A Six-month Phase 2 Study of Oral PTH in Postmenopausal Women with Low Bone Mass – 6 Month Bone Mineral Density (BMD) results

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EnteraBio

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Background

- Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue that leads to decreased bone strength and increased risk of fracture

- Teriparatide [hPTH(1-34)] for injection (Forteo®) is an osteoanabolic treatment that reduces the risk of vertebral fractures up to 80%

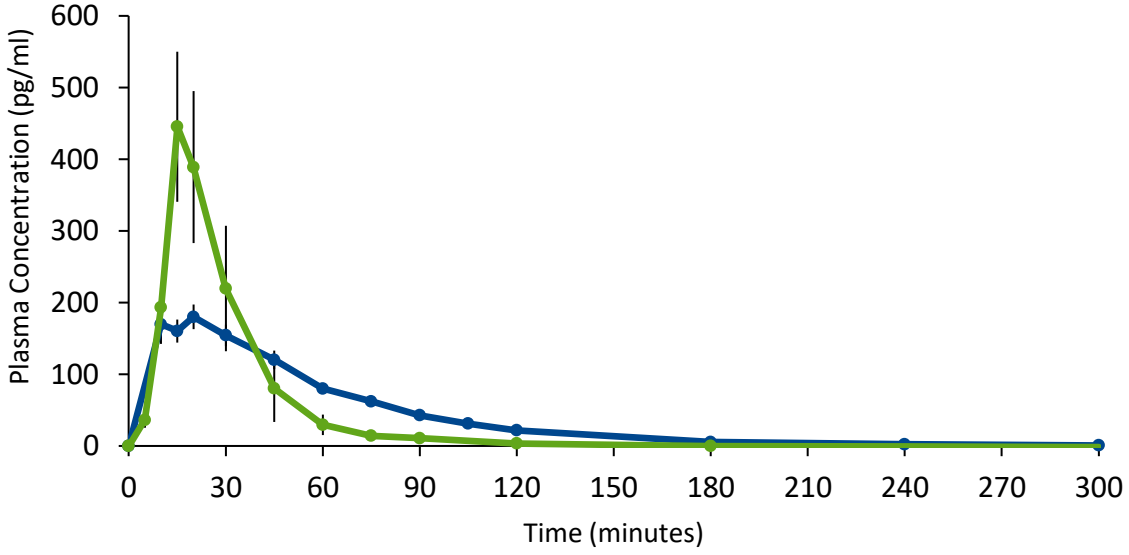
- Injections deter older patients from using the drug, contributing to a treatment gap in high-risk patients

- An oral formulation of PTH with adequate bioavailability, and similar safety and effect on BMD may address this unmet clinical need.

Background

- EBP05 is an oral formulation of hPTH(1-34), based on the proprietary drug delivery technology which promotes enteric absorption and stabilizes the teriparatide in the gastrointestinal tract

Pharmacokinetics of 1.5mg oral PTH(1-34) formulation (EBP05) and of Forteo® 20ug in healthy volunteers (n=9) (mean±SE)



Data presented at ASBMR 2018 Annual Meeting: "An oral PTH(1-34) formulation with a pharmacokinetic profile optimized for the treatment of osteoporosis"; Gregory Burshtein, Hillel Galitzer, Ariel Rothner, Phillip Schwartz, Roger Garceau, Eric Lang , Jonathan C. Y. Tang, William D. Fraser, Yoseph Caraco

Study Design

- A Phase 2, 6-month, randomized, dose-ranging, placebo-controlled study
- Conducted at 4 sites in Israel between June 2019 and May 2021

Screening

Key inclusion criteria

- >50 yr old and >3+ yr post menopause
- BMD T-score ≤ -2; >-3.5

Key exclusion criteria

- Osteoporosis treatment within last 2 yr
- Other disorders of bone or mineral metabolism
- Severe osteoporosis that precludes placebo

