Design and topline results of TransCon PTH, a long-acting PTH, phase 2 trial in subjects with hypoparathyroidism

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BACKGROUND

- PTH (parathyroid hormone) is important for the regulation of serum calcium, phosphate, urinary calcium and bone turnover[1,2] (Figure 1)
- Conventional therapy for hypoparathyroidism includes calcium and active vitamin D (e.g. calcitriol, alfacalcidol) supplementation[1]
- The ideal PTH replacement therapy would restore physiologic levels of PTH and thus also restore downstream physiologic levels of calcitriol promoting independence from calcium and active vitamin D supplementation and normalization of quality of life[1,3]
- TransCon PTH is a sustained-release prodrug designed to provide stable PTH levels in the physiological range for 24 hours/day; TransCon PTH is designed to normalize blood and urinary calcium levels, serum phosphate, bone turnover, and quality of life[4] (Figure 2)
- In a phase 1 study in healthy adults, TransCon PTH provided a flat, infusion-like profile of Free PTH within the normal physiological range, with a half-life of ~60 hours[4]
- Here, we report results from the initial 4-week double blind period of the phase 2 PaTH Forward Trial evaluating TransCon PTH in adults with hypoparathyroidism

Figure 1. PTH Replacement for Hypoparathyroidism

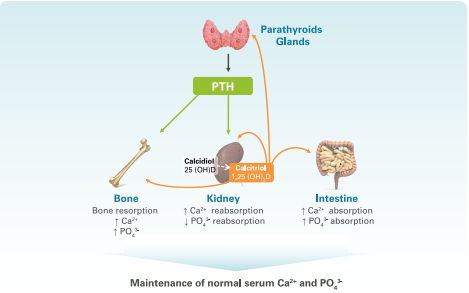
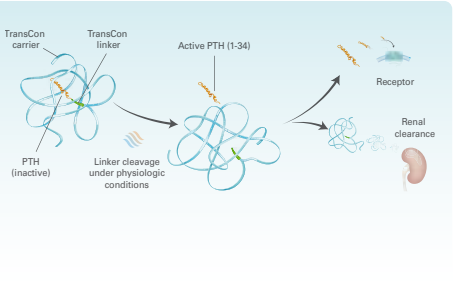


Figure 2. TransCon PTH Design



METHODS

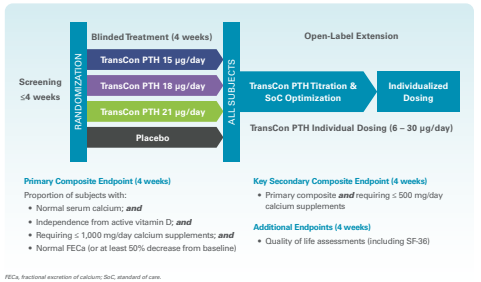
STUDY DESIGN

- The PaTH Forward Trial consists of a 4-week double-blinded treatment period followed by an ongoing open label extension (Figure 3)
- For the double-blinded period, adult subjects with hypoparathyroidism treated with conventional therapy were randomized 1:1:1:1 to TransCon PTH 15, 18, 21 µg/day or placebo and received fixed dosing of TransCon PTH or placebo for 4 weeks

STATISTICAL ANALYSIS

- Efficacy analyses were based on the Per Protocol Population, which included subjects from the full analysis set who met inclusion/exclusion criteria and completed the full double-blind trial period
- Safety analyses were based on the Safety Population, which included all randomized subjects who received at least 1 dose of randomized treatment

Figure 3. TransCon PTH Phase 2 Trial Design



FECa, fractional excretion of calcium; SoC, standard of care.

RESULTS

- This trial enrolled 59 subjects; 57 subjects met criteria for the Per Protocol Analysis
- Demographics, baseline characteristics, disease characteristics, and baseline supplementation were generally comparable across groups (Table 1 and 2)
  - The majority of subjects were female, Caucasian, 30-65 years old, and diagnosed with post-surgical hypoparathyroidism
  - TransCon PTH subjects had slightly higher mean total daily dose of calcium at baseline

Table 1. Demographics and Baseline Characteristics

	TransCon PTH 15 µg/day (n=14)	TransCon PTH 18 µg/day (n=15)	TransCon PTH 21 µg/day (n=15)	All TransCon PTH Subjects (n=44)	Placebo (n=13)
Age (years), mean (SD)	47 (13)	47 (11)	54 (11)	49 (12)	50 (13)
Age group (years), %					
< 30	7	7	0	5	8
≥ 30 - < 65	79	93	87	86	85
≥ 65	14	0	13	9	8
Sex, %					
Female	86	80	80	82	77
Race, %					
White	100	80	87	89	100
Geographical Region, %					
North America	50	80	67	66	54
Europe	50	20	33	34	46

