# The Oral Calcilytic Encaleret Decreased the Fractional Excretion of Calcium (FECa) and Normalized Blood and Urinary Calcium in Individuals with Post-surgical Hypoparathyroidism: Preliminary Findings from an Ongoing Open-label Phase 2 Study

Sun-LB 591


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## Background

### The actions of PTH and the calcium-sensing receptor (CaSR) on renal calcium handling are intertwined

- PTH activity and CaSR activation have opposing effects on renal calcium reabsorption
- CaSR activation impacts PTH secretion, confounding the ability to isolate the PTH-independent effects of renal CaSRs on calcium regulation

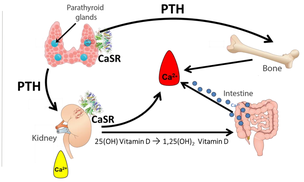



**Figure 1:** PTH and the CaSR are the primary regulators of blood and urinary calcium

### Calcilytics: Antagonists of the CaSR

- Encaleret is an investigational oral calcilytic (negative allosteric modulator of the CaSR).
- In post-menopausal women and patients with Autosomal Dominant Hypocalcemia Type 1 (ADH1) due to activating *CASR* variants, calcilytics ↑blood calcium,↑PTH, and ↓urine calcium (Caltabiano et al., *Bone*, 2013; Gafni et al., *NEJM*, 2023).
- In patients with functioning parathyroid glands, calcilytics reduce fractional calcium excretion through the combined effects of increased PTH and direct inhibition of renal CASRs.

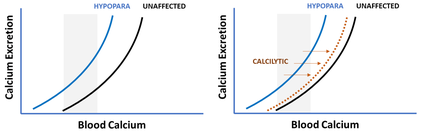
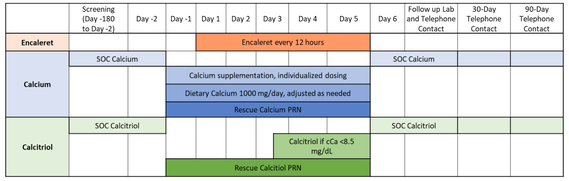



**Figure 2:** Calcium excretion curve in unaffected (black) vs. hypoparathyroid (blue) individuals. Calcilytics would be expected to shift the curve towards normal (orange) in patients with intact parathyroid glands.
(Figure adapted from Peacock et al., *Endocrinol Metab Clin North Am,* 2018)

### Calcilytics in Post-surgical Hypoparathyroidism (PSH)

- Current treatment of PSH is inadequate:
  - Calcium and active vitamin D requires a balance between blood calcium, urinary calcium, and symptoms.
  - Approved and investigational PTH analogs require daily injections.
- Pre-clinical studies in thyroparathyroidectomized rats show that calcilytics ↑blood calcium by ↓urinary calcium excretion without changes in PTH (Loupy et al., *J Clin Invest,* 2012).
- Hypothesis: Encaleret administration to individuals with PSH may reveal the PTH-independent effects of CaSR modulation on renal calcium handling and clarify the potential therapeutic role of calcilytics as an orally administered alternative in PSH.

## Study Design




- Open-label, phase 2, proof-of-principle study (NCT05735015)
- Up to 15 adult patients with post-surgical hypoparathyroidism
  - Up to 10 with permanent PSH (>1 year)
  - Up to 5 with recent PSH (<1 year)
- Encaleret 162 mg dosed every 12 hours for up to 5 inpatient days
- Primary endpoint: Change in FECa
- Secondary endpoint: Proportion of participants to achieve concomitant normal fasting blood calcium and 24-hour urine calcium
- Option to discontinue encaleret to observe PK-PD of encaleret withdrawal.

## Study Participants

**Table 1: Baseline Characteristics**

| Baseline Characteristics | n=7, median(range) |
|---|---|
| Age | 53 (26-69) |
| Female, n (%) | 7 (100%) |
| Permanent PSH (>1 year), n (%) | 7 (100%) |
| Corrected calcium (mg/dL, nl 8.4-10.2)* | 8.4 (7.9-9.3) |
| Intact PTH (pg/mL, nl 15-65)* | 6.8 (4.3-12.2) |
| 24h Urine Calcium (mg/24h, nl <250)* | 345 (204-504) |
| Nephrocalcinosis/nephrolithiasis, n (%) | 3 (43%) |
| **Supplement Doses** | |
| Elemental Calcium (mg/day)** | 1000 (85-3600) |
| Calcitriol (mcg/day) | 0.5 (0.25-1) |

*Measurements taken fasting Day -1; **Home regimen prior to Day -1, averaged over 1 week

## Adverse Events

**Table 2: Treatment-Emergent Adverse Events (AEs)**

| Treatment-Emergent AEs | Total=20; n(%) |
|---|---|
| Mild | 18 (90%) |
| Moderate | 2 (10%) |
| Severe | 0 (0%) |

- No serious AEs
- The only treatment-related AEs were mild hypercalcemia and mild headache in 1 participant. Her blood calcium was mildly elevated for 60 hours after the last dose of encaleret even after calcium/calcitriol was stopped (Peak corrected calcium 10.7 mg/dL). 24-hour urine calcium remained <200 mg/day.

