EB613 (Oral PTH(1-34) Tablet Treatment) – Does PK Drive Bone Modeling versus Bone Remodeling?

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BACKGROUND

While approved anabolic drugs have shown greater bone mineral density (BMD) increases, microarchitectural repair and fracture risk reduction compared with anti-resorptive therapies, these treatments are not widely used in part due to poor patient acceptance of subcutaneous injections. EB613 is being developed by Entera Bio Ltd. as a first-in-class oral daily tablet treatment of PTH(1-34), a bone anabolic peptide analog with a sequence identical to the 34 N-terminal amino acids of human parathyroid hormone. In a 6-month Phase 2 study (NCT04003467) in 161 postmenopausal women with low BMD or osteoporosis, EB613 showed dose-dependent increases in BMD at the lumbar spine, total hip, and femoral neck and a dual mechanism of increases in bone formation (P1NP) and decreases in bone resorption (CTx) (Tripto-Shkolnik L et al. JBMR 2024). Here, we report Phase 1 pharmacokinetic (PK) data of the two EB613 doses, which will be advanced to Phase 3, versus Forteo® with a discussion on bone turnover marker outcomes.

STUDY DESIGN

- In a randomized, cross-over Phase 1 study (NCT05965167), EB613 2.5 mg and 1.5 mg tablets as well as a SC injection of Forteo 0.02 mg were administered once-daily in the morning following an overnight fast. All subjects signed informed consent
- Oral tablets were administered with 100 ml water
- Plasma levels of PTH(1-34) were quantified by a validated LC-MS/MS method (LLOQ=15 pg/ml)
- This study was sponsored by Entera Bio Ltd (Jerusalem, Israel)

RESULTS

Participants included 15 healthy males, with mean (SD) age of 22 (1.2) years, weighing 72.5 (8.5) kg, and 173.7 (6.2) cm tall.

Treatment	C_{max} (pg/ml; mean, SE)	AUC_{last} (pg/ml*min; mean, SE)	T_{max} (min, median, range)	T_{last} (min, median, range)
EB613 1.5 mg	270 (109)	4590 (2200)	15 (10-20)	20 (10-90)
EB613 2.5 mg	488 (122)	7590 (2000)	15 (10-20)	30 (20-90)
Forteo 0.02 mg	89.3 (10.5)	4080 (466)	20 (5-45)	75 (30-120)

***Table 1**. Main PK parameters of PTH(1-34) following administration of 2.5 mg and 1.5 mg oral EB613 tablets, and Forteo SC injection (0.02 mg).*

RESULTS

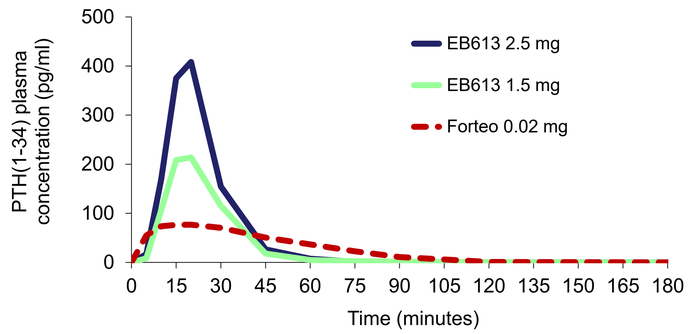

***Figure 1**. Mean plasma concentration of PTH(1-34) following administration of 2.5 mg and 1.5 mg oral EB613 tablets, and Forteo SC injection (0.02 mg).*

EB613:

- The PK profile of oral PTH(1-34) EB613 tablets 1.5 mg and 2.5 mg was characterized by a rapid increase in plasma PTH(1-34), achieving T_{max} within 20 minutes post dose (Figure 1)
- The elimination rate was rapid with $t_{1/2}$ of 11.1 and 8.8 minutes for the 1.5 and 2.5 mg doses, respectively
- The lower limit of quantification was reached within 60 minutes following drug administration for both doses

Forteo:

- The PK profile of SC Forteo was characterized by a rapid increase in plasma PTH(1-34) levels, similar to that observed after a single oral dose of EB613 tablets (Figure 1)
- The C_{max} was lower than after administration of oral tablets, and AUC_{last} was similar to that achieved with EB613 1.5 mg

The overall duration of exposure was substantially longer following SC administration compared with oral administration as assessed by T_{last} (75 minutes vs 20 and 30 minutes for EB613 1.5 and 2.5 mg, respectively, Figure 1)

Safety:

- The 1.5 mg and 2.5 mg oral EB613 doses were well tolerated, and there were no SAEs. All observed adverse events (mild or moderate palpitations, abdominal pain, nausea and dysgeusia) were previously reported for Forteo and EB613
- No safety differences were observed between both doses of EB613 and Forteo

CONCLUSION

- The PK profile of oral EB613 is characterized by a shorter systemic exposure versus both the once-daily and the once-weekly SC injections of teriparatide
- EB613 has previously been shown to have a consistent PK profile across healthy men and women of pre- and post-menopausal age with osteopenia, osteoporosis and hypoparathyroidism
- While C_{max} of maximal clinical EB613 dose (2.5 mg) is more similar to that reported for weekly PTH(1-34) (Figure 2), its AUC is much closer to that of daily Forteo injection
- In contrast to daily Forteo injection, daily EB613 and the weekly PTH(1-34) injection appear to have a dual anabolic and antiresorptive effect, maintaining bone formation while reducing bone resorption (Figure 3). A potentially ideal osteoanabolic treatment (Brown JP. JBMR 2024)
- EB613 will be further evaluated in a Phase 3 study as a potential new oral osteoanabolic treatment for women at high risk for fracture who continue to have important needs for treatment

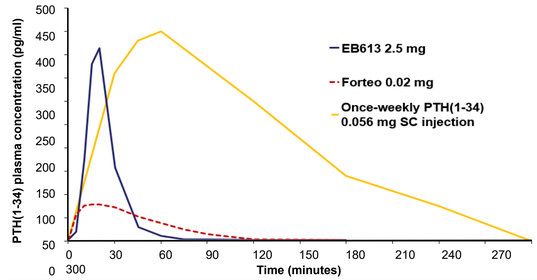

***Figure 2**. PK profile of once-weekly PTH(1-34) 0.056 mg SC injection (adapted from Kumagai Y et al. CPDD 2020) superimposed on the PK profiles of 2.5 mg EB613 and Forteo injection obtained in the recent Phase 1 study (NCT05965167).*

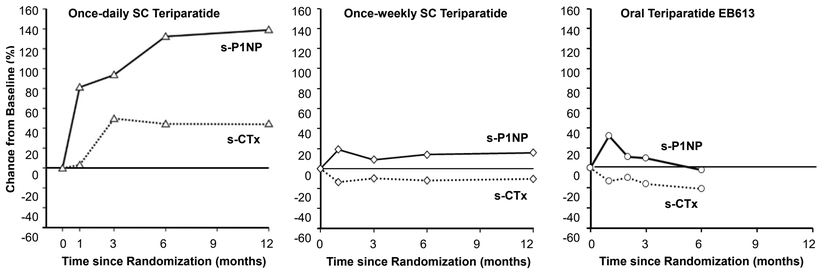

***Figure 3**. Data for bone turnover markers following once-daily SC teriparatide are adapted from Miller PD et al. JAMA 2016; data for once-weekly SC teriparatide injection are adapted from Tower and TWICE studies (Nakamura T et al. JCEM 2012 and Sugimoto T et al. Osteoporosis Int 2019). Oral Teriparatide data obtained from Phase 2 study (Tripto-Shkolnik L et al. JBMR 2024).*