TransCon PTH for Hypoparathyroidism – Design and Results of a Phase 1 TransCon PTH Trial in Healthy Volunteers

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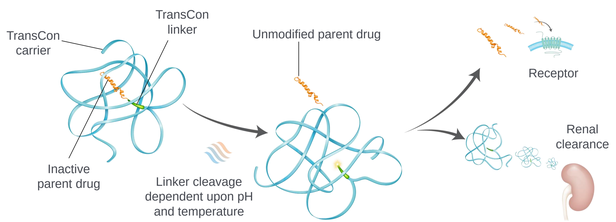
BACKGROUND

Hypoparathyroidism (HP), a condition of parathyroid hormone (PTH) deficiency, leads to abnormal calcium metabolism. The downsides of standard of care (SOC), ie, large and frequent doses of oral calcium and active vitamin D, include hypercalciuria, renal disease, and increased calcium x phosphate product resulting in ectopic calcifications in many tissues. Recently approved daily injections of Natpara, [PTH(1-84)], do not fully control urinary calcium excretion or symptomatic hypo- and hypercalcemia due to its half-life of only 3 hours.[1] NIH-sponsored studies in children and adults with HP have shown that in terms of serum calcium (sCa), serum phosphate (sP), urinary calcium (uCa), serum magnesium, and bone turnover:

- Daily PTH(1-34) injections are superior to SOC,[2]
- Twice daily PTH(1-34) injections are superior to SOC or once daily injections,[3-5]
- Continuous PTH(1-34) infusion via an insulin pump is superior to BID PTH(1-34) injections, despite a 65% lower dose of daily PTH.[6,7]

Ascendis Pharma is developing TransCon PTH, a sustained-release prodrug, as a replacement therapy for HP. In its inert prodrug form, PTH(1-34) is transiently bound to the TransCon carrier via the TransCon linker. Through autocleavage, TransCon PTH is designed to provide stable free PTH levels with a flat, infusion-like profile in the physiological range for 24 hours a day.



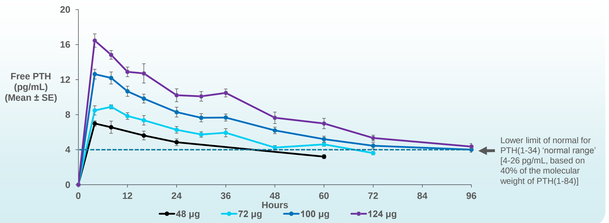
METHODS

This phase 1, randomized, placebo-controlled, single and multiple ascending dose (SAD and MAD, respectively) trial evaluated safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of TransCon PTH in 130 healthy adults. SAD and MAD cohorts consisted of 10 subjects each (8 active, 2 placebo) who received up to 7 single or 6 multiple ascending doses (administered daily for 10 days) of TransCon PTH, respectively. The doses ranged from TransCon PTH 3.5 to 124 µg PTH(1-34) for the SAD cohorts and TransCon PTH 3.5 to 24 µg PTH(1-34)/day for the MAD cohorts. The primary PK endpoints included TransCon PTH and free PTH [PTH(1-34) and PTH(1-33)]. The primary PD endpoints included sCa, sP, FECa (fractional excretion of calcium), serum magnesium, intact PTH(1-84), 1,25 dihydroxyvitamin D3, and bone turnover markers.

RESULTS

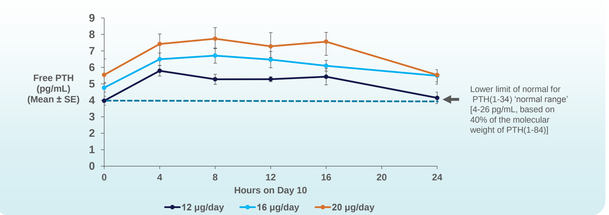
In the 7 SAD cohorts, free PTH demonstrated a dose-dependent response with a half-life of approximately 60 hours, shown for cohorts 3-7 administered TransCon PTH 32, 48, 72, 100, and 124 µg.

Figure 1: Free PTH Exposure After Single Doses of TransCon PTH (n=4-8)



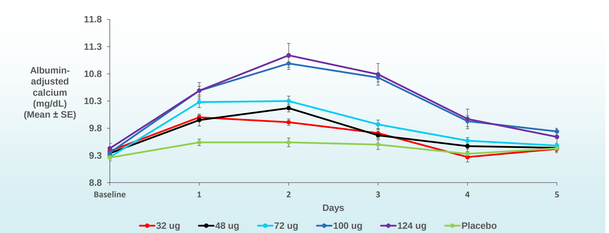
The MAD cohorts demonstrated a dose-dependent, flat, infusion-like profile at steady-state over 24 hours at day 10 for cohorts 3-5 administered TransCon PTH 12, 16, and 20 µg/day, respectively.