Endpoints

Primary – at 3 months

- Serum P1NP change from baseline at 3 months

Secondary – at 6 months

- BMD change from baseline at 6 months
- P1NP, Osteocalcin, Bone Alkaline Phosphatase
- Serum CTX, Urine NTX/Creatinine
- Plasma hPTH(1-34) at $T_{15\ min}$

Study Design

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Treatment – Oral PTH

Randomization N=161

Arm 1: Placebo tablets QD

Arm 2: 0.5 mg *

Arm 3: 1.0 mg *

Arm 4: 1.5 mg QD

Arm 5: 2.5 mg QD * **

Arm 6: 2.5mg titrated QD **

* Following an interim analysis, a 2.5mg arm was added and recruitment to the 0.5mg & 1.0 mg arms was stopped

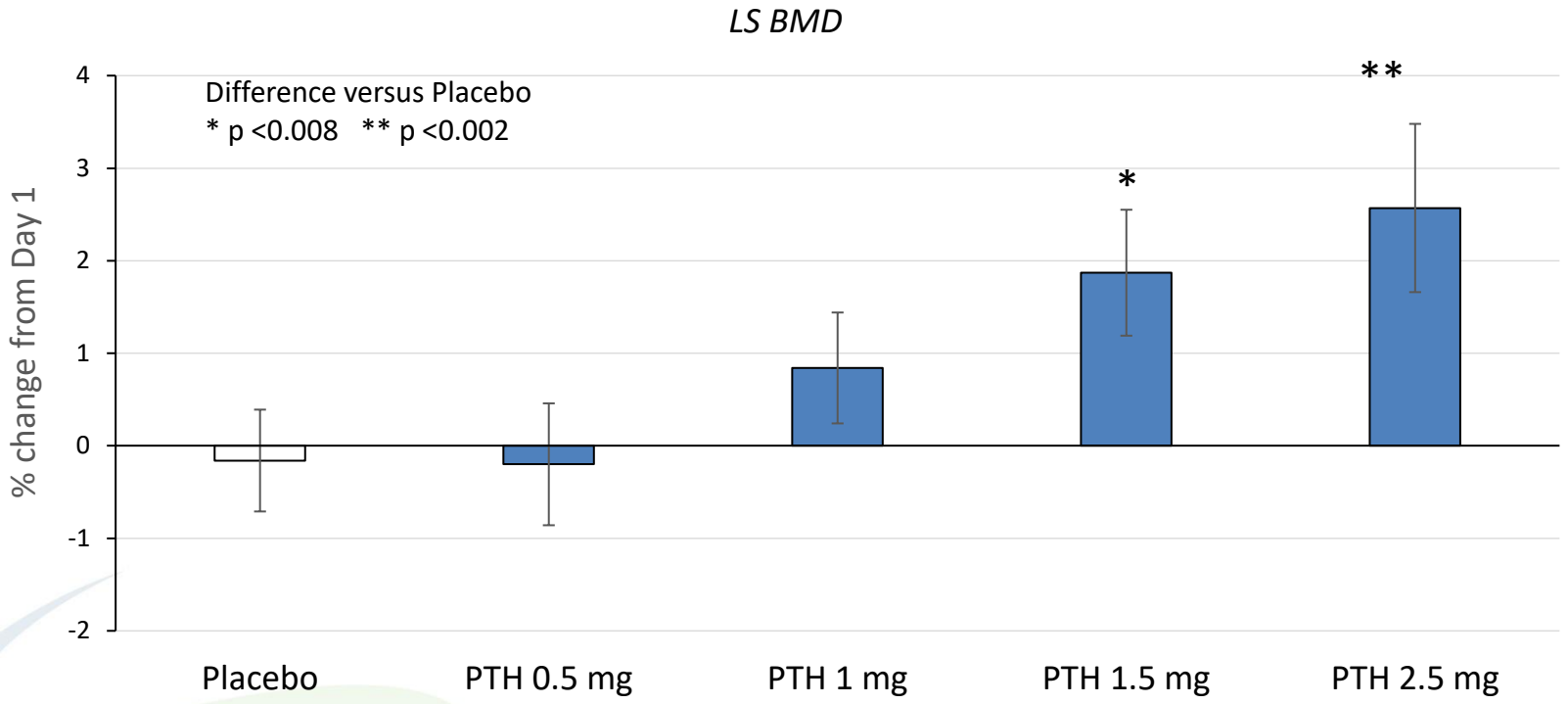
** Following AEs typical of orthostasis additional subjects in the 2.5mg group received 1.5mg for 1 month, 2.0mg for the next month and 2.5mg during months 3 to 6 (Titrated).

