

**Effects of Encaleret (CLTX-305) on Mineral Physiology in
Autosomal Dominant Hypocalcemia Type 1 Demonstrate Proof-of-
Concept: Early Results from a Phase 2B, Open-Label, Dose-
Ranging Study [NCT04581629]**

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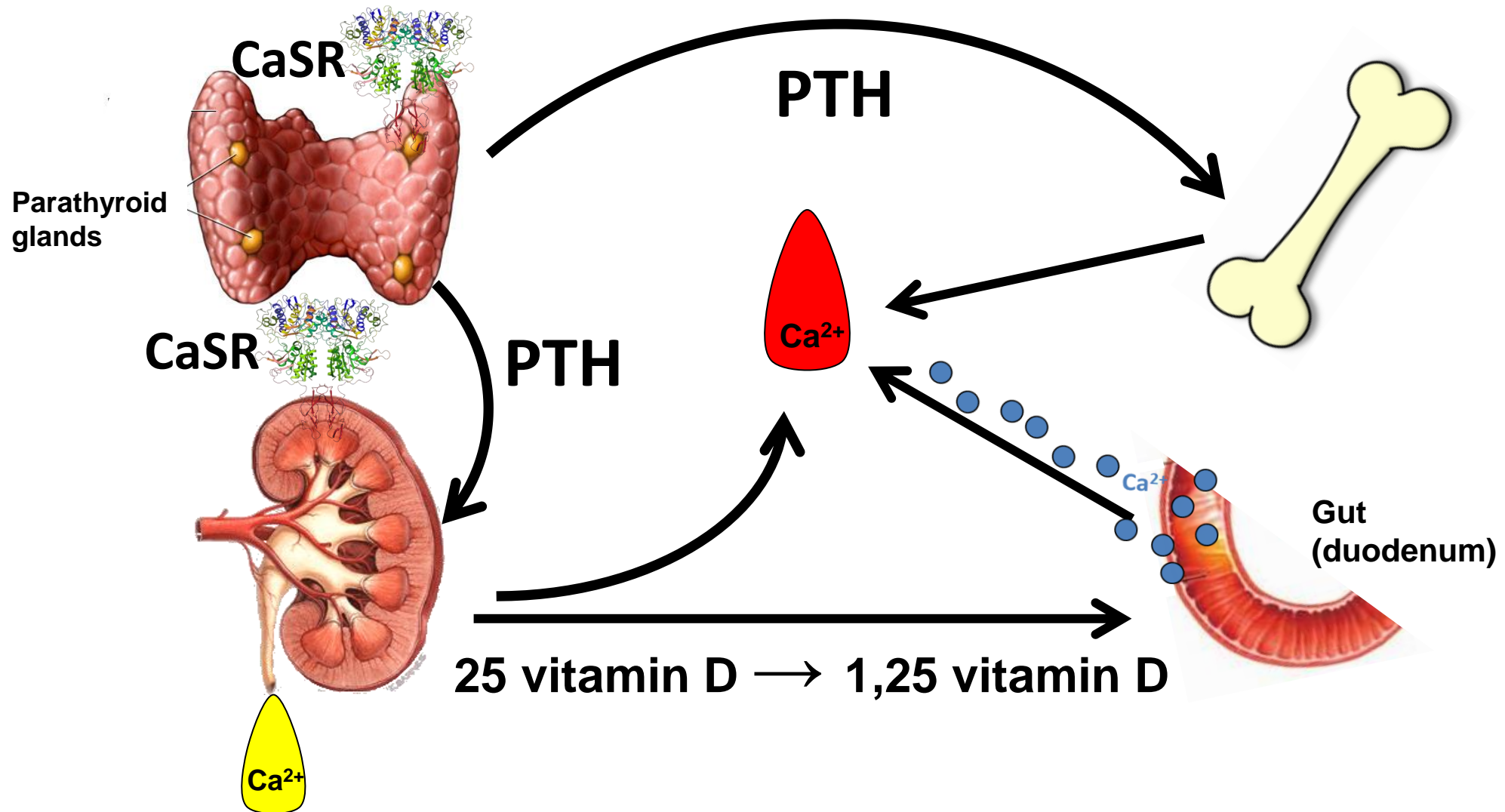
National Institute of Dental
and Craniofacial Research



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.

