First Oral hPTH(1-34) Tablet Treatment for Osteoporosis Demonstrates Rapid Pharmacodynamic Effect on Plasma Levels of Endogenous PTH(1-84)

Arthur C Santora[1], Gregory Burshtein[1], Constantin Itin[1], Hillel Galitzer[1], Anke Hoppe[1], Chana Sternberg[2], Miranda Toledano[1], Yoseph Caraco[3]

[1] Entera Bio Ltd., Israel, [2] CSC Ltd., Israel, [3] Hadassah Clinical Research Center, Jerusalem, Israel

BACKGROUND

Entera Bio is developing EB613 [hPTH(1-34) tablets of EBP05 formulation] as the first oral anabolic therapy for the treatment of osteoporosis. In a 6-month, 161-patient, placebo-controlled Phase 2 study, EB613 produced rapid dose-proportional changes in biochemical markers and increased Bone Mineral Density (BMD) in postmenopausal women with low BMD or osteoporosis. A Phase 1 study (ENT-11-2023) comparing EB613, subcutaneous (SC) injection hPTH(1-34) 20 μg (Forteo®) and a new generation of Entera's oral peptide delivery platform is ongoing.

One of the objectives of this study is to rapidly evaluate the pharmacodynamic (PD) effects of Entera's oral hPTH(1-34) tablets. Having a simple and rapid assessment of the pharmacologic effects of PTH treatment may be an important tool for chronic treatment and titration of osteoporosis patients, especially when analysis of hPTH(1-34) is not readily available in a clinical set-up. An increase in plasma ionized calcium should result in decreased secretion and plasma concentrations of endogenous PTH(1-84). **Thus, a reduction in plasma PTH(1-84) should provide an early PD marker indicating systemic exposure and pharmacologic activity with Entera's oral hPTH(1-34) tablets.**

METHODS

The Phase 1 open-label, exploratory, study evaluating PK, PD and safety in young adult healthy male volunteers is being conducted at Hadassah Clinical Research Center, Jerusalem, Israel. In the 1st phase of the study, 0.5 mg hPTH(1-34) EB613 tablets at doses of 1.5 mg and 2.5 mg (3 and 5 tablets respectively), and SC injection Forteo were administered in a randomized order to 15 subjects (mean age 22 years, range 19-24) in the morning following 8 hours of fasting. Oral tablets were administered with a glass of water. Endogenous PTH(1-84) was measured with an intact PTH immunoassay [Elecsys PTH(1-84), Cobas® e 601, Roche Diagnostics GmbH] as an early PD marker of the pharmacologic effect of the treatments. Phosphorus, calcium, albumin, and 1,25-dihydroxyvitamin D [1,25(OH)2D] were measured as well. The latter measured by IDS-iSYS 1,25 VitD^{Xp} assay (Immunodiagnostic Systems Ltd, UK).

RESULTS

Mean plasma PTH(1-84) levels following a single administration of both oral EB613 doses and Forteo rapidly and significantly decreased [Fig 1, mean (SD) % of plasma concentration at 120 min to baseline: 59.2 (14.5), 54.3 (13.6), and 52.3 (10.2) for 1.5 mg, and 2.5 mg EB613, and 20ug Forteo, respectively]. Individual profiles are presented in Fig 2, showing the effect for all subjects. EB613 showed comparable maximal decreases in levels of PTH(1-84) to Forteo. Decrease was rapid and prolonged, as shown by significant difference ($p<0.01$) compared to baseline levels.

Additional PD parameters (Fig 3) showed a significant, although less pronounced, responses following EB613 and Forteo administration. Phosphorus reduced rapidly but also returned fast to baseline levels. 1,25(OH)2D increased markedly, however statistical significance was achieved only at the 6 hours time-point tested. Calcium (albumin corrected) plasma levels change from baseline was hard to detect, due to low sensitivity and robustness of the test.

