Eneboparatide, A Novel Investigational PTH1R Agonist, Maintains Calcium Homeostasis Without Deleterious Effects on Bone

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BACKGROUND

Eneboparatide is a novel PTH type 1 receptor (PTH1R) agonist with a short half-life and high affinity for the R^0 receptor conformation. This profile is expected to result in maintenance of serum calcium (sCa) in chronic hypoparathyroidism (cHP) by recycling Ca from the glomerular filtrate and enhanced intestinal Ca absorption while avoiding the net bone resorptive effects of continuous PTH1R exposure.

METHODS

Data were examined from studies in non-human primates (NHP), healthy human volunteers (HV) and patients with cHP.

Non-Human Primates

NHPs received daily sc eneboparatide injections for 39 weeks at doses within and above the anticipated human therapeutic dose range (Table 1).

	Dose (µg/kg/day)	Number of animals (males+females) 39-week study
1. Control (saline)	-	6+6
2. Low dose	1 (22µg/day)*	4+4
3. Mid dose	2.5 (55µg/day)*	4+4
4. High dose	10 (220µg/day)	6+6

Human equivalent dose for 70 kg individual
**Within intended human clinical dose range*

Bone biomarkers were collected at baseline, and weeks 4, 8, 13, 26, and 39. In life bone mineral density (BMD) was evaluated by quantitative computed tomography (qCT) at baseline and weeks 26 and 39. Histopathological examination of bone was performed at week 39.

Healthy Volunteers

HVs were administered eneboparatide at doses up to 80 µg/day for 2 weeks. Serum calcium, 1,25 dihydroxy vitamin D (1,25(OH) vit D), bone biomarkers, and 24h urinary Ca (24hr-uCa) were measured.

	Dose (µg/day)	Number of subjects (males+females) 2-week study
Placebo	-	10 (9+1)
Cohort B1	10	8 (8+0)
Cohort B2	20	8 (6+2)
Cohort B3	40	10 (9+1)
Cohort B4	60	8 (8+0)
Cohort B5	80	8 (8+0)

Patients with chronic hypoparathyroidism

cHP 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.

sCa, 1,25(OH) vit D, bone biomarkers, 24hr-uCa and BMD were measured.

RESULTS

Bone (NHP)

In NHP, BMD, bone structure and turnover markers remained unchanged over 39 weeks.

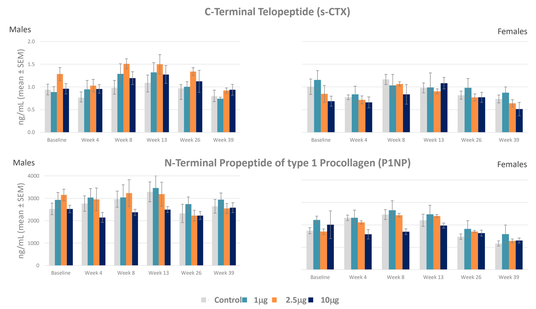

Figure 1. Bone biomarkers in NHP

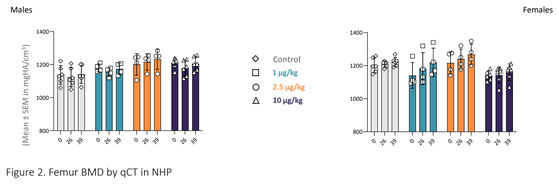

Figure 2. Femur BMD by qCT in NHP

Figure 3. Tibia BMD by qCT in NHP

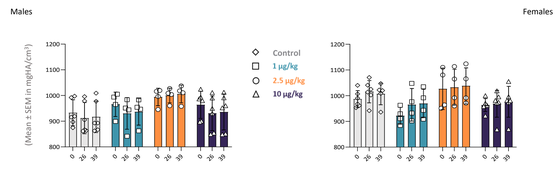

Figure 4. L4 BMD by qCT in NHP

Histological examination of the femur at the end of the 39-week of treatment revealed no noteworthy findings.

Bone (Healthy Volunteers)

In healthy volunteers, bone biomarkers remained stable at all dose levels during 14 days of daily dosing.

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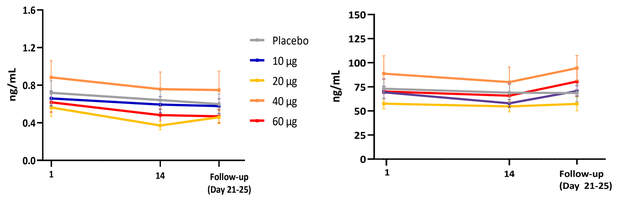


Figure 5. Bone biomarkers in healthy subjects during 14 days of eneboparatide treatment

Bone (cHP patients)

In cHP patients, eneboparatide induced a modest, balanced increase in bone biomarkers s-CTX and P1NP (Figure 6) and had no significant effect on BMD (Figure 7). Of note, T-scores for cHP patients revealed that 6 of 14 (43%) were osteopenic at baseline (Figure 8).

