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Eneboparatide, a Novel PTH-1 Receptor Agonist, Has No Impact on Bone Parameters Following Chronic Treatment of Non-Human Primates

Guillaume Ravel[1], Thomas Delale[1], Stéphane Milano[1], Sophie Chirat[2], Michael Verset[2], Emilie Latronico[3], Soraya Allas[1], Michael D. Culler[4]

[1]Amolyt Pharma, Ecully, France, [2]Charles River Laboratories France, Saint Germain Nuelles, France, [3]Voxcan, Dommartin, France, [4]Amolyt Pharma, Cambridge, Massachusetts, United States

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CONFLICT OF INTEREST

Michael D. Culler

X I have the following potential conflicts of interest to report:

☐ Research Contracts

☐ Consulting

X Employment in the Industry **(Employee of Amolyt Pharma)**

X Stockholder of a healthcare company

☐ Owner of a healthcare company

☐ Other(s) *– please include details*

No commercial logos or product names to be included please.

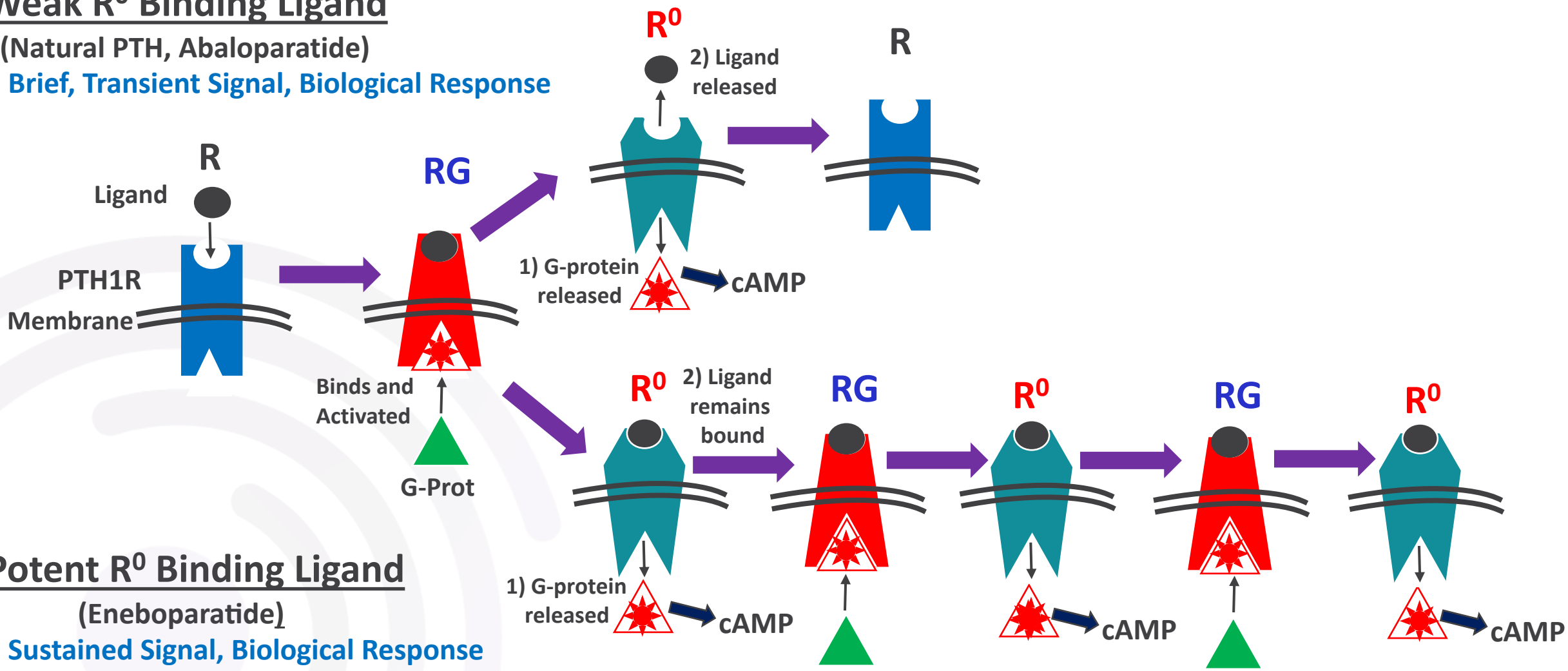
☐ **I declare that I have no potential conflict of interest.**

Upon Ligand Binding, the PTH1-Receptor Changes Its Conformation Corresponding to the the Binding (RG) or Release (R^0) of G-Protein – Biological Effect Depends on R^0 Affinity

Weak R^0 Binding Ligand

(Natural PTH, Abaloparatide)

= Brief, Transient Signal, Biological Response



Potent R^0 Binding Ligand

(Eneboparatide)

= Sustained Signal, Biological Response

Eneboparatide is a Unique Hybrid Analog of PTH and PTHrP Engineered for High Affinity for the R^0 Conformation of the PTH1 Receptor

Eneboparatide (AZP-3601)

