Temporal Effects of Encaleret (CLTX-305) on Mineral Physiology in Autosomal Dominant Hypocalcemia Type 1 (ADH1): Results from a Phase 2B, Open-Label, Dose-Ranging Study [NCT04581629]

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Background

- Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism caused by gain-of-function pathogenic variants in the calcium-sensing receptor gene (*CASR*).[1]
- The estimated U.S. prevalence is 3.9/100,000 with > 100 gain-of-function *CASR* variants reported.[1-2]
- Biochemical features of ADH1 include low parathyroid hormone (PTH), hypocalcemia, hypercalciuria, hyperphosphatemia, and hypomagnesemia.[3]
- Conventional therapy for ADH1 (calcium and active vitamin D) can lead to or exacerbate hypercalciuria, increasing risk of nephrolithiasis, nephrocalcinosis, and renal insufficiency.
- Calcilytics (investigational negative allosteric antagonists of the CaSR) shift the concentration-response relationship between extracellular calcium and the cellular response of cells expressing CaSR to the right (Figure 1).[3]
- Encaleret (CLTX-305), an investigational oral calcilytic, has the potential to restore normal mineral homeostasis in ADH1 without calcium and active vitamin D supplementation.
- Period 1 of the Phase 2b study was a 5-day inpatient dose-escalation course, designed to evaluate the safety and tolerability of encaleret.

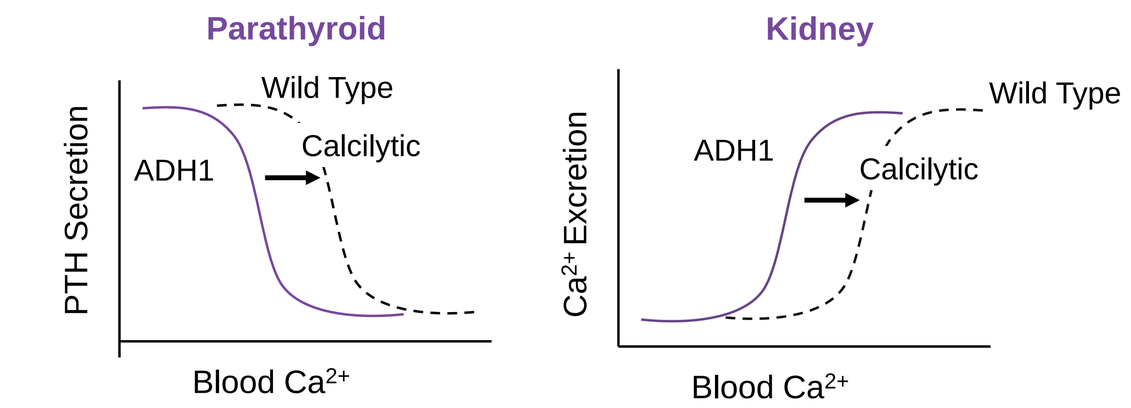

Figure 1: The effects of calcilytics on parathyroid and renal physiology
Calcilytics decrease the sensitivity of CaSRs to extracellular calcium, resulting in increased PTH secretion (left) and decreased calcium excretion (right). [Figure adapted from Tfelt-Hansen, 2002].[4]

