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.

- Parathyroid glands
- CaSR
- Gut (duodenum)

25 vitamin D → 1,25 vitamin D

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**
- PTH
- CaSR
- Ca²⁺
- Gαq + Gαi
- PTH mRNA
- Nucleus

CaSR decreases PTH synthesis and secretion in response to ↑ blood Ca²⁺.

**Renal Tubule**
- Urine
- Blood
- CaSR
- Ca²⁺

CaSR decreases renal tubular Ca²⁺ reabsorption in response to ↑ blood Ca²⁺.
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
**Encaleret Phase 2B Study Design – CLTX-305-201**

**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)

**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)
  - October 2021
  - Phase 2 Period 2 results

**LTE**
- **Long-term extension**
  - Outpatient
## 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

- Elemental Calcium (mg/day) [mean (range)] 2628 (750-4800)
- Calcitriol (µg/day) [mean (range)] 0.8 (0.2-2.0)

### 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.

Encaleret was well-tolerated with no serious adverse events reported.

<table>
<thead>
<tr>
<th></th>
<th>Period 1 (N = 6)</th>
<th>Period 2 (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></td>
<td></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><strong>Number of Adverse Events Reported</strong></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><strong>Treatment-related Adverse Events</strong></td>
<td></td>
<td></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 (54%)</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.
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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