Encaleret (CLTX-305) Restored Mineral Homeostasis in a Phase 2 Study in Autosomal Dominant Hypocalcemia Type 1 (ADH1) [NCT04581629]

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Prepared for presentation at the ENDO 2022 Annual Meeting
• This study was supported by a public/private partnership between the NIDCR Intramural Research Program and BridgeBio affiliate Calcilytix Therapeutics, Inc.
• Encaleret is currently under clinical development, and its safety and efficacy have not been evaluated by any regulatory authority.
Blood calcium is maintained by four organs regulated by the CaSR and PTH

- Kidney: \( \uparrow \text{Ca}^{2+} \text{ reabsorption} \)
- Intestine: \( \uparrow \text{1-\(\alpha\)-hydroxylase} \) on 25(OH) Vitamin D, \( \uparrow \text{Ca}^{2+} \text{ absorption} \)
- Bone: \( \uparrow \text{Bone resorption} \), \( \uparrow \text{Ca}^{2+} \)

\( \downarrow \text{Blood Ca}^{2+} \text{ detected by CaSRs} \)

\( \text{Ca}^{2+} = \text{ionized calcium}; \ PTH = \text{parathyroid hormone}; \ \text{CaSR} = \text{calcium-sensing receptor} \)
Activating variants in the CASR cause Autosomal Dominant Hypocalcemia (ADH1)

**Clinical Manifestations**

**Acute symptoms**
- Hypocalcemic seizures
- Paresthesia
- Tetany
- Muscle cramps

**Long-term complications**
- Nephrolithiasis
- Nephrocalcinosis
- Chronic Kidney Disease

Conventional therapy with calcium and activated vitamin D does not correct the underlying pathophysiology and has the potential to worsen long-term complications

**Activating variants in the CASR increase tissue sensitivity to Ca\(^{2+}\)**

- **Parathyroid**
  - Wild Type
  - ADH1
  - PTH Secretion
  - Blood Ca\(^{2+}\)

- **Kidney**
  - Wild Type
  - ADH1
  - Ca\(^{2+}\) Excretion
  - Blood Ca\(^{2+}\)

**Hyperactive CaSR causes dysregulation of Ca homeostasis**

- Decreased parathyroid hormone (PTH) secretion
- Decreased blood calcium
- Increased urinary calcium

Encaleret, an investigational oral calcilytic, may be a potential treatment for ADH1

- Calcilytics are negative allosteric modulators of the CaSR that decrease CaSR sensitivity to extracellular calcium
- Normalizing CaSR sensitivity could correct hypocalcemia, hypercalciuria, and low PTH in individuals with ADH1

Figure adapted from Tfelt-Hansen J, et al. Curr Med Chem. 2002.
Standard of care (calcium and active vitamin D) was discontinued prior to the first encaleret dose.

**Additional measures:**
- Blood 1,25-(OH)_2-vitamin D, magnesium, and phosphate
- Urine creatinine, cAMP, citrate, phosphate, sodium, magnesium
- Bone turnover markers (serum collagen C-telopeptide, serum procollagen Type 1 N-propeptide)

**Key study objectives:**
- Safety and tolerability
- Blood calcium concentration
- Urine calcium concentration
- Intact parathyroid hormone concentration

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population (N = 13)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, yr (range)</td>
<td>39 (22-60)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>8 (62%)</td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis/Nephrolithiasis, n (%)</td>
<td>10 (77%)</td>
<td></td>
</tr>
<tr>
<td>ECG QTcF (msec)</td>
<td>435 ± 16</td>
<td>&lt; 460 Female; &lt; 450 Male</td>
</tr>
<tr>
<td>Calcium¹,² (mg/dL)</td>
<td>7.1 ± 0.4</td>
<td>8.4 –10.2</td>
</tr>
<tr>
<td>Intact PTH² (pg/mL)</td>
<td>6.3 ± 7.8</td>
<td>15 – 65</td>
</tr>
<tr>
<td>Phosphate² (mg/dL)</td>
<td>4.5 ± 1.1</td>
<td>2.3 – 4.7</td>
</tr>
<tr>
<td>Magnesium² (mg/dL)</td>
<td>1.7 ± 0.2</td>
<td>1.6 – 2.6</td>
</tr>
<tr>
<td>24h Urine Calcium (mg/24h)</td>
<td>384 ± 221</td>
<td>&lt; 250 - 300</td>
</tr>
</tbody>
</table>

### Supplements

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental Calcium (mg/day)</td>
<td>2120 (750-4800)</td>
</tr>
<tr>
<td>Calcitriol (µg/day)</td>
<td>0.7 (0.2-2.0)</td>
</tr>
</tbody>
</table>

### CASR Variants

- C131Y (2)
- P221L (2)
- E604K (1)
- A840V (3)
- F788C (1)
- T151M (1)
- Q245R (1)
- I692F (1)
- E228K (1)

