Encaleret Normalized Mineral Homeostasis in Autosomal Dominant Hypocalcemia Type 1 (ADH1) in a Phase 2 Study

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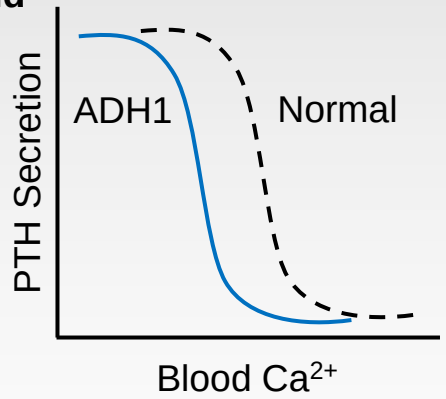
Disclosures

- 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.

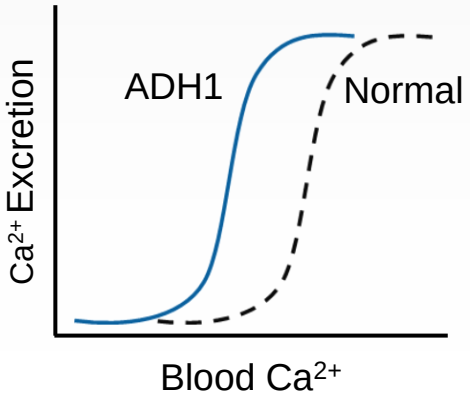
CASR activating variants cause Autosomal Dominant Hypocalcemia (ADH1)

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

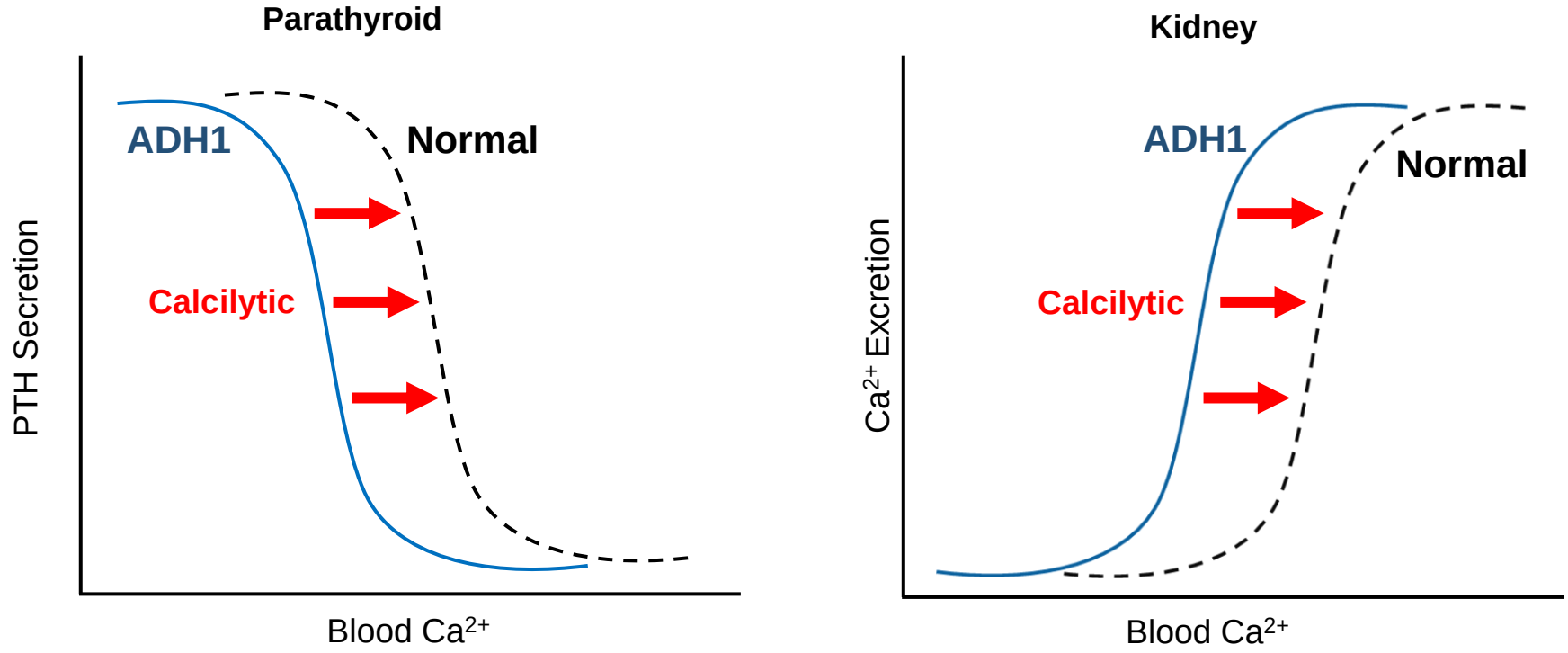
Chronic Kidney Disease

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.

