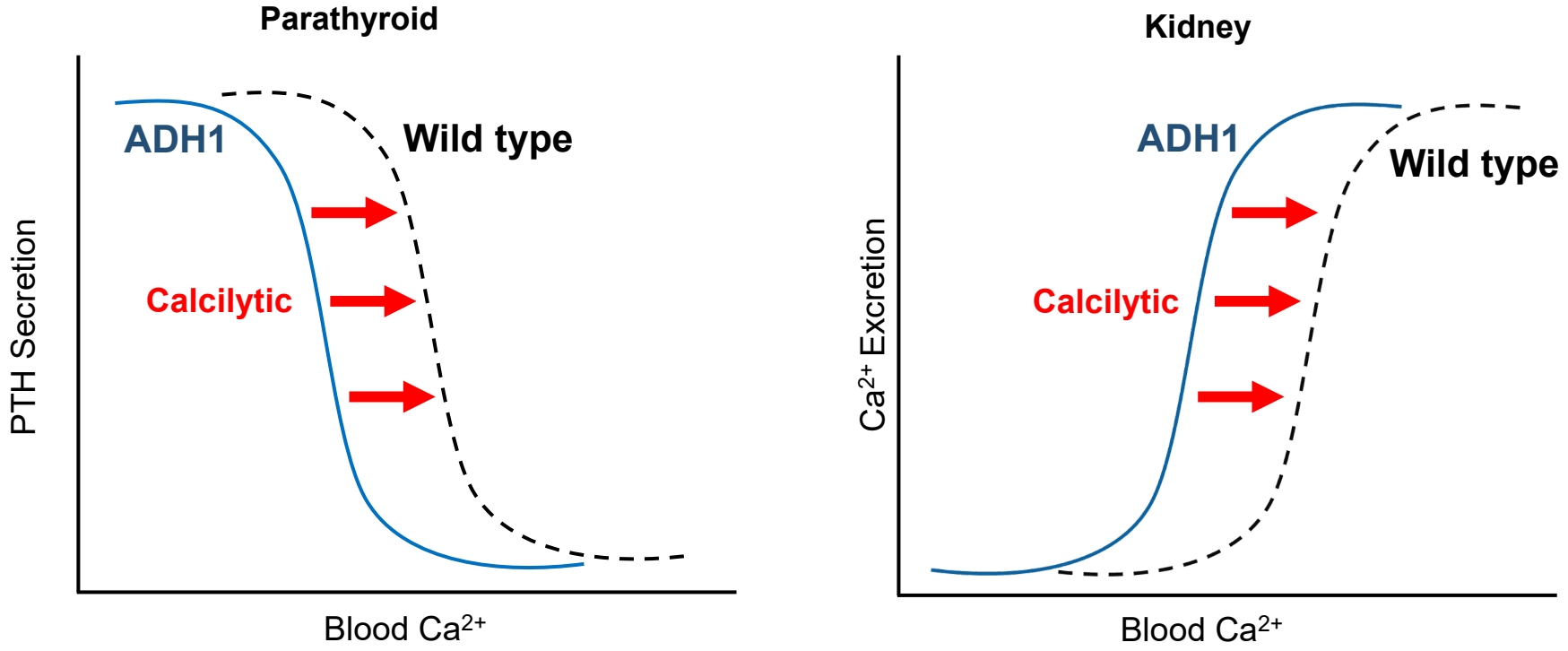
Chronic Kidney Disease

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.