Table 2. Disease Characteristics and Baseline Supplementation

	TransCon PTH 15 µg/day (n=14)	TransCon PTH 18 µg/day (n=15)	TransCon PTH 21 µg/day (n=15)	All TransCon PTH Subjects (n=44)	Placebo (n=13)
Cause of HP, %					
Acquired from neck surgery	71	80	80	77	85
Autoimmune disease	7	0	0	2	0
Idiopathic disease	21	20	20	21	15
Duration of HP (years), mean (range)	12 (1-39)	9 (2-29)	12 (3-25)	11 (1-39)	13 (3-30)
Calcium					
Mean TDD (mg)	**1643**	**2395**	**2334**	**2129**	**1636**
Calcium ≤ 1000 mg TDD, %	36	13	7	18	23
Calcium ≤ 2000 mg TDD, %	79	60	40	59	69
Calcitriol (Active Vitamin D), %	71	79	87	79	67
Mean TDD (µg)	**1.03**	**0.75**	**0.75**	**0.83**	**0.72**
Alfacalcidol (Active Vitamin D), %	29	21	13	21	33
Mean TDD (µg)	**2.75**	**2.00**	**2.00**	**2.33**	**2.50**

HP, hypoparathyroidism; TDD, total daily dose.
No subjects had known baseline brain or vascular calcification or cataract. 1 subject (2.3%) in Total PTH had history of ectopic calcification. 1 subject each in Total PTH (2.3%) and placebo group (7.7%) has history of seizure.
HP Supplements at Baseline collected by eDiary/TDD; 2 subjects did not have eDiary information confirmed by prescription information.

EFFICACY

- After 4 weeks of fixed-dosing during the double-blind period, significantly more TransCon PTH subjects met the primary composite endpoint compared to placebo (50% vs 15%, respectively; *P*=0.03) (Table 3)
- All subjects in the 21 µg/day arm and 82% of all subjects across all TransCon PTH dosage arms were able to eliminate conventional therapy (no active vitamin D and ≤500 mg/day of calcium supplements) (Table 4)
  - Almost all subjects across all 3 arms of TransCon PTH were independent of active vitamin D by week 2 and remained independent at 4 weeks unlike the minimal change seen with placebo (Figure 4)
  - The TransCon PTH subjects across all three arms required <1000 mg of calcium by week 2 and continued to require lesser doses of calcium by week 4 (Figure 4)
- Subjects treated with TransCon PTH had greater decreases in serum phosphate and calcium x phosphate product and exhibited reduced fractional excretion of calcium (FECa) despite increased serum calcium (Figure 5)
- By Week 4 of treatment, TransCon PTH had normalized FECa in an additional 8 subjects compared to none with placebo (Figure 6)

Table 3. Primary Composite Endpoint at Week 4 (Fixed-Dosing)

	TransCon PTH 15 µg/day (n=14)	TransCon PTH 18 µg/day (n=15)	TransCon PTH 21 µg/day (n=15)	All TransCon PTH Subjects (n=44)	Placebo (n=13)
Subjects Meeting Primary Composite Endpoint, n	7	6	9	22	2
Proportion, %	50	40	60	50	15
P-value	0.10	0.22	0.02	0.03	
Subjects Meeting Each Component, %					
Serum calcium within the normal range	86	80	93	86	92
Active vitamin D = 0 µg/day	100	93	100	98	31
Calcium ≤1000 mg/day	93	87	100	93	46
Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline	71	53	60	61	38

Table 4. Elimination/Reduction of Conventional Therapy

Proportion of subjects meeting each component, %	TransCon PTH 15 µg/day (n=14)	TransCon PTH 18 µg/day (n=15)	TransCon PTH 21 µg/day (n=15)	All TransCon PTH Subjects (n=44)	Placebo (n=13)
Active vitamin D = 0 µg/day	100	93	100	98	31
Calcium ≤1000 mg/day	93	87	100	93	46
Calcium ≤500 mg/day	86	60	100	82	15
Calcium = 0 mg/day	50	47	53	50	0
Active vitamin D = 0 µg/day **and** Calcium ≤500 mg/day	86	60	100	82	15
Active vitamin D = 0 µg/day **and** Calcium = 0 mg/day	50	47	53	50	0

Figure 4. Mean Active Vitamin D and Calcium Dose by Visit

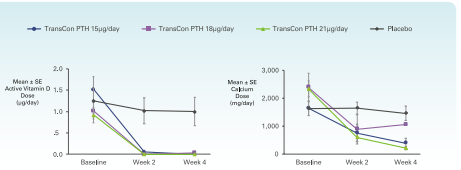
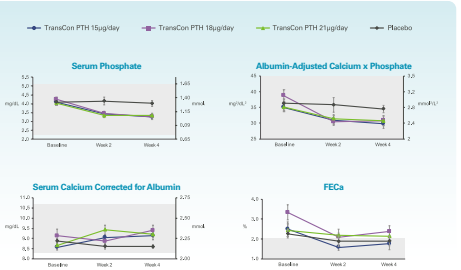
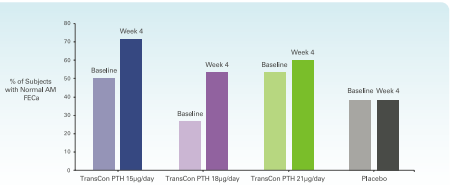


Figure 5. Mean Serum Phosphate, Calcium x Phosphate, Serum Calcium, and FECa by Visit



Values shown are mean ± SE.
Grey boxes indicate normal reference range.

