• PTH (parathyroid hormone) is important for the regulation of serum calcium, phosphate, urinary calcium and bone turnover (Figure 1).

• Conventional therapy for hypoparathyroidism includes calcium and active vitamin D (e.g., alfalcacidol) supplementation.

• The ideal PTH replacement therapy would restore physiological levels of PTH and thus also restore downstream physiological levels of calcium promoting independence from calcium and active vitamin D supplementation and normalization of quality of life.

• TransCon PTH is a sustained-release prosthetic designed to provide stable PTH levels in the physiological range for 24 hours/day; TransCon PTH is designed to normalise blood and urinary calcium levels, serum phosphate, bone turnover, and quality of life (Figure 2).

• In a phase 1 study in healthy adults, TransCon PTH provided a flat, inclusion-free profile of PTH within the normal physiological range, with a half-life of ~60 hours.

• Here, we report results from the initial 8-week double-blind period of the phase 2 iPATH Forward Trial evaluating TransCon PTH in adults with hypoparathyroidism.

**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=0.04) (Table 3).

• All subjects in the 21 µg/day arm and 90% of all subjects across all TransCon PTH dosage arms were able to discontinue conventional therapy (no active vitamin D or ≤ 500 mg/day of calcium supplements) (Table 6).

• Almost all subjects across all 3 arms of TransCon PTH were independent of active vitamin D by week 4 and remained independent for 8 weeks, unlike the minimal change seen with placebo (Figure 6).

• The TransCon PTH subjects across all three arms required < 100 mg of calcium by week 2 and continued to require lower doses of calcium by week 4 (Figure 6).

• Subjects treated with TransCon PTH had greater decreases in serum phosphorus and calcium + 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).

**Quality of Life Assessments**

• At baseline, most subjects had low/average SF-36 scores, suggesting there was a reduced health-related quality of life in this patient population (Figure 7).

• For both summary scores and all domain scores, increases for TransCon PTH subjects from baseline to Week 4 and approached the population average convergence, all scores except the “General Health” domain score decreased for placebo subjects (Figure 7).

**Safety**

• No serious adverse events occurred.

• No TEAE related to hypercalcemia led to an Early Urgent Care visit and/or hospitalization.

**CONCLUSIONS**

• This trial enrolled 50 subjects; 17 subjects met criteria for the Per Protocol Analysis.

• Demographic, baseline characteristics, disease characteristics, and baseline supplementation were generally comparable across groups (Table 1).

• The majority of subjects were female, Caucasian, 30-44 years old, and diagnosis with post-surgical hypoparathyroidism.

• TransCon PTH subjects had slightly higher mean total daily dose of calcium supplements requiring ≤ 500 mg/day (Table 6).

**METHODS**

• The PaTH Forward Trial consists of a 4-week double-blind treatment period followed by an ongoing open-label extension (Figure 3).

• For the double-blind period, with subjects who had hypoparathyroidism treated with conventional therapy were randomized 1:1:1 to TransCon PTH 15, 18, 21 µg/day and placebo and fixed dosing of TransCon PTH or placebo for 4 weeks.

• Safety analyses were based on the Safety Population, which included all randomized subjects who received at least 1 dose of randomized treatment.

• The PaTH Forward Trial continues with excellent subject retention and planned follow-up for 4 years.

**RESULTS**

• This study enrolled 50 subjects; 17 subjects met criteria for the Per Protocol Analysis.

• Demographic, baseline characteristics, disease characteristics, and baseline supplementation were generally comparable across groups (Table 1).

• The majority of subjects were female, Caucasian, 30-44 years old, and diagnosis with post-surgical hypoparathyroidism.

• TransCon PTH subjects had slightly higher mean total daily dose of calcium supplements requiring ≤ 500 mg/day (Table 6).

**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=0.04) (Table 3).

• All subjects in the 21 µg/day arm and 90% of all subjects across all TransCon PTH dosage arms were able to discontinue conventional therapy (no active vitamin D or ≤ 500 mg/day of calcium supplements) (Table 6).

• Almost all subjects across all 3 arms of TransCon PTH were independent of active vitamin D by week 4 and remained independent for 8 weeks, unlike the minimal change seen with placebo (Figure 6).

• The TransCon PTH subjects across all three arms required < 100 mg of calcium by week 2 and continued to require lower doses of calcium by week 4 (Figure 6).

• Subjects treated with TransCon PTH had greater decreases in serum phosphorus and calcium + 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).

**Quality of Life Assessments**

• At baseline, most subjects had low/average SF-36 scores, suggesting there was a reduced health-related quality of life in this patient population (Figure 7).

• For both summary scores and all domain scores, increases for TransCon PTH subjects from baseline to Week 4 and approached the population average convergence, all scores except the “General Health” domain score decreased for placebo subjects (Figure 7).