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Efficacy and Safety of Encaleret in Autosomal Dominant Hypocalcemia Type 1

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To the Editor:

Autosomal dominant hypocalcemia type 1 (ADH1) is a monogenic form of hypoparathyroidism caused by gain-of-function variants of *CASR*, which encodes the calcium-sensing receptor (CaSR).[1] The CaSR primarily regulates parathyroid hormone (PTH) secretion and renal calcium and magnesium reabsorption.[2] Gain-of-function *CASR* variants increase the sensitivity of the CaSR to extracellular calcium, reducing PTH secretion and renal calcium reabsorption and resulting in hypocalcemia, hyperphosphatemia, hypomagnesemia, and hypercalciuria. Symptoms range from none to paresthesia, muscle cramps, seizures, and laryngospasm.[3]

Conventional therapy for ADH1 with calcium and active vitamin D increases blood calcium levels but worsens hypercalciuria, thus increasing the risk of renal disease.[3] There are no approved ADH1-specific treatments that address its underlying molecular pathophysiological features. CaSR antagonists (calcilytics) are negative allosteric modulators of the CaSR that have normalized mineral levels in animal models of ADH1.[4] Furthermore, calcilytics increased PTH secretion in a small proof-of-concept study involving adults with ADH1,[5] a finding that supports their potential as molecularly targeted therapies for ADH1.

We treated 13 adults with ADH1 (caused by nine different *CASR* variants) with encaleret, an investigational oral calcilytic, in an open-label, phase 2b study (ClinicalTrials.gov number, NCT04581629). Details regarding the study design are provided in the Supplementary Appendix, including Fig. S1, and in the protocol, both available with the full text of this letter at NEJM.org. Although ADH1 is not limited to specific races or ethnic groups (Table S1), participants were all non-Hispanic White, with clinical characteristics typical of ADH1 (Table S2). Participants completed one or two 5-day inpatient dose-ranging periods, followed by a 24-week outpatient period. Encaleret was administered twice daily

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with doses adjusted to achieve normal albumin-corrected blood calcium levels (Fig. S2). Calcitriol and supplemental calcium were with-held during encaleret treatment.

Encaleret corrected hypocalcemia and reduced hypercalciuria during the inpatient periods and the 24-week outpatient period. Mean blood levels of intact PTH, magnesium, and 1,25-dihydroxy-vitamin D increased, whereas phosphorus levels and tubular reabsorption of phosphate decreased (Fig. 1 and Figs. S4, S5, and S6). The dose range that was required to maintain eucalcemia was wide (5 to 190 mg twice daily), but individual doses were mostly stable, with minimal adjustments needed. Renal function and preexisting renal calcifications did not worsen (Table S3). As expected with increasing PTH levels, levels of bone-turnover markers rose during the outpatient period, with levels in 9 of 13 participants remaining normal (Fig. S7). Short-term effects on bone density were negligible (Table S4); longer study assessing skeletal effects is ongoing.

No serious adverse events were reported with encaleret. Treatment-related adverse events were limited to infrequent mild, transient, asymptomatic hypophosphatemia, hypercalcemia, or both that resolved either spontaneously or with dose adjustment (Table S5). No treatment discontinuations or study withdrawals occurred.

