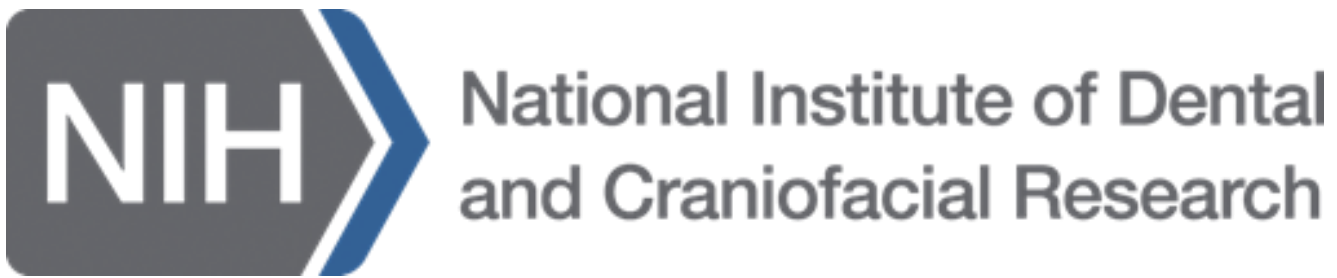


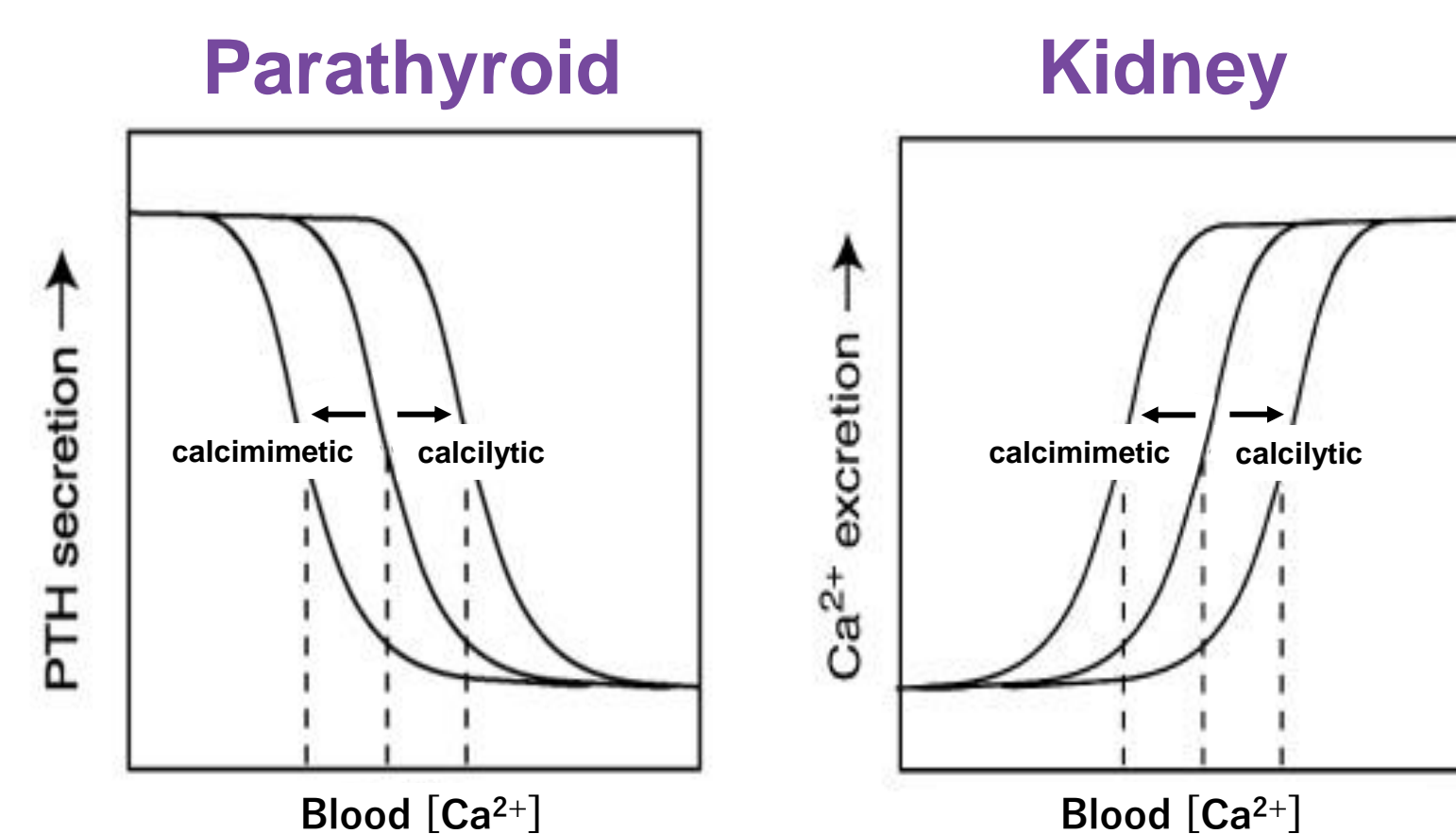
# The Effects of Encaleret (CLTX-305) on Mineral Physiology in Autosomal Dominant Hypocalcemia Type 1 (ADH1) Demonstrate Proof-of-Concept: Early Results from an Ongoing Phase 2B, Open-Label, Dose-Ranging Study



