Autosomal dominant hypocalcemia type 1 (ADH1) is a rare form of hypoparathyroidism caused by gain-of-function pathogenic variants in the gene encoding the calcium-sensing receptor (CaSR). It is characterized by variable degrees of hypocalcemia, hyperphosphatemia, and hypomagnesemia, with inappropriately low levels of parathyroid hormone (PTH) and hypercalciuria. Conventional therapy includes oral calcium and activated Vitamin D supplementation, which can lead to or exacerbate hypercalciuria. As a result, patients may develop nephrolithiasis and/or nephrocalcinosis, which can progress to renal insufficiency. Calcilytics (antagonists of the CaSR) have demonstrated in *in vitro* and *in vivo* models of ADH1, as well as in a small clinical trial (Roberts et al, JBMR 2019), the ability to shift the dose-response relationship between extracellular calcium and the cellular response of cells bearing the mutant CaSR towards normal. This shift has the potential to increase endogenous PTH secretion which in turn may promote skeletal release of calcium into the bloodstream, production of endogenous calcitriol, renal excretion of phosphate, and renal reabsorption of calcium. Additionally, direct effects of calcilytics on renal CaSRs may further reduce renal calcium and magnesium excretion in ADH1. Taken together, this class of drugs has the capacity to restore normal mineral homeostasis, without calcium and activated vitamin D supplements and without attendant risks of iatrogenic hypercalciuria. This Phase 2b, open-label, dose-ranging study will evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of the calcilytic encaleret (CLTX-305) in up to 16 participants with ADH1 (NCT04581629). The study will consist of 3 periods. In periods 1 and 2, participants will undergo a 1-week inpatient evaluation to study the safety and tolerability of daily and twice-daily doses of encaleret. Period 3 will follow participants for up to 24 weeks of continuous outpatient dosing, with periodic inpatient and outpatient assessments. The primary endpoint of period 3 is the change from baseline in albumin-corrected blood calcium concentration. Secondary endpoints of the study include the change in urine calcium (fractional and 24-hour excretion), 1,25-dihydroxy-Vitamin D, phosphate, magnesium, and other blood/urine biomarkers. Enrollment for this study at the National Institutes of Health (NIH) began in September 2020 with topline results expected in 2021. This study is supported by Calcilytix Therapeutics, Inc. and the NIH Intramural Research Program.

Bone and Mineral Metabolism
PARATHYROID AND RARE BONE DISORDERS

A Single Administration of AZP-3601, a Novel, Long-Acting PTH Analog, Induces a Significant and Sustained Calcemic Response: Preliminary Data From a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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Hypoparathyroidism is a rare disease characterized by a deficiency in parathyroid hormone (PTH) that results in hypocalcemia and hyperphosphatemia. Current treatment approaches, including high dose oral calcium and active vitamin D, as well as recombinant human PTH (1–84), do not provide adequate or consistent control of either serum calcium or clinical symptoms over a full 24-hour period. AZP-3601 is a novel 36 amino-acid PTH analog that has been designed to potently bind to the R^0 conformation of the PTH1 receptor, which results in prolonged signaling responses in vitro and prolonged calcemic responses in animals despite having a short circulating half-life. A Phase 1 double-blind, placebo-controlled, single and multiple ascending dose study is being conducted to evaluate the safety, tolerability and pharmacodynamics of AZP-3601 in healthy adults. Here we report data from the first cohorts of the single ascending dose portion of the study. Sequential cohorts of 4 (cohort 1) to 8 (cohort 2 to 4) healthy male subjects aged 18–60 years, with a body mass index of 19–28 kg/m^2, were assigned to receive 5, 10, 20 or 40µg of AZP-3601 or placebo at a ratio of 3:1. The study drug was administered in the morning by subcutaneous injection in the abdominal wall and was well tolerated with no remarkable adverse events. As compared with placebo controls, AZP-3601 treatment produced a clear, dose-dependent increase in mean albumin-adjusted serum calcium values from baseline. The normal physiological diurnal variation of albumin-adjusted serum calcium was gradually attenuated with 5 and 10µg AZP-3601, and was completely eliminated with 20µg. With the dose of 40µg AZP-3601, mean albumin-adjusted serum calcium values were significantly increased but stayed within normal laboratory range and remained elevated through at least 24 hours post-administration. We observed a dose-dependent decrease in mean endogenous serum PTH that was significantly correlated with the concomitant increase in mean serum calcium. These data provide initial evidence of the pharmacodynamic effect of AZP-3601 in healthy humans characterized by a sustained calcemic response for at least 24 hours following a single administration.

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PARATHYROID AND RARE BONE DISORDERS

Appropriate Cutoff for 25OHD Levels in the Diagnosis of Normocalcemic Primary Hyperparathyroidism (NPHPT): A Systematic Review.

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Introduction: The Fourth International Workshop in 2014 delineated guidelines for the diagnosis of NPHPT which include ruling out secondary causes of hyperparathyroidism, and recommended cutoffs for 25 vitamin D (25OHD) to be ≥20ng/mL. Keeping in mind that the exact levels to optimize 25OHD in hyperparathyroid states are unknown, we aim to review possible variation in the prevalence of NPHPT if 25OHD cutoffs were to be raised to rule out vitamin D deficiency with more specificity. **Methods: A** PubMed search was conducted with key