Treatment of chronic hypoparathyroidism by eneboparatide, a novel PTH1 receptor agonist: results from a phase 2a study

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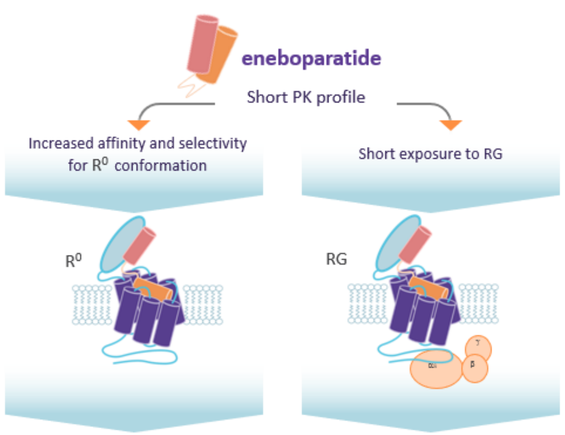
INTRODUCTION

- Hypoparathyroidism (HP) is a rare disease characterized by a deficiency in parathyroid hormone (PTH) that results in hypocalcemia, hyperphosphatemia, hypercalciuria and low bone turnover.
- Conventional therapy for chronic hypoparathyroidism (cHP) is often unable to maintain stable normal serum calcium (Ca) levels for a full 24h, to control symptoms, to prevent the detrimental long-term effects on the kidney and to preserve normal bone architecture.
- 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) in animals[1,2] and in healthy humans[3].
- We report the results of two consecutive cohorts (C1 and C2) of cHP patients enrolled in a phase 2a multi-center open-label study (CT.gov Id: NCT05239221).

MECHANISM OF ACTION

The PTH1 receptor (PTHR1) exists in two conformationally-distinct forms:

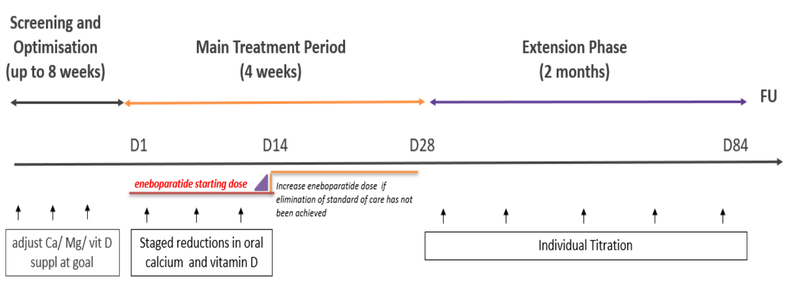
- RG, which rapidly releases the ligand once the G-protein is activated and released, ending its signal transduction, and resulting in a transient cAMP signal and transient calcium elevation.
- R^0, which allows continued association with the ligand and thereby multiple cycles of G-protein coupling and 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.

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.



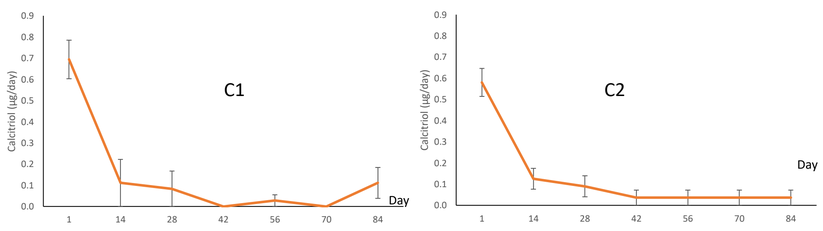
PATIENTS BASELINE CHARACTERISTICS

	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%)
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

SAFETY AND TOLERABILITY

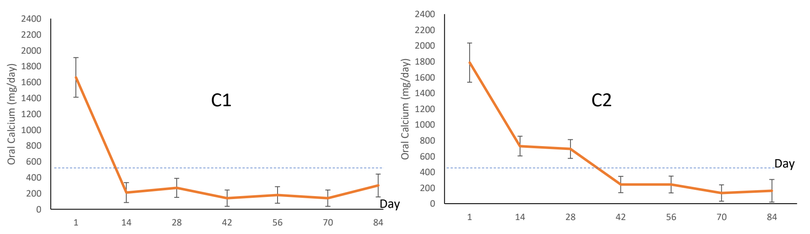
Eneboparatide treatment was well tolerated. No safety concerns. No serious events were reported. All adverse events were of mild or moderate intensity and included a few episodes of hypocalcemia or hypercalcemia (C1 only, during first half of treatment when patients were still on standard of care that was progressively removed) and injection site reactions (all resolved).

ACTIVE VITAMIN D AND ORAL CALCIUM



Active vitamin D dose (calcitriol dose equivalent). Data are means ± SEM.

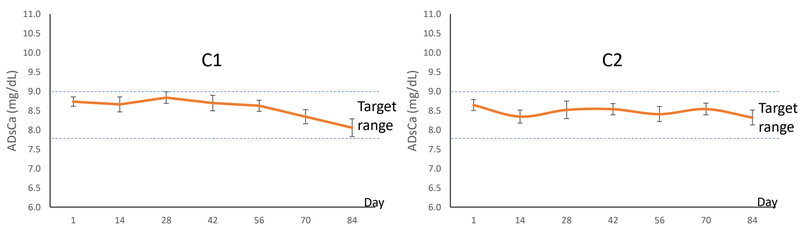
Eneboparatide enabled discontinuation of active vitamin D in 8/10 patients in C1 and 13/14 patients in C2.