Adapted from Noda et al. JBMR Plus 4:e10367 2020

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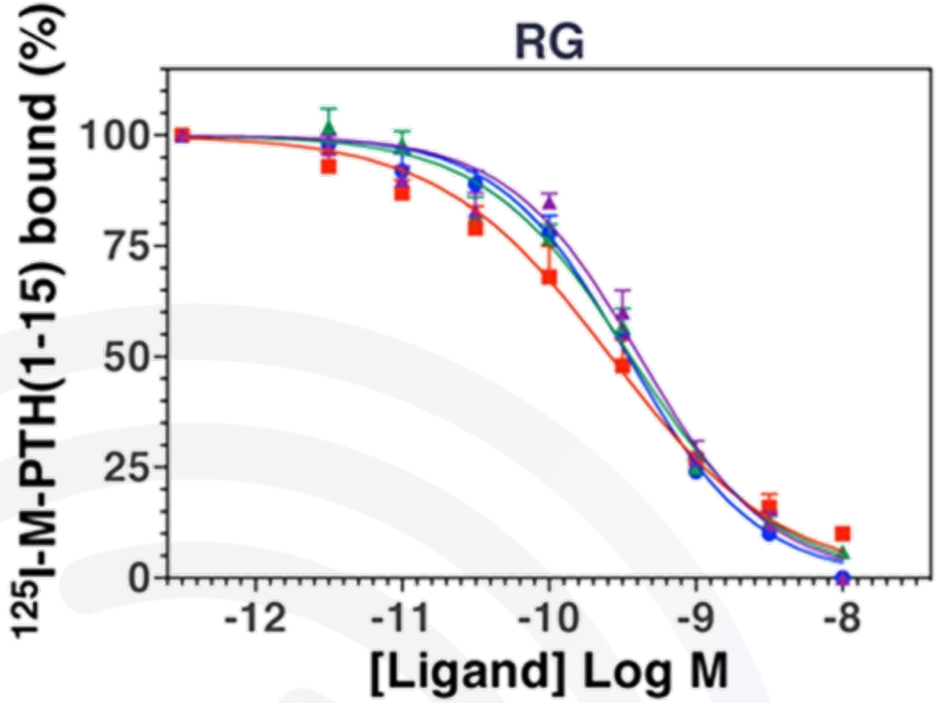
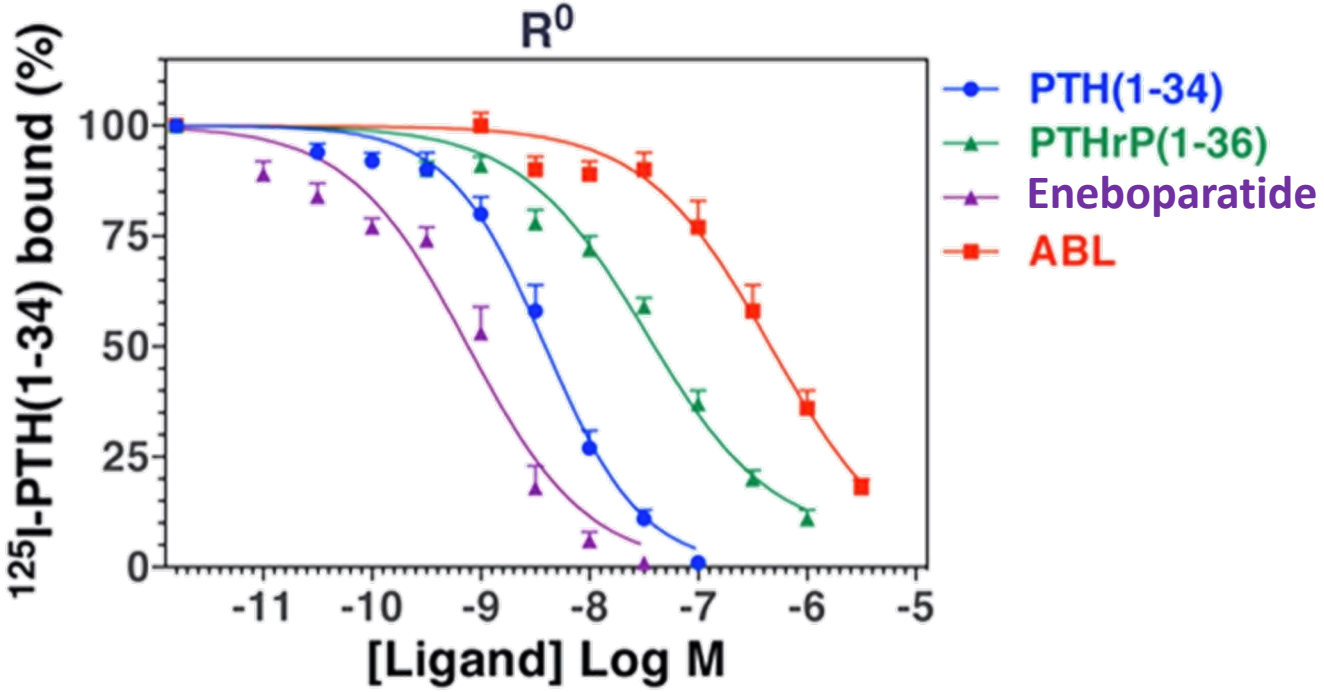
Comparative Binding of PTH Ligands to RG and R^0 Conformations of PTH1 Receptor - Eneboparatide Significantly More Potent for R^0 Than Natural PTH1-R Ligands





Comparable Affinities for RG Conformation

Compounds Differentiated by Affinity for R^0 Conformation

Hattersley et al. Endocrinology 157:141, 2016

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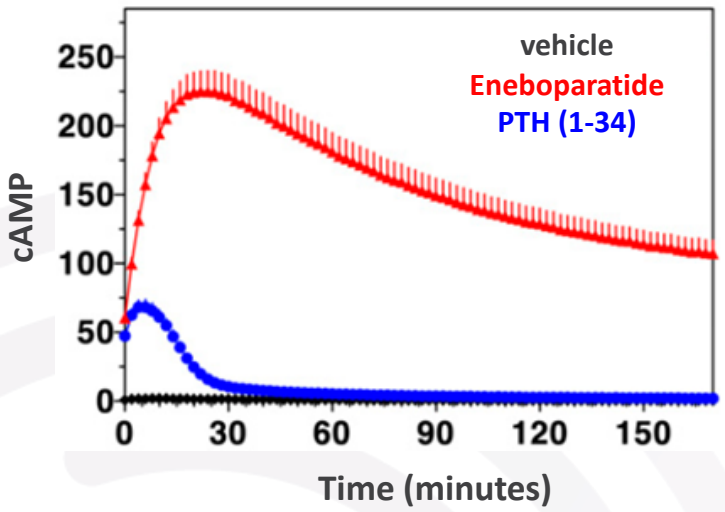
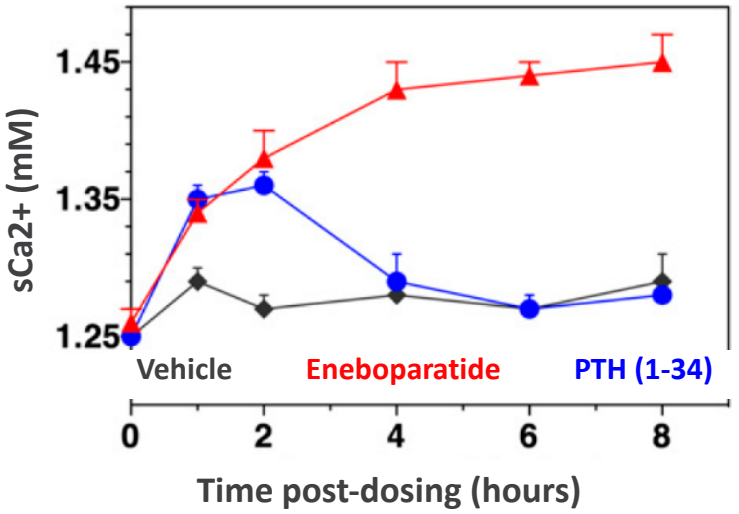
High Affinity for R^0 Conformation Translates to Enhanced and Prolonged Signaling Resulting in a Sustained Biological Response