Demographics & Baseline T-Scores

		Placebo (N=43)	EBP05 0.5 mg QD (N=25)	EBP05 1.0 mg QD (N=29)	EBP05 1.5 mg QD (N=28)	EBP05 2.5 mg QD (N=19)	EBP05 2.5 mg titrated QD (N=17)
Age (years)	Mean (SD)	59.9 (5.1)	61.2 (6.0)	62.4 (4.7)	61.4 (6.5)	62.4 (4.1)	61.9 (5.3)
Weight (kg)	Mean (SD)	65.6 (13.0)	68.7 (10.9)	65.9 (13.7)	65.2 (12.0)	70.0 (10.6)	65.1 (10.2)
BMI (kg/m2)	Mean (SD)	25.0 (5.2)	27.0 (4.0)	25.9 (4.7)	25.3 (4.9)	27.7 (3.6)	26.0 (4.6)
T-Score (Spine)	Mean (SD)	**-2.37 (0.65)**	**-2.45 (0.8)**	**-2.35 (0.71)**	**-2.32 (0.88)**	**-2.21 (0.74)**	
T-Score (T. Hip)	Mean (SD)	-2.17 (0.54)	-2.16 (0.55)	-2.1 (0.62)	-2.02 (0.46)	-2.27 (0.48)	
T-Score (F. Neck)	Mean (SD)	-1.94 (0.61)	-1.94 (0.57)	-1.72 (0.61)	-1.77 (0.52)	-1.86 (0.68)	

6 Months BMD Results

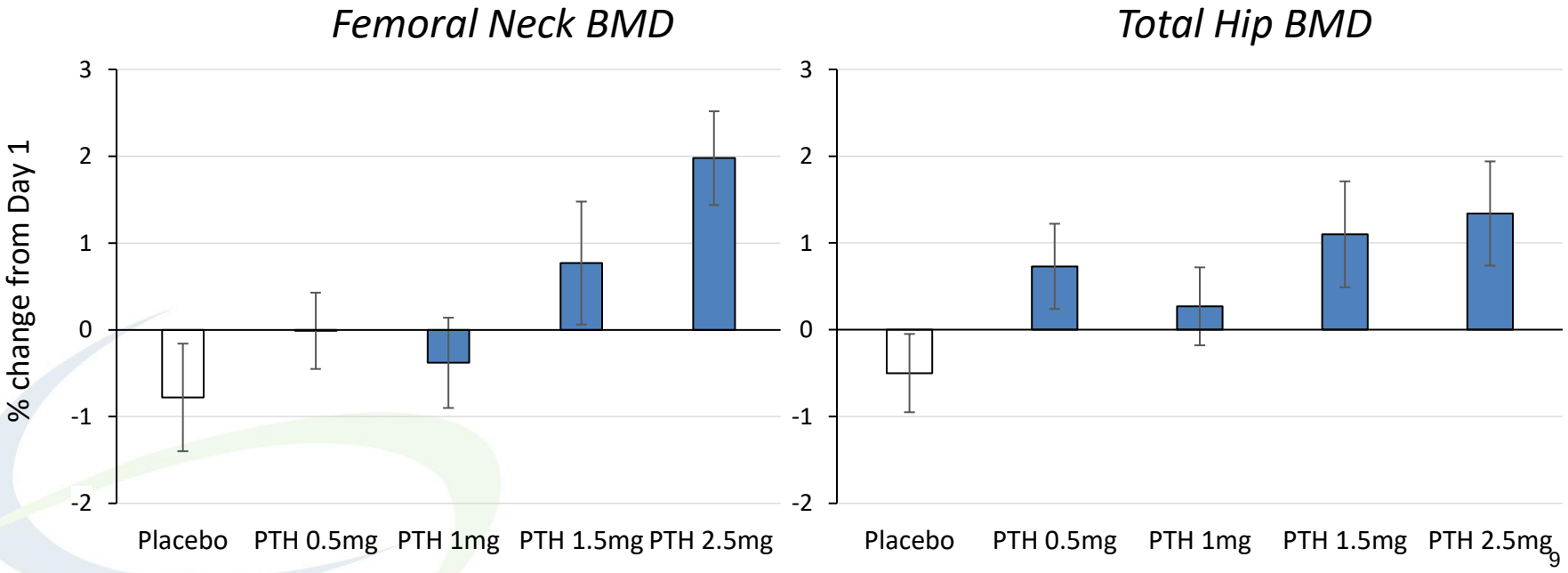
- Oral PTH produced a statistically significant **dose response** in lumbar spine BMD (p<0.0001)