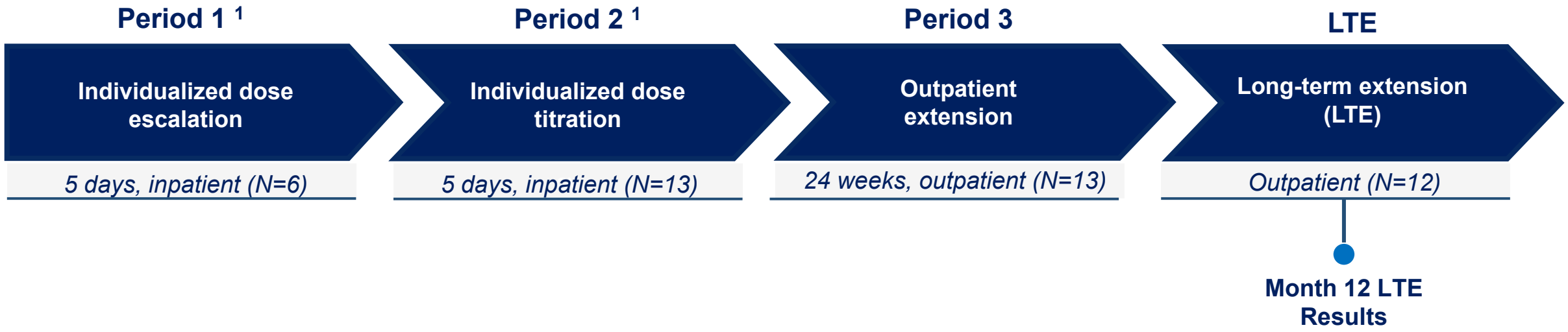
# Encaleret, an investigational oral calcilytic, may be a potential treatment for ADH1

- 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 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

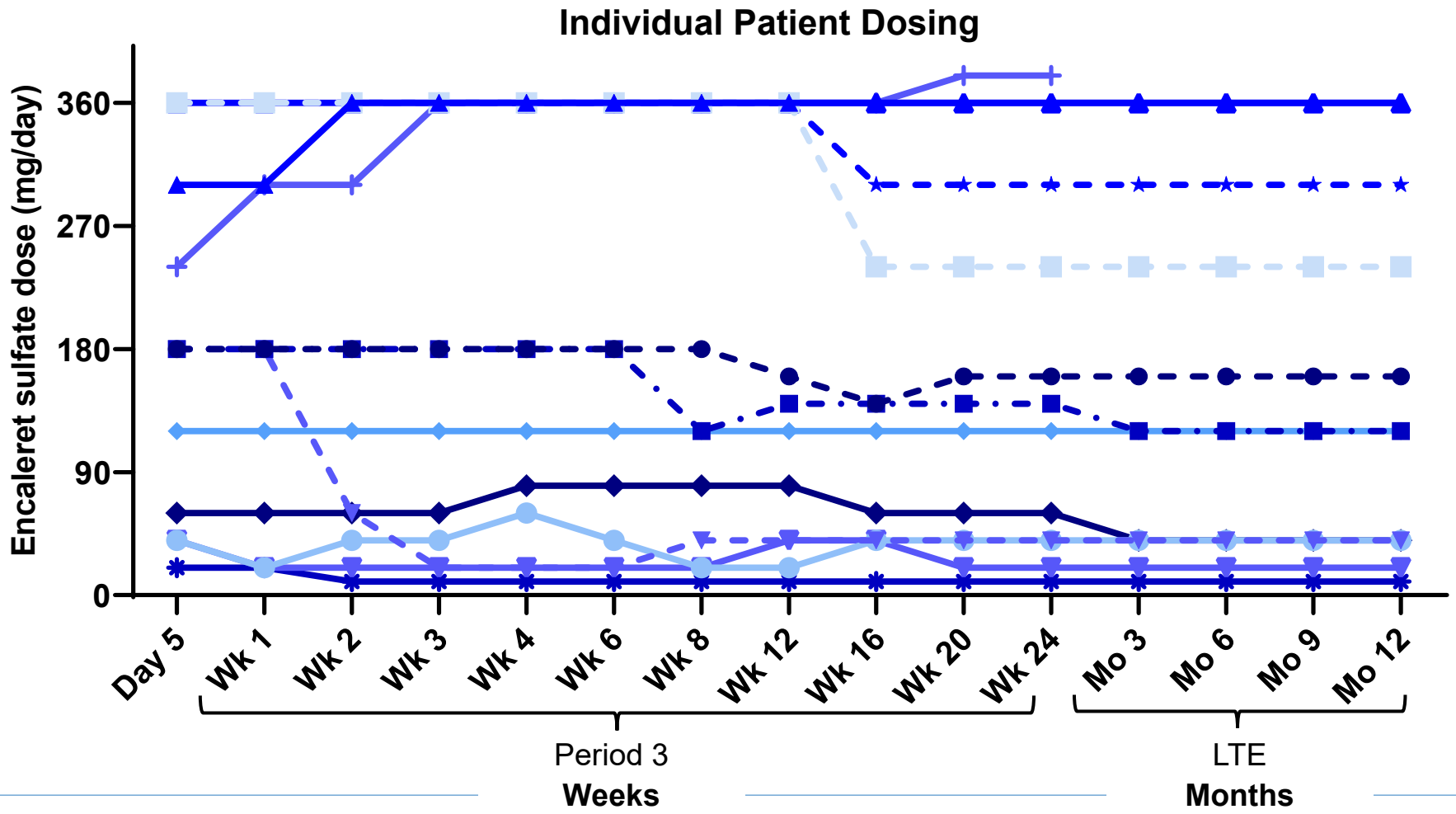
| Characteristic | Study Population (N = 13) | *Normal Range* |
|---|---|---|
| Age, mean, yr (range) | 39 (22-60) | |
| Female, n (%) | 8 (62%) | |
| Corrected Calcium[1,2] (mg/dL) | 7.1 ± 0.4 | 8.4 –10.2 |
| Intact PTH (pg/mL) | 6.3 ± 7.8 | 15 – 65 |
| Phosphate (mg/dL) | 4.5 ± 1.1 | 2.3 – 4.7 |
| 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: 172.0±140 mg/day

