Poster #8669

Characteristics of Adults with Autosomal Dominant Hypocalcemia Type 1 (ADH1) Enrolled in the CLARIFY Disease Monitoring Study

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Background

- Autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function calcium-sensing receptor gene (*CASR*) variants, is characterized by low parathyroid hormone (PTH) concentrations, hypocalcemia, hypercalciuria, hyperphosphatemia and hypomagnesemia[1].
- ADH1, a rare disease with an estimated prevalence of 3.9 per 100,000[2], is one of the most common causes of monogenic hypoparathyroidism[3].
- Standard-of-care (SoC) therapy for ADH1, which includes calcium and/or active vitamin D, may alleviate symptoms of hypocalcemia but increases in blood calcium lead to hypercalciuria and may result in renal complications including nephrocalcinosis, nephrolithiasis, and chronic kidney disease[1].

Study Design

- The CLARIFY disease monitoring study [NCT05227287] is a global, multicenter, longitudinal, non-interventional study to understand disease burden, management, and progression in pediatric and adult participants with ADH1 or ADH2 over a 5-year period.
- All participants must have a documented activating variant or variant of uncertain significance (VUS) of the *CASR* gene (for ADH1) or documented activating variant or VUS of the *GNA11* gene (for ADH2) associated with a clinical syndrome of hypoparathyroidism prior to enrollment.
- Study visits occur every 6 months for the first three years and yearly thereafter. Study visits comprise of medical history assessment, lab sampling, and/or imaging.

Methods

- Any SoC treatment that participants received was directed by their treating physicians. The Sponsor did not provide any medication, including SoC, as part of the study.
- Blood and urine samples for clinical laboratory tests were collected at pre-specified time points and testing was performed at a central laboratory.
- Blood samples were collected after a minimum of 4-hour fasting period and prior to AM dosing of SoC therapy for ADH1 (if applicable).
- Urine samples were collected over 24 hours and assessed for completeness at the central laboratory using pre-specified criteria.

Analysis Population

Data include a subset of baseline (at Day 1 study visit) characteristics of those participants aged ≥18 years (adults) with ADH1, enrolled as of Nov 2023.

The analysis population is comprised of 44 participants [54.5% (n=24) female; 45.5% (n=20) male] with a mean±SD age of 42.5 ± 16.5 years (range 18-80). The mean±SD age of a hypocalcemia diagnosis was 20.2 ± 19.7 years, and the mean±SD age for a diagnosis of ADH1 was 28.6 ± 20.2 years.

Medical History

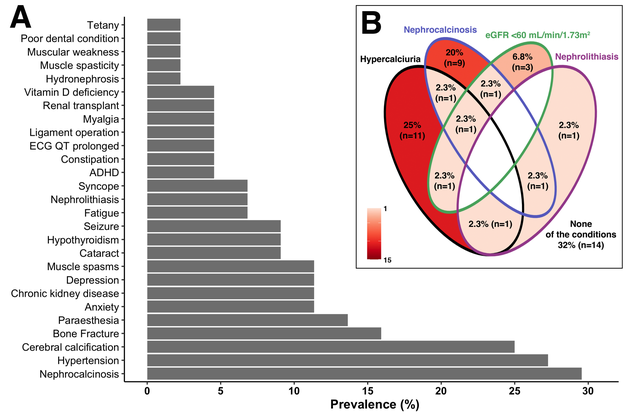

FIGURE 1. (A) Prevalence of select self-reported medical conditions. Conditions, reported as Medical History (MHx), have been coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Conditions potentially related to hypoparathyroidism or related morbidities are shown. Of note, as the MHx data was self-reported, hypocalcemia-related symptoms may not have been reported distinctly from diagnoses of ADH1, hypocalcemia, or hypoparathyroidism, and therefore, may be underrepresented in the analysis. **(B) Intersection of participants with renal complications at baseline.** In the analysis population, 68% (n=30) have at least one of the renal complications assessed – hypercalciuria, nephrocalcinosis (NC), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, or nephrolithiasis (NL). Of the n=2 participants with a MHx of renal transplant, the first participant also has eGFR <60 mL/min/1.73m^2 at baseline and a MHx of NC; the second participant has none of the renal complications assessed. NC and NL are based on self-reported MHx; hypercalciuria is defined as elevated baseline urine calcium excretion [women: ≥250 mg/24hrs; men: ≥300 mg/24hrs]; eGFR value is based on baseline labs. n=0 is represented by empty white-colored intersections.

Real-World Tx Patterns

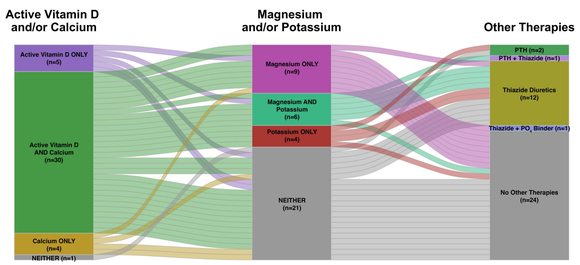

FIGURE 2. Standard-of-care treatment for ADH1. Standard-of-Care (SoC) therapies at baseline are grouped into 7 classes of medication/supplements – active vitamin D, calcium, magnesium, potassium, phosphate (PO_4) binder, thiazide diuretics, and parathyroid hormone (PTH) replacement. SoC includes active vitamin D and/or calcium 91% (n=39) [active vitamin D only 12% (n=5); calcium only 9.3% (n=4); both 70% (n=30)]; magnesium 35% (n=15), potassium 23% (n=10), thiazide diuretics 33% (n=14), PTH replacement 7.0% (n=3), phosphate binder 2.3% (n=1), and no treatment 7.0% (n=3). Data is shown for n=40 participants. Plot excludes participants who are not receiving any treatment for ADH1 (n=3) or for whom treatment data is not available (n=1).