Data reported as mean±SD. ECG QTcF = electrocardiogram Fridericia-corrected Q-T interval. The encaleret starting dose was either 180mg BID or 90mg BID in Period 2. 1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1, Period 2.
Phase 2B Oral Encaleret Dosing Summary

**Period 1 Dosing**  
*Defined dose escalation*  
Day 5 Mean: 350.0±22.4 mg/day

**Period 2 Dosing**  
*Individualized dose titration*  
Day 5 Mean: 178.3±123.7 mg/day

**Period 3 Dosing**  
*Optimized dose adjustments*  
Wk 24 Mean: 172.0±140 mg/day

Periods 1 and 2 data reported as mean±SD.
Encaleret was well-tolerated with no serious adverse events reported

<table>
<thead>
<tr>
<th>Number of Adverse Events Reported</th>
<th>Period 1 N=6</th>
<th>Periods 2 and 3 N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects experiencing any Serious Adverse Event</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Number of subjects experiencing any Adverse Event</strong></td>
<td>6 (100%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (100%)</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of Adverse Events Reported</strong></td>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>Mild</td>
<td>8 (100%)</td>
<td>76 (97%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treatment-related Adverse Events</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2 (33%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (100%)</td>
<td>10 (63%)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0 (0%)</td>
<td>6 (37%)</td>
</tr>
</tbody>
</table>

Data as of Mar 8, 2022. 1. Treatment-related adverse events were transient and 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.
Period 1 Results (n=6): Encaleret increased PTH secretion and normalized blood and urine calcium

1. Encaleret dose adjusted to 180/120 in 1 subject on Day 5.
2. Values below limit of assay quantitation recorded as "0".
3. Day 4 values used in two subjects given Day 5 values unavailable. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. ** p-value < 0.01.

1. Encaleret dose adjusted to 180/120 in 1 subject on Day 5. 2. Values below limit of assay quantitation recorded as "0". 3. Day 4 values used in two subjects given Day 5 values unavailable. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. ** p-value < 0.01.
Periods 2 and 3 Results (n=13): BID Encaleret restored and maintained mean blood and urine calcium in the normal range over a 24-week period.

Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. ULN = upper limit of normal; LLN = lower limit of normal. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women. cCa values shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.
Period 2 and 3 Results (n=13): BID encaleret increased mean PTH and decreased mean blood phosphate into the normal range

Data as of Mar 8, 2022 reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. The measures shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.
Period 2 and 3 Results (n=13): BID encaleret increased mean blood magnesium and mean 1,25-(OH)$_2$-vitamin D

Data as of Mar 8, 2022 reported as mean+SD. Gray shading reflects normal range. The measures shown for weeks 8, 16, and 24 are pre-encaleret. ** p-value < 0.01 Week 24 mean compared to Baseline.
Period 3 Results (n=13): BID encaleret increased bone turnover markers

Data as of Mar 8, 2022. CTX and P1NP reported as individual participant data and were corrected for sex and menopausal status. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-encaleret.
Period 3 Results (n=11): BID encaleret had minimal short-term effects on bone density

<table>
<thead>
<tr>
<th>DXA Anatomical Site</th>
<th>Screening Z-score Mean ± SD</th>
<th>Period 3, Week 24 Z-score Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body</td>
<td>2.1 ± 1.4</td>
<td>2.0 ± 1.3</td>
</tr>
<tr>
<td>AP Lumbar Spine</td>
<td>2.6 ± 1.5</td>
<td>2.3 ± 1.7</td>
</tr>
<tr>
<td>Total Hip</td>
<td>2.2 ± 1.4</td>
<td>2.0 ± 1.4*</td>
</tr>
<tr>
<td>1/3 Distal Radius</td>
<td>0.2 ± 0.9</td>
<td>0.3 ± 0.9</td>
</tr>
</tbody>
</table>

Data as of Mar 8, 2022. DXA data not available on 2 participants due to surgical hardware. * p< 0.05
Summary

• In patients with ADH1, encaleret administered twice daily for 24 weeks restored mineral homeostasis as demonstrated by:
  • Increase in PTH
  • Correction of hypocalcemia
  • Normalization of mean 24-hr urine calcium
  • Reduction in blood phosphate
  • Increase in mean magnesium and 1,25-(OH)_2-vitamin D
  • Increase in bone turnover while remaining in the normal range in most participants

• Encaleret was well-tolerated over 24 weeks, with no serious adverse events reported

• Outpatient evaluation of encaleret in the Phase 2b long-term extension is ongoing

• Phase 3 study is planned for initiation in 2022
Acknowledgements

Thanks to the patients, referring physicians, and the support staff at the National Institutes of Health
Back-up Slide
Data as of Mar 8, 2022. CTX and P1NP reported as individual participant data and were corrected for sex and menopausal status. Gray shading reflects normal range. Measures shown for weeks 8, 16, and 24 are pre-encaleret. Individual participant number is provided to the right of each graph.