First in Man Studies of Pharmacokinetic Profiles of a Novel Oral Parathyroid Hormone PTH (1-34) delivery system

Jonathan C.Y. Tang¹, Hillel Galițzer², Christopher J. Washbourne¹, Isabelle Piec¹, Naifang Wang², Gregory Burshtien², Phillip Schwartz², Joseph Caraco³, Ehud Arbi³ and William D. Fraser³

¹BioAnalytical Facility, Biomedical Research Centre, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, United Kingdom NR4 7TJ. ²Entera Bio Ltd, Hadassah Ein-Kerem, Jerusalem Bio Park, POB 12117, Jerusalem 91120, Israel. ³Hadassah Hospital Jerusalem, Israel.

Abstract

Showed a triple profile of effects of teriparatide, glucocorticoids and bisphosphonates on bone cells.

Introduction

- PTH(1-34) [Teriparatide] is an anabolic agent used in treatment of osteoporosis. It promotes bone formation and reduces the risk of vertebral and some non-vertebral fractures.
- The route of administration by daily subcutaneous (sc) injection can cause problems in certain patients. A new oral delivery system for human PTH(1-34) has been developed as a possible treatment option.
- Galițzer et al. first presented pre-clinical data (ASBMR 2012, MO0402) and first-in-human results (ASBMR 2013, FR0378) on safety, tolerability and absorption dynamics of oral PTH(1-34) in various dosages.

Aims and Objectives

- A single-center, double blinded, triple crossover study was designed to compare the 1.8 mg optimal dose of oral PTH(1-34) against standard dosage of teriparatide injection and oral placebo.
- The study was conducted following and in accordance with the Hadassah Medical Center ethical approval committee.
- 12 healthy volunteers (6m/6f), 18-50y, received three treatments: single subcutaneous injection of 20µg FORTEO®, 1.8 mg oral PTH(1-34), or placebo.
- Blood samples were collected at time 0, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300 minute post dose.
- Plasma concentration of PTH(1-34) (IDS, Tyne and Wear, UK) and cyclic adenosine 3',5' monophosphate (cAMP) were measured on all samples.

Methods

- The study was conducted following and in accordance with the Hadassah Medical Center ethical approval committee.
- 12 healthy volunteers (6m/6f), 18-50y, received three treatments: single subcutaneous injection of 20µg FORTEO®, 1.8 mg oral PTH(1-34), or placebo.
- Blood samples were collected at time 0, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300 minute post dose.
- Plasma concentration of PTH(1-34) (IDS, Tyne and Wear, UK) and cyclic adenosine 3',5' monophosphate (cAMP) were measured on all samples.

Sample analysis

Ab Sciex API 4000 LC-MS/MS system

IDS iSYS automated immunoassay

PTH(1-34)

- Linear 4-1000 pg/mL
- Intra-assay imprecision: mean 11.7 pg/mL SD ±0.82, CV 5.4%, 46.7 pg/mL SD ±2.52, CV= 5.4%.
- Inter-assay imprecision: mean 18.5 pg/mL SD ±0.78, CV 4.2%, 46.7 pg/mL SD ±3.2, CV= 7.0%.

Cyclic Adenosine 3',5' Monophosphoric acid (cAMP)

- Negative ion mode
- 13CS-cAMP as internal standard.
- cAMP m/z transition 328 > 134

Results

- All 12 subjects completed the study, no serious adverse events (SAE) were reported. Frequency of AEs were moderate.
- Serum adjusted calcium in all subjects remained within normal limits throughout the studies.
- All 12 subjects on oral PTH(1-34) showed rapid, post dose increase then decrease of PTH(1-34), from baseline mean (±SD) of 5.9 (1.8) pg/mL to peak mean of 185.3 (±128.8) pg/mL.
- PK profiles of oral PTH(1-34) showed Cmax (pg/mL), Tmax (mins), AUC₀₋₃₄ of 238.3 (110.8), 17.5 (5.4) and 6161.7 (2726.7), respectively; whereas sc group showed mean Cmax (pg/mL), Tmax (mins), AUC₀₋₃₄ of 172.3 (55.7), 20.8 (8.7) and 13965.9 (2984.8), respectively.
- A transient increase in plasma cAMP was observed in all subjects in response to PTH(1-34) treatment. Although the increase is less apparent in oral than sc both showed a similar PK profile and a significant difference in plasma concentration (p<0.05) compared to placebo group 20 minutes post treatment.
- Increase in cAMP is indicative of PTH bioactivity, suggesting that the administered peptide is pharmacologically active and not degraded during GI transport.

Conclusions

- PK profiles showed that a single oral dose of 1.8 mg PTH(1-34) is rapidly absorbed, and there is no significant difference in Cmax and Tmax when compared with 20µg of Forteo injection.
- A significant difference in the rate of plasma clearance and AUC₀₋₃₄ value was observed between oral and sc groups. These differing profiles and modality of administration of PTH(1-34) could offer unique advantages in the treatment of calcium and metabolic bone disorders.