6 Months BMD Results

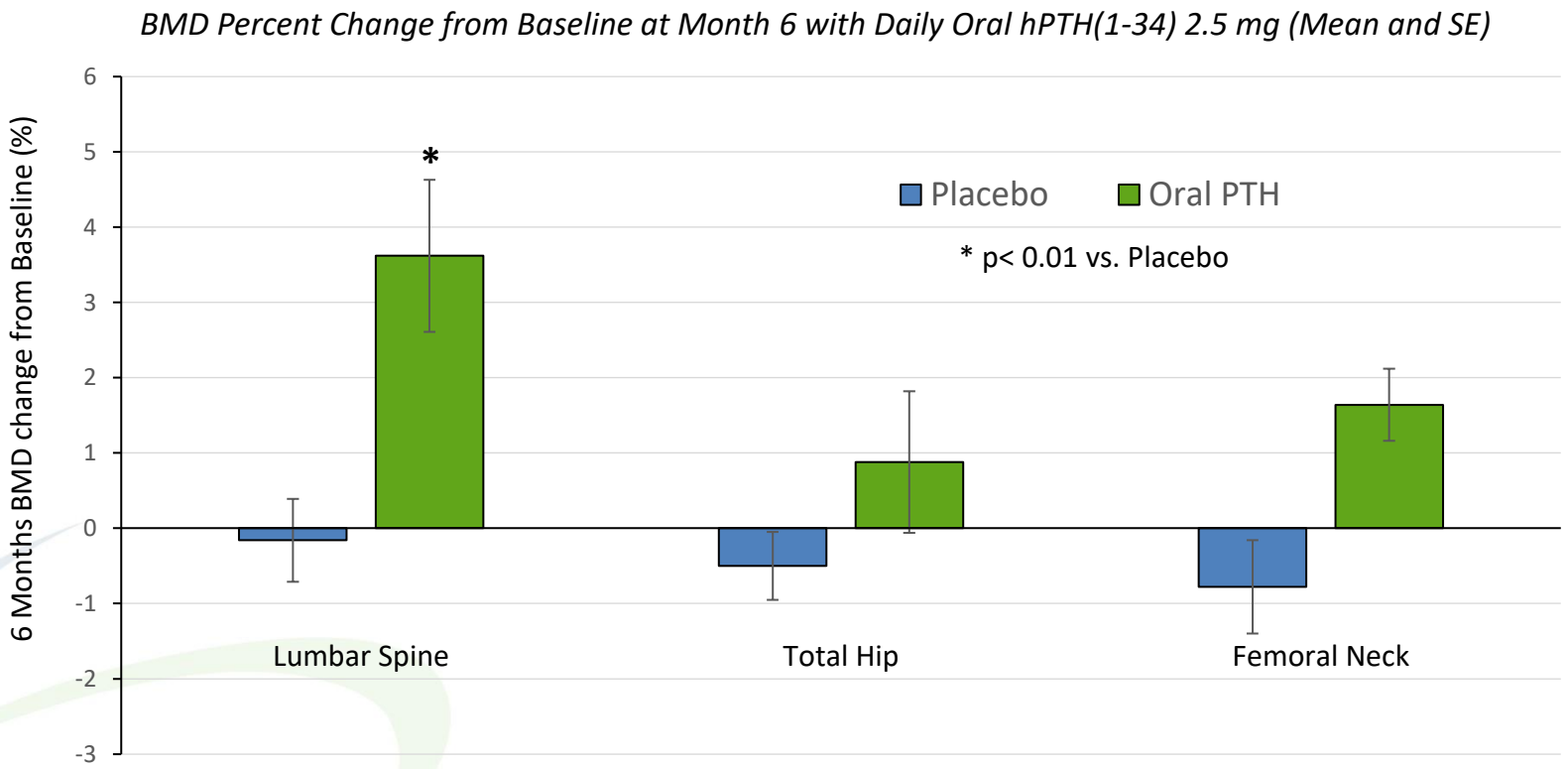
- Oral PTH produced a statistically significant **dose response** in femoral neck (**FN**) ($p<0.002$) and total hip (**TH**)($p<0.008$) BMD

