Eneboparatide, a novel PTH1 receptor agonist, induces rapid reduction and normalization of urinary calcium in hypoparathyroid patients

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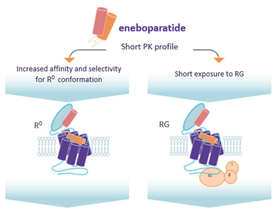
INTRODUCTION

- Conventional therapy with oral calcium (Ca) and active vitamin D (vitD) supplementation for chronic hypoparathyroidism (cHP) can induce or aggravate hypercalciuria and may lead to detrimental long-term renal complications.
- Eneboparatide (AZP-3601) is a novel 36-amino-acid peptide specifically designed to preferentially activate the R^0 conformation of the PTH1 receptor that results in a prolonged calcemic response and a sustained reabsorption of urinary calcium (uCa) as shown in animals and in humans.
- Here we report data on uCa excretion from a multicenter open label phase 2a study (CT.gov Id: NCT05239221) that examined the effects of 3-month treatment with eneboparatide in two consecutive cohorts (C1 and C2) of cHP patients.

MECHANISM OF ACTION

The PTH1 receptor (PTHR1) exists in two conformationally-distinct forms: RG and R^0



Eneboparatide (AZP-3601) has been designed to bind with high affinity to the R^0 conformation of the PTH1 receptor in order to produce a sustained serum Ca elevation despite having a short PK half-life. This enables eneboparatide to induce potent calcium reabsorption in the renal tubules and exert a physiological impact on bone turnover, as observed in both animal research and human studies.

MATERIALS AND METHODS

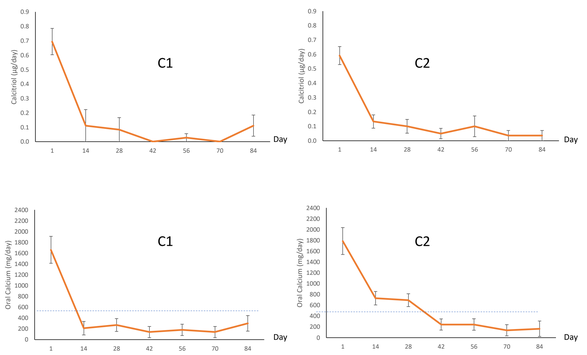
- Eligible patients included male and female patients aged 18 to 75 years with cHP for ≥12 months and treated with calcitriol ≥ 0.25 µg/day or alphacalcidol ≥ 0.50 µg/day and oral calcium ≥ 1000 mg/day.
- Conventional therapy was adjusted to have albumin-adjusted serum calcium (ADsCa) within the target range of 7.8 to 9.0mg/dL before treatment with eneboparatide.
- Patients received a daily sc. administration of eneboparatide for 3 months at a starting dose of 20µg (C1; n=12) or 10µg (C2; n=16) for 14 days, while progressively reducing oral calcium and active vitamin D intake. In C1, the majority of patients remained at dose 20µg, only a few had their dose titrated up to 60µg. In C2, the majority of patients were rapidly titrated to 20µg and then up to 80µg.

PATIENTS BASELINE CHARACTERISTICS

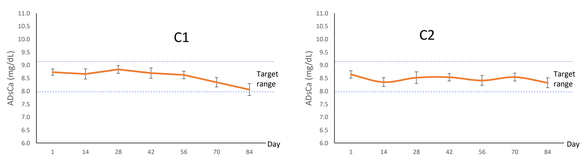
	Cohort 1 N=12	Cohort 2 N=16	All N=28
Mean age, years (SD) **min-max**	62.7 (9.7) 44-72	54 (11.2) 26-72	57.7 (11.3) 26-72
Female, n (%)	9 (75%)	12 (75%)	21 (75%)
Post-menopausal women, n (%)	7 (58.3%)	7 (43.8%)	14 (50%)
Mean time since menopause, years **min-max**	20.1 10-33	13.5 2-20	17.1 2-33
Etiology of cHP **Post-surgery, n (%)** **Idiopathic, n (%)** **Genetic, n (%)**	 10 (83.3%) 2 (16.7%) -	 13 (81.3%) 2 (12.5%) 1 (6.3%)	 23 (82.1%) 4 (14.3%) 1 (3.6%)
Mean oral vitamin D, µg/day *(calcitriol dose equivalent)* **min-max**	0.67 0.25-1	0.60 0.25-1	0.63 0.25-1
Mean oral calcium dose, mg/day **min-max**	1,625 1,000-3,500	1,688 1,000-7,800	1,661 1,000-7,800
Mean 24-hour urinary calcium, mg/24h min-max	329 143-614	331 57-729	330 57-729

ACTIVE VITAMIN D AND ORAL CALCIUM

Eneboparatide was well tolerated and enabled rapid and sustained reduction of active vitamin D and oral calcium ≤500mg/d in the great majority of patients of both cohorts.



