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

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Autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function variants in the gene encoding the calcium-sensing receptor (CaSR), is characterized by hypocalcemia, hyperphosphatemia, hypomagnesemia, low parathyroid hormone (PTH), and hypercalciuria. Conventional therapy (calcium and activated Vitamin D) worsens hypercalciuria and can lead to renal morbidity. Calcilytics (negative allosteric modulators of the CaSR) decrease the sensitivity of hyperactive receptors to extracellular calcium and normalize blood and urine abnormalities in ADH1 rodent models. Encaleret is an oral calcilytic under investigation as a potential treatment for ADH1.

Thirteen adults (22-60y) with ADH1 due to 9 unique CASR variants participated in a 3-period, Phase 2b, open-label, dose-ranging study. Conventional therapy was discontinued prior to encaleret initiation. Period 1 (P1) was a 5-day inpatient dose-escalation course (n=6). Period 2 (P2) was a 5-day inpatient course (n=13) in which doses were individually titrated to normalize albumin-corrected blood calcium (cCa) and minimize hypercalciuria and

hypophosphatemia. All 13 participants continued into Period 3 (P3), a 24-week outpatient maintenance period. Patients underwent serial 24hr blood and urine sampling in P1, P2, and in P3 at Weeks 8, 16, and 24, with additional outpatient laboratory timepoints.

The mean±SD encaleret dose at the end of P2, Day 5 (P2D5) was 94±64mg BID (range: 10-180 BID); by P3, Week 24 (P3W24), the mean was 78±67mg BID (5-190 BID). Encaleret was well-tolerated with no serious adverse events reported; there were no treatment discontinuations or study withdrawals.

Twenty-four hour mean±SD values from P2D5 (n=13) and P3W24 (n=12) compared to baseline are presented. Baseline PTH was low at 6.3±7.8 pg/mL (nl 10-65) and had normalized by P2D5 (40.5±37.5, $p<0.01$); this was sustained through P3W24 (31.3±20.8, $p<0.01$). Likewise, baseline hypocalcemia (cCa=7.1±0.4 mg/dL [nl 8.4-10.2]) corrected to 8.6±0.7 by P2D5 ($p<0.01$) and remained normal through P3W24 (9.0 ±0.6, $p<0.01$). Baseline urinary calcium was 395±216 mg/d (nl <250-300) and decreased to 179±108 by P2D5 ($p<0.01$) and 189±72 at P3W24 ($p<0.05$); urinary calcium excretion was normal in 10/12 patients at P3W24. Baseline phosphate decreased from 4.5±1.1 mg/dL (nl 2.3-4.7) to 3.2±0.7 on P2D5 ($p<0.01$) and was maintained through P3W24 (3.5±0.6, $p<0.05$). Magnesium increased from low- to mid-normal (baseline 1.7±0.2 mg/dL [nl 1.6-2.6]; P2D5 1.9±0.2 [$p<0.01$]; P3W24 2.0±0.2, [$p<0.01$]). 1,25-dihydroxy-Vitamin D increased from 19.5±4.4 pg/mL (nl 20-70) to 32.0±16.7 on P2D5 ($p<0.05$) and 30.2±14.0 on P3W24 ($p<0.05$). Bone turnover markers were not different between baseline (n=7, CTX=253±111 pg/mL; P1NP=34±10 mcg/L) and P2D5 (CTX=241±181, p=NS; P1NP=26±12, p=NS) but had increased by P3W24 (CTX=784±686, $p<0.01$; P1NP=102±87, $p<0.01$).

In conclusion, this study represents a molecularly targeted, precision medicine approach to the treatment of ADH1. The consistent and sustained results from all periods of this Phase 2 study establish a clinically meaningful efficacy, tolerability, and safety profile for encaleret as a potential treatment of adults with ADH1.

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