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 Study Number: CLTX-305-201; ClinicalTrials.gov Identifier: NCT04581629

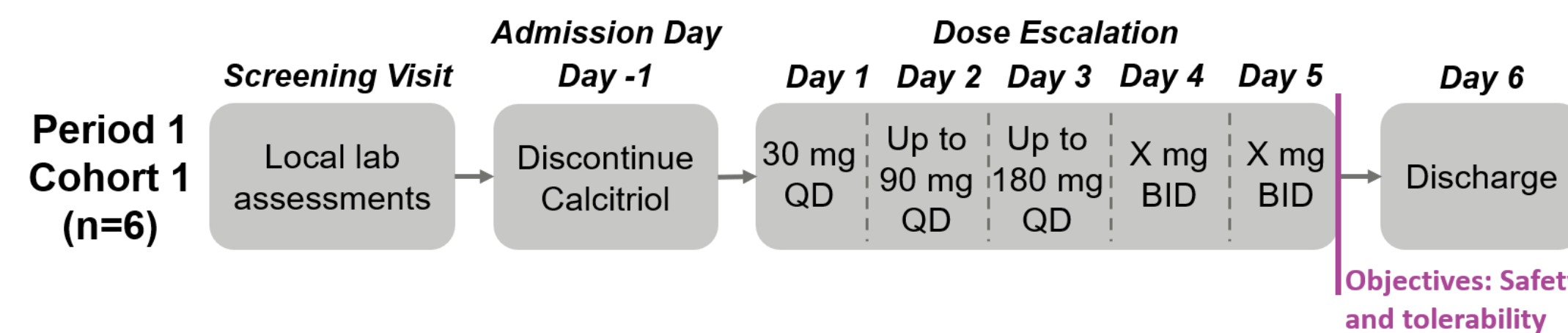
## Background

- Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism caused by gain-of-function pathogenic variants in the gene encoding the calcium-sensing receptor (CaSR).<sup>1</sup>
- The estimated U.S. prevalence is 3.9/100,000 with > 90 gain-of-function CASR variants reported.<sup>1,2</sup>
- Biochemical features of ADH1:<sup>3</sup>
  - hypocalcemia and hypercalciuria
  - hyperphosphatemia
  - inappropriately low parathyroid hormone (PTH)
  - hypomagnesemia
- Conventional therapy for ADH1 (calcium and calcitriol) can lead to or exacerbate hypercalciuria, increasing risk of nephrolithiasis, nephrocalcinosis, and renal insufficiency.
- Calcilytics (investigational allosteric antagonists of the CaSR) are designed to shift the concentration-response relationship between extracellular calcium and the cellular response of cells bearing the CaSR to the right (Figure 1).<sup>3</sup>
- Through direct renal effects, calcilytics may further reduce calcium and magnesium excretion in ADH1.
- Calcilytics increase plasma levels of PTH and normalize mineral metabolism in animal models of ADH1.<sup>5,6</sup>
- A small clinical trial demonstrated that the calcilytic NPSP795 increased plasma levels of PTH and decreased calcium excretion in patients with ADH1.<sup>7</sup>
- Encaleret (CLTX-305), an investigational oral calcilytic, has the potential to restore normal mineral homeostasis without calcium and vitamin D supplementation.



