Encaleret (CLTX-305) Normalized Mineral Homeostasis Parameters in Patients with Autosomal Dominant Hypocalcemia Type 1: Results over 12 months in a Phase 2 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 of genetic variants is 3.9/100,000 with > 100 unique 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 modulators 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, an investigational oral calcilytic, has the potential to restore normal mineral homeostasis in ADH1 without calcium and active vitamin D supplementation.
- This Phase 2b open-label study of encaleret in ADH1 was comprised of 3-periods followed by a long-term extension (LTE).

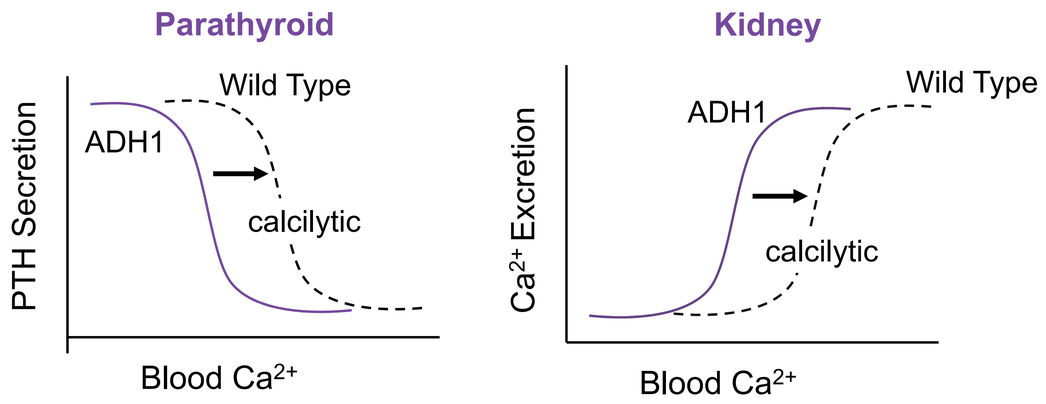
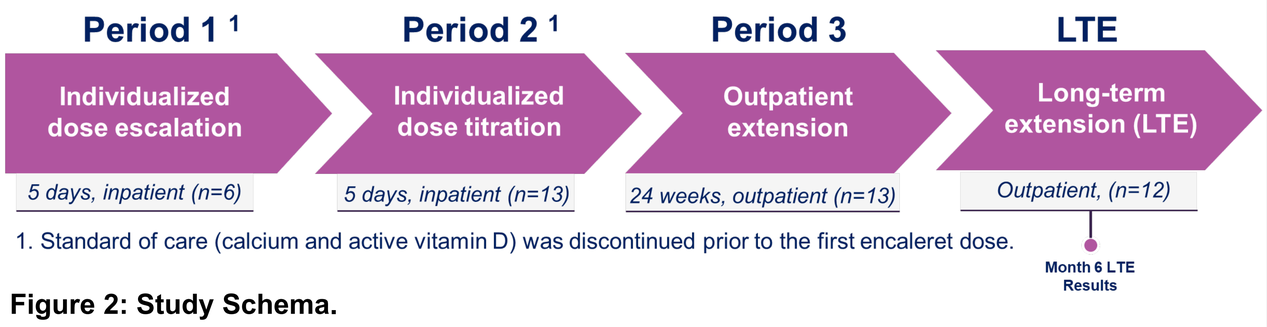


Figure 1: The effects of calcilytics on parathyroid and renal physiology
Calcilytics decrease the sensitivity of CaSRs to extracellular calcium, resulting in increased PTH secretion (left) and decreased calcium excretion (right). [Figure adapted from Tfelt-Hansen, 2002].[4]

Phase 2b Study Design



1. Standard of care (calcium and active vitamin D) was discontinued prior to the first encaleret dose.

Figure 2: Study Schema.

Subject Characteristics

Table 1: Baseline Characteristics

Characteristic	N=13	*Normal Range*
Age, mean (range)	39 (22-60)	
Female, n (%)	8 (62%)	
Nephrocalcinosis/Nephrolithiasis, n (%)	10 (77%)	
eGFR (mL/min/1.73 m^2)	84 ± 25	*> 60*
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*
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)

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	2 (15%)	4 (33%)
Severe	0 (0%)	0
Number of AEs Reported	**78**	**66**
Mild	76 (97%)	57 (86%)
Moderate	2 (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. 1. Treatment-related adverse events were transient & 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.

