CALIBRATE: A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Encaleret (CLTX-305) Compared to Standard of Care in Participants with Autosomal Dominant Hypocalcemia Type 1 [NCT05680818]

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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]
- ADH1 is emerging as the most common genetic form of non-syndromic hypoparathyroidism for which there are currently no approved interventions indicated[2]
- Estimated prevalence is 3.9/100,000 with > 100 known unique GoF *CASR* variants[1,3]
- Current standard-of-care (SoC) is calcium and active vitamin D
- Individuals with ADH1 are particularly prone to hypercalciuria and negative renal effects from SoC due to the combination of oversensitive CaSR in the kidney, and parathyroid hormone (PTH) suppression
- Calcilytics are negative allosteric CaSR modulators that may offer potential for the treatment of ADH1
- An investigational oral calcilytic, encaleret (CLTX-305), was studied in an open-label, Phase 2b study [NCT04581629][4]
- Encaleret administered twice daily rapidly increased intact parathyroid hormone secretion (iPTH), corrected hypocalcemia, reduced hypercalciuria, restored other parameters of mineral homeostasis, and was well-tolerated in 13 adult patients with ADH1[4]

Study Design

- CALIBRATE is a multi-center, randomized, open-label, two-arm, global Phase 3 study with a long-term extension (LTE) designed to evaluate the efficacy and safety of encaleret compared to SoC
- Approximately 60 participants with ADH1 and biochemical evidence of hypoparathyroidism will be enrolled

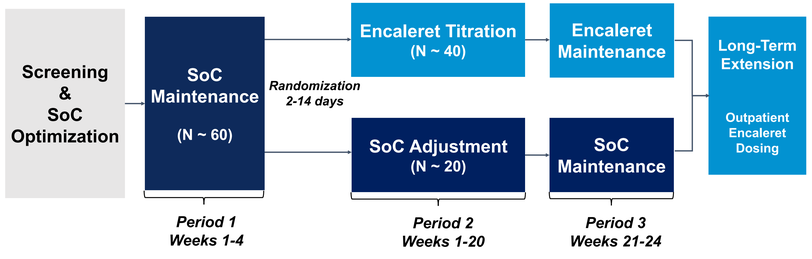


Figure 1. CALIBRATE Study Schema

- **Screening & SoC Optimization Period:** SoC treatment regimen will be assessed and optimized with the goal of achieving normal albumin-corrected blood calcium (cCa) and 24-hr urine calcium (UCa) excretion
- **Period 1 [P1]:** 4-week SoC maintenance
- **Randomization:** Participants will be randomized 2:1 to encaleret or SoC
- **Period 2 [P2]:** Doses will be adjusted as needed to achieve target cCa levels while minimizing UCa excretion
- **Period 3 [P3]:** Encaleret or SoC doses will remain fixed and only adjusted to address potential safety concerns
- **Long-Term Extension [LTE]:** All participants may enter LTE and receive encaleret treatment

Efficacy Endpoints & Analyses

- **Primary Endpoint:** The proportion of participants at the completion of P3 achieving:
  - cCa within the target range (8.3-10.7 mg/dL) **AND**
  - 24-hr UCa within the reference range (< 300 mg/day for men, < 250 mg/day for women)
- Participants who meet both criteria will be considered responders
- The primary analysis is a within-patient comparison of the proportion of responders at the completion of P3 compared to the completion of P1
- Additional endpoints include between-treatment arm comparisons as well as the evaluation of mineral homeostasis parameters, renal health, bone health, and patient-reported outcomes
  - blood iPTH
  - blood phosphate
  - blood magnesium
  - 1,25-$(OH)_2$ Vitamin D
  - bone mineral density
  - bone turnover markers
  - renal ultrasound
  - 36-item short form health survey
  - ADH1 questionnaire

Key Eligibility Criteria

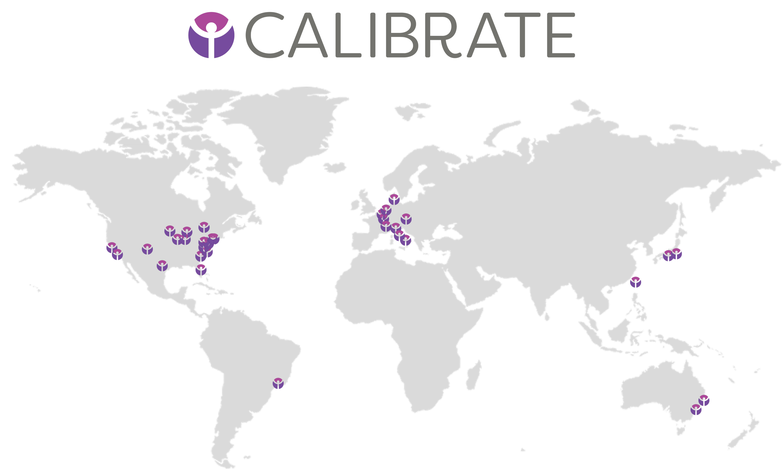
Inclusion

- Age ≥ 16 years (EU: ≥ 18 years)
- Documented *CASR* variant associated with biochemical findings related to hypoparathyroidism at Screening or a documented history of both:
  - cCa < 8.6 mg/dL (2.2 mmol/L) in participants 16 to < 18 years, or < 8.5 mg/dL (2.1 mmol/L) in participants ≥ 18 years
  - iPTH < 40 pg/mL (4.2 pmol/L)
- Documented history of signs or symptoms of ADH1
- Discontinued thiazides for at least 14 days prior to SoC Optimization

Exclusion

- History of hypocalcemic seizure within the 3 months preceding Screening
- History of thyroid or parathyroid surgery
- Pregnant or nursing (lactating) women
- History of treatment with PTH 1-84 or 1-34 within the 2 months preceding Screening
- Blood 25-OH Vitamin D level < 25 ng/mL
- Estimated glomerular filtration rate < 30 mL/minute/1.73 m^2
- Participants planning to conceive a child prior to the LTE

Participating Global Investigational Sites



USA
Bethesda, MD
Indianapolis, IN
Rochester, MN
Greenville, NC
Boston, MA
Columbus, OH
Baltimore, MD
Aurora, CO
Philadelphia, PA
Oakland, CA
New York, NY
Houston, TX
Los Angeles, CA
Jacksonville, FL
Chicago, IL

Australia
Brisbane
St Leonards

Brazil
São Paulo

Canada
Ontario

Czech Republic
Prague

Denmark
Aarhus

France
Lille
Paris
Lyon

Italy
Milan
Rome
Pisa

Japan
Osaka
Tokyo

Netherlands
Rotterdam

Taiwan
Tainan

Figure 2. Investigational sites planned as of October 2023

Summary

- The compelling results from the Phase 2 study provide evidence to support the continued development of encaleret to be a first-in-class molecularly targeted therapy for the treatment of ADH1[4]
- CALIBRATE is the largest global prospective, interventional study in ADH1 and is currently enrolling in 11 countries

References

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2. Mannstadt M. Next-Generation Sequencing for Detection of Underlying Genetic Causes of Nonsurgical Hypoparathyroidism: Preliminary Results from a Sponsored Testing Program. Poster presented at: Endocrine Society's Annual Meeting; June 17, 2023; Chicago, IL.
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