Mineral Homeostasis Profile

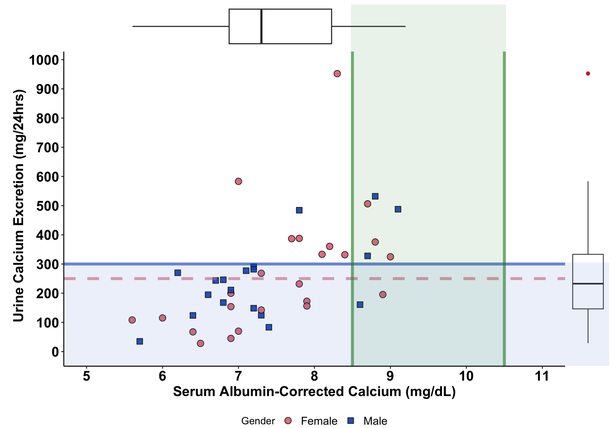

FIGURE 3. Distribution of serum albumin-corrected calcium (cCa) and 24-hr urine calcium (uCa) excretion at baseline. 4.7% (n=2) participants (pts) have normal cCa and normal uCa excretion; 14% (n=6) pts have normal cCa and hypercalciuria; 60% (n=26) pts have hypocalcemia and normal uCa excretion; 21% (n=9) pts have hypocalcemia and hypercalciuria. Green vertical lines indicate reference range of cCa (8.5-10.5 mg/dL); horizontal lines indicate upper normal limit of uCa excretion for men (blue solid line; < 300 mg/day) and women (pink dotted line; < 250 mg/day). Each pt is represented by a pink circle (female) or a blue square (male) based on the self-reported gender. Outliers are represented by red dots in box plot. Plot excludes n=1 pt due to missing uCa excretion value.

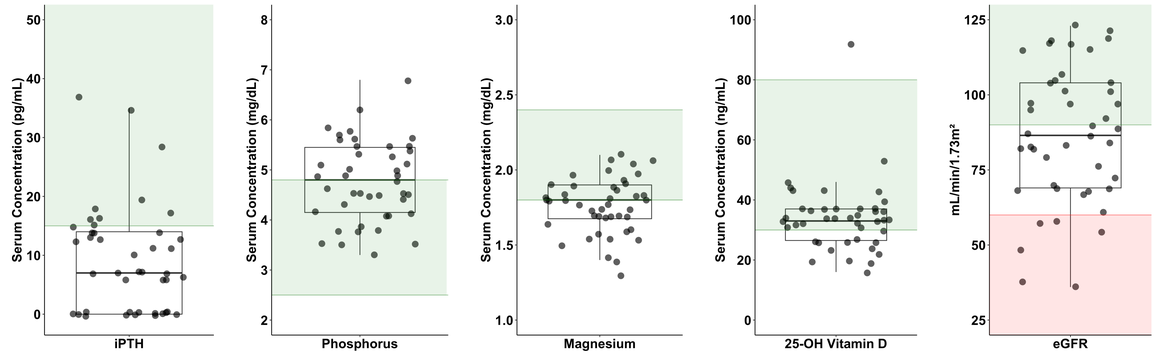

FIGURE 4. Mineral homeostasis profile of adult participants with ADH1. Laboratory tests at baseline show that 77% (n=33) have low intact parathyroid hormone (iPTH) concentrations, 49% (n=21) have hyperphosphatemia, 45% (n=20) have hypomagnesemia, and 28% (n=12) have vitamin D deficiency. 14% (n=6) have reduced kidney function, defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 (red horizontal line) and assessed by the CKD-EPI equation. iPTH concentrations below the limit of detection (<6 pg/mL) are substituted with the constant value 0 for this analysis. Green horizontal line(s) indicate reference range of each assay per the central laboratory reference manual.

Summary

- The CLARIFY study represents the largest cohort of adults with ADH1 described to date.
- Baseline data highlight variability in therapeutic approaches in a real-world setting with the majority of participants receiving at least 2 different medications/supplements.
- Despite being followed in expert centers, and treated with available therapies, amongst the adult participants with ADH1, 4.7% have normal blood and urine calcium concentrations, and 68% have at least one of the renal complications assessed at baseline.
- The study provides an opportunity to better understand the progression and burden of disease in participants with ADH1 through continued prospective and standardized CLARIFY data collection (including blood and urine labs, renal ultrasounds, DXAs, SF-36/SF-10, and ECGs).

References

1. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. *J Bone Miner Res* 2022; 37(12):2568-2585. doi:10.1002/jbmr.4691.
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3. Mannstadt, M, Mathew A, Sridhar A, et al. SAT231 Next-generation Sequencing For Detection Of Underlying Genetic Causes Of Nonsurgical Hypoparathyroidism: Preliminary Results From A Sponsored Testing Program. *J Endocr Soc* 2023; 7(Suppl 1): bvad114.527.