cAMP signaling
after ligand washout



Sustained cAMP signal with Eneboparatide
Compared with PTH(1-34) in HEK293 (kidney) cell line expressing the hPTH1 receptor

Mouse serum Ca^{2+}



Sustained sCa^{2+} with Eneboparatide
Blood ionized calcium responses in mice

Eneboparatide and PTH(1-34) have comparable in vivo half-lives

Shimizu M et al., *JBMR.* 2016
Gardella TJ et al., *Pharmacol. Rev.* 2015

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Key Therapeutic Goals for Optimal Medical Treatment of Hypoparathyroidism

Current Standard of Care does *NOT Achieve These Therapeutic Goals*

Therapeutic goal #1 - Normalization of Serum Calcium Levels and Symptom Relief

- Sustained and stable sCa levels within normal range over full 24 hours to:
  - Eliminate Ca/VitD supplementation
  - Decrease frequency and severity of symptoms

Therapeutic goal #2 - Preserve Kidney Function

- Decrease in urinary Ca (uCa) excretion, in particular in patients with elevated uCa

Therapeutic goal #3 - Ensure Bone Safety

- Neutral impact on the bone; ideally restore normal and physiological bone turnover without bone loss

- ***53%*** HP patients are peri- or post-menopausal women
- ***17%*** have osteopenia or osteoporosis

Eneboparatide has been demonstrated both preclinically in animal models and clinically in hypoparathyroid patients to induce and maintain sustained normalization of serum and urinary calcium

In this study, we focus on the impact of chronic Eneboparatide treatment on bone

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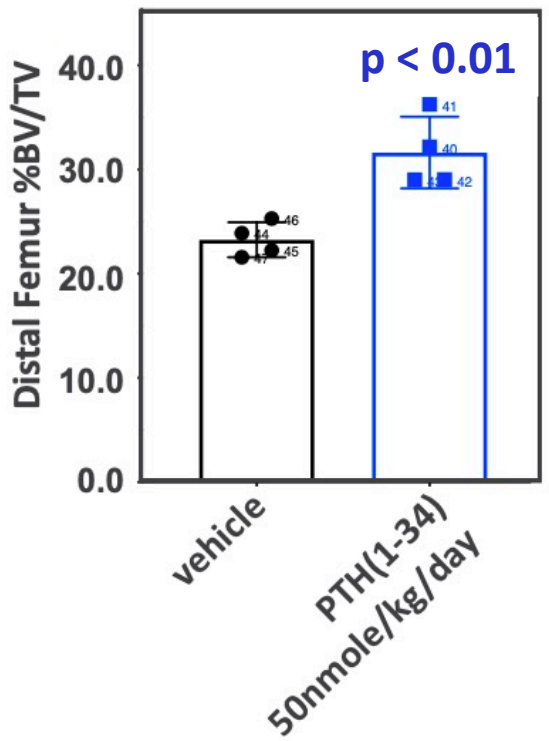
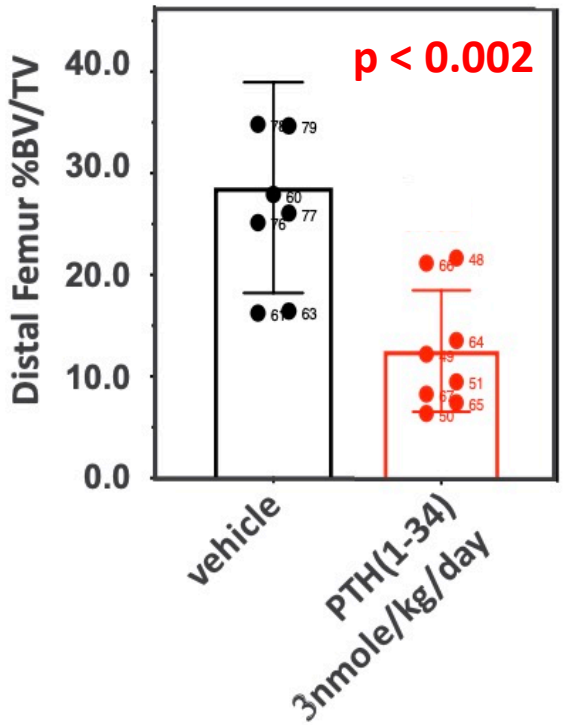
Direct Comparison of Distal Femur in TPTX Rats Following 14-Day Treatment with Either Daily PTH(1-34) Injection, Continuous PTH(1-34) Infusion or Daily Eneboparatide Injection, at Doses that Normalize Serum Calcium

