The Effects of Encaleret (CLTX-305) on Mineral Physiology in Autosomal Dominant Hypocalcemia Type 1 (ADH1) Demonstrate Proof-of-Concept: Early Results from an Ongoing Phase 2B, Open-Label, Dose-Ranging Study

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Disclosures

- This study was supported by a public/private partnership between the NIDCR Intramural Research Program and BridgeBio affiliate Calcilytix Therapeutics, Inc.
- Non-FDA approved investigational agent will be discussed
Blood calcium is maintained by four organs regulated by PTH and the CaSR

PTH = parathyroid hormone; CaSR = calcium-sensing receptor
CaSR maintains physiological calcium homeostasis primarily through its activity in the parathyroid cell and renal tubule.

**Parathyroid cell**

- CaSR decreases PTH synthesis and secretion in response to \( \uparrow \) blood \( \text{Ca}^{2+} \)

**Renal Tubule**

- CaSR decreases renal tubular \( \text{Ca}^{2+} \) reabsorption in response to \( \uparrow \) blood \( \text{Ca}^{2+} \)
Activating variants in the CASR cause Autosomal Dominant Hypocalcemia (ADH1)

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

- **Parathyroid**
  - **PTH**
  - **Blood Ca\(^{2+}\)**
  - ADH1
  - WT

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

**Hyperactive CaSR causes dysregulation of Ca homeostasis**

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

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

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

![Graph showing PTH secretion and Ca²⁺ excretion](image_url)
Key study objectives:
- Safety and tolerability
- Blood calcium concentration
- Urine calcium concentration
- Intact parathyroid hormone concentration

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)

Encaleret Phase 2B Study Design – CLTX-305-201

Period 1
Individualized dose escalation
5 days, inpatient (N=6)
March 2021
Proof of concept early results

Period 2
Individualized dose titration
5 days, inpatient (N=13)
October 2021
Phase 2 Period 2 results

Period 3
Outpatient extension
6 months, outpatient (N=13)

LTE
Long-term extension
Outpatient

Complete
## 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, n (%)</td>
<td>10 (77%)</td>
<td></td>
</tr>
<tr>
<td>ECG QTcB (msec)</td>
<td>452 ± 16</td>
<td>&lt;440</td>
</tr>
<tr>
<td>Calcium1 (mg/dL)2</td>
<td>8.0 ± 0.7</td>
<td>8.4 –10.2</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)2</td>
<td>2.8 ± 3.4</td>
<td>15 – 65</td>
</tr>
<tr>
<td>Phosphate (mg/dL)2</td>
<td>5.1 ± 1.1</td>
<td>2.3 – 4.7</td>
</tr>
<tr>
<td>Magnesium (mg/dL)2</td>
<td>1.8 ± 0.1</td>
<td>1.6 – 2.6</td>
</tr>
<tr>
<td>24h Urine Calcium (mg/24h)</td>
<td>425 ± 253</td>
<td>&lt;250-300</td>
</tr>
</tbody>
</table>

### Supplements

<table>
<thead>
<tr>
<th>Calcium Elemental (mg/day) [mean (range)]</th>
<th>2628 (750-4800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol (µg/day) [mean (range)]</td>
<td>0.8 (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 QTcB = electrocardiogram Bazett-corrected Q-T interval.
1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1 in Period 1 or Period 2.
Period 1 and Period 2 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: 187.7±128.2 mg/day

Data reported as mean±SD.
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.

<table>
<thead>
<tr>
<th></th>
<th>Period 1 (N = 6)</th>
<th>Period 2 (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects experiencing any Serious Adverse Event</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of subjects experiencing any Adverse Event</td>
<td>6 (100%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (100%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of Adverse Events reported</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Mild</td>
<td>18 (95%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Treatment-related Adverse Events*</td>
<td>3 (16%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (67%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0 (0%)</td>
<td>1 (12%)</td>
</tr>
</tbody>
</table>

*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. Gray shading reflects normal range. ** p-value < 0.01.

**Baseline Value (Day 1)**  
**Mean Value (Day 5) on encaleret 180 mg BID**

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**Albumin-corrected blood calcium**  
mg/dL

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

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**Urine calcium**  
mg/day

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
<td>30</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>5</td>
<td>120</td>
<td>6</td>
<td>150</td>
</tr>
</tbody>
</table>

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**Intact parathyroid hormone**  
pg/mL

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
<th>Subject</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
<td>30</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>
| 4       | 90       | 5       | 120      | 6       | 150      | **

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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. Gray shading reflects normal range. ** p-value < 0.01.
Period 2 Results (n=13): BID Encaleret normalized mean blood and urine calcium

Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range. Solid line for urine calcium reflects the upper limit for men and dashed line reflects upper limit for women.
**Period 2 Results (n=13):** BID encaleret increased mean PTH and decreased mean blood phosphate

Data reported as mean+SD. Values below limit of assay quantitation recorded as "0". Gray shading reflects normal range.
Summary

- In 13 participants, encaleret normalized mean corrected blood calcium and 24-hour urine calcium excretion during Periods 1 and 2
- Mean PTH increased and phosphate decreased into the normal range during Periods 1 and 2
- Compared with Period 1, individualized BID dosing in Period 2 resulted in a decrease in the mean Day 5 dose
- Encaleret was well-tolerated when administered once or twice daily over 5 days, with no serious adverse events reported
Conclusions

- Consistent improvements in mineral homeostasis suggest encaleret may become an effective treatment for ADH1
- Outpatient evaluation of encaleret in this Phase 2b study remains ongoing
- Data support further investigation of encaleret in ADH1 patients
Acknowledgements

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