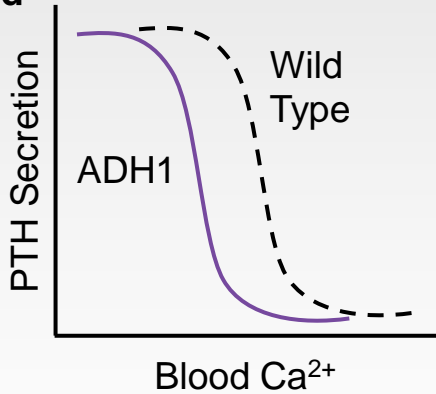
Blood calcium is maintained by four organs regulated by PTH and the CaSR



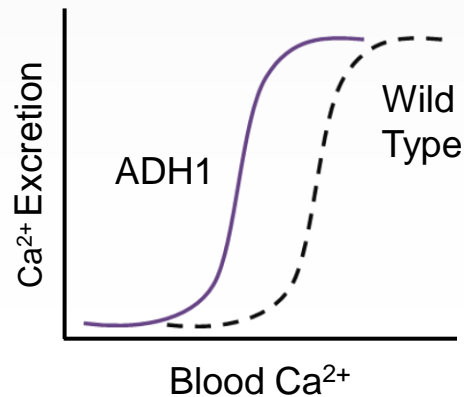
Activating variants in the *CASR* cause Autosomal Dominant Hypocalcemia (ADH1)

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

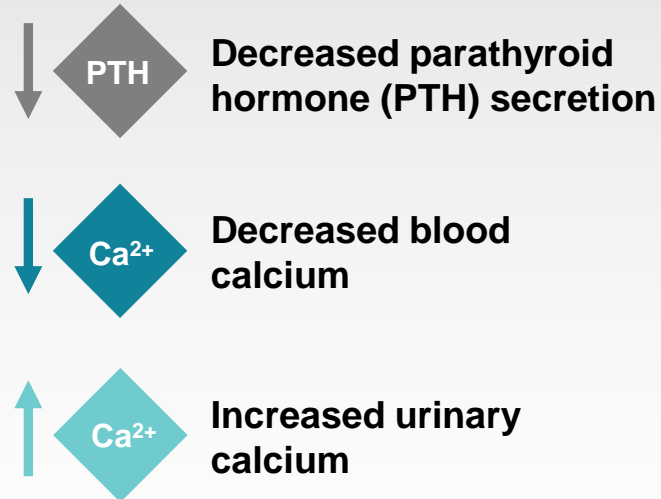
Parathyroid



Kidney



Hyperactive *CaSR* causes dysregulation of Ca homeostasis



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

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

- Calcilytics are negative allosteric modulators of the CaSR and decreases CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1