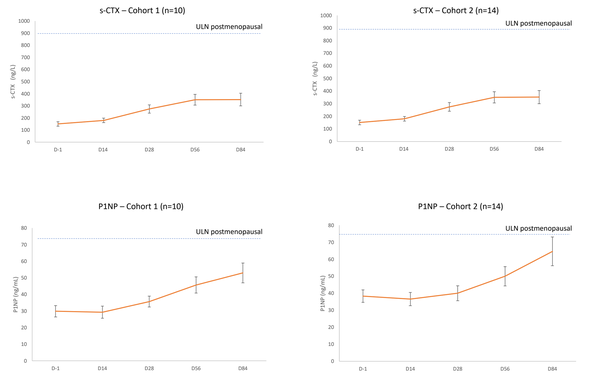


Figure 6. Bone biomarkers in cHP patients treated with eneboparatide for 84 days

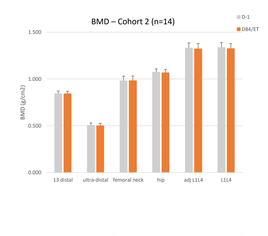


Figure 7. Bone Mineral Density in cHP patients (cohort 2) treated with eneboparatide for 84 days

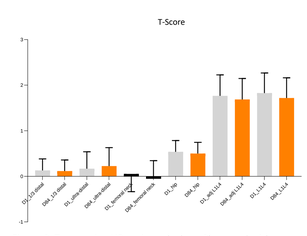
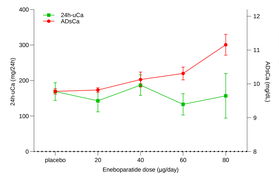


Figure 8. T scores in cHP patients (cohort 2) treated with eneboparatide for 84 days

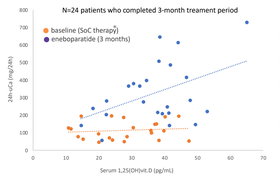
Kidney (Healthy Volunteers)



In HV, there was no increase in 24hr-uCa despite marked elevation of sCa at higher doses of eneboparatide (Figure 9).

Figure 9. Serum calcium and urinary calcium values across escalating doses of eneboparatide

Kidney (cHP patients)



SoC therapy: standard of care therapy

Figure 10. Relationship between serum 1,25 (OH) vit D and 24-hour urinary calcium levels

In patients with cHP, at baseline, 24hr-uCa is correlated with 1,25(OH) vit D. because urinary excretion of calcium primarily depends on intestinal absorption of calcium facilitated by 1,25(OH) vit D but is not influenced by PTH1R-mediated reabsorption of urinary calcium.

However, on treatment with eneboparatide, 24hr-uCa is no longer directly proportional to 1,25(OH) vit D but also dependent on the eneboparatide-induced reabsorption of calcium (Figure 10).

Eneboparatide treatment resulted in a rapid and profound decrease in urinary calcium levels (Figure 11), especially notable in patients with hypercalciuria at baseline (Figure 12).

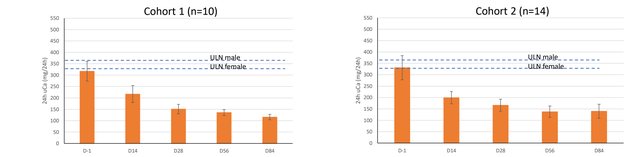


Figure 11. 24-hour urinary calcium levels on treatment with eneboparatide (both cohorts of cHP patients)

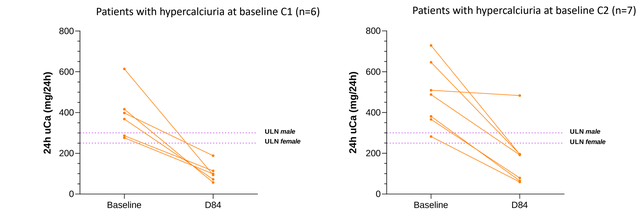


Figure 12. 24-hour urinary calcium levels on eneboparatide treatment (patients with hypercalciuria at baseline)

In addition to stimulation of renal tubular reabsorption of calcium, eneboparatide is likely to increase absorption of dietary calcium by increased endogenous production of 1,25(OH) vit D. After removal of active vit D supplements, levels are maintained at a stable level on treatment.

CONCLUSION

The collective data from NHP, HV and cHP patients do not suggest that eneboparatide induces net bone loss. Further, treatment of HV with eneboparatide promotes renal capacity to reabsorb filtered calcium as serum calcium increases, while in cHP patients, eneboparatide restores normal renal calcium reabsorption. Eneboparatide-stimulated renal conversion of 25(OH) vit D to 1,25(OH) vit D allows continued intestinal Ca absorption despite the removal of supplements. These data suggest that restoration of Ca homeostasis with eneboparatide in cHP is likely due to a sustained effect on renal calcium reabsorption and intestinal calcium uptake without deleterious effects on bone.

Poster LB SUN-652, presented at ASBMR Annual Meeting October 13-16, 2023, Vancouver