RESULTS

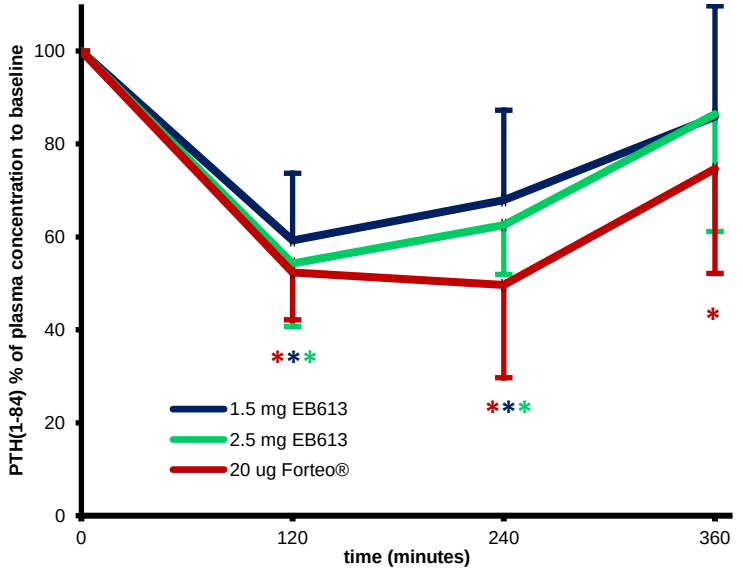

Figure 1. *PTH(1-84) % of plasma concentration to baseline. Mean (SD). N=15 healthy male volunteers. Asterisk signifies statistical difference compared to baseline, p<0.01, ANOVA with Tukey post-hoc.*

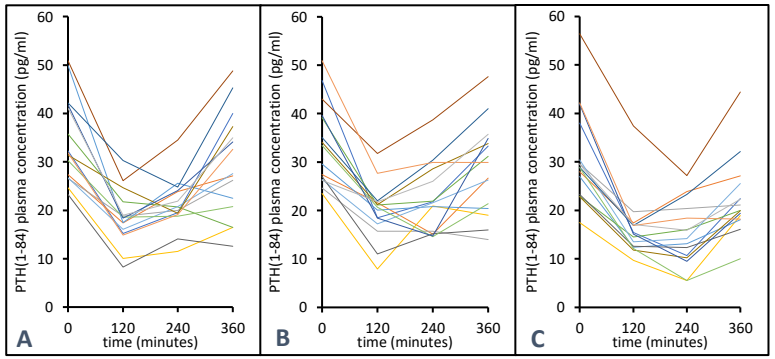

Figure 2. *PTH(1-84) plasma concentrations. Individual profiles following administration of A: EB613 2.5 mg oral tablets, B: EB613 1.5 mg oral tablets, C: Forteo SC injection.*

RESULTS

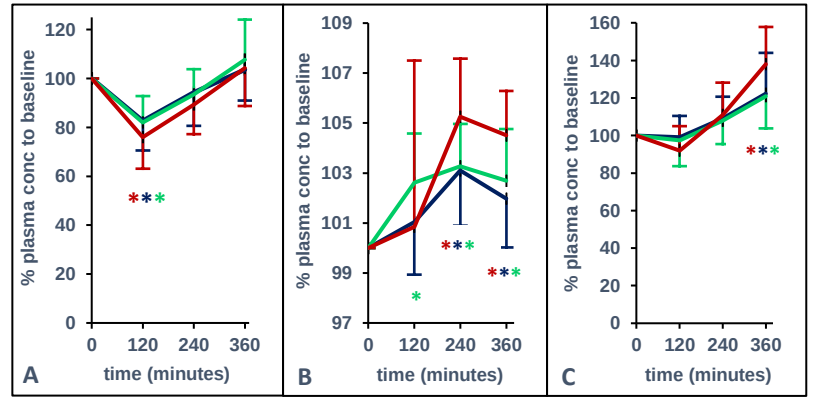

Figure 3. *% of plasma concentration to baseline for A: Phosphorus, B: Calcium (albumin corrected), C: 1,25-dihydroxyvitamin D. Mean (SD) blue: 1.5 mg EB613, green: 2.5 mg EB613, red: 20 ug Forteo SC injection. N=15 healthy male volunteers. Asterisk signifies statistical difference compared to baseline, p<0.05, ANOVA with Tukey post-hoc.*

DISCUSSION

The ability to rapidly evaluate PD effects as early markers of therapeutic response is crucial to monitoring compliance and optimizing future management of patients. While response of conventional PD markers of bone metabolism may take several months, intact endogenous PTH(1-84) effect is rapid. Endogenous PTH(1-84) is also advantegeous over other potential early PD markers. Its effect is more rapid and robust as compared to small changes in plasma calcium and delayed changes in 1,25(OH)2D and is prolonged, as compared to short-lived changes of phosphorus levels. In addition, immunoassay of endogenous PTH(1-84) is readily available in clinical set-up as compared to expensive and not common 1,25(OH)2D test.

CONCLUSIONS

In this ongoing PK study, EB613 oral tablets (1.5 mg and 2.5 mg dose) rapidly decreased plasma concentrations of PTH(1-84) in all subjects and in a dose proportional manner.

The results indicate that decrease in plasma PTH(1-84) may serve as an early PD marker of systemic exposure, pharmacologic activity and therapeutic response to Entera's orally administered hPTH(1-34) tablets.

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