Daily PTH(1-34) Injection



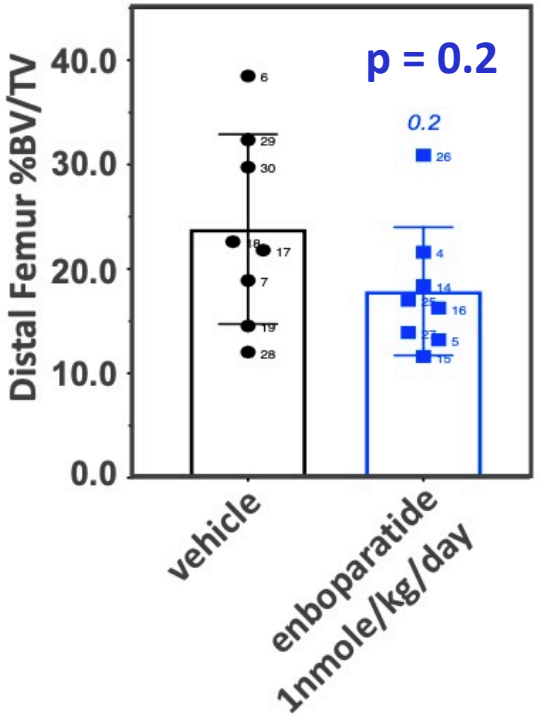
Significant anabolic effect

Continuous PTH(1-34) Infusion



Significant catabolic effect

Daily Eneboparatide Injection



Neutral effect

Aksu et al. ECE Abstract 978 2022

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13- and 39-Week Studies in Non-Human Primates

Daily SC injections of vehicle or eneboparatide in healthy Cynomolgus monkeys

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

Human equivalent dose for 70kg individual

***Within intended human clinical dose range**

13-week study

. Ex-vivo bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) at week 13

. Histopathological examination of bone at week 13

39-week study

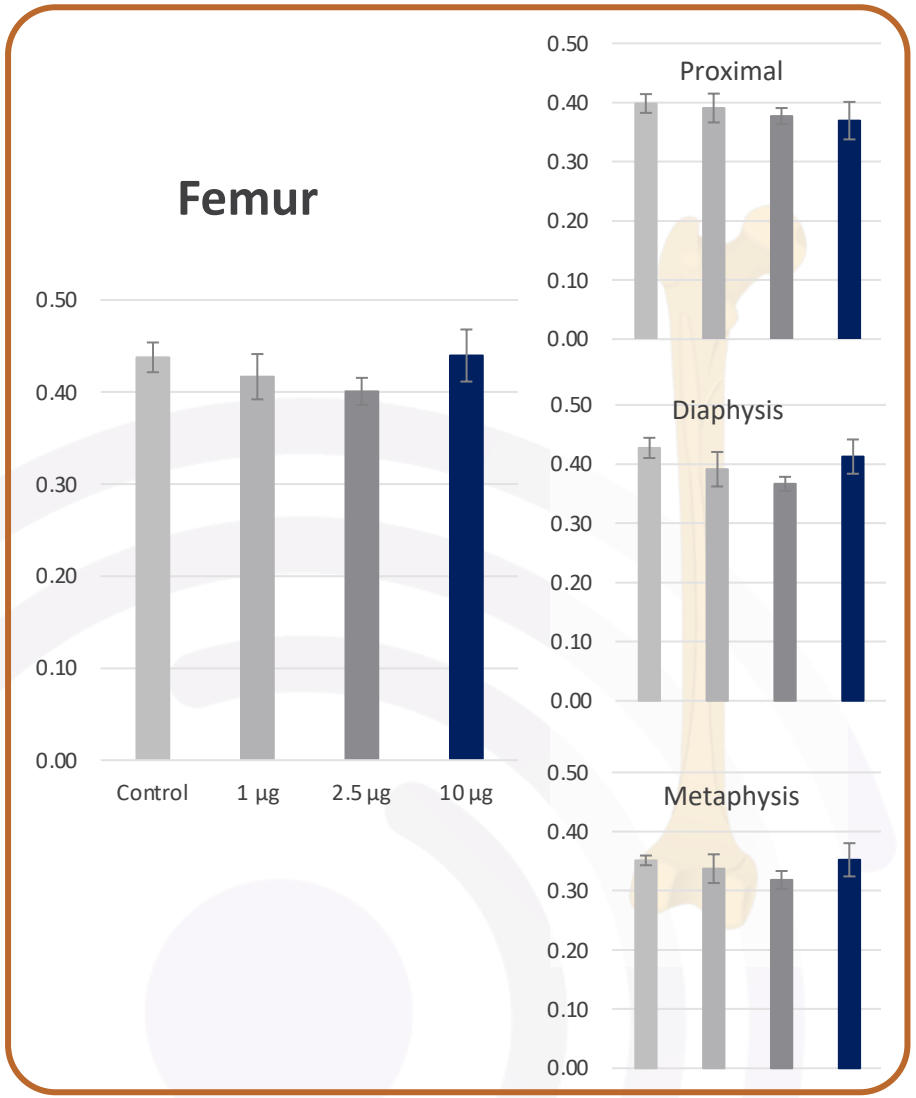
. Serum bone biomarkers at baseline and weeks 4, 8, 13, 26 and 39