Mineral Parameters

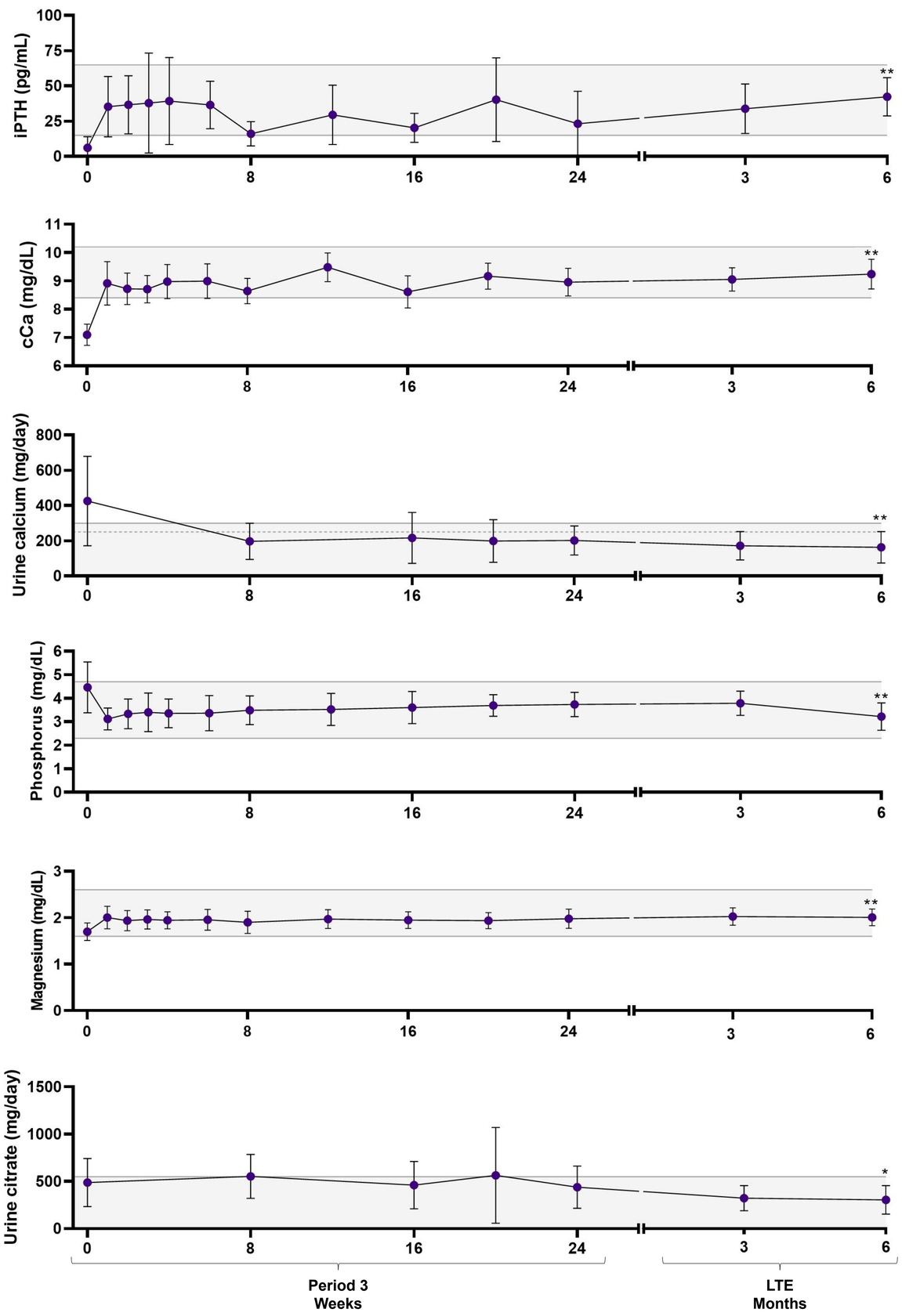


Figure 3: Encaleret restored mineral homeostasis in patients with ADH1, which was maintained over 12 months. Data reported as mean±SD. Gray shading = normal range. Solid line for urine calcium = upper limit for men, dashed line = upper limit for women. Values below limit of assay quantitation recorded as "0". The measures shown for weeks 0, 8, 16, and 24 are pre-AM encaleret dose. ** p-value < 0.01, * p-value < 0.05 LTE Month 6 mean compared to Baseline.

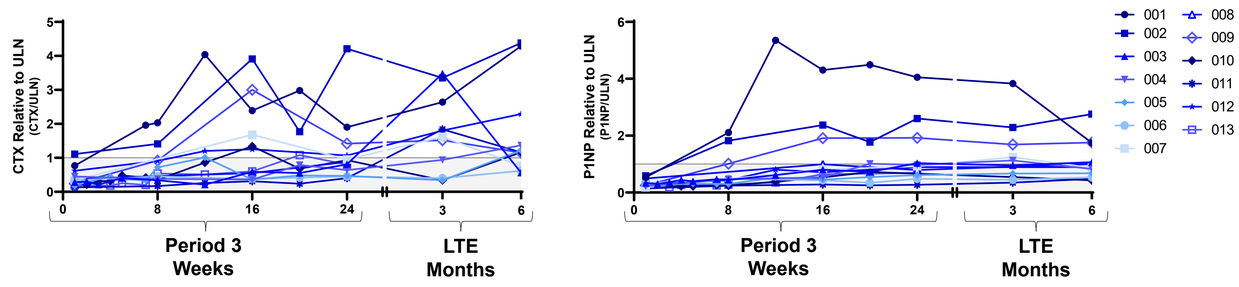


Figure 4: Encaleret increased bone turnover in patients with ADH1. Individual participant corrected for sex and menopausal status reported as relative to sex/age upper limit of normal; "1" = upper limit of normal. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-AM encaleret dose.

Conclusions

- In patients with ADH1, encaleret administered twice daily for 12 months restored mineral homeostasis as demonstrated by:
  - ✓ Increase in PTH
  - ✓ Correction of hypocalcemia
  - ✓ Normalization of mean 24-hr urine calcium
  - ✓ Reduction in mean blood phosphate
  - ✓ Increase in mean blood magnesium
  - ✓ Increase in bone turnover with some participants above the normal range
- Encaleret was well-tolerated over 12 months with no serious adverse events reported
- Outpatient evaluation of encaleret in the Phase 2b long-term extension is ongoing
- Phase 3 study initiated in late 2022

Acknowledgements

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References

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