**Figure 1: The effects of allosteric modulators on the CaSR**  
 Calcilytics decrease the sensitivity of CaSRs to extracellular calcium, resulting in increased PTH secretion (left panel) and decreased calcium excretion (right panel). Calcimimetics (CaSR agonists) have the opposite effect [Figure adapted from Tfelt-Hansen, 2002].

## Period 1 Study Design



**Figure 2: Period 1 Cohort 1 Study Schema**  
 For full Phase 2B study design see Abstract #7288

## Subject Characteristics

**Table 1: Baseline Characteristics**

Characteristic	N=6	Normal Range
Age, mean (range)	40 (22-60)	
Male, n (%)	3 (50%)	
Nephrocalcinosis, n (%)	4 (67%)	
ECG QTcB (msec)	452 ± 9	< 440
Corrected calcium (mg/dL)*	7.6 ± 0.6	8.4–10.2
Intact PTH (pg/mL)*	3.4 ± 4.5	15–65
Phosphorus (mg/dL)*	4.5 ± 0.7	2.5–4.5
Magnesium (mg/dL)*	1.6 ± 0.4	1.6–2.6
24h Urine Calcium (mg/24h)	436 ± 255	< 250-300
<b>Supplement Doses</b>		
Elemental Calcium (mg/day) [mean (range)]	2317 (800-4000)	
Calcitriol (µg/day) [mean (range)]	0.9 (0.5-2.0)	

ECG QTcB = electrocardiogram Bazett-corrected Q-T interval.  
 \*Measurements taken pre-dose Day 1 (mean±SD)  
 CASR variants (n): C131Y (2), P221L (2), A840V (1), E604K (1).