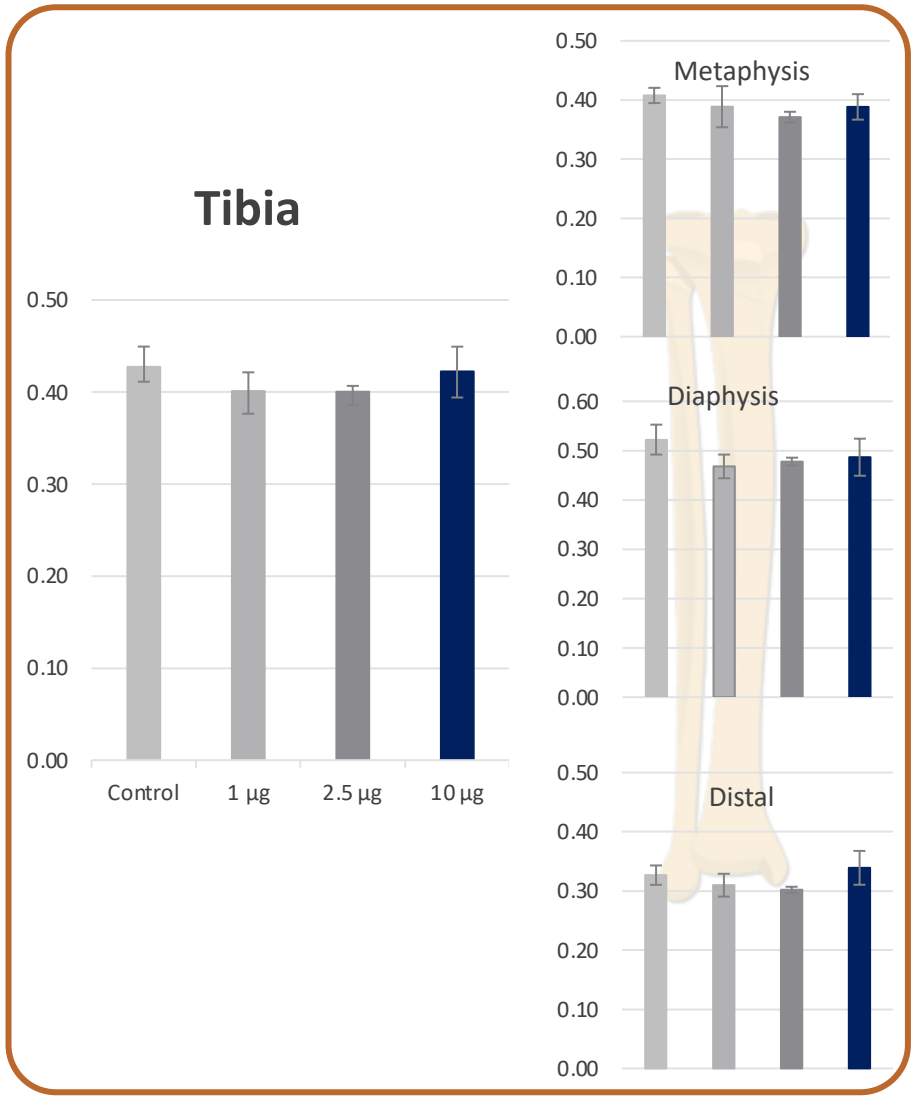
. In-life BMD by quantitative computed tomography (qCT) at baseline and weeks 26 and 39

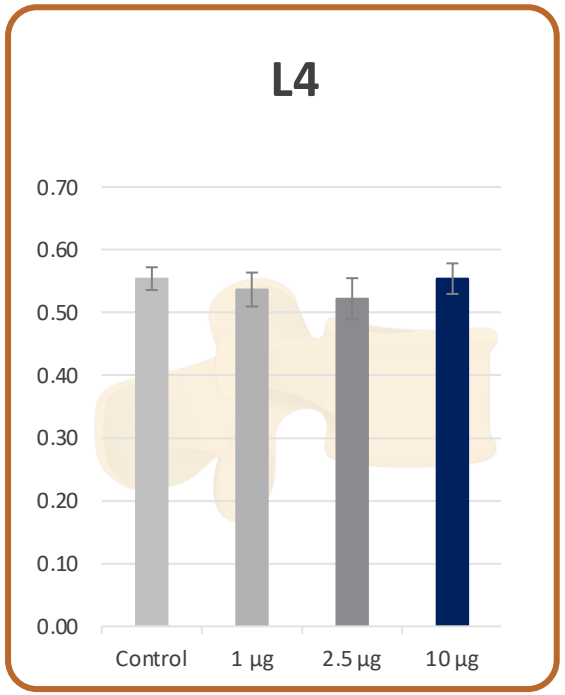
. Histopathological examination of bone at week 39

BMD by DXA in Males after 13 weeks

(Mean ± SEM in g/cm²)