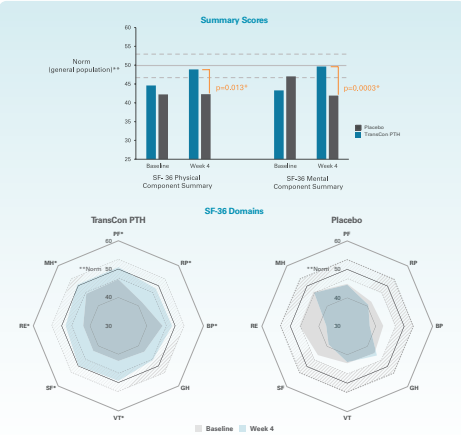
Figure 6. TransCon PTH Associated with Improvement in Proportion of FECa Responders



QUALITY OF LIFE ASSESSMENTS

- At baseline, most subjects had lower-than-average SF-36 scores, suggesting that there was a reduced health-related quality of life in this patient population (Figure 7)
- For both summary scores and all domains, scores increased for TransCon PTH subjects from baseline to Week 4 and approached the population average; conversely, all scores except the "General Health" domain score decreased for placebo subjects (Figure 7)

Figure 7. Treatment Effect on SF-36 Functional Health and Well-Being Outcomes



BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
**P<0.05 for TransCon PTH vs. placebo at week 4 (ANCOVA model including baseline as a covariate and treatment as a fixed factor).*
***The dashed lines (—) indicate the upper (52) and lower (47) bounds of T scores considered to be in the range of average functioning for the U.S. general population of group level data. Group mean scores lower than 47 indicate impairment. Source: Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated.*

SAFETY

- Similar rates of treatment emergent adverse events (TEAEs) were observed across arms (Table 5)
  - No serious adverse events occurred
  - No TEAE related to hyper- or hypocalcemia led to an ER/Urgent Care visit and/or hospitalization

Table 5. Treatment-Emergent Adverse Event Summary

TEAE, n (%)	TransCon PTH 15 µg/day (n=14)	TransCon PTH 18 µg/day (n=15)	TransCon PTH 21 µg/day (n=15)	All TransCon PTH Subjects (n=44)	Placebo (n=13)
Any TEAE*	6 (43)	3 (20)	8 (53)	17 (39)	5 (33)
Headache	3 (21)	1 (7)	2 (13)	6 (14)	0
Nausea	2 (14)	1 (7)	1 (7)	4 (9)	1 (7)
Serious TEAE	0	0	0	0	0
Severity**					
Severe TEAE	0	0	0	0	0
Moderate TEAE	1 (7)	1 (7)	1 (7)	3 (7)	3 (20)
Mild TEAE	5 (36)	2 (13)	7 (47)	14 (32)	2 (13)
Related TEAE	3 (21)	1 (7)	5 (33)	9 (21)	1 (7)
TEAE Related to Hyper- or Hypocalcemia Leading to ER/Urgent Care Visit and/or Hospitalization	0	0	0	0	0

**Specific TEAEs reported by ≥5% of subjects in total PTH or placebo groups.*
***Subjects are counted only in the highest severity category.*
TEAE, treatment-emergent adverse event.
None of the TEAEs led to discontinuation of the study drug or trial or death.

CONCLUSIONS

- The population recruited in this trial reflected the known epidemiology and characteristics of patients with chronic hypoparathyroidism, with typical doses of conventional therapy at baseline[5,6]
- Data from the end of the 4-week blinded period of the PaTH Forward Trial supports the potential for TransCon PTH as a replacement therapy
  - The majority of subjects randomized to fixed doses of TransCon PTH demonstrated independence from conventional supplements while
    - Maintaining serum calcium in the normal range
    - Reducing serum phosphate and urine calcium excretion
    - Demonstrating enhanced quality of life
  - All 3 fixed TransCon PTH doses were well-tolerated, with no adverse events of hypocalcemia or hypercalcemia requiring visit to hospital, emergency room, or urgent care
- The PaTH Forward Trial continues with excellent subject retention and planned follow-up for 4 years
- TransCon PTH will be evaluated in the global phase 3 PaTHway Trial

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