**LTE (n=12)**
*Maintenance dose*
Month 12 Mean: 150.8±132.6 mg/day

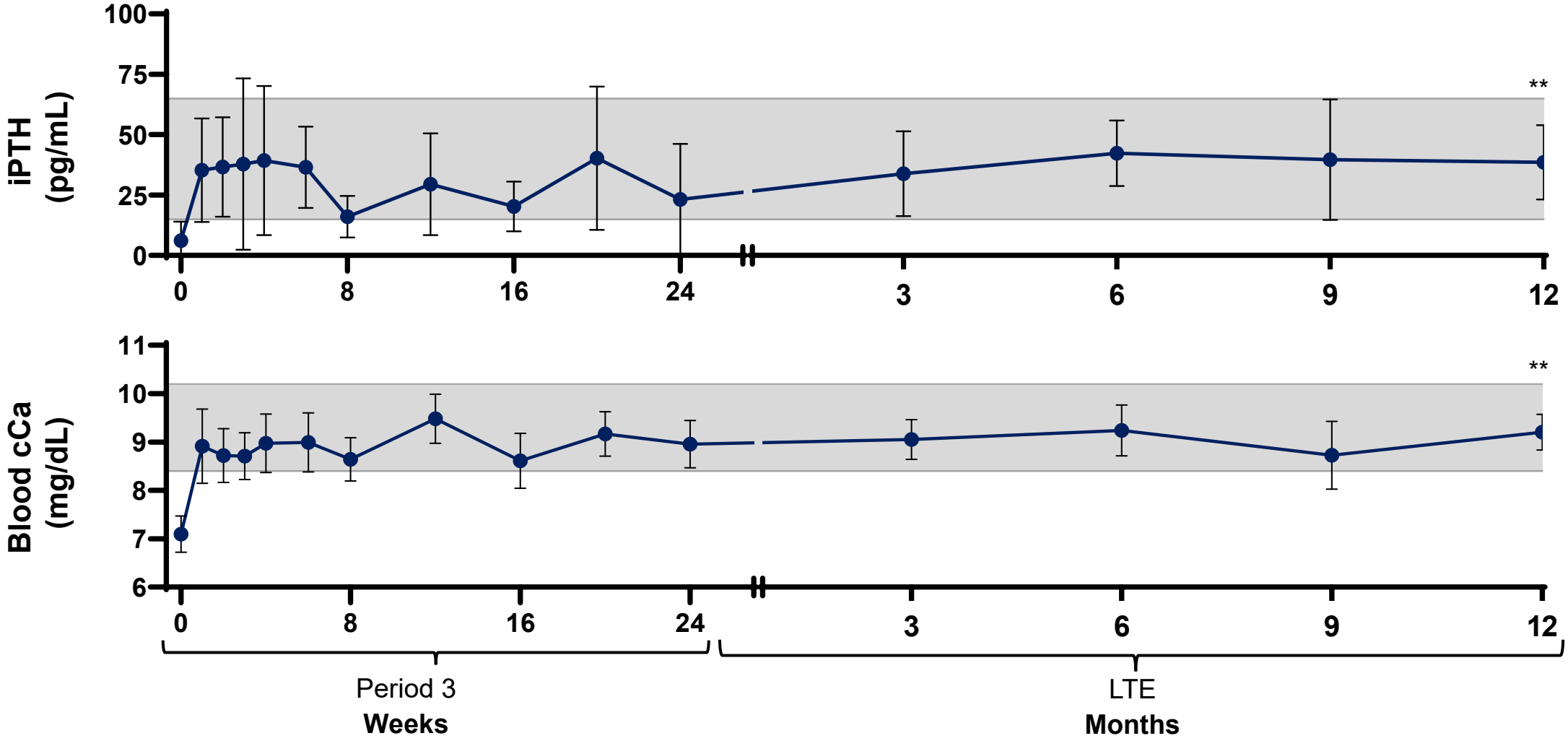


# Encaleret was well-tolerated with no serious adverse events reported

| | 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 Adverse Event** | **13 (100%)** | **12 (92%)** |
| Mild | 13 (100%) | 12 (100%) |
| Moderate | 3 (23%) | 4 (33%) |
| Severe | 0 | 0 |
| **Number of Adverse Events Reported** | **86** | **66** |