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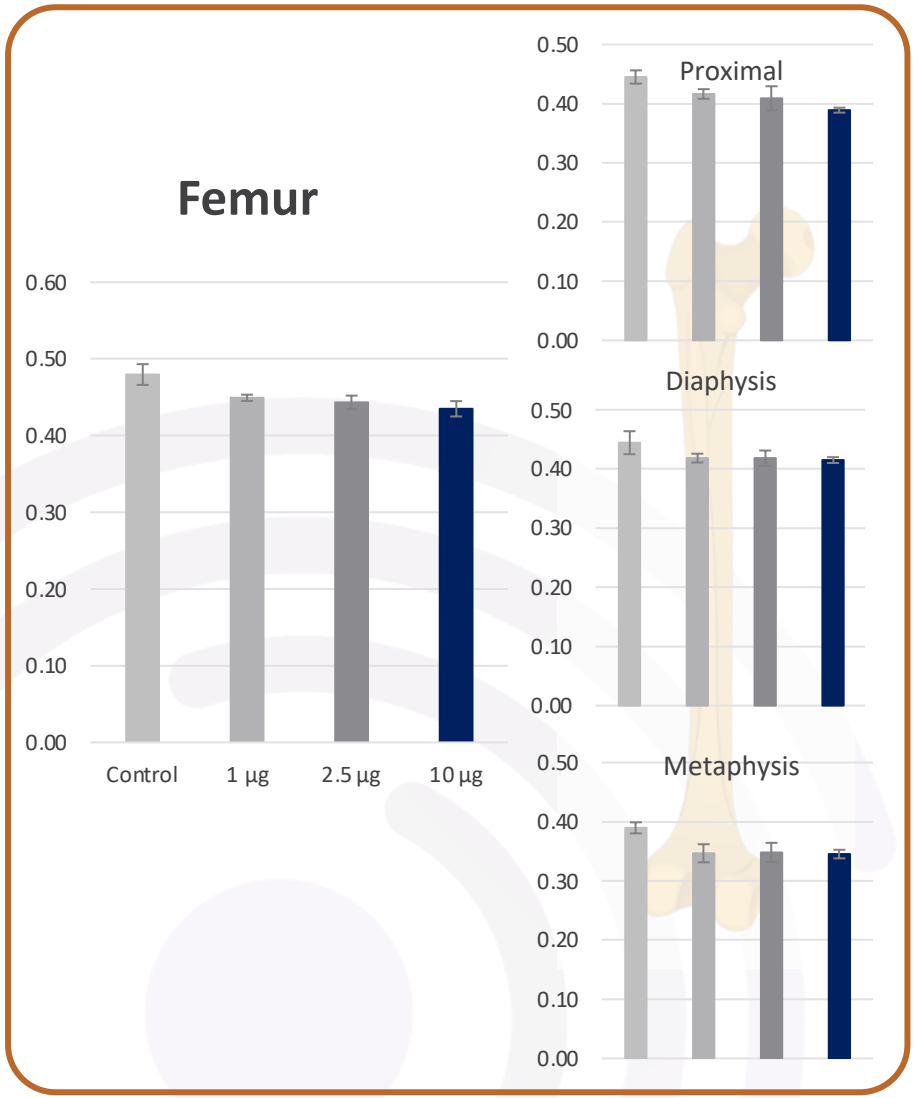
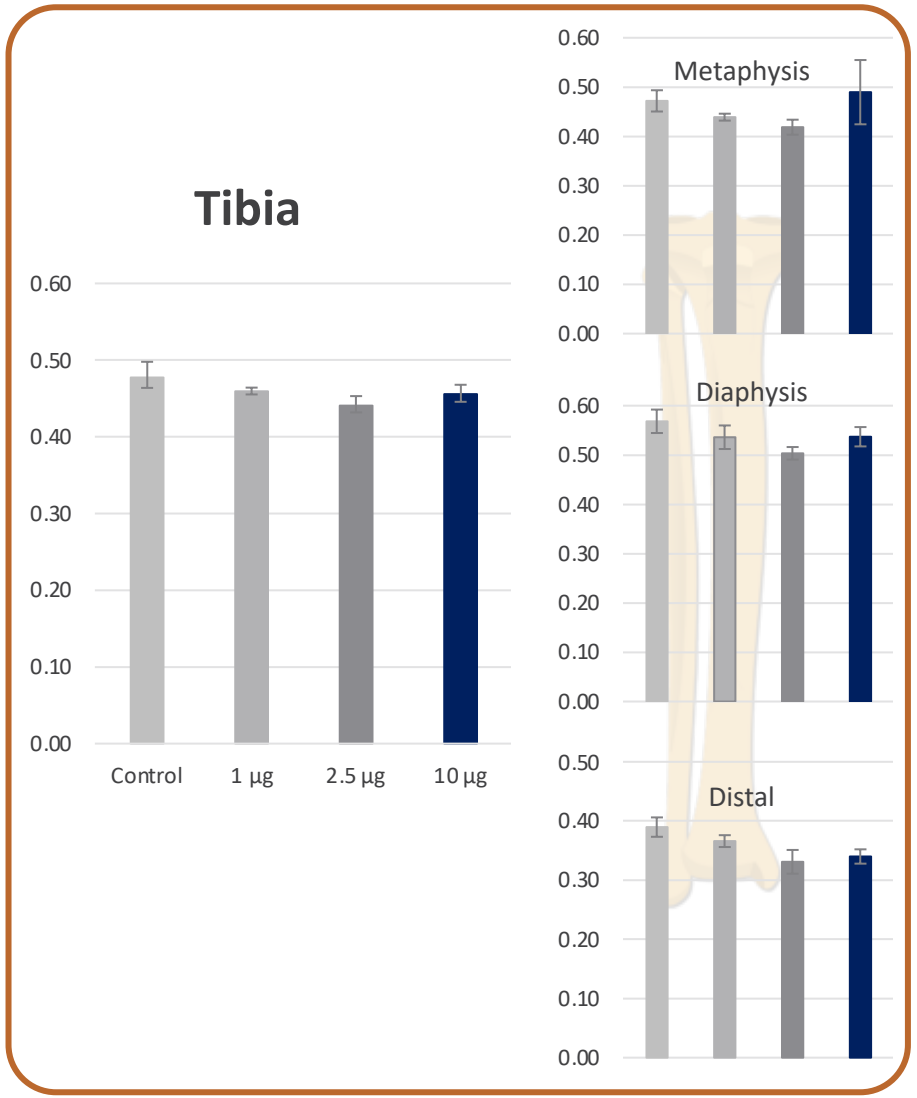
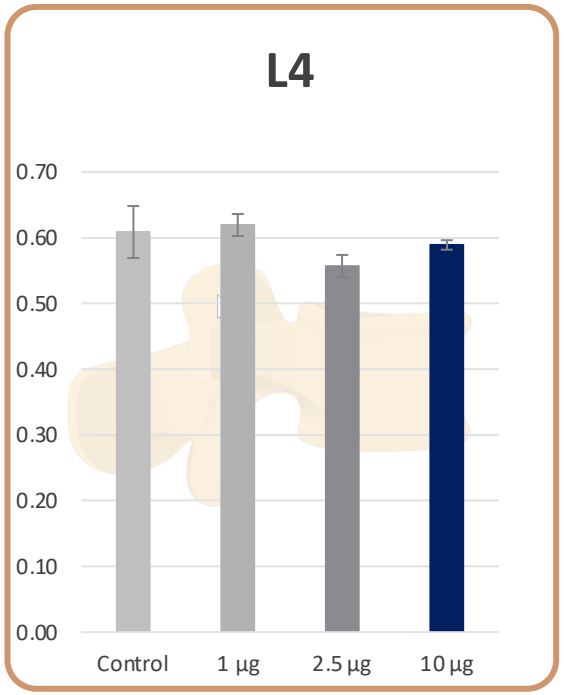
BMD by DXA in Females after 13 weeks

(Mean ± SEM in g/cm²)





