A Six-month Phase 2 Study of Oral PTH (EBP05/EB613) in Postmenopausal Women with Low Bone Mass – Dose Proportional Absorption and Effect on Lumbar Spine BMD

Liana Tripto-Shkolnik[1], Auryan Szalat[2], Gloria Tsvetov[3], Vanessa Rouach[4], Chana Sternberg[5], Phillip Schwartz[6], Anke Hoppe[6], Gregory Burshtein[6], Hillel Galitzer[6], Arthur Santora[6]

[1] Chaim Sheba Medical Center, Israel, [2] Hadassah Medical Center, Israel, [3] Rabin Medical Center, Israel, [4] Tel Aviv Sourasky Medical Center, Israel, [5] Chana Sternberg Consultancy Ltd., Israel, [6] Entera Bio Ltd., Israel

BACKGROUND

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. Entera Bio is developing oral hPTH(1-34) formulation (EBP05 / EB613) as the first potential osteoanabolic agent to treat osteoporosis.

STUDY DESIGN

The presented results are from a 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 conducted in 161 postmenopausal women with low bone mineral density (BMD) or osteoporosis. The study was conducted at 4 different sites in Israel. All subjects were white, mean (SD) age 61.3 (5.4) years old, 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.) once daily in the morning following an overnight fasting period. After adverse events typical of orthostasis were observed in some subjects on the 2.5 mg dose (Constant), a titration period was added for patients subsequently recruited, starting with 1.5 mg for month 1, 2.0 mg for month 2 and 2.5 mg during months 3 to 6 (Titrated).

BMD was measured with a Dual-energy X-ray absorptiometry at the start of study on Day 1 and at the end of study. Serum P1NP levels were evaluated at Day 1 (D1), end of Month 1 (M1), Month 3 (M3) and Month 6 (M6) with a validated chemiluminescence based method. Plasma levels of hPTH(1-34) at the single time point of 15 minutes post-dose were measured on D1, M1, M3 and M6 of the study using a validated High Performance Liquid Chromatography Tandem Mass Spectrometry method.

Table 1. *Summary of treatment regimens and subjects (N) in each arm completing the study on Study Medication per protocol (PP)*

Treatment	N
Placebo Once Daily	38
EBP05 Oral hPTH(1-34) 0.5 mg Once Daily	22
EBP05 Oral hPTH(1-34) 1.0 mg Once Daily	26
EBP05 Oral hPTH(1-34) 1.5 mg Once Daily	21
EBP05 Oral hPTH(1-34) 2.5 mg Once Daily – Constant	7
EBP05 Oral hPTH(1-34) 2.5 mg Once Daily – Titrated	14

ENDPOINTS and OBJECTIVES

The primary endpoint of change in P1NP at 3 months, and secondary endpoints of change in lumbar spine (LS), total hip and femoral neck BMD were met, as previously reported (ASBMR 2021 poster FRI-237). Pharmacokinetic analysis of plasma levels of hPTH(1-34) was defined as a secondary endpoint. We are now presenting the results of additional analysis performed to evaluate the relationship between the dose of EBP05 and the following parameters: hPTH(1-34) plasma concentrations at 15 minutes post-dose, change in LS BMD following 6 months of treatment, and change in serum P1NP levels following 1 month of treatment.

RESULTS

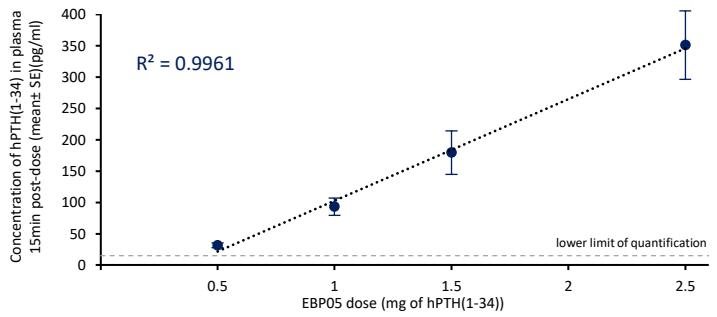

Figure 1. Correlation between EBP05 dose and plasma concentration of hPTH(1-34) at 15min time point. The mean of all pharmacokinetic samples per EBP05 dose administered on PK testing days was calculated. All available pharmacokinetic data (including the data of the patients that were excluded from PD analysis and of the patients that have an incomplete set of PK data) was used for the correlation analysis (n= 91 for EBP05 0.5 mg, n=104 for EBP05 1mg, n=96 for EBP05 1.5 mg, n=65 for EBP05 2.5 mg). The LOQ was 15 pg/ml and results that were below LOQ were set to 15 pg/ml for the correlation analysis. The correlation is statistically significant (p<0.005).