| Mild | 83 (97%) | 57 (86%) |
| Moderate | 3 (3%) | 9 (14%) |
| Severe | 0 | 0 |
| **Treatment-related Adverse Events[1]** | **16 (21%)** | **1 (2%)** |
| Hypophosphatemia | 10 (63%) | 0 |
| Hypercalcemia | 6 (37%) | 1 (100%) |

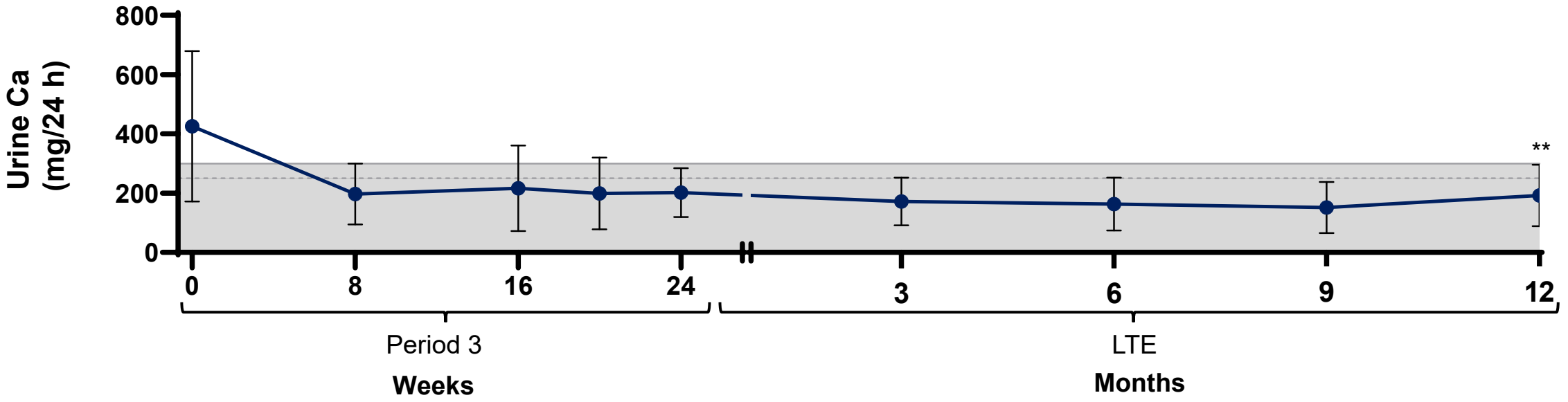
Data as of Feb 8, 2023. 1. Treatment-related adverse events were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs.