Oral Calcium Dose. Data are means ± SEM.

Eneboparatide enabled rapid and sustained reduction of oral calcium supplementation <500mg/d in 8/10 patients in C1 and 13/14 patients in C2. In C2, discontinuation of oral calcium supplementation was delayed and required up-titration due to the lower starting dose (10 µg), supporting a dose-related effect.

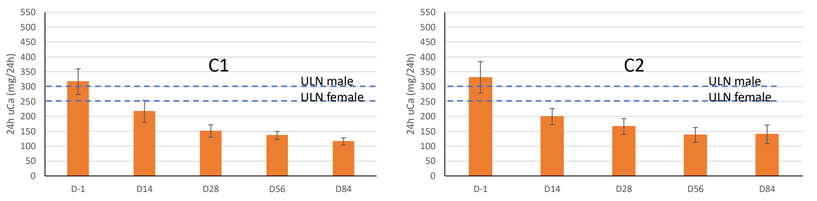
ALBUMIN-ADJUSTED SERUM CALCIUM



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.

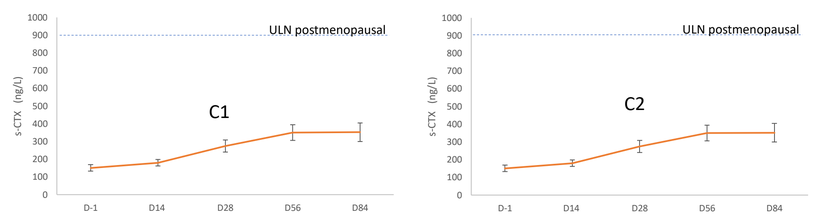
24H URINARY CALCIUM



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

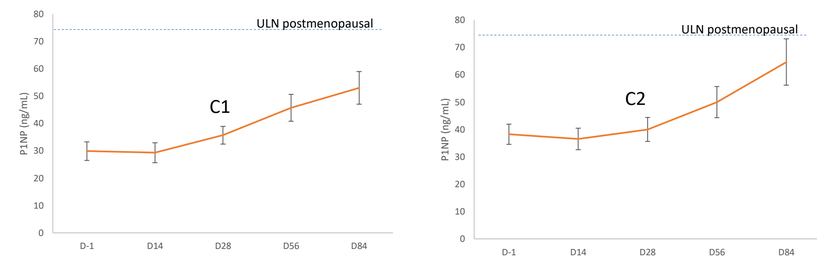
In both cohorts, eneboparatide induced a rapid, profound and sustained reduction of 24h urinary excretion of calcium, including in patients with hypercalciuria at baseline (refer to Poster 2634 for more details).

SERUM BONE MARKERS



Catabolic Bone Biomarker (s-CTX). Data are means ± SEM.

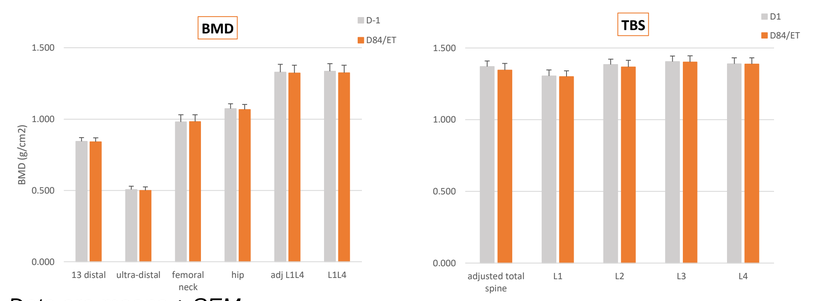
Eneboparatide induced a smooth and progressive increase of the low baseline CTX levels into the mid-normal range.



Anabolic Bone Biomarker (P1NP). Data are means ± SEM.

Eneboparatide induced a progressive increase of P1NP with mean value remaining within normal range.

BONE MINERAL DENSITY



Data are means ± SEM.

BMD and TBS as assessed by DXA with central readings (C2 only) remained stable during eneboparatide treatment. Z-scores and T-scores (calculated from BMD) also remained stable throughout the study treatment duration, including in osteopenic patients (data not shown).

SUMMARY AND CONCLUSION

- In both cohorts of cHP, eneboparatide treatment for 3 months was well tolerated with no safety concerns.
- Standard of care was rapidly eliminated while mean ADsCa was maintained within the target range.
- Mean urinary calcium decreased to within the normal range including in those patients with hypercalciuria at baseline.
- Bone turnover data were consistent with a balanced resumption of bone turnover.
- These data support eneboparatide as a potential treatment of chronic hypoparathyroidism targeting urinary calcium reabsorption rather that bone resorption, and advancement to Phase 3 with 20 µg as starting dose.
- A multicenter, randomized, placebo-controlled, double-blind Phase 3 study is underway in North America and Europe (CT.gov Id: NCT05778071).

Poster 2251 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