A Six-month Phase 2 Study of Oral PTH in Postmenopausal Women with Low Bone Mass – An Interim Three-Month Analysis

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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 has been shown to reduce the risk of vertebral fractures by 65 to 80%. Injections deter many older osteoporotic patients from either starting or continuing the drug, contributing to the treatment gap in high-risk patients. An oral formulation of hPTH(1-34) (PTH) with adequate bioavailability, and similar safety and effects on BMD may address this unmet clinical need.

STUDY DESIGN

Phase 2, 6-month, dose-ranging, placebo-controlled study to evaluate oral hPTH(1-34) formulation (EBP05) 0.5, 1.0, 1.5, or 2.5 mg daily doses was conducted in 161 postmenopausal women with low bone mineral density (BMD) or osteoporosis. The study was conducted at 4 sites in Israel. All subjects were white, mean (SD) age 61.3 (5.4) yr, weight 66.6 (12) kg, height 160.3 (5.8) cm.

The total dose of oral hPTH(1-34) was administered as 1 to 5 EBP05 0.5 mg tablets (Entera Bio Ltd.) daily.

The initial treatment regimen included a top dose of 1.5 mg. (**Table 1**) A planned limited analysis of the first 80 subjects indicated that a dose higher than 1.5 mg should produce greater effects on bone formation. A 2.5 mg dose was added and enrollment of subjects in the 0.5 and 1.0 mg groups was ended. After adverse events typical of orthostasis were observed in subjects starting 2.5 mg (Constant), additional subjects in the 2.5 mg group received 1.5 mg for 1 month, 2.0 mg for the next month and 2.5 mg during months 3 to 6 (Titrated).

Table 1. *Summary of treatment regimen and subjects (N) in each group*

Treatment	N
Placebo Once Daily	43
Oral hPTH(1-34) 0.5 mg Once Daily	25
Oral hPTH(1-34) 1.0 mg Once Daily	29
Oral hPTH(1-34) 1.5 mg Once Daily	28
Oral hPTH(1-34) 2.5 mg Once Daily – Constant	19
Oral hPTH(1-34) 2.5 mg Once Daily – Titrated	17

ENDPOINTS

Bone Formation
P1NP - N-terminal propeptide of Type 1 collagen and Osteocalcin

Bone Resorption
CTX - Serum C-telopeptides of Type 1 collagen (CTX)

Safety
Adverse Events (AE), Clinical and Laboratory Exams

The primary endpoint was change in P1NP at Month 3. Secondary endpoints included change in P1NP and Months 1 and 2, and osteocalcin and serum CTX at Months 1, 2, and 3.

RESULTS

A significant increase in P1NP at Month 3 was observed in the oral PTH 2.5 mg treatment group [10 ± 5% (mean, SE)] vs. placebo (2 ±4%) (p<0.04) (**Figure 1**). Increases in P1NP from baseline at Months 1 [32 ± 7%] and 2 [12 ± 5%] were also greater vs. placebo (p<0.0001 and p<0.003). At Month 1 the increase in P1NP was dose-related (**Table 2**).

A significant increase in osteocalcin at Month 3 was observed in the oral PTH 2.5 mg treatment group [15 ± 4% (mean, SE)] vs. placebo (1 ± 3%) (p<0.006). Increases in osteocalcin from baseline at Months 1 [29 ± 8%] and 2 [20 ± 4%] were also greater vs. Placebo (p<0.0001).

A significant decrease in serum CTX at Month 3 was observed in the oral PTH 2.5 mg treatment group [-16± 6% (mean, SE)] vs. placebo (10± 7%) (p<0.015). Decreases in serum CTX from baseline at Months 1 [-13 ±7%] and 2 [-10 ±7%] were also greater vs. placebo (p<0.0007 and p<0.07). The decrease in CTX was sustained through Month 3

Figure 1. *Percent change from baseline (mean and SE). P1NP, Osteocalcin and Serum CTX * P < 0.05 vs. Placebo; ** P < 0.01*