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

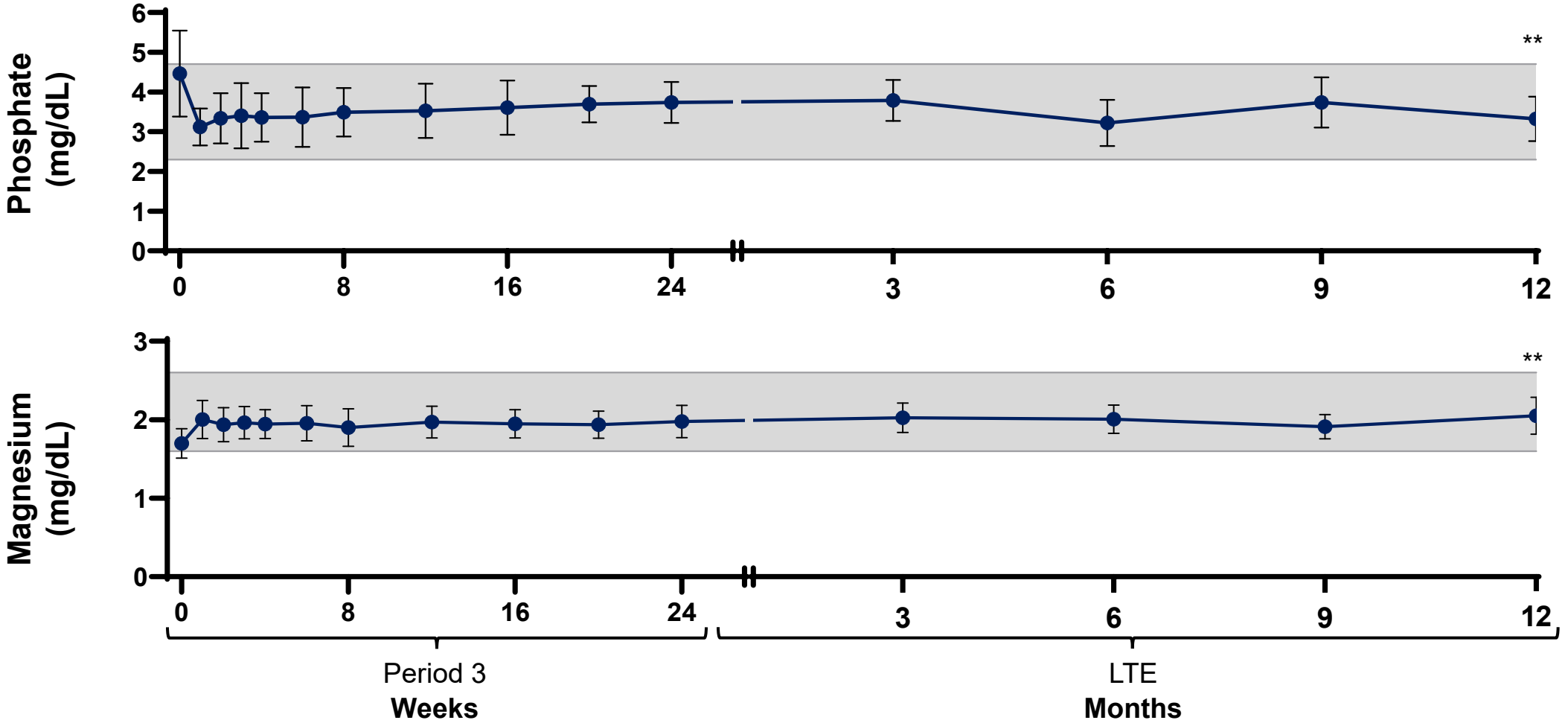
# Encaleret decreased mean urine calcium into the normal range




