Effects of Encaleret on Corrected QT Interval in Autosomal Dominant Hypocalcemia Type 1: Early Results from an Ongoing Phase 2b, Open-Label, Dose-Ranging Study

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Disclosures

• This study represents a collaboration between the NIDCR Intramural Research Program of the NIH and Calcilytix Therapeutics, a BridgeBio Company.
• NIDCR investigators and staff helped design and are responsible for the clinical conduct of the trial at the NIH Clinical Center.
• Calcilytix Therapeutics is the sole sponsor of the study and provided encaleret, an investigational agent which has not been approved for routine use by the FDA or any other competent health authority.
Blood calcium is maintained by four organs regulated by PTH and the CaSR.

- Parathyroid glands
- Gut (duodenum)
- Kidney

PTH = parathyroid hormone; CaSR = calcium-sensing receptor
Autosomal Dominant Hypocalcemia, type 1 (ADH1) causes hypocalcemia and hypomagnesemia which slows ventricular repolarization resulting in QT interval prolongation.

### Activating variants in the CASR increase tissue sensitivity to Ca²⁺

- **Parathyroid**
  - PTH Secretion
  - ADH1
  - WT
  - Blood Ca²⁺

- **Kidney**
  - Ca²⁺ Excretion
  - ADH1
  - WT
  - Blood Ca²⁺

### Hyperactive CaSR causes dysregulation of Ca homeostasis

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

- **Slows cardiac repolarization resulting in QT prolongation**

[Graph showing changes in PTH and Ca²⁺ levels]
Calcilytics may restore normal calcium and magnesium homeostasis in patients with ADH1

- Calcilytics are antagonists of the CaSR with the potential to restore normal CaSR sensitivity in ADH1 and normalize blood calcium and magnesium.
- This study explored the biochemical and ECG effects of encaleret, an investigational oral calcilytic, in individuals with ADH1.
Encaleret Phase 2B Study Design – CLTX-305-201

Period 1
Individualized dose escalation
5 days, inpatient (N=6)
12-lead ECG
- Day -1 (baseline)
- Day 5 of therapy

Period 2
Individualized dose titration
5 days, inpatient (N=13)
12-lead ECG
- Day -1 (baseline)
- Day 5 of therapy

Period 3
Outpatient extension
6 months, outpatient (N=13)
12-lead ECG
- Every 8 weeks

LTE
Long-term extension
Outpatient
12-lead ECG
- Every 3 months

QT intervals were automatically corrected for heart rate using Bazett’s and Fridericia’s rate correction formulas
## 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>
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<tr>
<td>Female, n (%)</td>
<td>8 (62%)</td>
<td></td>
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<tr>
<td>ECG QT&lt;sub&gt;c&lt;/sub&gt;B (msec)</td>
<td>452 ± 16</td>
<td>&gt; 460 Female</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 450 Male</td>
</tr>
<tr>
<td>ECG QT&lt;sub&gt;c&lt;/sub&gt;F (msec)</td>
<td>432 ± 15</td>
<td>&gt; 460 Female</td>
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<tr>
<td></td>
<td></td>
<td>&gt; 450 Male</td>
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<tr>
<td>Calcium&lt;sup&gt;1&lt;/sup&gt; (mg/dL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8.0 ± 0.7</td>
<td>8.4 – 10.2</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.8 ± 3.4</td>
<td>15 – 65</td>
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<tr>
<td>Phosphate (mg/dL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5.1 ± 1.1</td>
<td>2.3 – 4.7</td>
</tr>
<tr>
<td>Magnesium (mg/dL)&lt;sup&gt;2&lt;/sup&gt;</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>

Data reported as mean±SD. ECG QTcB = electrocardiogram Bazett-corrected Q-T interval. ECG QTcF = electrocardiogram Fridericia-corrected Q-T interval.

1. Albumin-corrected calcium. 2. Measurements taken pre-dose Day 1 in Period 1 or Period 2.
Encaleret normalized mean blood calcium and magnesium

Period 1 Dosing (n=6)
*Defined dose escalation*

Period 2 Dosing (n=13)
*Individualized dose titration*

Over five days of encaleret treatment in periods 1 and 2, encaleret increased PTH secretion and normalized blood calcium and magnesium. Encaleret was well-tolerated and without serious adverse events.

*Encaleret dose adjusted to 180/120 in 1 subject on Day 5 in Period 1. Abbreviations: cCa – albumin-corrected calcium. Data reported as mean+SD. Values below limit of assay quantitation recorded as “0”. Gray shading reflects normal range.*
In parallel to the improvement in calcium and magnesium, Encaleret decreased QTcF into the normal range.

During Period 1, QTcF trended down from 433±13 msec at baseline to 413±19 (p=0.06). During period 2, QTcF significantly decreased from 435±15 msec at baseline to 413±12 msec (p<0.001). Change in QTcF correlated with change in calcium (p<0.0001) but not magnesium. There were no important changes or trends in blood potassium, heart rate, blood pressure, or other ECG intervals.

Gray shading reflects normal range for blood calcium and magnesium.
• ADH1 is caused by activating variants in the calcium sensing receptor resulting in hypocalcemia and hypomagnesemia.
• High-normal or mild prolongation of the QT interval, associated with hypocalcemia, was observed at baseline in ADH1 study participants.
• The QT response to encaleret in ADH1 participants provides preliminary evidence that encaleret, most likely by raising blood levels of calcium and magnesium, can improve cardiac repolarization in patients with ADH1.
• Longer-term evaluation of encaleret in ADH1 is ongoing.