- Oral PTH 2.5 mg produced a placebo-adjusted 2.76% increase in **FN** ($p<0.002$), and a 1.84% increase in **TH** BMD ($p<0.02$) at 6 months

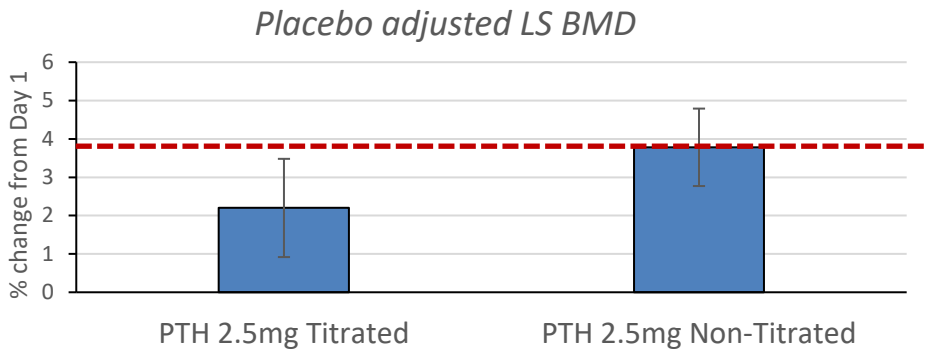


6 Months BMD Results

- There were placebo adjusted increases in BMD at the lumbar spine (**3.78%**), total hip (1.38%), and femoral neck (2.42%) at 6 months, in subjects **treated for 6 months** with 2.5 mg PTH.

