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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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).[1]
- The estimated U.S. prevalence is 3.9/100,000 with > 90 gain-of-function *CASR* variants reported.[1-2]
- Biochemical features of ADH1:[3]
  - 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).[3]
- 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.[5,6]
- A small clinical trial demonstrated that the calcilytic NPSP795 increased plasma levels of PTH and decreased calcium excretion in patients with ADH1.[7]
- Encaleret (CLTX-305), an investigational oral calcilytic, has the potential to restore normal mineral homeostasis without calcium and vitamin D supplementation.

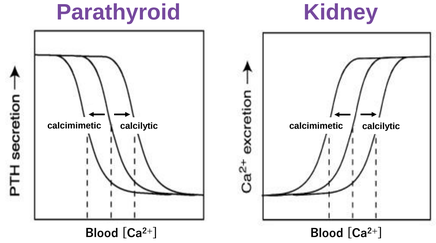

Figure 1: The effects of allosteric modulators on the CaSR
Calcilytics decrease the sensitivity of CaSRs to extracellular calcium, resulting in increased PTH secretion (left panel) and decreased calcium excretion (right panel). Calcimimetics (CaSR agonists) have the opposite effect [Figure adapted from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

Period 1 Study Design

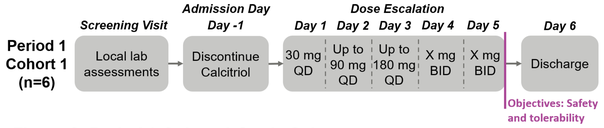

Figure 2: Period 1 Cohort 1 Study Schema
For full Phase 2B study design see Abstract #7288

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*
Supplement Doses		
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%)
Number of AEs	**9**
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

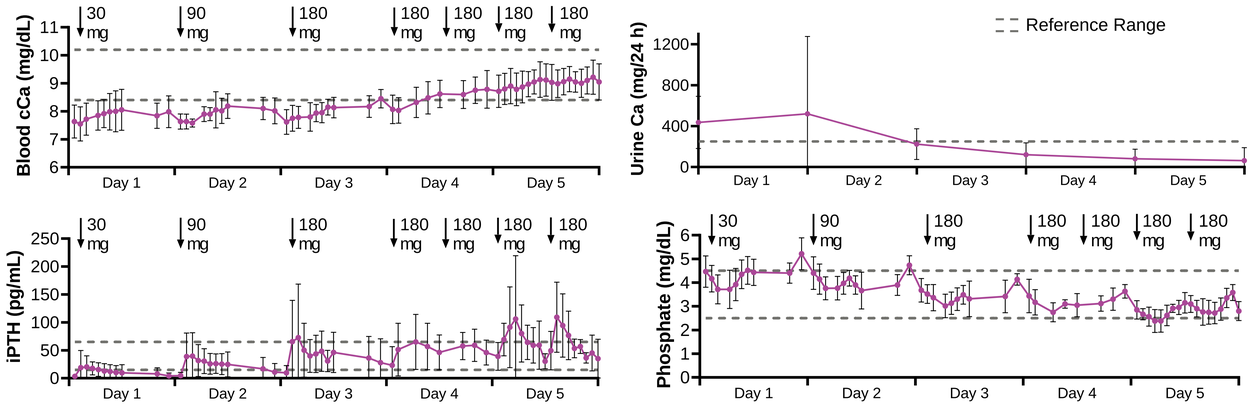

Figure 3: Mineral homeostasis normalized during Period 1 [mean±SD]. *One subject received second dose on Day 5 of 120 mg

Pharmacokinetics

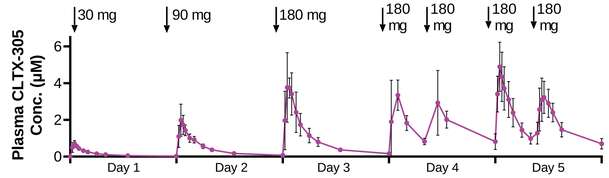

Figure 4: Pharmacokinetic profile for encaleret demonstrated dose proportional increase in plasma exposure over Period 1 [mean±SD].
* One subject received second dose on Day 5 of 120 mg.

Individual Subject Efficacy

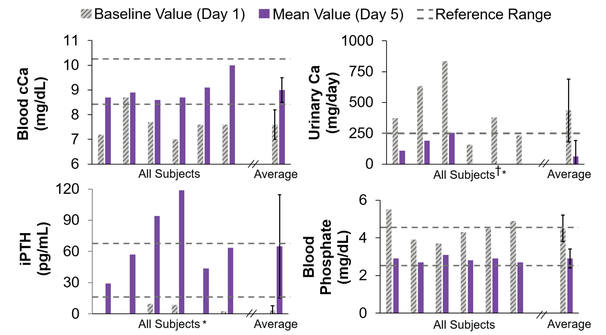

Figure 5: Summary of blood mineral levels following 5-day encaleret dosing.
† Where Day 5 values were unavailable, Day 4 values shown. * Values below limit of assay quantitation were plotted as "0".

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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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.
5. Dong B, et al. J Bone Miner Res. 2015; 30(11):1980-1993.
6. Hannan et al. J Bone Miner Res Plus. 2020; 4(10):e10402.
7. Roberts MS, et al. J Bone Miner Res. 2019; 34(9):1609-1618.