The Effects of TransCon PTH on Bone Turnover Markers in a Phase 1 Trial

BACKGROUND

Hyperparathyroidism (HP), a condition of parathyroid hormone (PTH) deficiency, leads to abnormal calcium and phosphate metabolism and a reduced rate of bone turnover. Standard-of-care (active vitamin D and calcium) does not correct decreased osteoblast activity and diminished bone turnover associated with HP. PTH replacement therapy is evolving with PTH analogues such as Natpara (PTH[1-84]) and Forteo (PTH[1-34]). However, due to intermittent exposure, they incompletely control the disease, increase bone resorption (which leads to decreased cortical bone), and, due to osteoblast exposure, are known to be anabolic to trabecular bone.

True replacement therapy would entail PTH exposure in the normal range 24 hours per day with an infusion-like profile. NIH studies in adults and children with HP showed continuous PTH[1-34] infusion. A HP infusion pump was superior to daily and twice daily PTH, including normalization of serum calcium, urinary calcium excretion, and bone turnover.3,11-13 Horwitz et al demonstrated that continuous PTH[1-34] infusion in healthy adults led to suppression of bone formation and increased resorption markers.2

TransCon PTH, a sustained-release produg of PTH[1-34], is in development for the treatment of HP. Through auto-clavage at physiological temperature and pH, unmodified PTH[1-34] is sustainably released.

METHODS

This phase 1, randomized, placebo-controlled, single and multiple ascending dose (SAD and MAD) trial evaluated safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of TransCon PTH in 130 healthy adults. Cohorts of 10 subjects (8 active, 2 placebo) received 7 SAD [TransCon PTH 3.5-124 µg PTH[1-34]] or 6 MAD [TransCon PTH 3.5-24 µg PTH[1-34]]/day for 10 days. The primary PK endpoint was free PTH (PTH[1-34]) and PTH(1-33).

The PD endpoints included serum calcium, osteoblastic bone formation markers (PINP and BAP), and osteoclastic bone resorption marker, CTx.

RESULTS

TransCon PTH was generally well-tolerated. TransCon PTH demonstrated a half-life of approximately 60 hours. The MAD cohorts demonstrated a dose-dependent, flat, infusion-like profile at steady-state over 24 hours, shown at day 10 for cohorts 3-5 administered TransCon PTH 12, 16, and 20 µg/day.

Compared to placebo, PINP decreased over 10 days of TransCon PTH 12, 16, and 20 µg/day.

Compared to placebo, BSAP did not increase over 10 days of TransCon PTH 12, 16, and 20 µg/day.

Compared to placebo, CTx increased over 10 days of TransCon PTH 12, 16, and 20 µg/day.

DISCUSSION

In healthy volunteers, TransCon PTH did not increase PINP or BSAP, suggesting that by producing a flat-infusion-like profile of PTH within the calculated normal range, the study drug is not anabolic. TransCon PTH did modestly increase CTx but less than that seen in published data with short-acting PTH.14 These data are similar to published literature illustrating the effects of continuous PTH administration.15

Future studies in patients with HP are needed to determine if treatment beyond 10 days leads to normalization of bone turnover and a decline in the elevated BMD seen in patients with HP treated with standard-of-care.

Due to their short half-lives, daily dosed PTH analogues provide intermittent PTH exposure, stimulating systemic bone formation as demonstrated by increases in PINP, BSAP, and trabecular bone mineral density (BMD).1 Due to coupling, this osteoblast stimulation is associated with a substantial increase in bone resorption (up to 200% increase).3

While anabolic activity resulting in increased BMD is the treatment goal in osteoporosis, HP is, due to decreased bone resorption, associated with increased BMD. The treatment objective is therefore to normalize bone turnover and modestly decrease BMD back to the normal level.

CONCLUSION

• Data from this phase 1 study in healthy volunteers supports an infusion-like PTH profile with TransCon PTH that may predict improved efficacy and long-term safety in the treatment of HP.

• The effect of TransCon PTH on bone formation markers were consistent with a continuous infusion of PTH[1-34] and lacked an anabolic effect.

• Based on these results, TransCon PTH is entering clinical development in patients with hyperparathyroidism.

REFERENCES