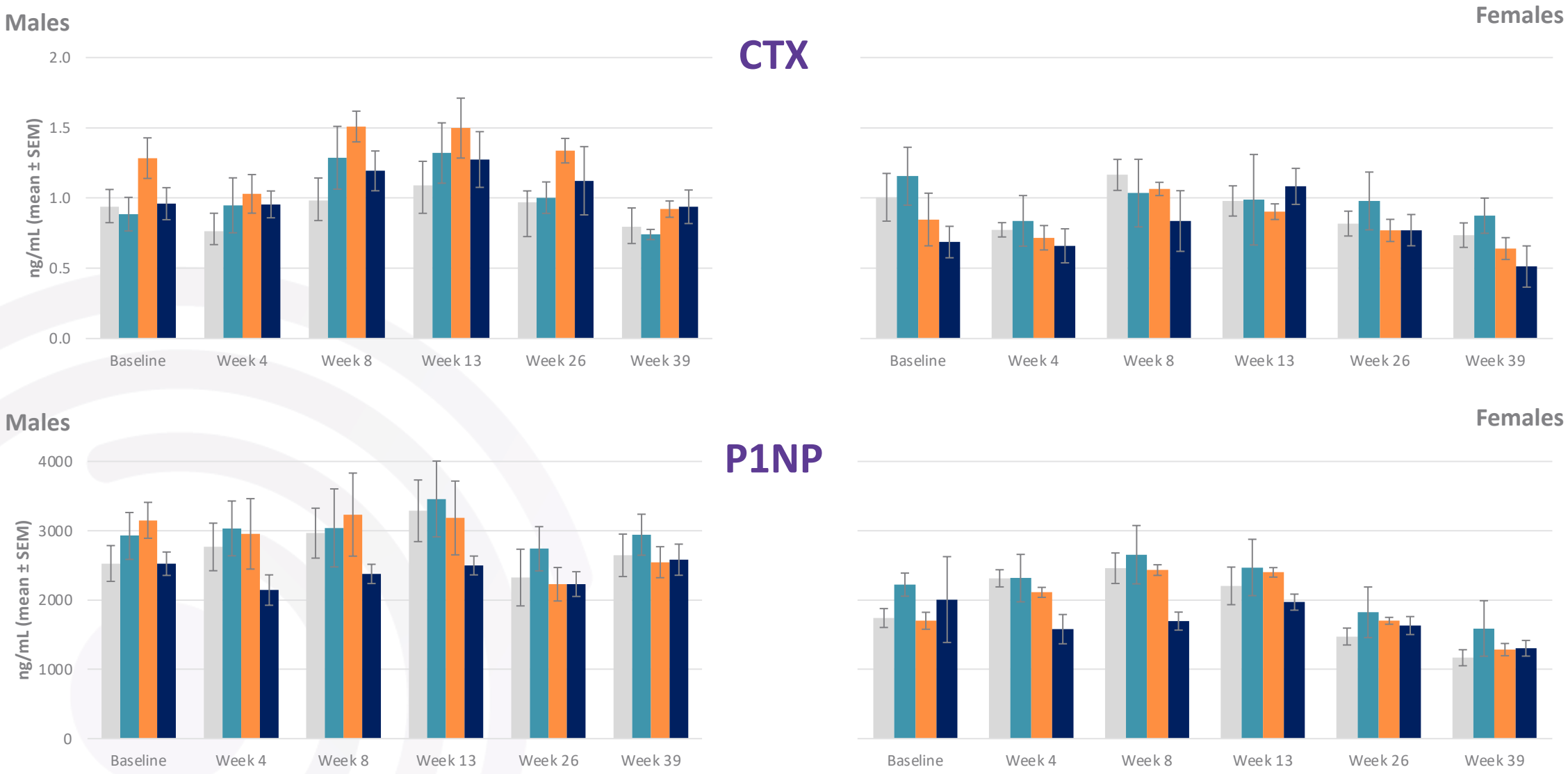


Bone biomarkers after 39 Weeks

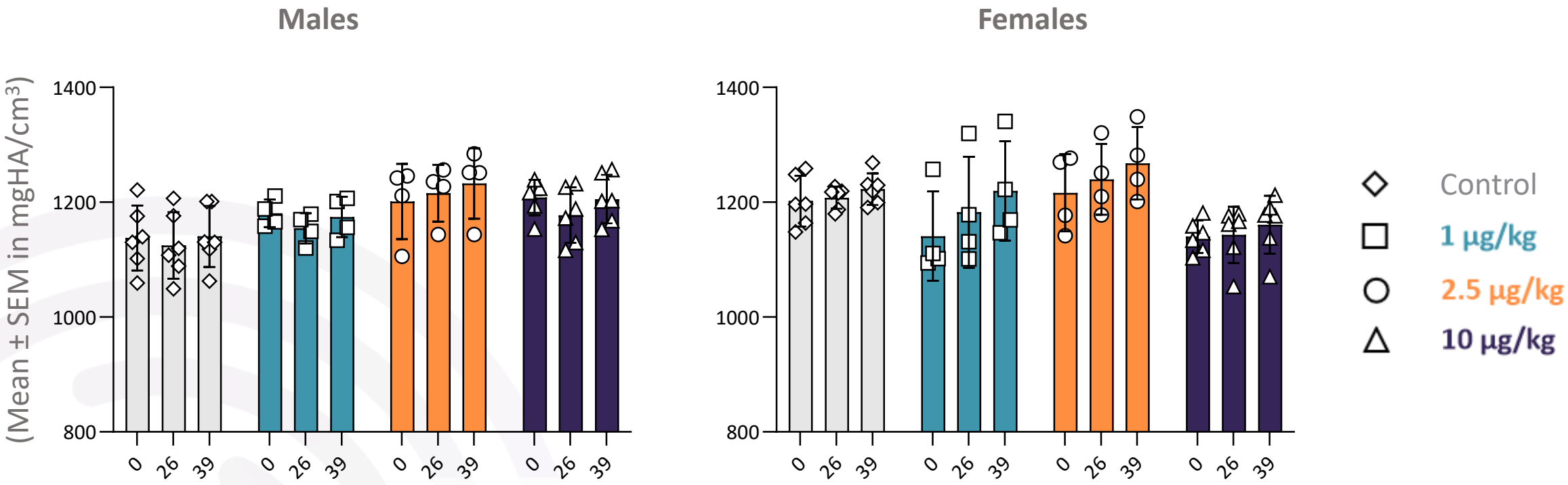
Control 1µg 2.5µg 10µg

C-Terminal Telopeptide (CTX)