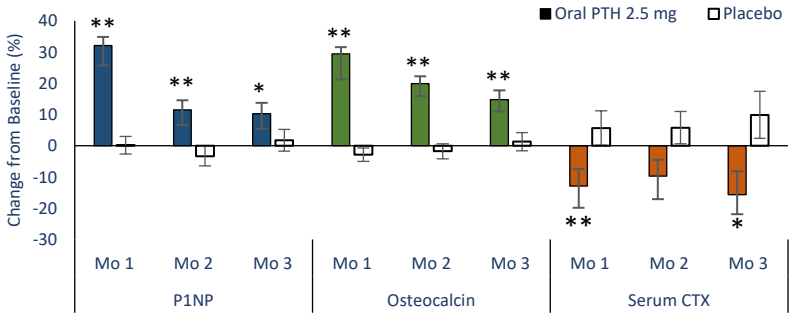
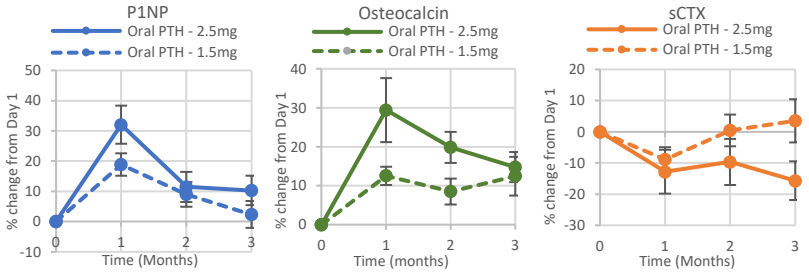


Table 2. *P1NP Percent change from baseline at Month 1*

Treatment	N	Mean	SE	P-value by Paired T-Test
Placebo	40	0.19	2.80	0.95
Oral hPTH(1-34) 0.5 mg QD	21	2.73	4.17	0.52
Oral hPTH(1-34) 1.0 mg QD	24	11.49	3.13	< 0.01
Oral hPTH(1-34) 1.5 mg QD	36	18.86	3.73	< 0.01
Oral hPTH(1-34) 2.5 mg QD	10	32.04	6.28	< 0.01

Regression of Month 1 P1NP relative change by dose showed a statistically significant dose response (P < 0.0001)

Figure 2. *Change in Bone Markers with a Dosage of 2.5 mg in Comparison to Change in Bone Markers with a dosage of 1.5 mg.*



ADVERSE EVENTS

The primary safety analysis of this study was planned for adverse event and laboratory safety data for the full 6-month period of treatment. The interim safety analysis of 3-month data was limited to evaluation of aggregate adverse event (AE) data blinded to treatment. Drug-related AEs (Investigator's rating of causality) were reviewed without unblinding. There were no drug-related Serious AEs. All AEs were mild or moderate in intensity. The most common drug-related AEs associated with discontinuation of study medication were headache, nausea, dizziness and presyncope. One subject in the oral hPTH(1-34) 2.5 mg titrated group did not tolerate 2.5 mg, and continued in the study with 1.5 mg.

DISCUSSION

The increases in P1NP and osteocalcin observed following treatment with the oral hPTH(1-34) formulation indicate an osteoanabolic response. The increase was greatest at Month 1 and gradually decreased in Months 2 and 3. While subcutaneous hPTH(1-34) increases bone remodeling, resulting in an increase in bone resorption, oral hPTH(1-34) 2.5 mg resulted in a decrease in bone resorption; At Month 3 serum CTX was about 25% lower than with placebo (**Figure 1**). This suggests that the anabolic effect on BMD might be greater than that estimated by the P1NP and osteocalcin response alone. The effect of oral hPTH(1-34) on P1NP is proportional to dose (**Table 2**). The adverse effect profile of oral hPTH(1-34) formulation was consistent with the known orthostatic effect of subcutaneously injected hPTH(1-34). Starting treatment at 1.5 mg with titration to 2.5 resulted in greater than 90% of subjects tolerating the full 2.5 mg dose.

Abstract Number: LB - 1116: A Six-month Phase 2 Study of Oral PTH in Postmenopausal Women with Low Bone Mass – 6 Month Bone Mineral Density (BMD) results will be presented **Monday, October 4** as an Oral Presentation in the Late-Breaking: Clinical Treatment Session **11:30 am - 12:45 pm PT**. Changes in BMD, Biochemical Markers and final Safety Data will be included.