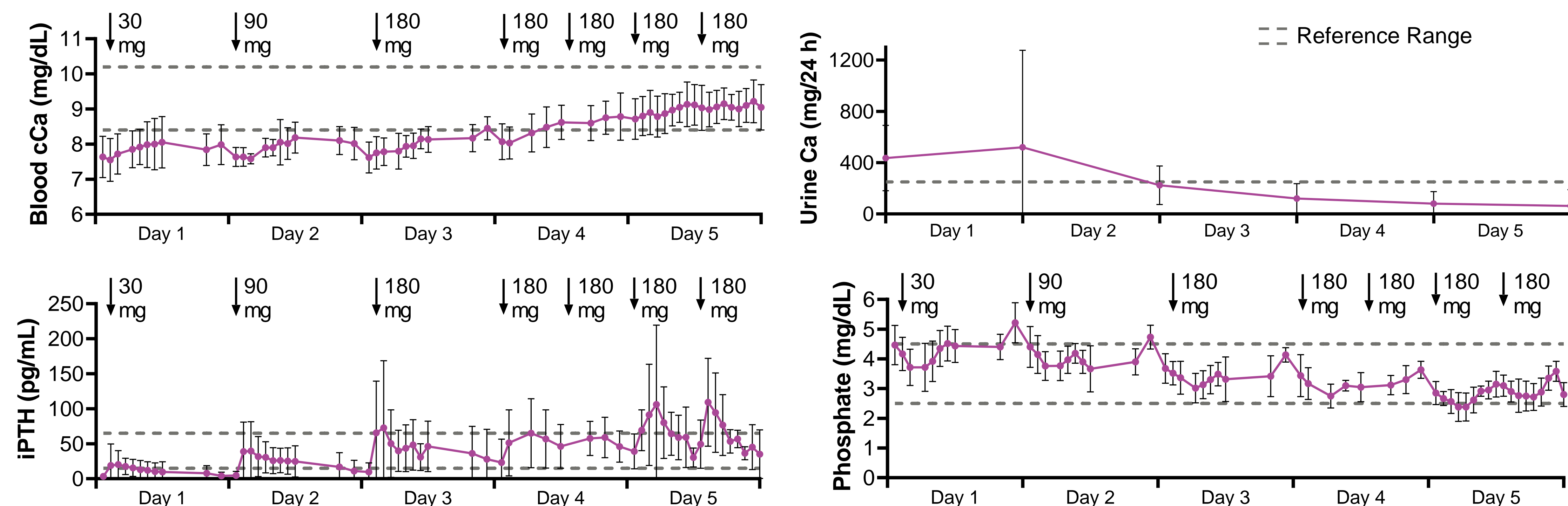
## Safety and Tolerability

**Table 2: Summary of Adverse Events (AEs), n (%)**

Subjects with Serious AEs	0 (0%)
Subjects with AEs	5 (83%)
Mild	5 (83%)
Moderate	0 (0%)
Severe	0 (0%)
<b>Number of AEs</b>	
Mild	9 (100%)
Moderate	0 (0%)
Severe	0 (0%)

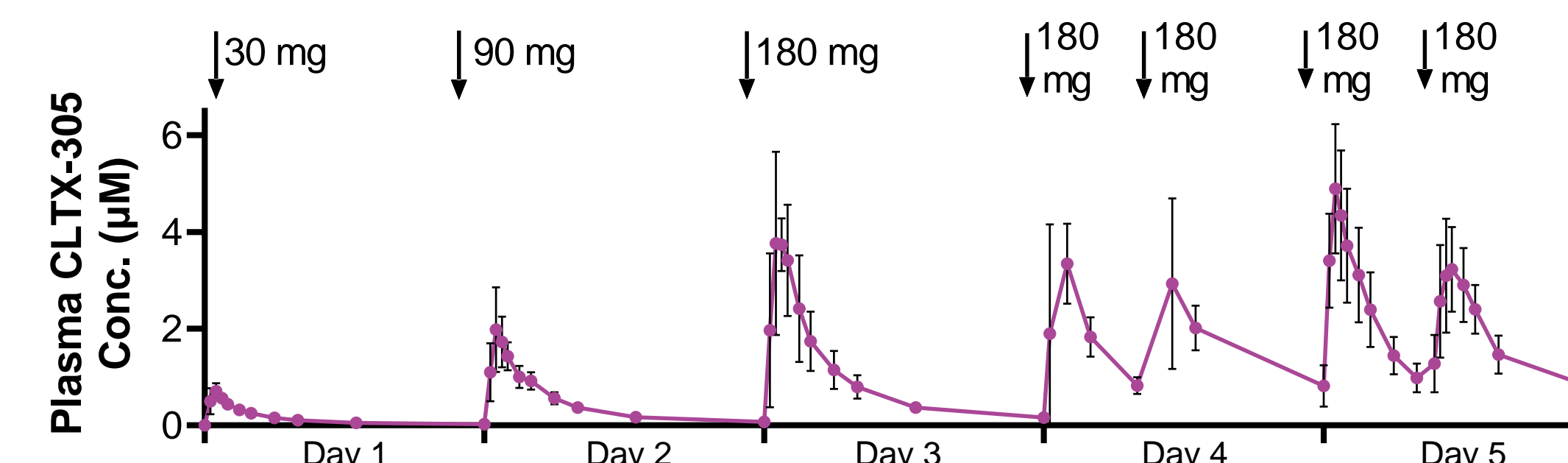
The only AE deemed to be related to encaleret was transient, asymptomatic hypophosphatemia < 2 mg/dL (n=2). Baseline prolonged QTcB normalized to 433 ± 11 msec on Day 5.

