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.

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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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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

words "normocalcemic primary hyperparathyroidism" to review studies about NPHPT and 25OHD status. 533 articles were found, and 127 articles were identified by title/abstract screening with year of publication between 2014 to 2020. Ten studies were identified for the systematic review based on full text review for relevance. **Results: S**tudies have been conducted in various countries across all continents to characterize NPHPT further. 5/10 studies used 25OHD cutoff of ≥20ng/mL and 4 studies had a cutoff of ≥30ng/mL and 1 study looked into the difference in prevalence with both cutoffs. All 3 studies from Italy used the higher cutoff. Rosario et al from Brazil reported a decrease in prevalence of NPHPT from 6.8% (25OHD≥20ng/mL) to 0.74% by supplementing those subjects to 25OHD ≥30ng/mL without any increase in serum calcium or parathyroid hormone (PTH) levels.[1] Wang et al found that when total 25OHD levels were kept between 30–40 ng/mL, free 25OHD levels were actually lower compared to normal subjects.[2] **Conclusion: T**he levels of 25OHD that would define deficiency in NPHPT remain undetermined and both >20 ng/mL and >30ng/mL have been studied as cutoffs. It is well known that vitamin D insufficiency (25D 20-30ng/mL) drives up PTH and supplementation to 30-40ng/mL is required to reduce such effects. Wang et al suggest that free 25OHD levels correlate better with PTH as compared to total 25OHD and maybe a more reliable marker of 25OHD status. We suggest that a diagnostic criterion of ≥30ng/mL would be more appropriate in ruling out 25OHD deficiency in this special population. The role of free 25OHD levels in PHPT needs further evaluation.
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Assessment of Hypercalcemia Management at an Academic Institution

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Background: Currently, there is no widely accepted clinical practice guideline for the management of severe hypercalcemia in hospitalized patients.
Objective: The purpose of this project was to analyze management of hypercalcemia in hospitalized patients at an academic medical center, then establish and implement a clinical practice guideline for hypercalcemia treatment.
Design: Retrospective chart review of all patients admitted for management of hypercalcemia over 37 consecutive months.
Setting: Urban academic tertiary referral center
Measurements: We examined which calcium- lowering medications were used, how often 2 medications were needed, average time to normocalcemia, incidence of hypocalcemia post treatment, serum phosphorus nadir and serum creatinine peak. We also assessed medication appropriateness (dose and frequency).
Results: Seventy-two patients were included; 58 patients with hypercalcemia of malignancy and 14 patients with hypercalcemia of other diagnoses. In the malignancy group the most common treatment was a combination of calcitonin + bisphosphonate (43%), followed by bisphosphonate alone (29%) and calcitonin alone (24%). In the non-malignancy group, calcitonin alone was used in 50%, calcitonin + bisphosphonate in 21% and a bisphosphonate alone in 14%. Denosumab was rarely used in both groups. The median time to normocalcemia was 3.0 days irrespective of diagnostic group. Seventy two percent of the patients with malignancy and 86% of the non-malignancy group achieved normocalcemia. The incidence of hypocalcemia was 21% (12/58) in the malignancy subgroup and 29% (4/14) in the others after treatment. Serum creatinine did not change from baseline to post-treatment in either population. Median serum phosphorus dropped from 2.9 mg/dL to 1.8 mg/dL in the malignancy group and 4.2 mg/dL to 2.1 mg/dL in the non-malignancy group. Only 41% of patients that received calcitonin, were given recommended dose, route, and frequency.
Conclusion: Based on the results of this study, a hypercalcemia treatment guideline was developed, highlighting appropriate medication dose and frequency. This guideline recommends zoledronic acid alone for asymptomatic malignancy patients, and in combination with calcitonin for symptomatic patients. In contrast, calcitonin alone is considered first line for non-malignant conditions.

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Basal Ganglia Calcification in Hypoparathyroidism Is Associated With Low Serum Calcium/Phosphate Ratio.

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Background: Basal ganglia calcification (BGC) is a well-known complication of hypoparathyroidism. It is currently thought that increased serum phosphate or calcium x phosphate product may be major risk factors. However, the pathophysiology of BGC is still unclear, since the literature is largely based on limited case series or case reports.
Methods: We identified a large cohort of patients with hypoparathyroidism diagnosed between 2000 and 2020 and evaluated those with head CT scans performed over this interval. Etiology and date of onset of hypoparathyroidism were determined by medical records review. All head CT scan images were reviewed to confirm radiology reports reporting BGC. We retrieved laboratory data within 10 years before the first head CT that showed incident BGC. Three age- and sex- matched controls with head CT scans were selected for each patient, and compared to the patients with hypoparathyroidism. **Results:** Of 1014 unique patients with a verified diagnosis of hypoparathyroidism, 142 had