Encaleret (CLTX-305) Normalizes Mineral Homeostasis Parameters in Patients with Autosomal Dominant Hypocalcemia Type 1 over 18 months in a Phase 2 Study (NCT04581629)

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Background

- Autosomal dominant hypocalcemia type 1 (ADH1) is caused by gain-of-function (GoF) variants in the calcium-sensing receptor (CaSR) gene (*CASR*)[1]
- Estimated U.S. prevalence: 3.9/100,000[1-2]
- > 100 unique GoF *CASR* variants reported[1-2]
- Biochemical features[3] include:
  - Inappropriately low parathyroid hormone (PTH)
  - Hypocalcemia
  - Hypercalciuria
  - Hyperphosphatemia
  - Hypomagnesemia
- Conventional therapy (calcium and active vitamin D) can exacerbate hypercalciuria, increasing risk of renal calcifications and insufficiency
- Calcilytics (negative allosteric CaSR modulators) 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 normalize mineral homeostasis in ADH1 without calcium (Ca) and active vitamin D supplementation[5]

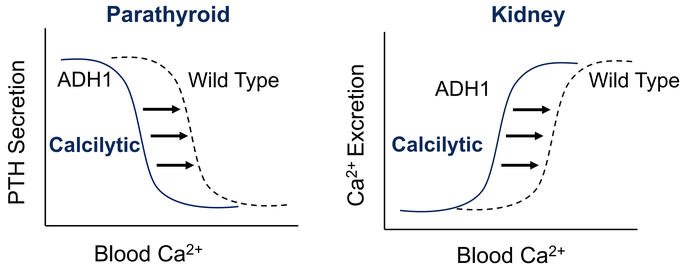
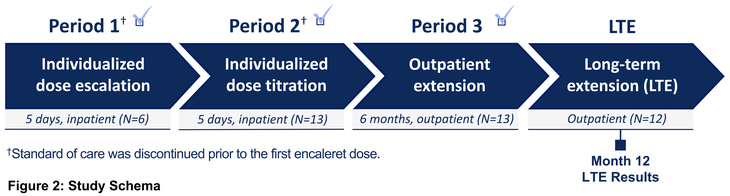


Figure 1: The effects of a calcilytic on the CaSR
Calcilytics decrease the sensitivity of the CaSR to extracellular calcium, resulting in increased PTH secretion (left) and decreased calcium excretion (right). [Figure adapted from Tfelt-Hansen, 2002].[4]
Ca^{2+} = ionized calcium

Phase 2b Study Design



†Standard of care was discontinued prior to the first encaleret dose.

Figure 2: Study Schema
This Phase 2b open-label study of encaleret in ADH1 was comprised of 3-periods followed by an LTE.

Acknowledgements

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References

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Subject Characteristics

Table 1: Baseline Characteristics

Characteristic	N=13	*Normal Range*
Age, mean (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Albumin corrected calcium (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*
Supplement Doses		
Elemental Calcium (mg/day) [mean (range)]	2120 (750-4800)	
Calcitriol (μg/day) [mean (range)]	0.7 (0.2-2.0)	

*Measurements taken pre-dose Day 1, Period 2. Data reported as (mean±SD). *CASR* variants (n): C131Y (2), P221L (2), E604K (1), A840V (3), F788C (1), T151M (1), Q245R (1), I692F (1), E228K (1)

Encaleret Dosing

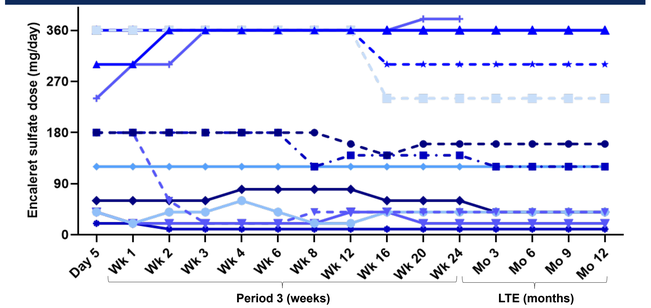

Figure 3: Individual encaleret sulfate dose needed to maintain albumin-corrected Ca (cCa) 8.4-10 mg/dL. Daily doses were divided BID.

Safety and Tolerability

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

	Periods 2 & 3	LTE
Subjects with Serious AEs	**0 (0%)**	**0 (0%)**
Subjects with AEs	**13 (100%)**	**12 (92%)**
Mild	13 (100%)	12 (100%)
Moderate	3 (23%)	4 (33%)
Severe	0 (0%)	0 (0%)
Number of AEs Reported	**86**	**66**
Mild	83 (97%)	57 (86%)
Moderate	3 (3%)	9 (14%)
Severe	0	0
Treatment-related Adverse Events[1]	**16 (21%)**	**1 (2%)**
Hypophosphatemia	10 (63%)	0
Hypercalcemia	6 (37%)	1 (100%)

Data as of 08-FEB-2023 and includes all available LTE data at time of data cut. Treatment-related AEs were transient & resolved either spontaneously or with encaleret dose adjustment. Treatment-related AEs counted as number of events per period and are presented as a percentage of the total number of AEs.