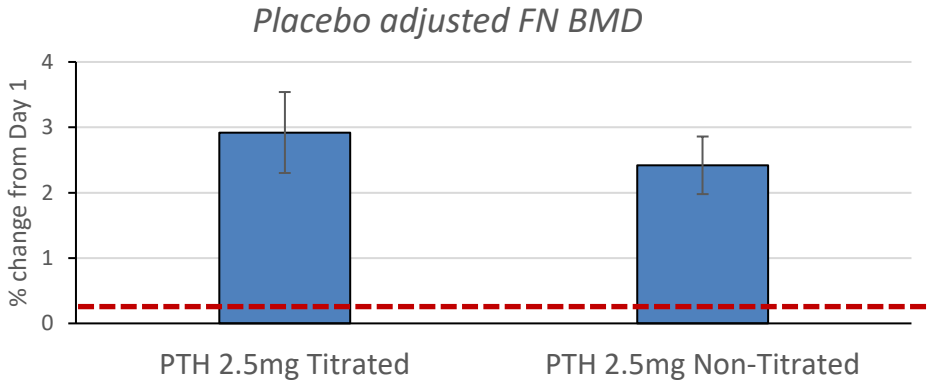


6 Months BMD - 2.5 Titrated vs Non-Titrated

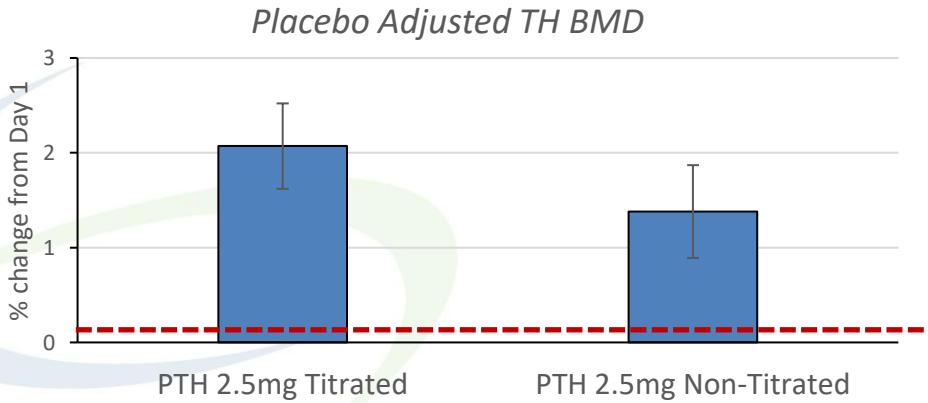


Historical data (Leder BZ et.al. JCEM 2015)

1.6% Placebo vs 5.5% Teriparatide
Difference = 3.9%



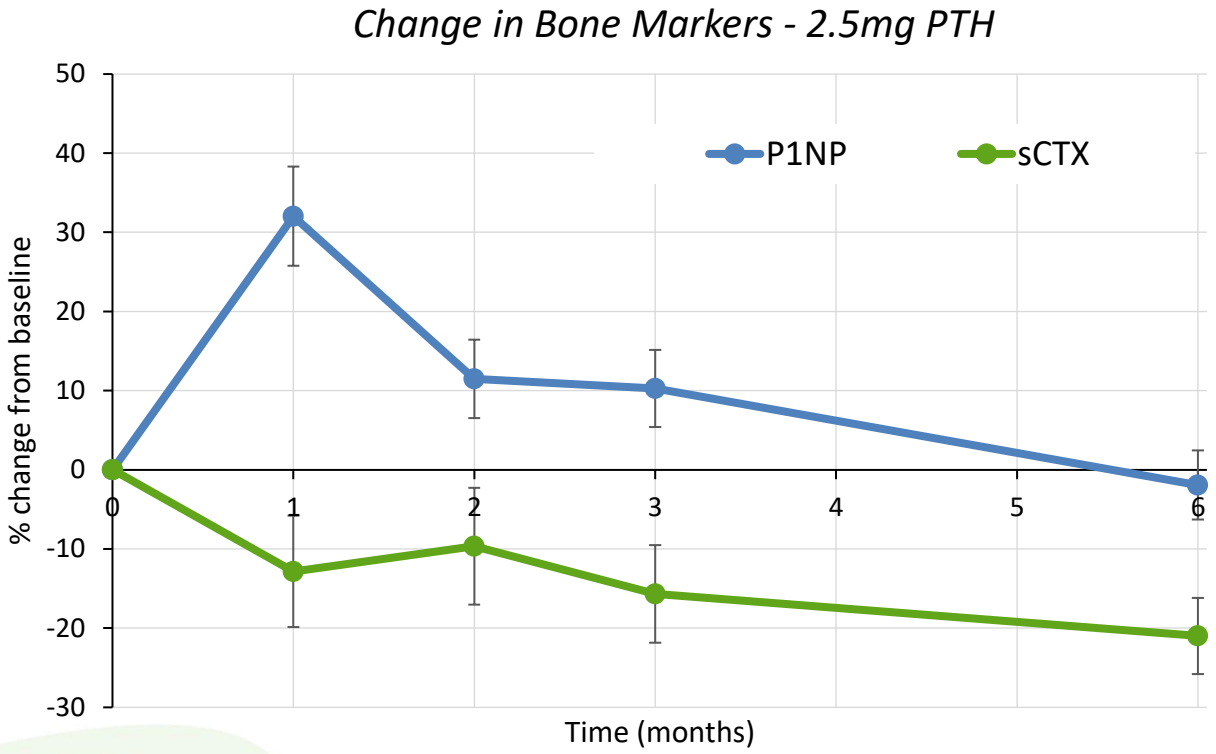
0.8% Placebo vs 1.1% Teriparatide
Difference = 0.3%



