Poster Number: P82

Long-Term Effects of Recombinant Human Parathyroid Hormone, rhPTH(1-84), on Bone Remodeling in Patients With Hypoparathyroidism: 3-Year Data From the Open-Label RACE Study

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BACKGROUND AND OBJECTIVE

- Hypoparathyroidism is a rare endocrine disorder caused by deficient or absent endogenous parathyroid hormone (PTH), a key regulator of calcium utilization and mineral homeostasis[1,2]
- Patients with hypoparathyroidism have reduced PTH-mediated bone remodeling, which can lead to increased bone mineral density (BMD) and abnormal bone microarchitecture[1]
- Management of hypoparathyroidism with oral calcium and activated vitamin D addresses attendant hypocalcemia, but this approach fails to correct the underlying PTH deficiency or to normalize skeletal metabolism[1,2]
- Recombinant human parathyroid hormone (rhPTH[1-84]) is structurally identical to full-length (84 amino acids) endogenous human PTH
- In the pivotal phase III placebo-controlled and the subsequent phase III dose-blind, fixed-dose studies (REPLACE and RELAY), rhPTH(1-84) restored mineral homeostasis and improved bone-remodeling characteristics in patients with hypoparathyroidism[3,4]
- The ongoing, long-term, open-label study (RACE) aims to assess safety, tolerability, and effects of flexible dosing of rhPTH(1-84) in adult patients with hypoparathyroidism
- This assessment reports the findings related to bone parameters from 38 patients who received 36 months of rhPTH(1-84) treatment in RACE

METHODS

- Patients in the United States who completed the double-blind randomized studies (REPLACE and/or RELAY) were eligible to participate in RACE
- Patients initiated open-label treatment with subcutaneous rhPTH(1-84) at 25 or 50 µg/day, with possible uptitration to 50, 75, or 100 µg/day if active vitamin D and oral calcium could be further reduced
  - Starting dose of rhPTH(1-84) was determined by baseline total serum calcium levels and oral calcium and vitamin D requirements
  - Baseline was defined as the start of treatment with rhPTH(1-84)
  - There was no pretreatment optimization period
- This interim analysis includes patients who received rhPTH(1-84) as of September 30, 2014. Analysis data sets for efficacy endpoints consisted of available data at the Month 36 study visit; no imputation or last-observation-carried-forward methods were applied

RESULTS

- 49 patients enrolled in the ongoing RACE study from 12 sites in the United States **(Table 1)**; 47 patients completed the 1-year period, and 43 patients are continuing treatment. This interim analysis included 38 patients who completed the Month 36 study visit.

Table 1. Demographics and Baseline Characteristics

Variable	N=49
Women, n (%)	40 (82)
Mean (SD) age, years	48.1 (9.8)
Mean (SD) duration of hypoparathyroidism, years	15.9 (12.5)
Prescribed calcitriol at baseline, n (%)	
Low dose (≤0.25 µg/day)	13 (27)
Medium dose (>0.25–0.50 µg/day)	16 (33)
High dose (>0.50 µg/day)	20 (41)
Prescribed oral calcium at baseline, n (%)	
0–2000 mg/day	31 (63)
>2000 mg/day	18 (37)

- Mean ± SD albumin-corrected serum calcium level was maintained between baseline (2.1±0.2 mmol/L; N=49) and Month 36 (2.1±0.2 mmol/L; n=36)
- Mean ± SD serum phosphate decreased from baseline (1.6±0.2 mmol/L; N=49) at all time points; at Month 36, mean serum phosphate was 1.4±0.2 mmol/L (n=36)

Changes in Bone Turnover Markers

- As shown in **Figure 1**, over the 36-month treatment period, mean serum bone turnover markers (BTMs) increased with rhPTH(1-84)

Figure 1. Mean Values for Serum BTMs*

*Month 36: n=37 (BSAP), n=36 (P1NP and CTX)
Mean ± SEM
Time points for Month 10 and 12 = data collected at Week 40 and 52

