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

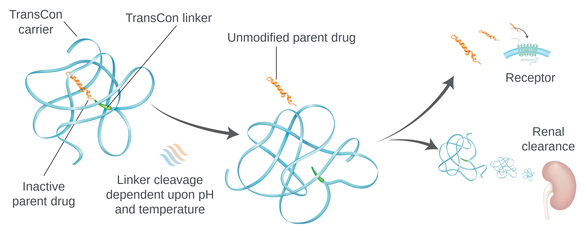
David B. Karpf, Susanne Pihl, Aimee Shu, Sanchita Mourya, Eva Mortensen, Jonathan A. Leff
Ascendis Pharma A/S

BACKGROUND

Hypoparathyroidism (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 osteoclast 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),[1] 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 via an infusion pump was superior to daily and twice daily PTH, including normalization of serum calcium, urinary calcium excretion, and bone turnover.[2,3] Horwitz et al demonstrated that continuous PTH(1-34) infusion in healthy adults led to suppression of bone formation and increased resorption markers.[4]

TransCon PTH, a sustained-release prodrug of PTH(1-34), is in development for the treatment of HP. Through auto-cleavage at physiological temperature and pH, unmodified PTH(1-34) is sustainably released.



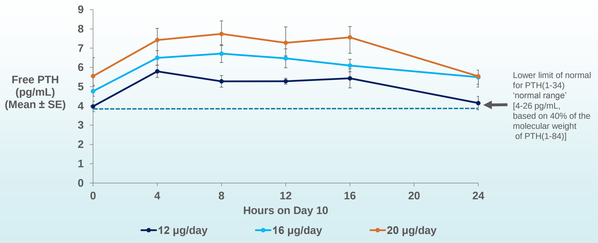
METHODS

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 (P1NP and BSAP), and osteoclastic bone resorption marker, CTx.

RESULTS

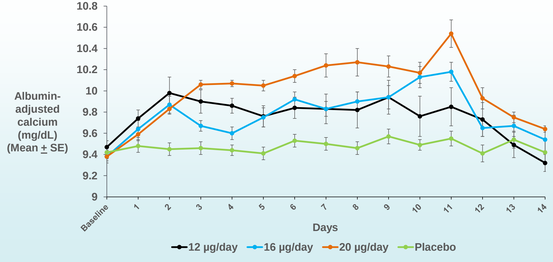
TransCon PTH was generally well-tolerated. TransCon PTH demonstrated a half-life of approximately 60 hours. The MAD cohorts demonstrated a dose-dependent, flat, infusion-like profile at steady-state over 24 hours, shown at day 10 for cohorts 3-5 administered TransCon PTH 12, 16, and 20 µg/day.

Figure 1: Free PTH Exposure After Multiple Doses of TransCon PTH (n=7-8)



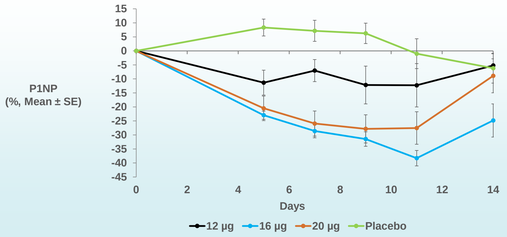
The MAD cohorts demonstrated a sustained, dose-dependent increase in albumin-adjusted serum calcium after 10 days, shown for cohorts 3-5 administered TransCon PTH 12, 16, and 20 µg/day.

Figure 2: Change in Albumin-adjusted Serum Calcium over 10 Days of TransCon PTH (n=8/group)



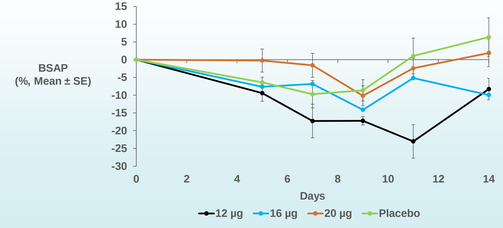
Compared to placebo, P1NP decreased over 10 days of TransCon PTH 12, 16, and 20 µg/day.

Figure 3: Suppression of P1NP over 10 days of TransCon PTH (n=8/group)



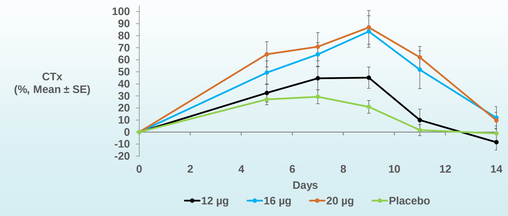
Compared to placebo, BSAP did not increase over 10 days of TransCon PTH 12, 16, and 20 µg/day.

Figure 4: Suppression of BSAP over 10 days of TransCon PTH (n=8/group)



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

Figure 5: Increase in CTx over 10 days of TransCon PTH (n=8/group)



DISCUSSION

In healthy volunteers, TransCon PTH did not increase P1NP 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 increased CTx but less than that seen in published data with short-acting PTH.[1] These data are similar to published literature illustrating the effects of continuous PTH administration.[2-4]

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 osteoblastic bone formation as demonstrated by increases in P1NP, 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).[1]

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 hypoparathyroidism.

REFERENCES:
[1]Rubin, M.R., et al., *Therapy of Hypoparathyroidism With PTH(1-84): A Prospective Six Year Investigation of Efficacy and Safety.* J Clin Endocrinol Metab, 2016. 101(7): p. 2742-50
[2]Winer, K.K., et al., *Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism.* J Clin Endocrinol Metab, 2012. 97(2): p. 391-9.
[3]Winer, K.K., et al., *Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism.* J Pediatr, 2014. 165(3): p. 556-63.e1.
[4]Horwitz, M.J., et al., *A 7-day continuous infusion of PTH or PTHrP suppresses bone formation and uncouples bone turnover.* J Bone Miner Res, 2011. 26(9): p. 2287-97.

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