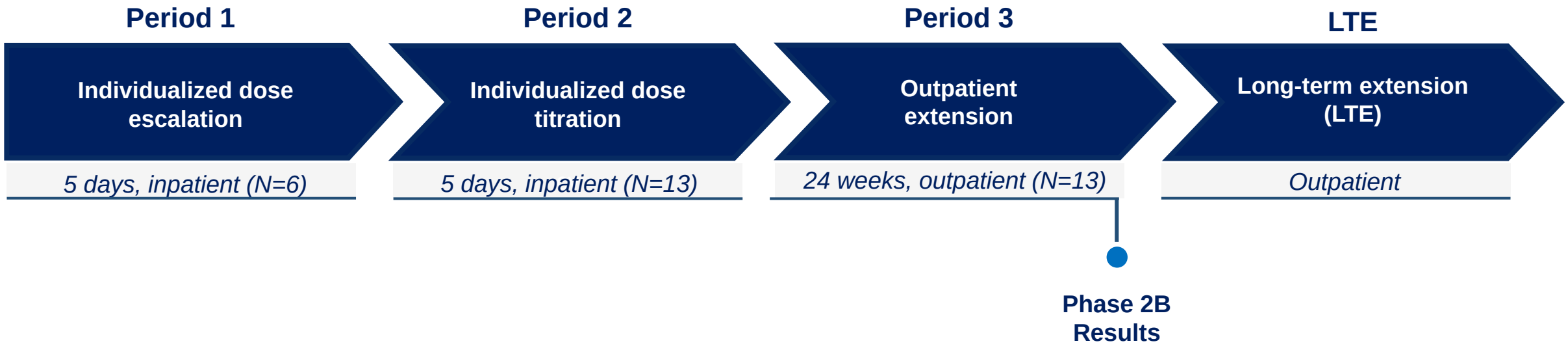
Encaleret, an investigational oral calcilytic, is a potential treatment for ADH1

- 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



Encaleret Dosing:

- Orally administered BID
- Individually titrated targeting normal cCa and phosphate

Key study objectives:

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

Additional measures:

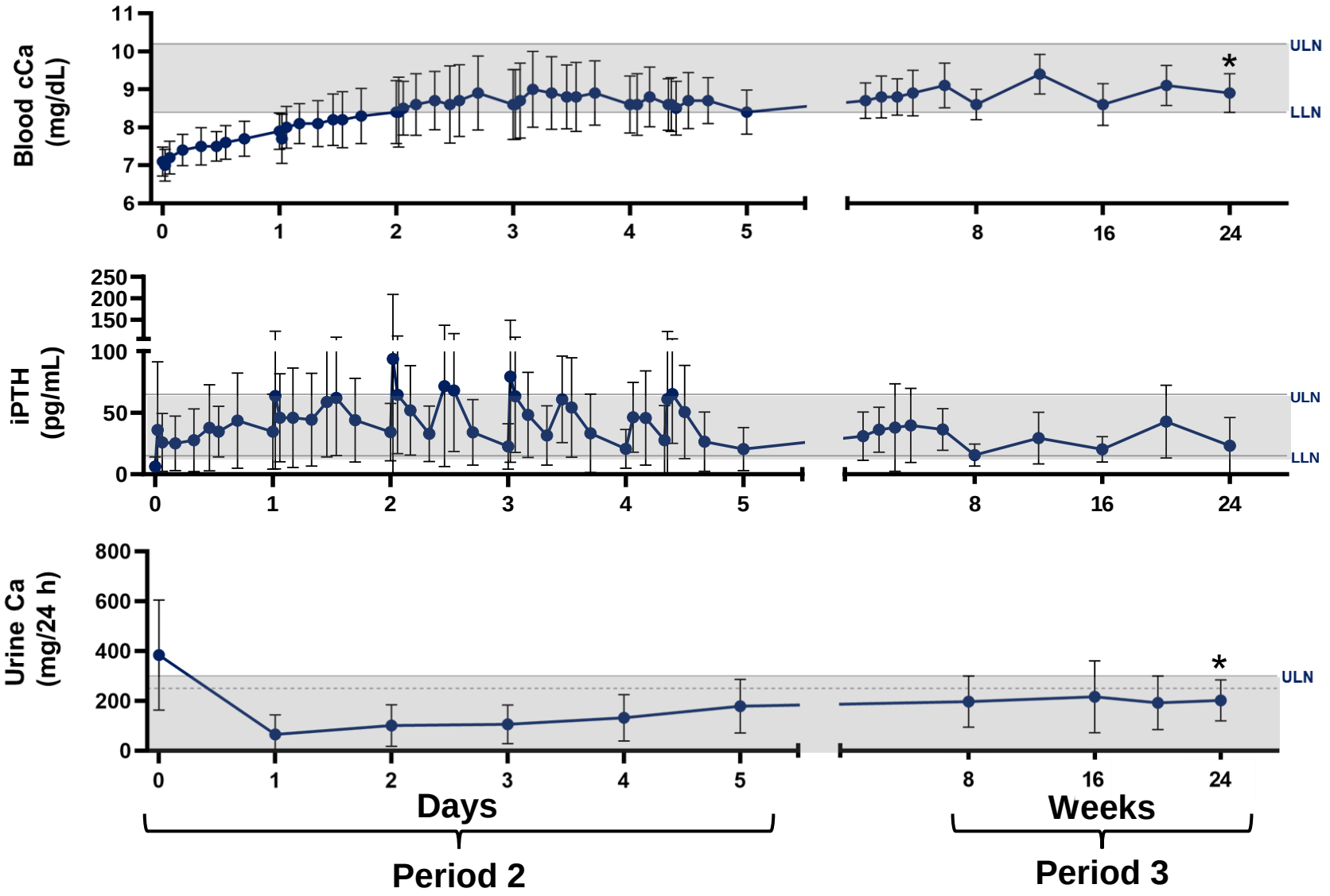
- Markers of bone and mineral metabolism

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)	
Magnesium, n (%)	8 (62%)	
Citrate, n (%)	5 (38%)	
***CASR* Variants**	C131Y (2), P221L (2), E604K (1), A840V (3), F788C (1), T151M (1), Q245R (1), I692F (1), E228K (1)	