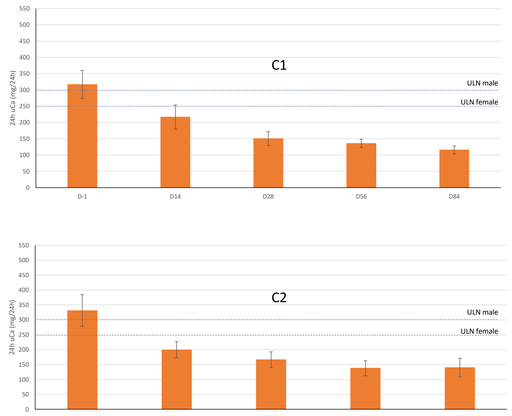
ALBUMIN-ADJUSTED SERUM CALCIUM



Data are means ± SEM. (mmol/L = mg/dL x 0,0259).

In both cohorts, eneboparatide maintained mean ADsCa within the target range through the study.

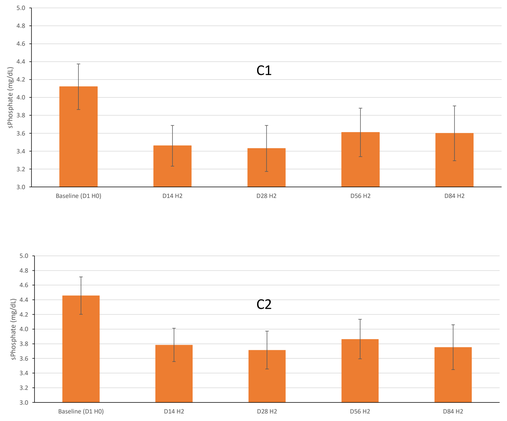
24H URINARY CALCIUM (All patients)



Data are means ± SEM. (mmol/24h = mg/24h x 0,0259).

In both cohorts, mean uCa decreased to within the normal range by Day 14 and continued to decrease through the end of the treatment period independent of associated serum calcium levels. Similarly, mean FECa decreased in the entire population and in patients with hypercalciuria.

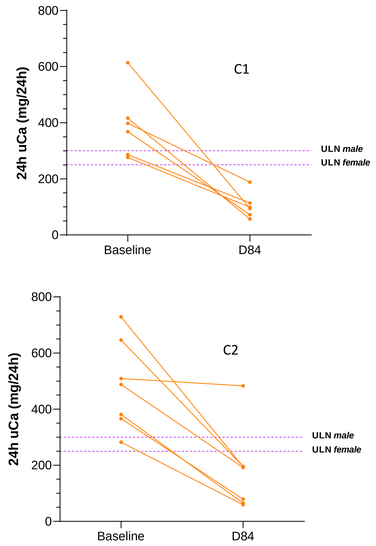
SERUM PHOSPHATE



Data are means ± SEM. (mmol/24h = mg/24h x 0,0259).
D=Day, H=Hours postdose

In both cohorts, mean serum phosphate decreased rapidly after the onset of eneboparatide treatment and remained reduced until the end of the study while 24h-urinary phosphate excretion increased from baseline to D84.

24H URINARY CALCIUM (Patients with hypercalciuria at baseline)



Each line represents an individual.

92.3% of patients with elevated 24h uCa at baseline had their values normalized by the end of the treatment period.

SUMMARY AND CONCLUSION

- In both cohorts of patients with cHP, eneboparatide treatment induced rapid, profound and sustained reduction and normalization in mean 24h urinary calcium.
- Importantly, this effect was observed in hypercalciuric patients who had their values normalized by the end of the treatment period.
- The observed significant improvement in uCa and sPh is expected to translate to a clinically meaningful benefit for cHP patients in the long-term.
- Together with previous findings in animals and humans, these data suggest that eneboparatide's effects on serum calcium are mainly achieved through a potent and sustained reabsorption of calcium from the kidney.
- A multicenter, randomized, placebo-controlled, double-blind Phase 3 study further evaluating the effects of eneboparatide on normalization of urinary calcium in cHP patients is underway (CT.gov Id: NCT05778071).

CALYPSO STUDY

Poster SAT-239 presented at ENDO, June 15-18, 2023, Chicago

References:[1]Bi et al, JBMR, 2015, [2]Shimizu et al, JBMR, 2016, [3]Allas et al, ASBMR, 2021