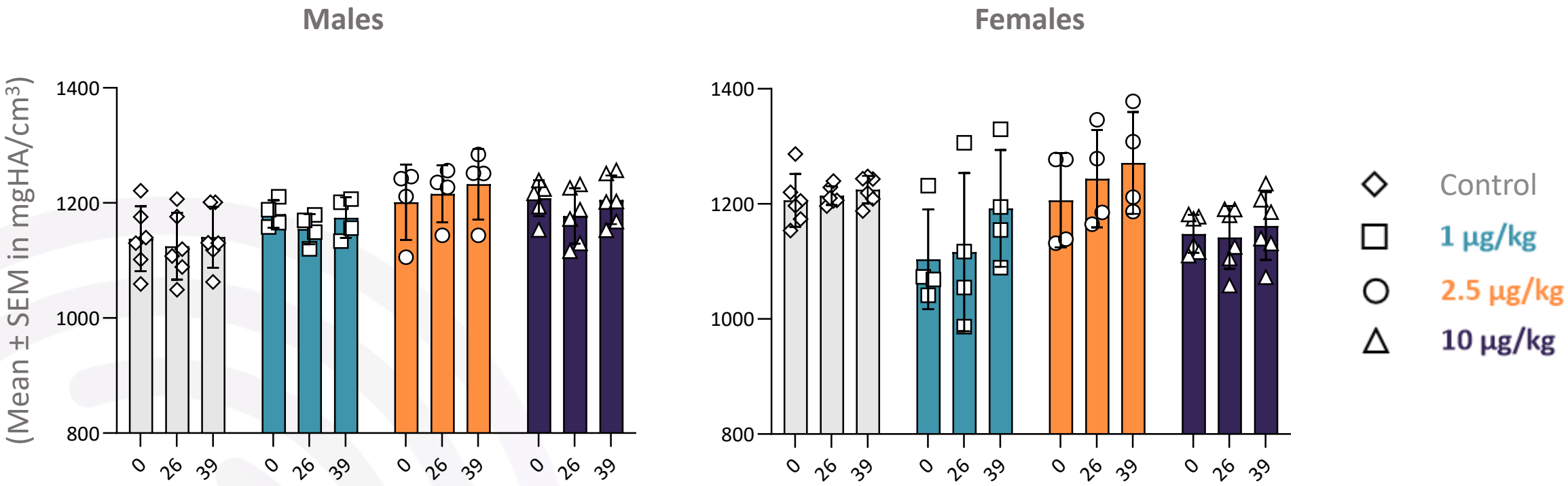
N-Terminal Propeptide of type 1 Procollagen (P1NP)



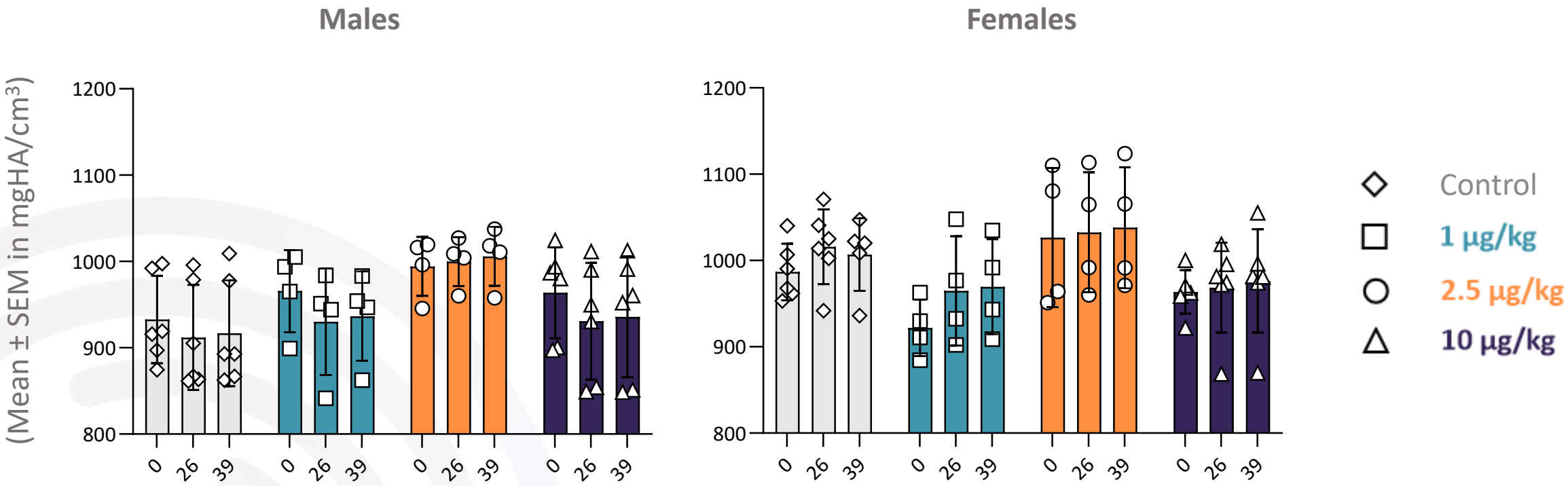
Femur BMD by quantitative computed tomography (qCT) after 39 weeks



Tibia BMD by qCT after 39 Weeks



L4 BMD by qCT after 39 Weeks



Summary and Conclusions

- **Eneboparatide is a unique hybrid analog of PTH and PTHrP engineered for high affinity to the R^0 conformation of the PTH1 receptor**
- **This mechanism of action results sustained biological responses in vivo despite having only a brief circulating half-life**
- **In the present study, eneboparatide was demonstrated to have no significant effect on bone parameters following chronic, daily treatment of non-human primates for up to 9 months**
- **These results, coupled with the observations on serum and urinary calcium from both preclinical models of hypoparathyroidism and clinical studies in hypoparathyroid patients, strongly support the development of eneboparatide as an optimal treatment for chronic hypoparathyroidism**
- **A Phase 3, multicenter, placebo-controlled, double-blind clinical study evaluating the efficacy and safety of eneboparatide in hypoparathyroid patients is underway**

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Thank you!