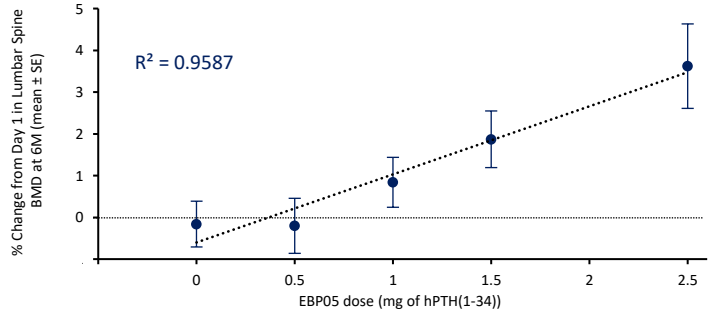

Figure 2. *Correlation between the dose and % change from day 1 in LS BMD following 6-month treatment with EBP05. Only patients who were administered a constant 2.5 mg dose for the entire duration of the study (6 months) were included in the 2.5 mg group. The correlation is statistically significant (p<0.005).*

RESULTS

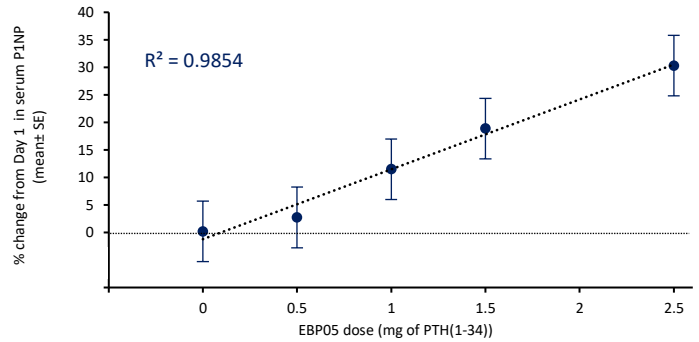

Figure 3. *Correlation between the dose and % change from baseline in serum P1NP levels following 1 month of treatment with EBP05. Only patients who were administered a constant 2.5 mg dose for the entire duration of the study (6 months) were included in the 2.5 mg group. The correlation is statistically significant (p<0.0001).*

Additional analysis of the results from a phase 2, 6-month, dose-ranging study with an oral hPTH(1-34) formulation in postmenopausal women with osteoporosis showed an excellent correlation (R^2 = 0.996) between the EBP05 dose and mean plasma levels of hPTH(1-34) found 15 minutes post dose. A strong correlation (R^2 =0.959) was also shown between the oral hPTH(1-34) dose and the mean change in lumbar spine BMD following 6 months of treatment. A similar correlation (R^2 = 0.985) was found between the EBP05 dose and the mean change in serum P1NP following 1 month of treatment.

DISCUSSION

Earlier pharmacokinetic studies with EBP05 showed that the median Tmax of the oral PTH formulation is 15 minutes post dose, with little variation between subjects[1]. Therefore, the single PK timepoint evaluated in this study provides a good estimate of maximal plasma levels (Cmax) of hPTH(1-34) in patients. Additional analysis of study results showed that the oral formulation of hPTH(1-34) has a dose proportional effect (R^2 = 0.959) on Lumbar Spine BMD in postmenopausal women with osteoporosis or low BMD following 6 months of treatment. At the 1-month time point, where the maximal increase in P1NP was observed, an excellent correlation (R^2 = 0.985) was shown between EBP05 dose and mean change in serum P1NP. A strong correlation (R^2 = 0.996) was also found between the dose of EBP05 and mean hPTH(1-34) plasma levels 15 minutes following drug administration.

In conclusion, dose proportional PK and PD effects observed in the current study are critical pharmacologic characteristics which further support the potential of Entera Bio's oral hPTH(1-34) to be the first oral anabolic drug for osteoporosis and a convenient alternative to the injectable formulation of hPTH(1-34).

1. Burshtein et al. *An oral PTH(1-34) formulation with a pharmacokinetic profile optimized for the treatment of osteoporosis* ASBMR 2018

 Hadassah Ein-Kerem, Jerusalem Bio Park, POB 12117 Jerusalem 9112002 Israel