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

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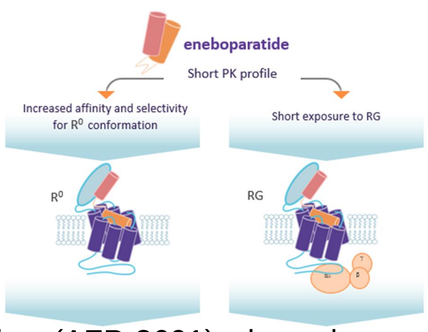
INTRODUCTION

- 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.
- In rodent models of HP, administration of eneboparatide led to prolonged increases in serum calcium and was not associated with an increase in urinary calcium excretion[1,2].
- In healthy subjects, eneboparatide treatment induced a dose-dependent increase in serum calcium with no increase in urinary calcium despite marked elevation of serum calcium[3].
- 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, which rapidly releases the ligand once the G-protein is activated and released, ending its signal transduction, and resulting in a transient cAMP signal and transient calcium elevation.
- R^0, which allows continued association with the ligand and thereby multiple cycles of G-protein coupling and activation, resulting in a sustained cAMP signal and sustained calcium elevation[3].

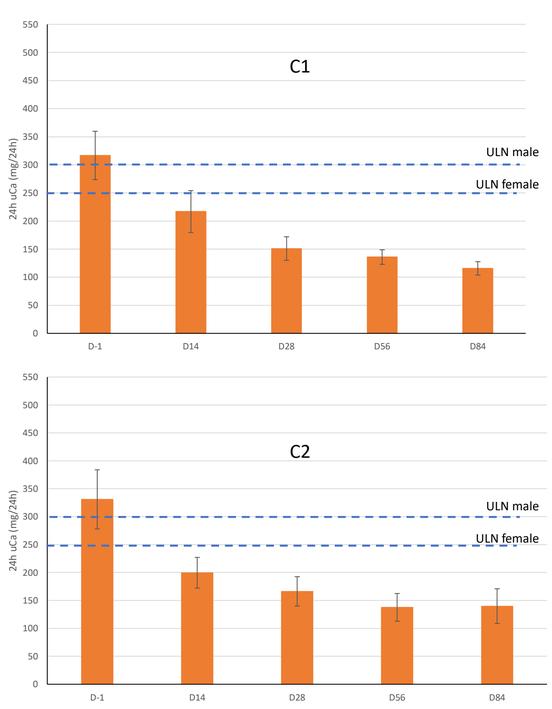


Eneboparatide (AZP-3601) has been designed to preferentially activate the R^0 conformation of the PTH1 receptor in order to produce a sustained serum Ca elevation despite having a short PK half-life. This enables eneboparatide to induce potent calcium reabsorption in the renal tubules and exert a physiological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

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%)
Mean BMI, kg/m² (SD) **min-max**	28.3 (4.4) 23.0-37.1	29.1 (5.4) 19.6-38	28.8 (4.9) 19.6-38
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
Mean time since cHP diagnosis, years *(overall population)* **min-max**	12.8 2-31	12.3 3-50	12.5 2-50
Mean time since cHP diagnosis, years, *(women only)* **min-max**	13 2-31	13 3-50	13 2-50
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 Alb-adjusted serum calcium, mg/dL **min-max**	8.67 8.10-9.20	8.70 7.72-9.6	8.71 7.72-9.6
Mean 24-hour urinary calcium, mg/24h **min-max**	329 143-614	331 57-729	330 57-729

24H URINARY CALCIUM (All patients)