Phase 2b Study Design

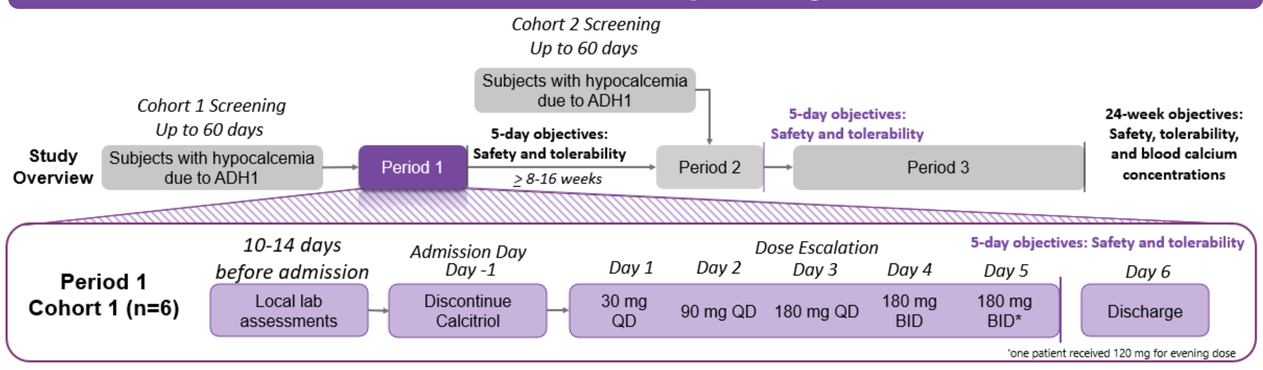

Figure 2: Period 1 Study Schema.

Subject Characteristics

Table 1: Baseline Characteristics

Characteristic	N=6	*Normal Range*
Age, mean (range)	40 (22-60)	
Male, n (%)	3 (50%)	
Nephrocalcinosis/Nephrolithiasis, n (%)	4 (67%)	
ECG QTcF (msec)	433 ± 13	*< 450 Male* *< 460 Female*
Corrected Calcium (mg/dL)*	7.6 ± 0.6	*8.4 – 10.2*
Intact PTH (pg/mL)*	4.0 ± 4.0	*15 – 65*
Phosphorus (mg/dL)*	4.5 ± 0.7	*2.5 – 4.5*
Magnesium (mg/dL)*	1.8 ± 0.2	*1.6 – 2.6*
24h Urine Calcium (mg/24h)	436 ± 255	*< 250-300*
Supplement Doses		
Elemental Calcium (mg/day) [mean (range)]	2433 (800-4800)	
Calcitriol (μg/day) [mean (range)]	0.8 (0.5-2.0)	

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

Period 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%)
Number of AEs Reported	**8**
Mild	8 (100%)
Moderate	0 (0%)
Severe	0 (0%)

The only AE deemed to be related to encaleret was transient, asymptomatic hypophosphatemia (n=2).