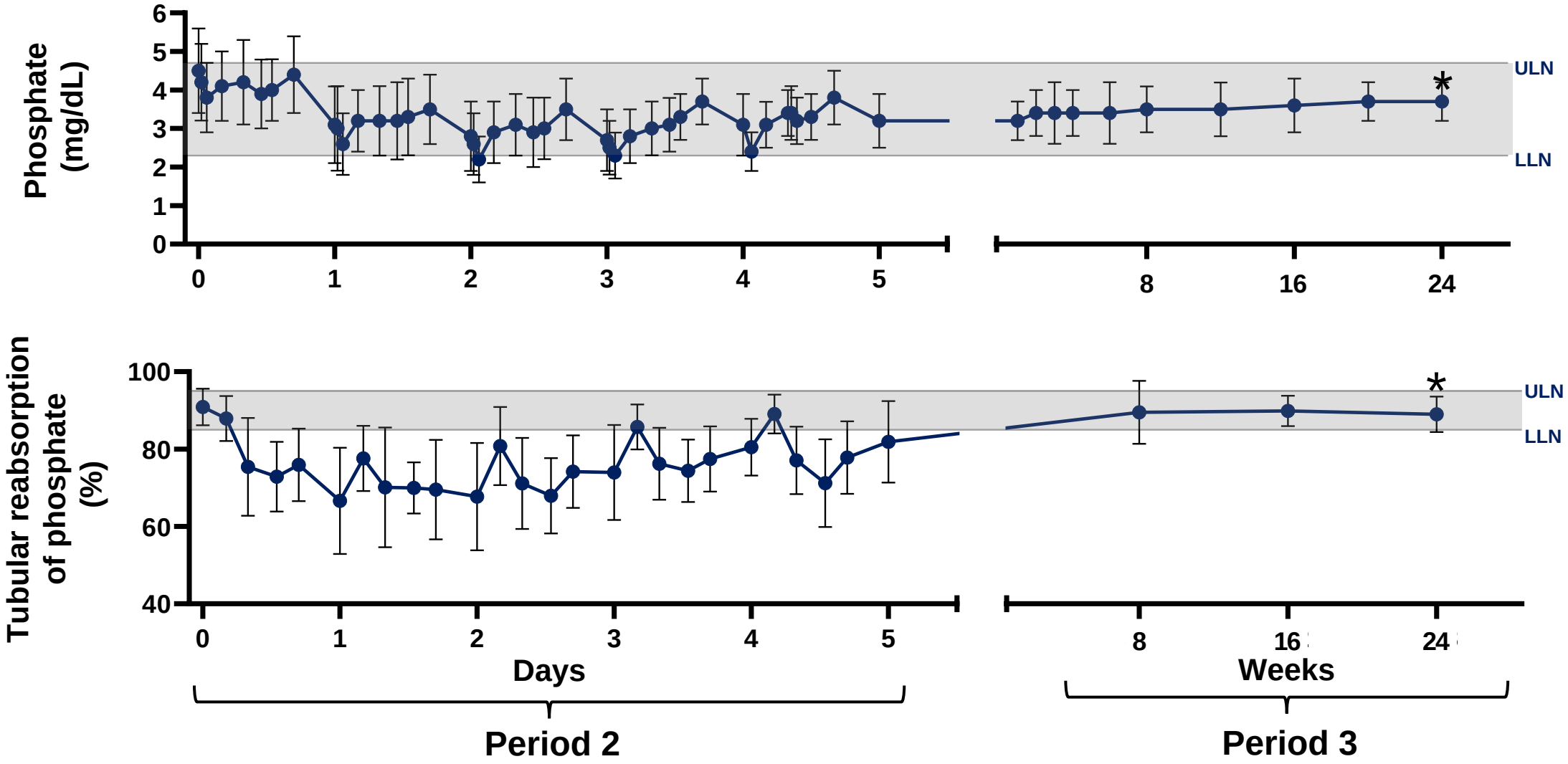
Data reported as mean±SD. eGFR = estimated glomerular filtration rate calculated by the CKD-EPI equation.
1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1, Period 2.

Encaleret increased mean blood calcium and parathyroid hormone and decreased mean urine calcium into normal ranges



*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. cCa values shown for weeks 8, 16, and 24 are pre-dose levels.