Bone and Mineral Parameters

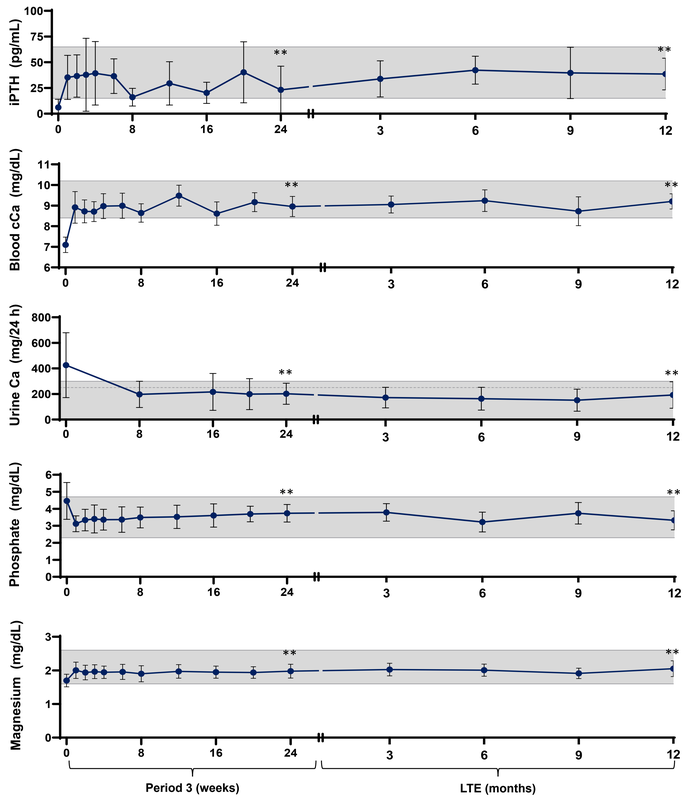

Figure 4: Encaleret restored and maintained mineral homeostasis in patients with ADH1 over 12 months.
Data reported as mean±SD. Gray shading = normal range. Solid line for urine calcium = upper limit for men, dashed line = upper limit for women. Values below limit of assay quantitation recorded as "0". Measures at weeks 0, 8, 16, and 24 are pre-encaleret dose. ** p-value < 0.01 Period 3 Week 24 or LTE Month 12 compared to Baseline.

Bone Turnover

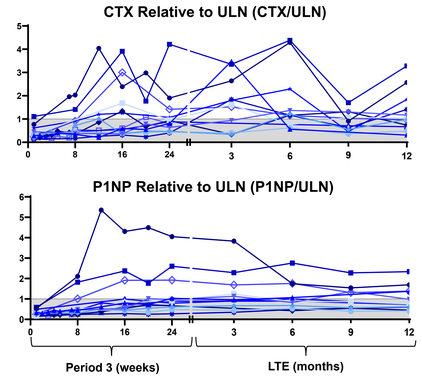

Figure 5: Encaleret increased bone turnover in patients with ADH1.
Individual participant corrected for sex and menopausal status reported as relative to sex/age upper limit of normal; "1" = upper limit of normal. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-AM encaleret dose. CTX = Collagen cross-linked C-telopeptide. P1NP = Procollagen type 1 N-terminal propeptide

Bone Density

DXA Anatomical Site n = 11	Screening Z-score n = 11	Period 3 Week 24 Z-score n = 11	LTE Month 12 Z-score n = 10
Total Body	2.1 ± 1.4	2.0 ± 1.3	N/A
AP Lumbar Spine	2.6 ± 1.5	2.3 ± 1.7	2.5 ± 1.7
Total Hip	2.2 ± 1.4	2.0 ± 1.4*	2.0 ± 1.3*
1/3 Distal Radius	0.2 ± 0.9	0.3 ± 0.9	0.5 ± 0.5

Figure 6: Encaleret had minimal short-term effects on bone density.
Data reported as mean±SD. DXA data not available on 2 participants due to surgical hardware. * p< 0.05 compared with screening

Conclusions

- In patients with ADH1, encaleret administered twice daily rapidly corrected and maintained mineral homeostasis within the normal range, as demonstrated by:[5]
  - ✓ Increase in PTH
  - ✓ Correction of hypocalcemia
  - ✓ Normalization of mean 24-hr urine calcium
  - ✓ Reduction in mean blood phosphate
  - ✓ Increase in mean blood magnesium
- Bone turnover markers increased with some participants above the normal range
- Encaleret was well-tolerated over 18 months, with no serious adverse events reported
- Outpatient evaluation of encaleret in a long-term extension is ongoing
- Phase 3 (CLTX-305-302) CALIBRATE study is underway **[NCT05680818]**

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