Mineral Parameters Over 24H on Day 4

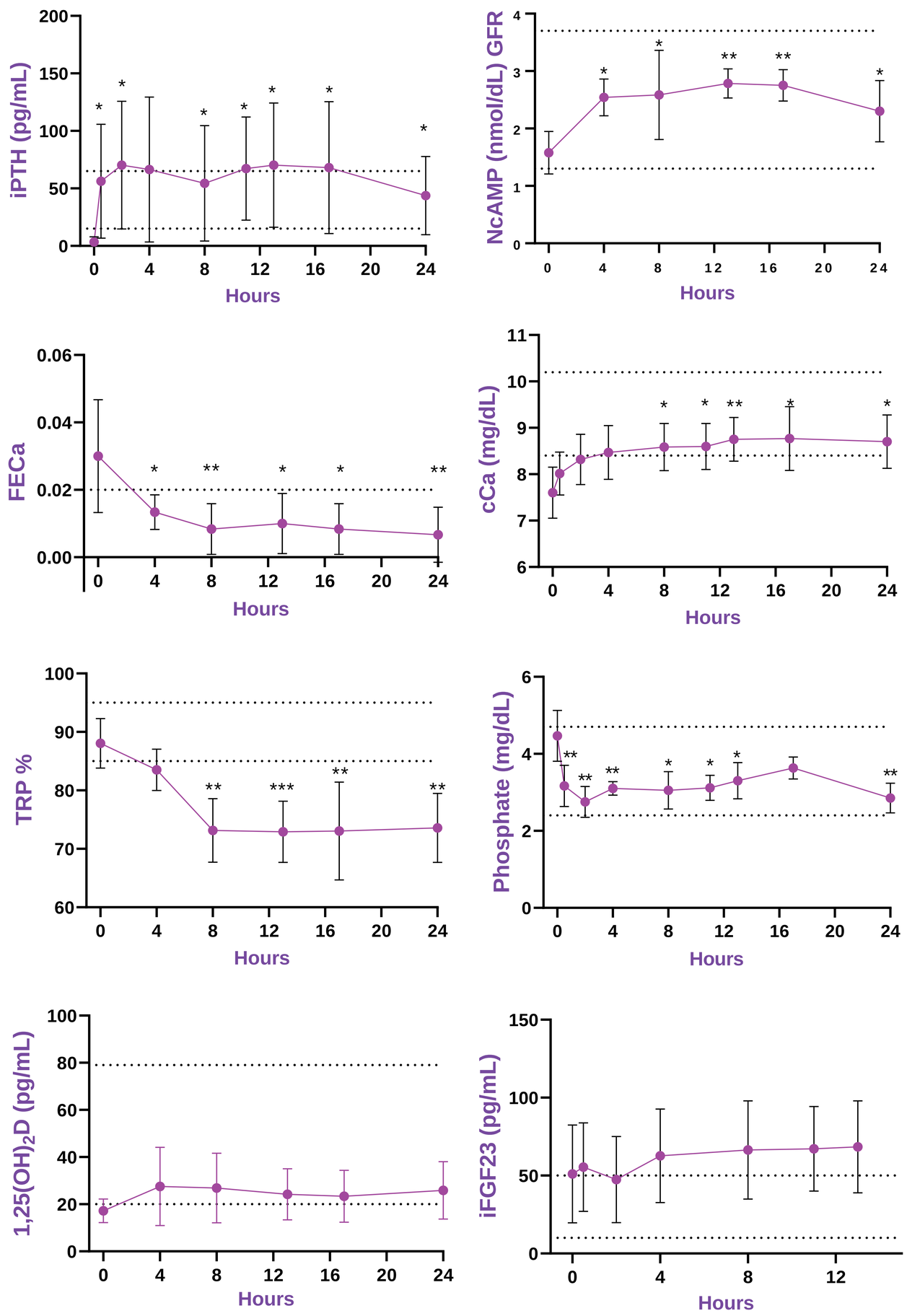

Figure 3: PTH rose rapidly and remained normal through the 24hrs measured. Nephrogenous cAMP (NcAMP) was significantly increased through the 24hrs measured. Fractional excretion of Ca (FECa) significantly decreased and was maintained through 24hrs. Blood albumin-corrected Ca (cCa) was normal by 4hr and remained significantly increased from 8-24hrs. Tubular reabsorption of phosphate (TRP) and blood phosphate decreased rapidly. 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) was below normal at 0hr, increased and remained in the normal range from 4-24hrs. Intact fibroblast growth factor 23 (iFGF23) was above normal at time 0hr and remained unchanged over the 13hrs monitored. Bone turnover markers CTX and P1NP were unchanged compared with day 1. Mean±SD values. *p<0.05, **p<0.01, ***p<0.001

Conclusions

- Encaleret was well-tolerated when administered in escalating oral doses once or twice daily over 5 days, with no serious adverse events reported.
- PTH, blood calcium, and phosphate were generally normalized and maintained within the normal range by day 5.
- Intact FGF23 was above normal at time 0hr and surprisingly remained unchanged over the 13hrs monitored, despite the reported changes in phosphate, PTH and $1,25(OH)_2D$.
- 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.
- Data support further development of encaleret in ADH1.

Acknowledgements

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References

1. Dershem R, et al. Am J Hum Genet. 2020; 106(6):734-747. **2.** Hendy G, et al. Prog Molec Biol Transl Sci. 2009; 89:31-95. **3.** Roszko KL, et al. Front Physiol. 2016; 7:458. **4.** Tfelt-Hansen J, et al. Curr Med Chem. 2002; 2:175-193.

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