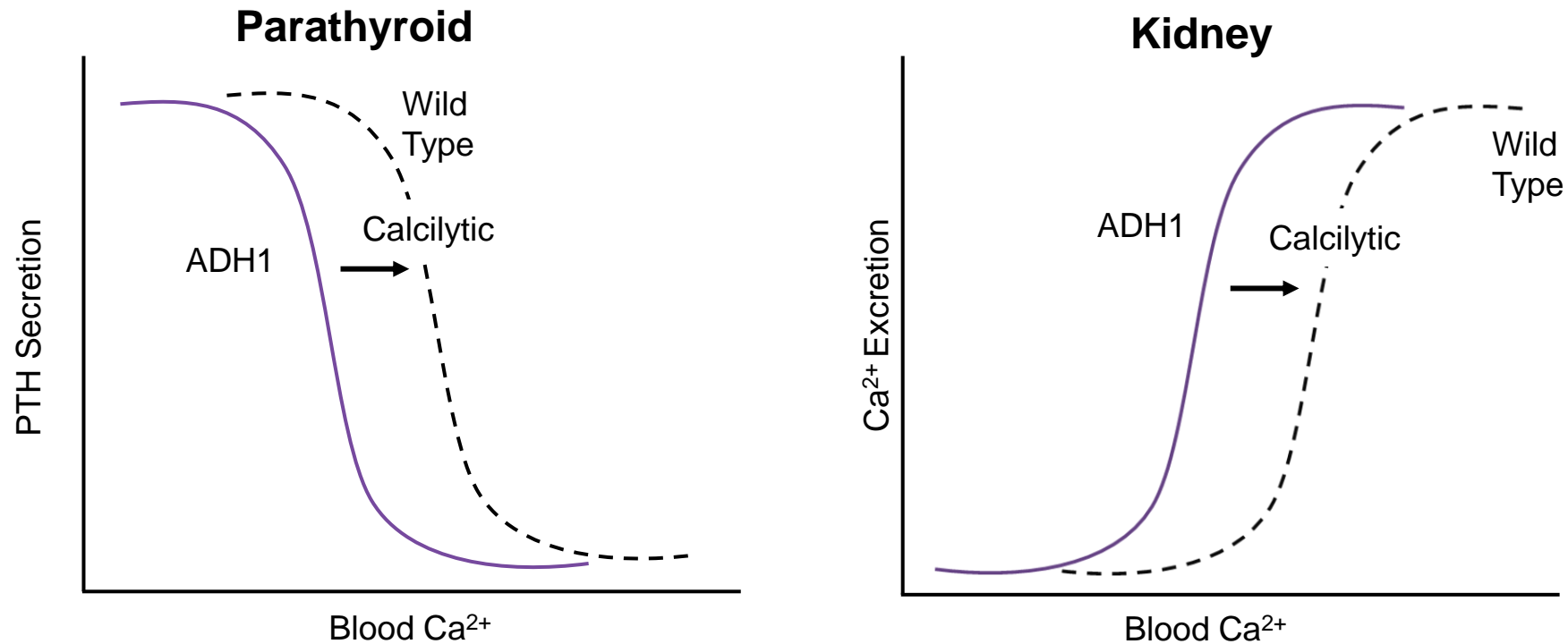
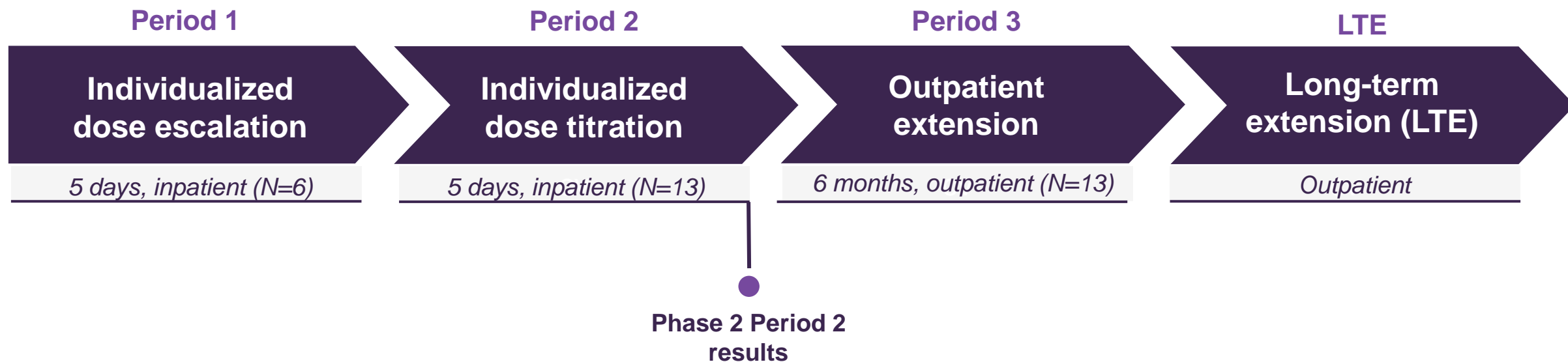


Figure adapted from Tfelt-Hansen J, et al. Curr Med Chem. 2002.

