An Evaluation of the Pharmacodynamic Effects of an Oral hPTH(1-34) formulation in Patients with Hypoparathyroidism

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BACKGROUND

Hypoparathyroidism is characterized by deficient PTH production, hypocalcemia and hyperphosphatemia. Standard treatments include oral calcium supplements and calcitriol (or analogs). Raising serum calcium to normal physiological levels frequently leads to elevated urinary calcium in the absence of PTH and is often associated with ectopic calcification, including nephrocalcinosis and renal failure. Subcutaneous hPTH(1–84) (Natpara®) once daily reduces supplementation requirements but provides adequate hormone blood levels for only part of the day. Entera Bio, utilizing its proprietary drug delivery platform, has developed an oral formulation of hPTH(1-34) which facilitates multiple daily dosing, thus more closely mimicking the pulsatile physiologic pattern of the hormone secretion throughout the day. Oral hPTH(1-34), when compared to a single daily subcutaneous hPTH(1-84) injection, can potentially result in both greater patient acceptance, as well as improved control of serum and urine calcium, both important to quality of life.

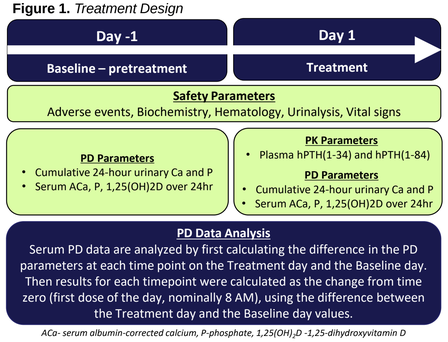
STUDY DESIGN

Table 1. *Summary of treatment regimen, dosing time and total patient number to receive each dose*

Treatment	Time of Dose			
	8:00	13:00	18:00	23:00
SC Natpara® 100 µg	7*	-	-	-
Oral hPTH(1-34) TID 0.75 mg	8	-	8	7*
Oral hPTH(1-34) BID 2.25 mg	8	-	8	-
Oral hPTH(1-34) TID 2.25 mg	8	-	8	8
Oral hPTH(1-34) QID 2.25 mg	8	8	8	7*

** Three patients did not receive one dose of study drug due to reasons unrelated to the study drug (hypercalcemia before the intended dose, technical problems with blood sampling)*

Figure 1. *Treatment Design*



ACa- serum albumin-corrected calcium, P-phosphate, 1,25(OH)$_2$D -1,25-dihydroxyvitamin D

A Phase 2, open-label, 2-period partial crossover study to evaluate the PK and PD profiles of two doses - 0.75 and 2.25 mg, and three regimens (BID, TID and QID) of Oral hPTH (1-34) and Natpara® [hPTH(1-84)] 100 µg SC injection QD (the maximum approved dose) was conducted at the Hadassah Clinical Research Center in Jerusalem, Israel in 16 patients with hypoparathyroidism. 12 patients were allocated to receive 2 treatments each and 4 patients were allocated to receive 4 treatments. The study design and parameters assessed for each treatment is displayed in Figure 1. All patients continued to receive their usual therapy (calcium supplements plus alfacalcidol or calcitriol). In addition, each patient received either SC hPTH(1-84) or Oral hPTH(1-34) as shown in Table 1.

Meals were administered 30 minutes post-drug administration, ensuring a minimum of 4-hour fast prior to each drug administration, and concomitant medications were not taken 1 hour before or 30 minutes after study drug administration. Meals and concomitant medications were administered at the same times on both study days.

RESULTS

Demographics

Table 2. *Subject Demographics on Enrollment. Values are for 16 patients at the time of enrollment in the study.*

Number of Patients	Age *Mean (range) - yr*	Male / Female	Serum ACa *Mean (range) - mg/dL*	Serum Phosphate *Mean (range) - mg P/dL*	Serum 1,25(OH)$_2$D *Mean (range) - ng/L*
16	**46** (18-63)	**4 / 12**	**7.9** (6.6-10.2)	**4.8** (3.6-6.5)	**33.7** (7.5-73.5)

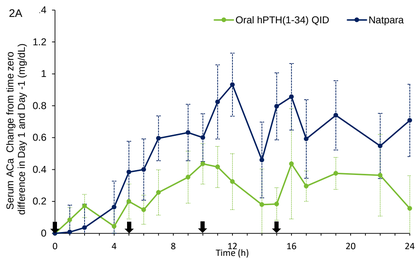
Pharmacokinetics

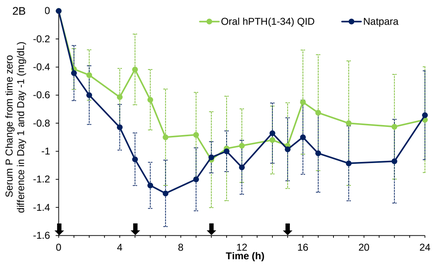
Total daily AUC$_{0\text{-}24hr}$ of hPTH(1-34) following Oral hPTH(1-34) 2.25 mg QID was 104±30 h*pmol/L and AUC$_{0\text{-}24hr}$ of hPTH(1-84) following a single dose of SC hPTH (1-84) injection (Natpara®) 100 µg was 147±57 h*pmol/L.