Encaleret decreased mean blood phosphate and acutely lowered mean TRP



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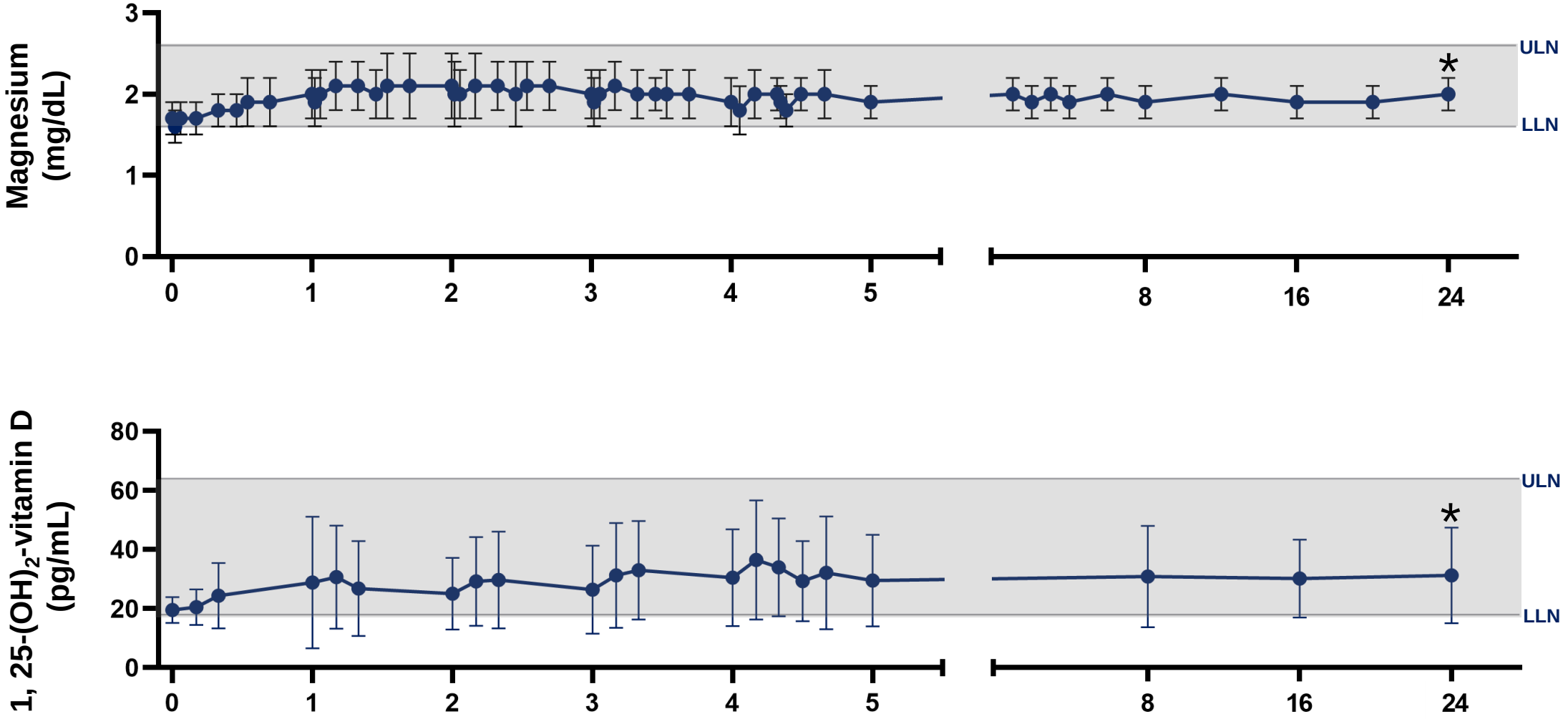
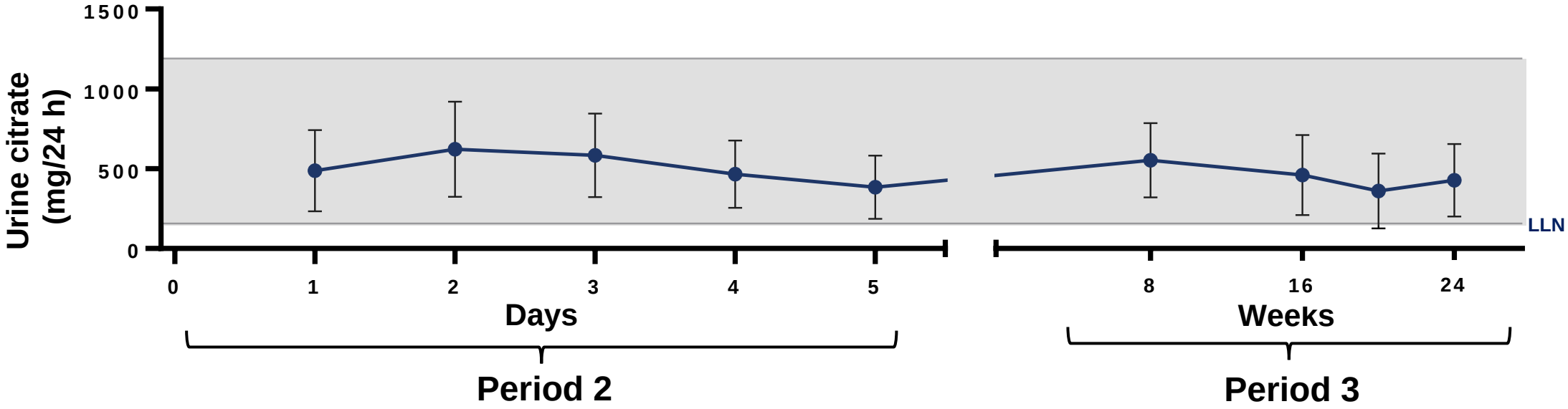
Encaleret increased mean blood magnesium and 1,25-$(OH)_2$-vitamin D



*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.

There was no change in urine citrate on Encaleret treatment



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 was well-tolerated with no serious adverse events (SAEs) reported

	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.

Summary

- Encaleret restored mineral homeostasis in 13 individuals with ADH1, as demonstrated by:
  - Normalization of the following mean values:
    - Blood calcium
    - iPTH
    - 24-hr urine calcium
    - Blood phosphate
    - Blood magnesium
    - $1,25(OH)_2$-vitamin D
- 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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