Preliminary Findings From an Ongoing Open-label Phase 2 Study Demonstrate that the Calcilytic Encaleret Can Improve the Relationship Between Blood and Urinary Calcium in Individuals with Post-surgical Hypoparathyroidism

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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

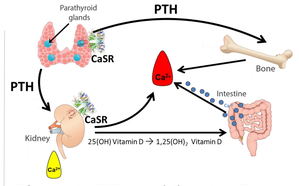


Figure 1: PTH and the CaSR are the primary regulators of blood and urinary calcium

Calcilytics: Antagonists of the CaSR

- Encaleret is an investigational oral calcilytic (negative allosteric modulator of the CaSR)
- In both healthy post-menopausal women and patients with Autosomal Dominant Hypocalcemia Type 1 (ADH1) due to activating variants of *CASR*, calcilytics ↑blood calcium and ↑PTH, while ↓urinary calcium (Caltabiano et al. 2013; Gafni et al, 2023).
- The decrease in fractional calcium excretion in these populations is due to the impact of calcilytics on *both* parathyroid and renal CaSRs.

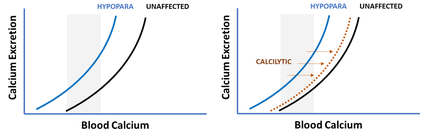
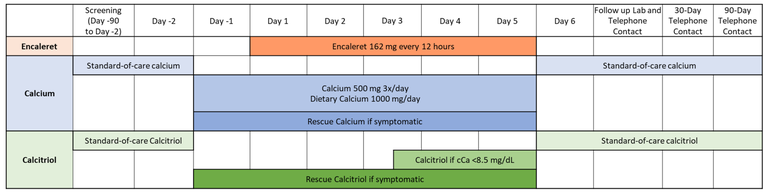


Figure 2: Calcium excretion curve in unaffected (black) vs. hypoparathyroid (blue) individuals. Calcilytics would be expected to shift the curve towards normal (orange) in patients with intact parathyroid glands. This study aims to determine if this effect persists in the absence of PTH (Figure adapted from Peacock et al. 2018)

Calcilytics in Post-surgical Hypoparathyroidism (PSH)

- Current treatment of PSH is inadequate, requiring a balance between blood calcium, urinary calcium, and symptoms
- Pre-clinical studies in thyroparathyroidectomized rats suggest calcilytics ↑blood calcium and ↓urinary calcium excretion (Loupy et al. 2012)
- We hypothesize that calcilytic 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 in PSH.

Study Design



- Open-label, phase 2, proof-of-principle study (NCT05735015)
- Encaleret 162 mg dosed every 12 hours for up to 5 inpatient days
- Option to discontinue encaleret early if specific achievement thresholds for endpoints are met to observe PK-PD of encaleret withdrawal

Study Participants

Plan to enroll 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)

Table 1: Baseline Characteristics

Baseline Characteristics	n=5, mean(range)
Age	47 (26-69)
Female, n (%)	5 (100%)
Permanent PSH (>1 year), n (%)	5 (100%)
Corrected calcium (mg/dL, nl 8.4-10.2)*	8.4 (7.9-8.6)
Intact PTH (pg/mL, nl 15-65)*	8.3 (4.7-12.2)
24h Urine Calcium (mg/24h, nl <250)*	379 (204-503)
Nephrocalcinosis/nephrolithiasis, n (%)	4 (80%)
Supplement Doses	
Elemental Calcium (mg/day)**	1260 (85-3600)
Calcitriol (mcg/day)	0.6 (0.25-1)

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

Adverse Events

Table 2: Summary of Adverse Events (AEs)

Number of Treatment-Emergent AEs	Total=10; n(%)
Mild	7 (70%)
Moderate	3 (30%)
Severe	0 (0%)

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

Results

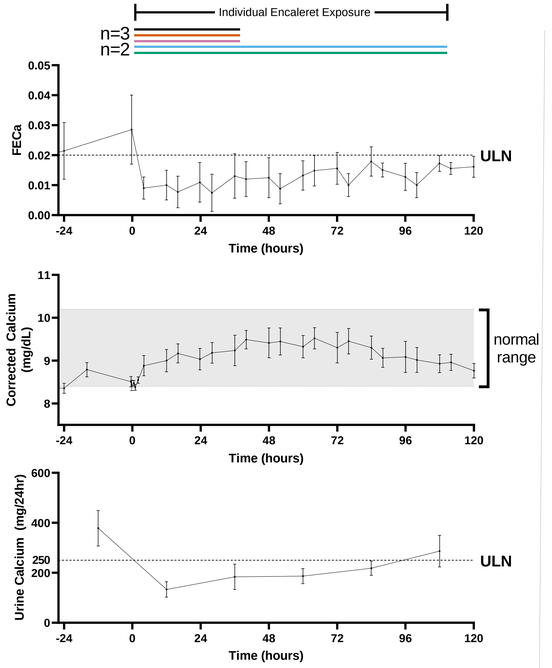


Figure 3: Fractional excretion of calcium (FECa), a measure of renal calcium handling, decreased on encaleret, reflecting a decrease in urinary calcium despite higher albumin-corrected blood calcium levels. Urinary calcium excretion normalized in 4 participants and decreased by 30% in the fifth. Mean±SEM; Colored lines = individual data; ULN = upper limit of normal

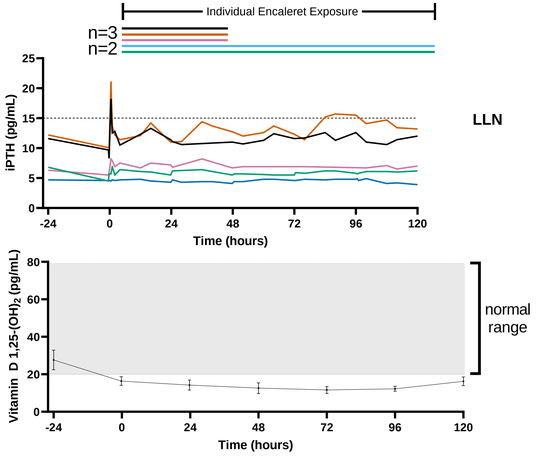


Figure 4: PTH increased transiently 30 minutes after the first dose of encaleret in 4 participants, then returned to near-baseline levels. 1,25(OH)$_2$-Vitamin D levels decreased reflecting the discontinuation of calcitriol on Day -1. Levels remained low despite 3 participants reinitiating low-dose calcitriol;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

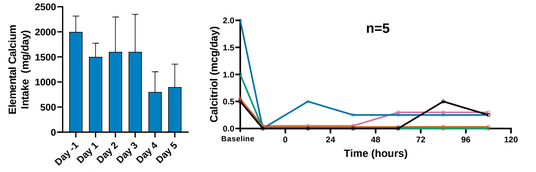


Figure 5: Calcium and calcitriol supplementation were titrated to mid-normal blood calcium levels. Mean±SEM; Colored lines = individual data;

Conclusions

- Encaleret reduced fractional excretion of calcium in the first 5 participants with post-surgical hypoparathyroidism, decreasing urinary calcium despite maintaining higher blood calcium levels.
- PTH levels remained low, apart from a small and transient rise after the initial dose in most participants suggesting that encaleret's effect likely occurred independent of PTH, primarily driven by renal CaSR inhibition.
- CaSR inhibition per se, 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