## Pharmacodynamics



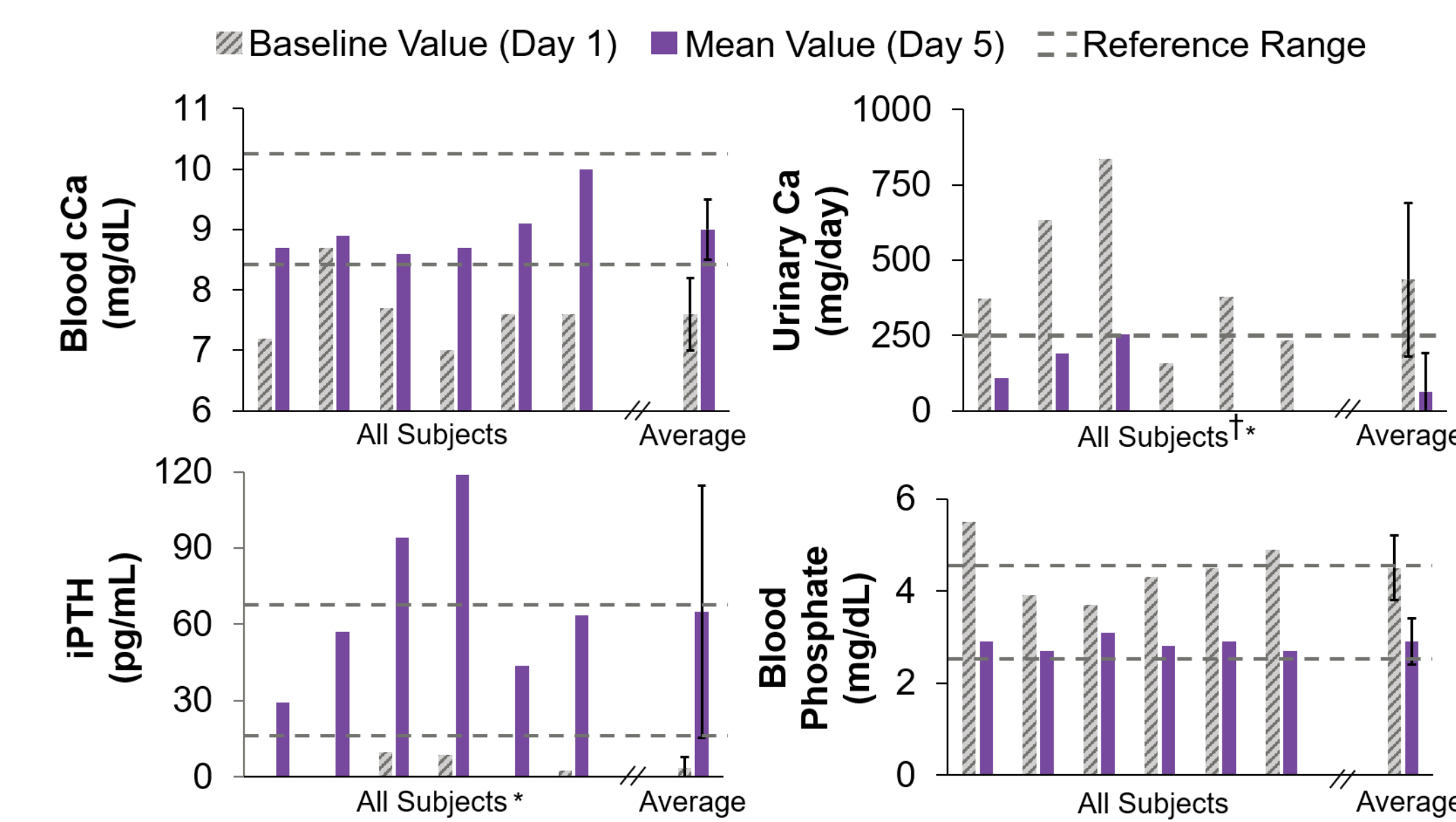
**Figure 3: Mineral homeostasis normalized during Period 1 [mean±SD].** \*One subject received second dose on Day 5 of 120 mg

## Pharmacokinetics



**Figure 4: Pharmacokinetic profile for encaleret demonstrated dose proportional increase in plasma exposure over Period 1 [mean±SD].** \* One subject received second dose on Day 5 of 120 mg.

## Individual Subject Efficacy



**Figure 5: Summary of blood mineral levels following 5-day encaleret dosing.** † Where Day 5 values were unavailable, Day 4 values shown. \* Values below limit of assay quantitation were plotted as "0".

## Conclusions

- Encaleret was well-tolerated when administered in escalating oral doses once or twice daily over 5 days, with no serious adverse events reported.
- Consistent changes from baseline in blood and urine mineral measurements provide preliminary proof-of-concept data that encaleret may be an effective treatment for ADH1.
- Blood calcium, PTH, and phosphate were generally normalized and maintained within the normal range by day 5.
- Urinary calcium excretion became normal or undetectable in all subjects while on encaleret and eucalcemic.
- Data support further development of encaleret in ADH1.

## Acknowledgements

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