Changes in BMD

- Changes in BMD by dual-energy x-ray absorptiometry (DXA) are shown in **Table 2**
  - Baseline BMD was greater than normal for age, sex, and ethnicity at all scan locations (mean Z-scores, +0.9 to +2.1), with high BMD at the lumbar spine (mean Z-score, +2.1)
  - At Month 36, there were decreases toward normal in BMD Z-scores at hip and forearm sites but not at lumbar spine

Table 2. Mean Change in BMD* From Baseline to Month 36

Location	BMD Parameter	Baseline		Month 36		Change From Baseline at Month 36		
		Mean (SD)	n	Mean (SD)	n	Mean (SD)†	n	*P* Value
Lumbar spine	g/cm²	1.27 (0.19)	45	1.29 (0.19)	38	0.01 (0.10)	36	0.52
	Z-score	2.14 (1.43)		2.46 (1.46)		0.24 (0.84)		0.09
Hip–total	g/cm²	1.12 (0.16)	44	1.10 (0.17)	36	–0.02 (0.07)	34	0.07
	Z-score	1.52 (1.10)		1.56 (1.17)		–0.05 (0.51)		0.53
Hip–femoral neck	g/cm²	0.99 (0.19)	44	0.98 (0.19)	36	–0.02 (0.08)	34	0.21
	Z-score	1.35 (1.24)		1.34 (1.16)		–0.05 (0.61)		0.65
Distal one-third radius	g/cm²	0.79 (0.11)	45	0.78 (0.12)	37	–0.03 (0.07)	35	0.02
	Z-score	0.94 (0.82)		0.49 (1.03)		–0.44 (0.76)		0.002

*Includes results from 6 patients who were assessed by different DXA machines at baseline vs Month 36 (Hologic and GE Lunar instruments, respectively) because a comparison of overall results including and excluding these 6 patients did not reveal meaningful differences
†The data are the same when the subset of patients who completed 36 months of treatment are analyzed

Safety and Tolerability

- Adverse events (AEs) were reported by 38/38 (100%) patients
  - Hypocalcemia, 14 (37%) patients
  - Nausea, 12 (32%) patients
  - Muscle spasms, 12 (32%) patients
  - Arthralgia, 10 (26%) patients
  - Paresthesia, 10 (26%) patients
  - Bronchitis, 10 (26%) patients
- Serious AEs were reported in 8/38 (21%) patients; none were treatment related
  - Hypocalcemia and gastroenteritis (1 patient, 2 events)
  - Viral infection (1 patient, 1 event)
  - Ulna and radius fracture (1 patient, 1 event)
  - Rectal cancer (1 patient, 1 event)
  - Urticaria (1 patient, 1 event)
  - Cellulitis on both legs, not injection-site related (1 patient, 1 event)
  - Tightness in upper chest, throat tightness and dyspnea; syncope (1 patient, 2 events)
  - Cholelithiasis and cholecystitis (1 patient, 1 event)
- There were no deaths

CONCLUSIONS

- **Long-term treatment of patients with rhPTH(1-84) was associated with continued improvements in mineral and bone homeostasis, evidenced by maintenance of serum calcium, decreases in serum phosphate, and increases in serum BTMs, as well as minor reductions in most BMD Z-scores**
  - **BTMs increased with rhPTH(1-84) treatment, reached a plateau, and then declined to new steady-state levels that were above normal for P1NP, and within normal range for BSAP and CTX**
- **rhPTH(1-84), administered for up to 36 months during the RACE study, had a safety profile similar to that observed in the pivotal phase III placebo-controlled REPLACE study[5]**
- **The results provide further evidence for the clinical utility and efficacy of rhPTH(1-84) in the treatment of hypoparathyroidism**

ABBREVIATIONS

AE = adverse event
BMD = bone mineral density
BSAP = bone-specific alkaline phosphatase
BTM = bone turnover marker
CTX = cross-linked C-telopeptide of type 1 collagen
DXA = dual-energy x-ray absorptiometry
P1NP = aminoterminal propeptide of type 1 collagen
PTH = parathyroid hormone
SD = standard deviation
SEM = standard error of the mean

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DISCLOSURES

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The interim results presented herein exclude data from 4 patients in this ongoing open-label study. The conclusions of this interim analysis did not change with the removal of these patients.

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