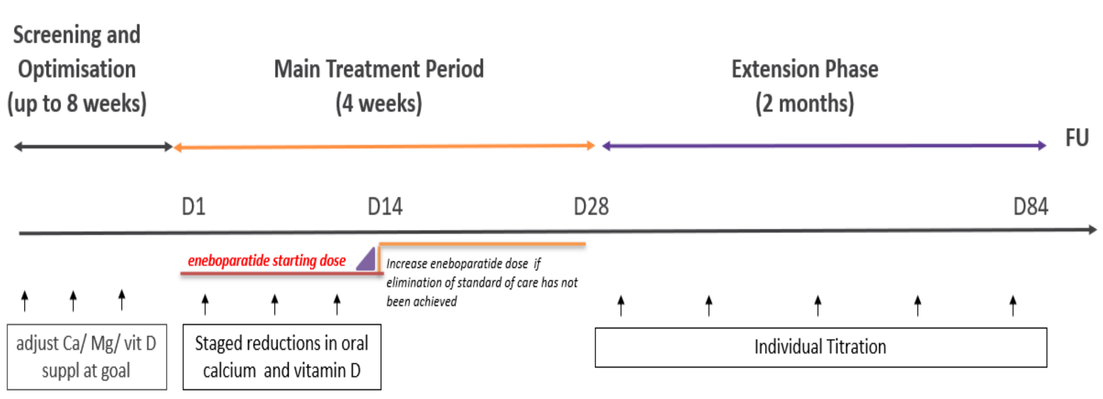


Data are means ± SEM. (mmol/24h = mg/24h x 0,0259).

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.

MATERIALS AND METHODS

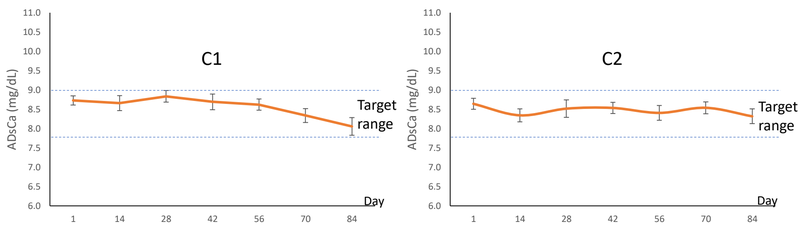
- Eligible patients included male and female patients aged 18 to 75 years with cHP for ≥12 months and treated with calcitriol ≥ 0.25 µg/day or alphacalcidol ≥ 0.50 µg/day and oral calcium ≥ 1000 mg/day.
- Conventional therapy was adjusted to have albumin-adjusted serum calcium (ADsCa) within the target 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.



ACTIVE VITAMIN D AND ORAL CALCIUM

Eneboparatide was well tolerated and enabled rapid and sustained reduction of oral calcium ≤500mg/d in the great majority of patients of both cohorts.
In C2, discontinuation of oral calcium was delayed and required up-titration due to the lower starting dose (10 µg), supporting a dose related effect (refer to Poster 2251 for more details).

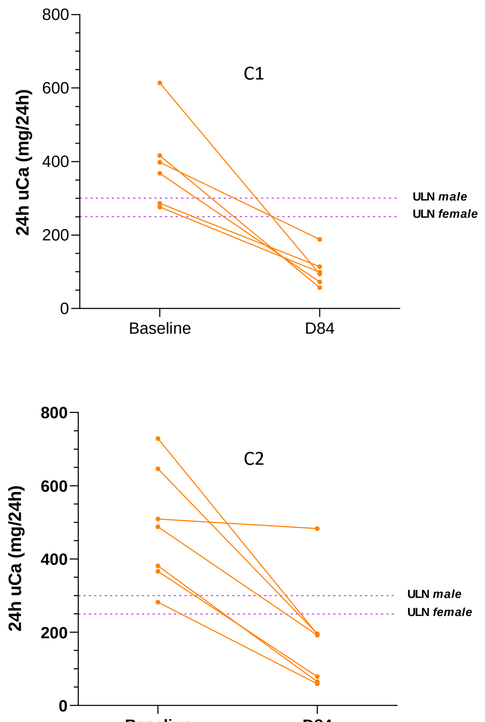
ALBUMIN-ADJUSTED SERUM CALCIUM



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. In C1, the lower mean at Day 84 was mainly due to 1 patient who had low ADsCa (6.72 mg/dL), this value was not associated with any symptoms.

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 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 indicate that eneboparatide effect 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).

Poster 2634 presented at ECE, May 13-16, 2023, Istanbul

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