Encalaret 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)

Baseline Characteristics

Characteristic	Study Population (N = 13)	Normal Range
Age, mean, yr (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Nephrocalcinosis, n (%)	10 (77%)	
ECG QT _c F (msec)	435 ± 16	< 460 Female < 450 Male
Calcium ¹ (mg/dL) ²	7.1 ± 0.4	8.4 – 10.2
Intact PTH (pg/mL) ²	6.3 ± 7.8	15 – 65
Phosphate (mg/dL) ²	4.5 ± 1.1	2.5 – 4.5
Magnesium (mg/dL) ²	1.7 ± 0.2	1.6 – 2.6
24h Urine Calcium (mg/24h)	384 ± 221	< 250 - 300
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)	

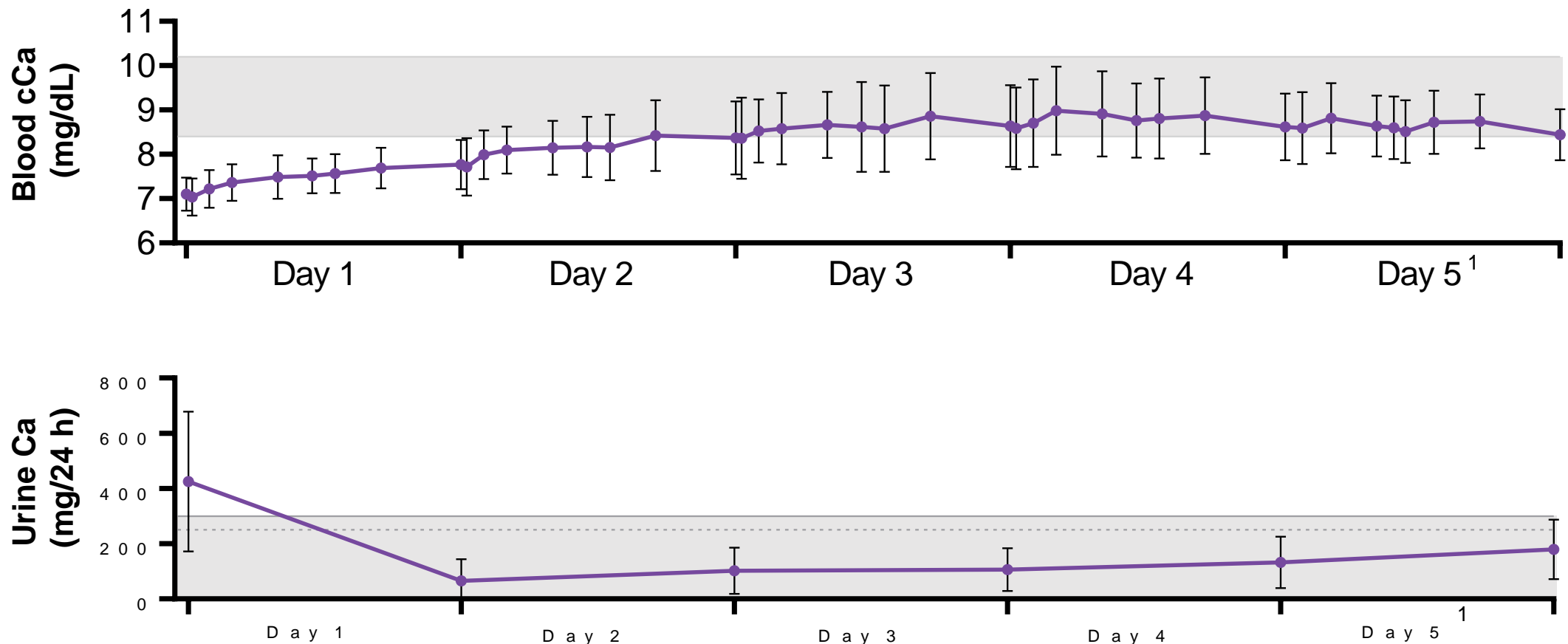
7 Data reported as mean±SD. ECG QT_cF = electrocardiogram Fridericia-corrected Q-T interval. The enalapril starting dose was either 180mg BID or 90mg BID in Period 2. 1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1, Period 2.

Encaleret was well-tolerated with no serious adverse events reported

	Period 2 N=13
Number of subjects experiencing any Serious Adverse Event	0 (0%)
Number of subjects experiencing any Adverse Event	10 (77%)
Mild	10 (77%)
Moderate	0 (0%)
Severe	0 (0%)
Number of Adverse Events Reported	13
Mild	13 (100%)
Moderate	0 (0%)
Severe	0 (0%)
Treatment-related Adverse Events¹	8 (62%)
Hypocalcemia	0 (0%)
Hypophosphatemia	7 (88%)
Hypercalcemia	1 (12%)