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

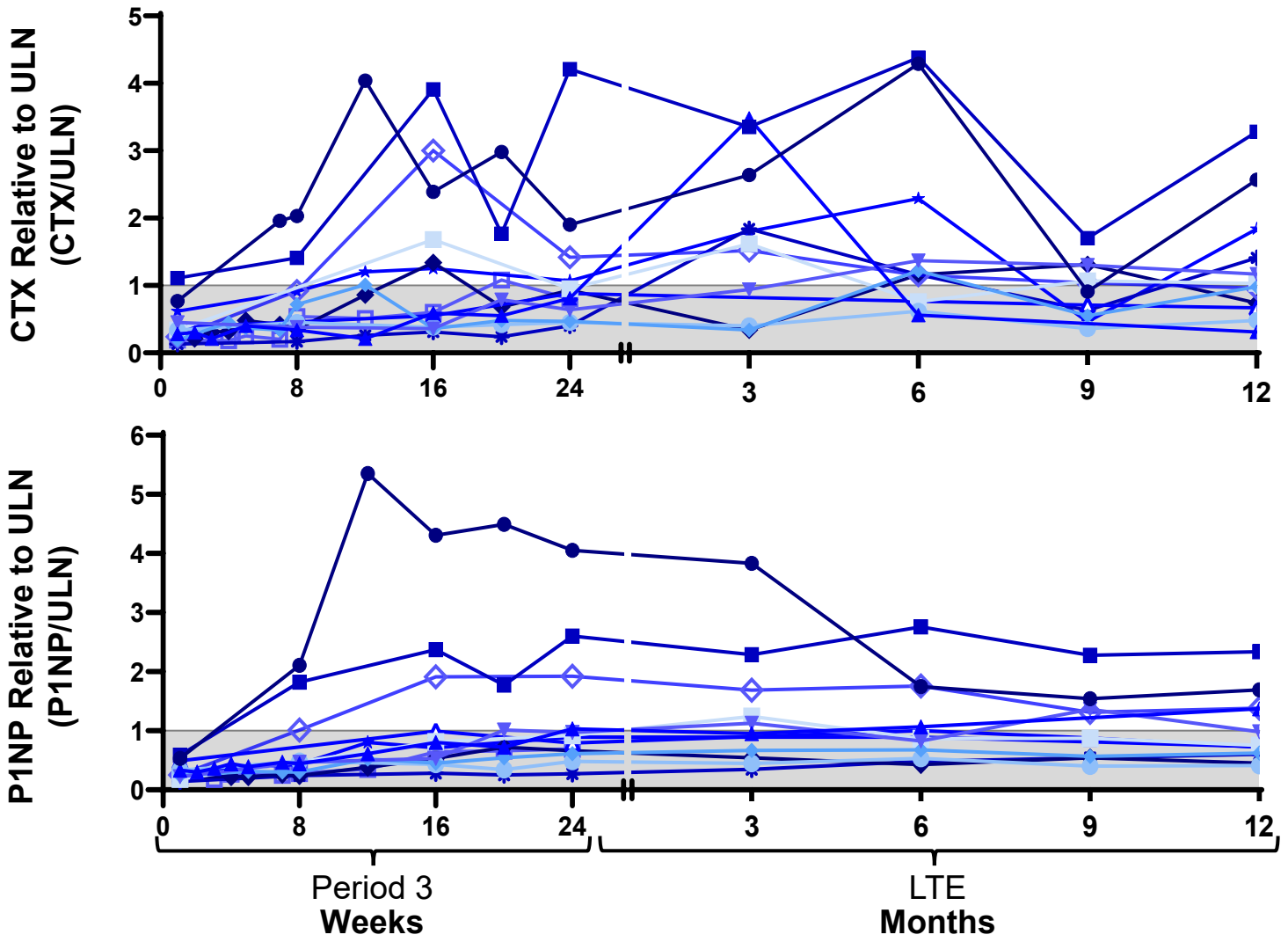
Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. ** p-value < 0.01 Month 18 compared to Baseline.

# 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 Month 18 mean compared to Baseline.

# Encaleret increased bone turnover markers




5/12 participants >1 at LTE Month 12

4/12 participants >1 at LTE Month 12

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 for 18 months restored mineral homeostasis 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 18 months, with no serious adverse events reported
- Outpatient evaluation of encaleret in the Phase 2b long-term extension is ongoing
- Phase 3 study is underway

# Acknowledgements

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