A Phase 2b, Open-Label, Dose-Ranging Study of Encaleret (CLTX-305) in Autosomal Dominant Hypocalcemia Type 1 (ADH1)

[1]RI Gafni, [1]IR Hartley, [1]KL Roszko, [2]EF Nemeth, [1]KA Pozo, [3]R Sani-Grosso, [3]AV Sridhar, [3]JC Fox, [1]MT Collins

1. NIDCR, NIH, Bethesda, MD, USA, 20892; 2. MetisMedica, Toronto, ON, Canada, M4V 2M7; 3. Calcilytix Therapeutics, Inc, San Francisco, CA, USA, 94104

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] (Figure 1)
- Estimated U.S. prevalence of ADH1 is 3.9/100,000 with over 90 unique gain-of-function *CASR* variants reported to date.[1-2]
- Clinical manifestations of ADH1 include variable degrees of hypocalcemia, hyperphosphatemia, inappropriately low levels of parathyroid hormone (PTH), hypomagnesemia, and hypercalciuria.[3]
- Conventional therapy of ADH1 includes oral calcium and vitamin D supplementation, which can lead to or exacerbate hypercalciuria, increasing the risk for nephrolithiasis, nephrocalcinosis, and renal insufficiency.

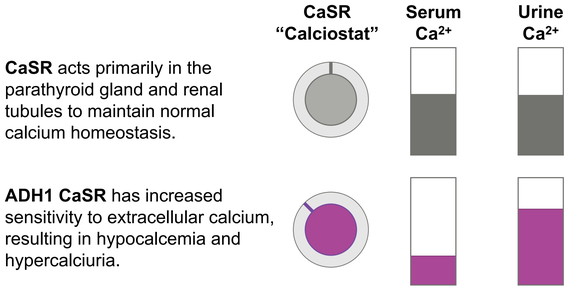


Figure 1: The CaSR as a "calciostat" and consequence of pathogenic activation in ADH1

Overview of Calcilytics

- Calcilytics (allosteric antagonists of the CaSR) shift the concentration-response relationship between extracellular calcium and the cellular response of cells bearing the CaSR to the right (Figure 2).
- Through direct effects on renal mineral reabsorption, 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.[4,5]

Overview of Calcilytics (continued)

- A small clinical trial demonstrated that a calcilytic can increase plasma levels of PTH and decrease renal calcium excretion in patients with ADH1.[6]
- Encaleret (CLTX-305), an orally available calcilytic, has the potential to restore normal mineral homeostasis in ADH1 patients in the absence of calcium and activated vitamin D supplementation.

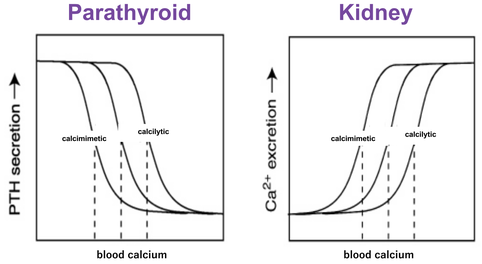


Figure 2: The effects of allosteric modulators on the CaSR
Calcilytics decrease the sensitivity of CaSRs to extracellular calcium, resulting in increased PTH secretion (left panel) and decreased calcium excretion (right panel). Calcimimetics have the opposite effect.

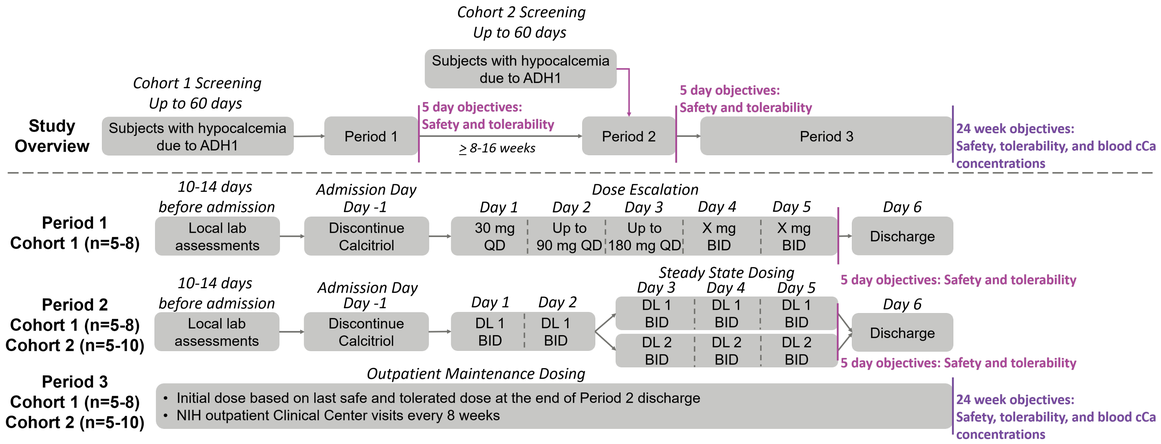
Key Inclusion Criteria

1. Age ≥16 years
2. Documented carrier of an activating *CASR* variant
3. BMI ≥ 18.5 and < 39 kg/m^2

Key Exclusion Criteria

1. History of treatment with PTH 1-84 or 1-34 within the previous 3 months
2. History of hypocalcemic seizures within the past 3 months
3. Blood 25-OH Vitamin D (Vit D) level < 25 ng/mL (repletion allowed)
4. Estimated glomerular filtration rate (eGFR) <25 mL/minute/1.73 m2
5. Clinically significant electrocardiogram (ECG) abnormalities
6. History of thyroid or parathyroid surgery

Study Design



Secondary endpoints include: Urinary calcium, serum levels of 1,25-$(OH)_2$ vitamin D, blood phosphate, bone turnover markers
Abbreviations: cCa – corrected calcium; DL – dose level

Figure 3: CLTX-305-201 Study Schema

Study Overview

- Single-site, open-label, dose-ranging Phase 2b study
- Calcitriol, calcium, and magnesium supplements discontinued while on CLTX-305
- **2 Cohorts and 3 Periods**
  - Cohort 1 (5-8 subjects) participate in all 3 Periods
  - Cohort 2 (5-10 subjects) participate in Periods 2 and 3
- **Period 1**
  - 5 inpatient CLTX-305 dosing days
  - 24-hr blood and urine sampling
- **Period 2**
  - 5 inpatient CLTX-305 BID dosing days
  - 24-hr blood and urine sampling
- **Period 3**
  - 24-week outpatient period with 3 inpatient visits and frequent outpatient assessments
  - Individualized CLTX-305 BID dosing

Objectives and Endpoints

- Safety and tolerability (adverse events, vital signs, safety labs)
- Treatment-related changes in:
  - Albumin-corrected blood calcium concentrations
  - iPTH blood concentrations
  - Urine calcium excretion (FECa and 24hr total)
  - Serum 1,25$(OH)_2$-vitamin D
  - Serum Mg, Pi, Na, K, Cr, cAMP, citrate
  - Bone turnover markers (serum collagen C-telopeptide and serum procollagen Type 1 N-propeptide)
- CLTX-305 PK profile

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

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