In our study, encaleret appeared to restore physiologic mineral homeostasis in 13 participants with ADH1. This molecularly targeted approach, pending further studies, may establish calcilytics as a potential treatment for ADH1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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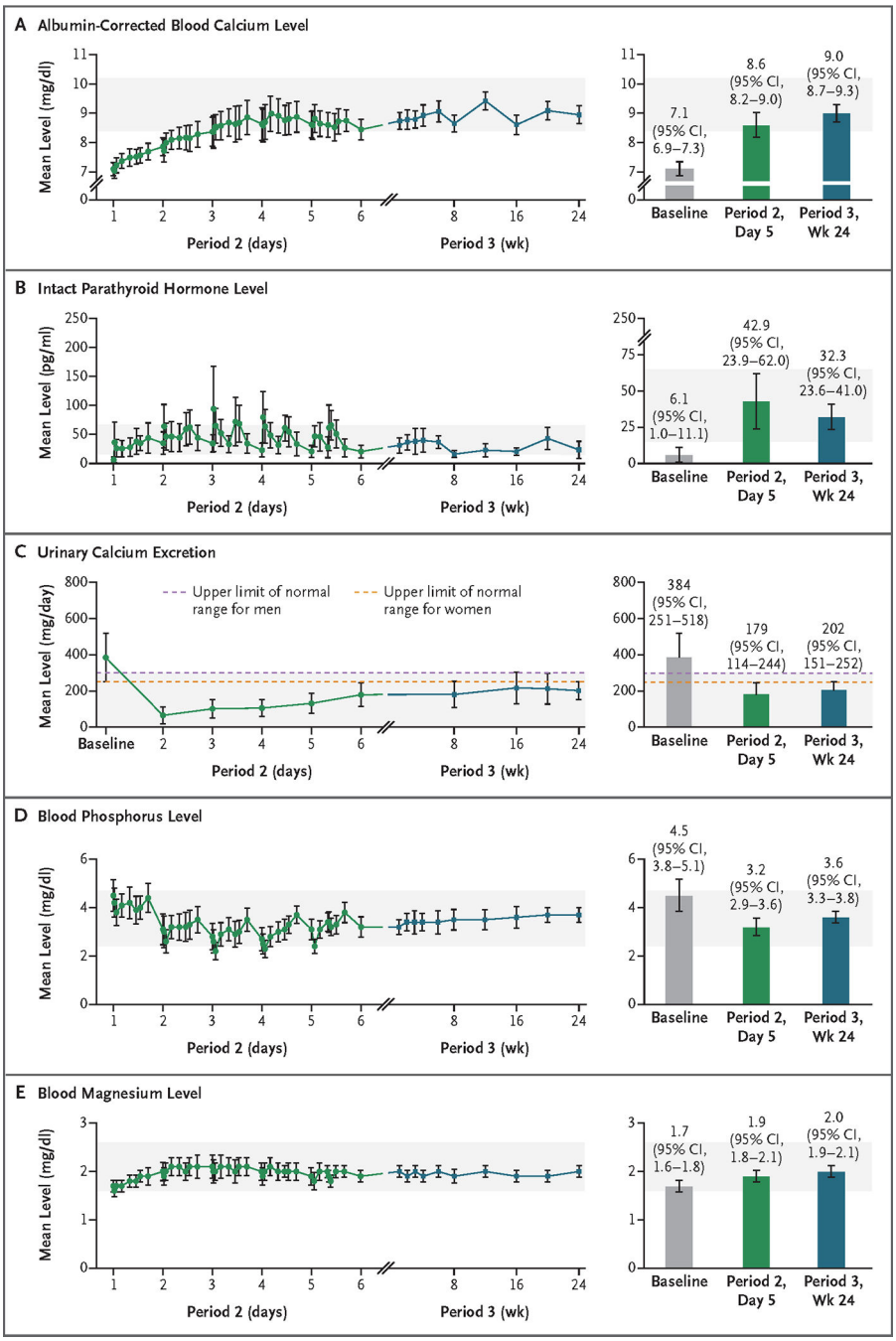

Figure 1. Effect of Encaleret on Mineral Homeostasis in 13 Participants with Autosomal Dominant Hypocalcemia Type 1.

The study included a 5-day inpatient dose-escalation period (period 1), a 5-day inpatient dose-adjustment period (period 2), and a 24-week outpatient dose-maintenance period (period 3). The line graph on the left side of each panel shows mean laboratory values and 95% confidence intervals (I bars) throughout periods 2 and 3. Period 2 included serial sampling. Period 3 included a combination of serial sampling (at weeks 8, 16, and 24) and outpatient laboratory measurements; results shown at serial sampling visits were obtained before the morning dose of encaleret, and the timing of samples outside these visits was

variable. Time points shown for period 2 in the line graphs (including throughout day 5) are provided in the Supplementary Appendix. The bar graph on the right side of each panel shows laboratory values at baseline; period 2, day 5; and period 3, week 24. With encaleret treatment, mean levels of albumin-corrected blood calcium, intact parathyroid hormone (PTH), and blood magnesium increased from baseline and were within the normal range at the later time points. The 24-hour urinary calcium excretion and blood phosphorus levels decreased with encaleret treatment. The values shown at period 2, day 5, and period 3, week 24, are means and 95% confidence intervals of serial measurements over a 24-hour period for blood variables. In both the line and bar graphs, normal ranges are indicated by shading. In Panel B, PTH values from one participant were excluded from the analysis owing to the variable presence of heterophile antibodies that interfered with the intact PTH assay. In Panel C, the baseline value was obtained at screening during standard care.