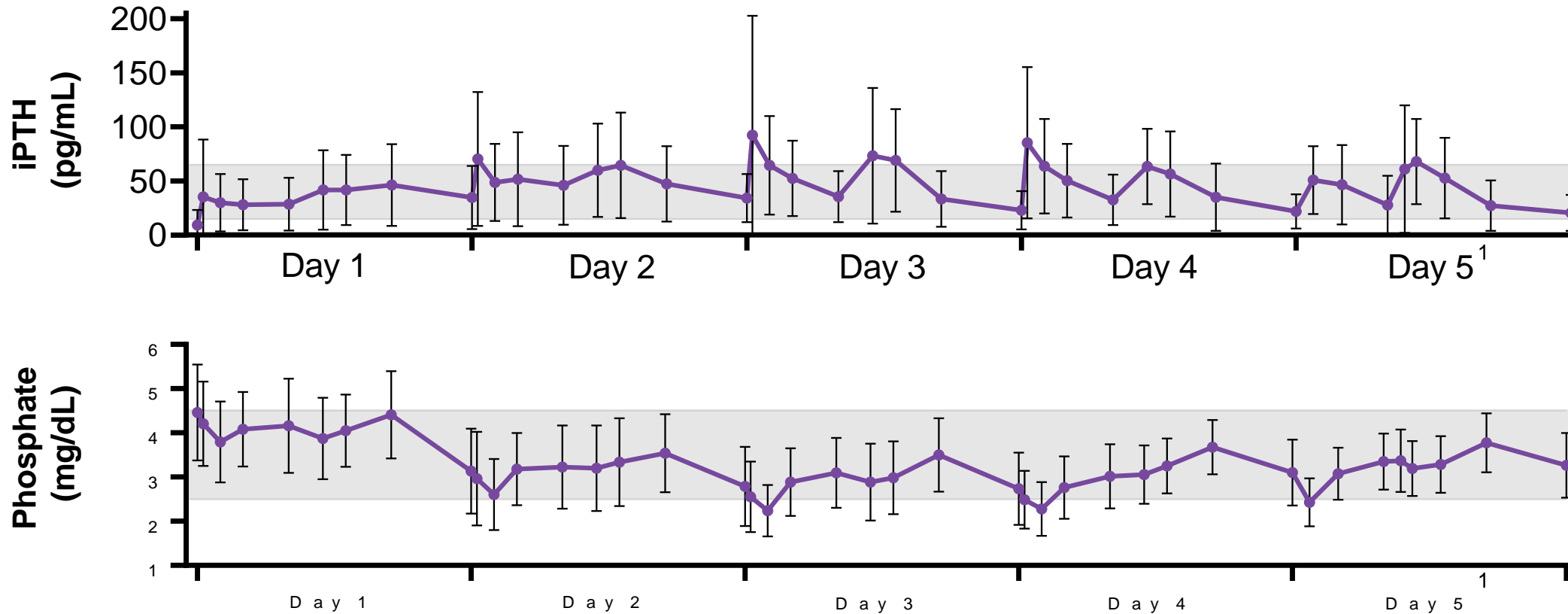
Data as of Mar 8, 2022. 1. Treatment-related adverse events were transient and resolved either spontaneously or with adjustment of the encaleret dose. Treatment-related AEs were counted as the number of events per period and are presented as a percentage of the total number of AEs.

Period 2 Results (n=13): BID Encaleret normalized mean blood and urine calcium



Data as of Mar 8, 2022 reported as mean±SD. 1. The mean±SD encaleret dose on Period 2 Day 5 was 94±64mg BID (range: 10-180 BID). 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.

Period 2 Results (n=13): BID encalaret increased mean PTH and decreased mean blood phosphate



Data as of Mar 8, 2022 reported as mean±SD. 1. The mean±SD encalaret dose on Period 2 Day 5 was 94±64mg BID (range: 10-180 BID). Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range.

Summary

- In 13 participants, encaleret normalized mean corrected blood calcium and 24-hour urine calcium excretion during Period 2
- Mean PTH increased and phosphate decreased into the normal range during Period 2
- Encaleret was well-tolerated when administered twice daily over 5 days, with no serious adverse events reported
- Consistent improvements in mineral homeostasis support further investigation of encaleret in ADH1 patients
- Outpatient evaluation of encaleret in this Phase 2b study remains ongoing

Acknowledgements



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