0.4% Placebo vs 0.5% Teriparatide
Difference = 0.1%

6 Months Bone Markers Results

- In the 2.5 mg PTH group, Serum CTX decreased 21% from baseline at **6 months** (p <0.01) while P1NP was unchanged



* *Biomarker data for Months 1-3 previously presented as a poster – ASBMR 2021 Preliminary Poster FRI-237*

Safety Results

- The safety profile of oral PTH was consistent with the known profile of subcutaneous PTH
- AEs commonly attributed to vasodilatation with subcutaneous PTH were observed - headache, nausea, presyncope and dizziness*.
- There were no serious drug-related AEs
- Mean serum calcium and changes exceeding PDLC were not increased and there were no treatment-emergent Hypercalcemia AEs

Subject disposition	*Placebo (N=43)*		*EBP05 0.5 mg orally QD (N=25)*		*EBP05 1 mg orally QD (N=29)*		*EBP05 1.5 mg orally QD (N=28)*		*EBP05 2.5 mg orally QD (N=19)*		*EBP05 2.5 mg titrated orally QD (N=17)*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Randomized	43	100	25	100	29	100	28	100	19	100	**17**	**100**
Discontinued Before Month 3	3	7	3	12	2	6.9	4	14.3	7	36.8	**1**	**5.9**
Discontinued from Study Before Month 6	5	11.6	3	12	3	10.3	6	21.4	9	47.4	**1**	**5.9**

Conclusions

In this study of postmenopausal women with osteoporosis or low BMD, Six months of treatment with oral PTH 2.5 mg:

- Increased lumbar spine, femoral neck and total hip BMD compared to placebo, and compared to start of treatment
- The increase in spine BMD was similar in magnitude to that previously reported with Forteo®
- Increases in total hip and femoral neck were greater than those previously reported with Forteo®
- Reduced serum CTX compared to placebo
- Adverse event profile similar to that observed with Forteo®, and typical of orthostatic hypotension
- Was not associated with serum calcium increases or Hypercalcemia Adverse Events
- Greater than 90% of subjects tolerated the 2.5 mg dose well, after titration starting with the 1.5, and progressing through 2.0 mg doses

Plans for Future Studies of Oral PTH

- Based on the results of this phase 2 dose ranging study Entera is preparing for a 1-year phase 3, head-to-head comparison study of Oral PTH versus Forteo® in 2022
- The six-month increases in BMD with the 2.5 mg dose position EBP05, Entera's oral hPTH(1-34), as potentially the first oral anabolic treatment

Thank you very much!