Serum Pharmacodynamic Endpoints

Oral hPTH(1-34) 2.25 mg QID increased serum ACa (Figure 2A) and serum 1,25(OH)$_2$D (Figure 2C) and decreased serum phosphate (Figure 2B). These PD effects persisted throughout the 24-hour observation period.

Figure 2A, 2B, and 2C. *Effect of Oral hPTH(1-34) 2.25 mg QID and SC Natpara® 100 µg QD on Change from time zero in the difference in Day 1 and Day -1 in ACa serum calcium (A), serum P (B) and 1,25-(OH)$_2$D (C) . Each data point represents the arithmetic mean ± SE of 4-7 patients (A and B) or 3-7 patients (C). Arrows represent dosing time or Oral hPTH(1-34) for QID dosing.*





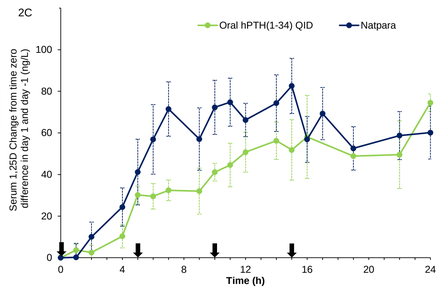


Table 3. *Summary of Oral hPTH(1-34) treatment effects on serum ACa, P and 1,25(OH)$_2$D levels. The ΔAUEC$_{0\text{-}24}$ was determined by first calculating the difference at each time point on the Treatment day and the Baseline day. The difference at each timepoint was then used to calculate the change from time 0 integrated over 24 hours. All data presented as mean ± SE.*

Treatment	N	Serum ACa ΔAUEC$_{0\text{-}24}$ (h*mmol/L)	Serum P ΔAUEC$_{0\text{-}24}$ (h*mg/dL)	Serum 1,25(OH)$_2$D ΔAUEC$_{0\text{-}24}$ (h*ng/L)
Natpara®	**7**	**3.2** ± 0.9	**-23** ± 4	**1290** ± 207
TID 0.75mg	**5**	**-0.3** ± 0.8	**4.2** ± 6	**116** ± 148
BID 2.25mg	**7**	**0.9** ± 0.7	**-11** ± 5	**393** ± 60
TID 2.25mg	**8**	**-0.1** ± 1.0	**-12** ± 2	**692** ± 112
QID 2.25mg	**4**	**1.9** ± 0.9	**-19** ± 7	**962** ± 134

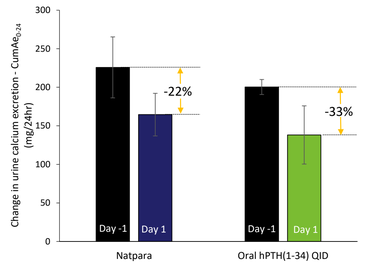
When expressed as a percentage of the mean integrated changes from time zero through hour 24 in the SC Natpara® 100 µg group, mean changes in the Oral hPTH (1-34) 2.25 mg QID group were 59%, 81% and 75% for serum ACa, P, and 1,25-(OH)$_2$D, respectively (Table 3).

RESULTS

Urine Pharmacodynamic Endpoints

Both Oral hPTH(1-34) QID treatment and SC Natpara® 100 µg QD treatment decreased the daily excretion of calcium in urine (Figure 3). In two patients who had baseline 24-hour calcium excretion above normal levels (>200 mg/dL in females,>250 mg/dL in males) treatment with Oral hPTH (1-34) QID lowered levels to within normal range. Oral hPTH(1-34) 2.25 mg administered BID and TID had no apparent effect on urine calcium.

Figure 3. *Effect of Oral hPTH(1-34) 2.25 mg QID (n=4) and subcutaneous Natpara® 100 µg QD (n=7) on 24-hour urine calcium excretion (CumAE$_{0\text{-}24}$) on pre-treatment (Day -1) and treatment (Day 1) day. Each column represents the average ± SE.*



Safety

There were no treatment-emergent Adverse Events of hypercalcemia reported. There were no treatment-emergent Serious Adverse Events.

CONCLUSIONS

- Oral hPTH(1-34) 2.25 mg QID for one day is associated with:
  - An increase in serum albumin-corrected calcium and 1,25(OH)$_2$D, decrease in serum phosphate, and decrease in urinary calcium in patients with hypoparathyroidism also receiving calcium supplements and either alfacalcidol or calcitriol.
  - All changes in these PD parameters are sustained over the 24-hour period of observation from time zero.
  - The magnitude of these changes are comparable to Natpara® 100 µg QD, the highest dose of hPTH(1-84) currently indicated for use in patients with hypoparathyroidism.
- BID, TID and QID regimens showed a dose-dependent increase in 1,25(OH)$_2$D indicating that the long-term treatment even with the less frequent regimens may be an effective treatment option.
- Treatment with Oral hPTH(1-34) dosed at multiple times during the day has the potential to reduce calciuria generally associated with maintenance of serum calcium within the normal range using calcium supplements and calcitriol analogs alone.
- Further clinical studies of longer treatment with Oral hPTH(1-34) are required to confirm its potential role in the treatment of hypoparathyroidism

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