## Results

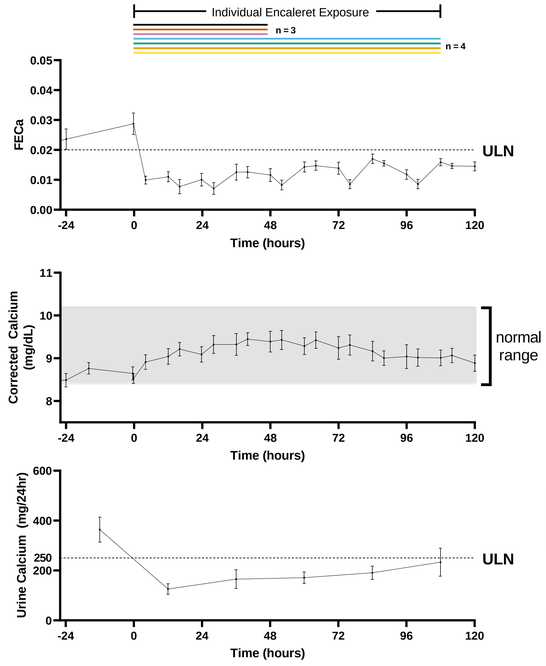



**Figure 3:** Fractional excretion of calcium (FECa), a measure of renal calcium handling, decreased on encaleret, reflecting a decrease in urinary calcium despite higher albumin-corrected blood calcium levels. 24-hour urinary calcium excretion normalized in 6 participants and decreased by 30% in the seventh. Mean±SEM; Colored lines = individual data; ULN = upper limit of normal

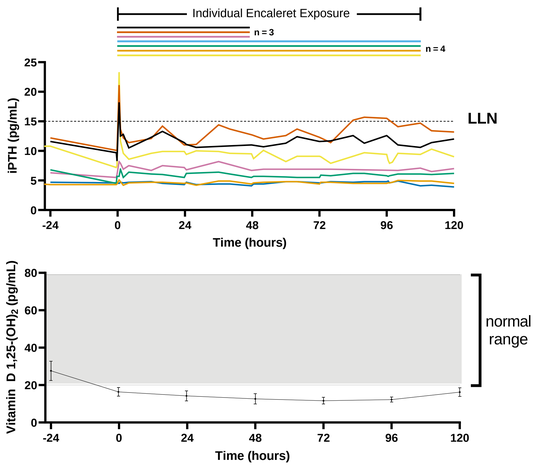



**Figure 4:** PTH increased transiently 30 minutes after the first dose of encaleret in 6 participants, then returned to near-baseline levels. 1,25(OH)$_2$-Vitamin D levels decreased reflecting the discontinuation of calcitriol on Day -1. Levels remained low despite 3 participants reinitiating low-dose calcitriol; Mean±SEM; LLN = lower limit of normal . Colored lines = individual data

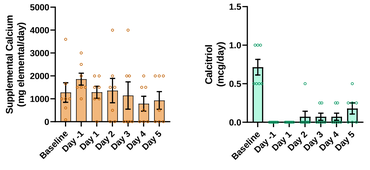



**Figure 5:** Calcium and calcitriol supplementation were titrated to maintain mid-normal blood calcium levels. On day 4 and 5, three participants received no supplemental calcium.

## Conclusions

- Encaleret reduced fractional excretion of calcium in the first 7 participants with post-surgical hypoparathyroidism and normalized concomitant blood and 24-hour urine calcium in 86% of participants with PSH.
- Apart from a small and transient rise after the initial dose, PTH levels remained low suggesting encaleret's sustained effect likely occurred independent of PTH, primarily driven by renal CaSR inhibition.
- CaSR inhibition did not appear to impact 1,25-(OH)$_2$-Vitamin D levels.
- Preliminary results from this Phase 2 study support continued evaluation of encaleret as an orally administered therapy for the treatment of patients with PSH.
- Recruitment is ongoing: https://clinicaltrials.gov/ct2/show/NCT05735015 or email: iris.hartley@nih.gov