Figure 2: Free PTH Exposure After Multiple Doses of TransCon PTH (n=7-8)



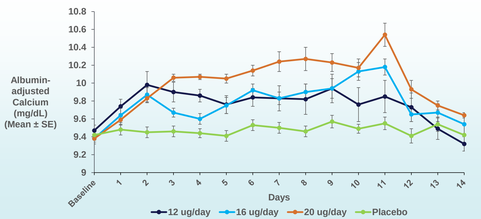
The SAD cohorts demonstrated a sustained, dose-dependent increase in albumin-adjusted serum calcium, shown for cohorts 3-7 administered TransCon PTH at 32, 48, 72, 100, and 124 µg.

Figure 3: Change in Albumin-adjusted Serum Calcium After Single Doses of TransCon PTH



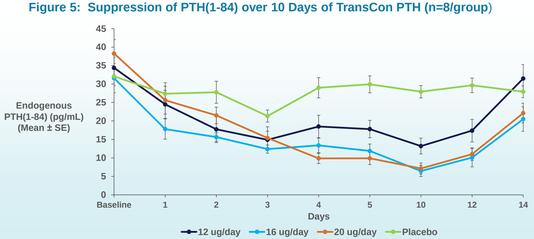
The MAD cohorts demonstrated a sustained, dose-dependent increase in albumin-adjusted serum calcium after 10 days, shown for cohorts 3-5 administered TransCon PTH 12, 16, and 20 µg/day.

Figure 4: Change in Albumin-adjusted Serum Calcium over 10 Days of TransCon PTH (n=8/group)



The MAD cohorts demonstrated a dose-dependent suppression of endogenous PTH(1-84) (intact PTH), shown for cohorts 3-5 administered TransCon PTH at 12, 16, and 20 µg/day, with full suppression at doses of ≥ 16 µg/day.

Figure 5: Suppression of PTH(1-84) over 10 Days of TransCon PTH (n=8/group)



In the SAD TransCon PTH 100 µg cohort (n=8), mean albumin-adjusted sCa increased to 10.5-11.2 mg/dL over 3 days. In the MAD TransCon PTH 20 µg cohort (n=8), adjusted sCa increased from 9.5 at baseline to 10.6 mg/dL on day 10. However, compared to the 6.5% fractional excretion of calcium (FECa) reported in healthy volunteers clamped by calcium IV infusion to a sCa of 10.3 mg/dL,[8] the FECa remained normal (1-2%) in TransCon PTH subjects despite hypercalcemia. This normal FECa reflects the continuous exposure of PTH on the renal receptors by TransCon PTH. In contrast, in the clamped healthy volunteers, endogenous PTH(1-84) was suppressed, causing their FECa to increase.

Figure 6: Spot FECa with Single Doses of TransCon PTH

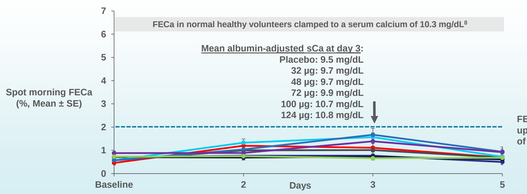
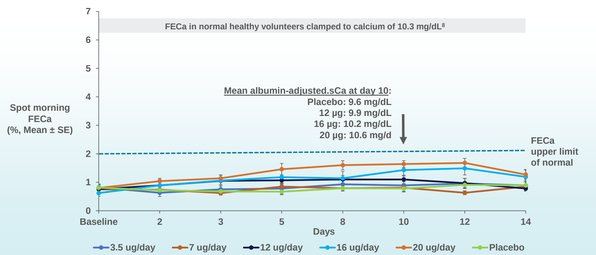


Figure 7: Spot FECa with daily doses of TransCon PTH (n=8/group) for 10 days



TransCon PTH was generally well tolerated, with no drug-related serious or severe adverse events (AE). Observed AEs leading to the maximum tolerated dose (MTD) reflected known PTH pharmacology. Minor non-AE injection site reactions, consisting primarily of erythema (without pain or pruritus), were observed, likely reflecting the known vasodilatory effects of PTH. For SAD, the MTD was TransCon PTH 124 µg, and for MAD, the MTD was Trans Con PTH 20 µg/day; 5 of 7 female MAD cohort participants who received TransCon PTH 24 µg/day had orthostatic hypotension, tachycardia, and/or palpitations, and 1 had syncope. Two of 3 males had asymptomatic hypercalcemia. Since participants were all healthy volunteers with normal baseline calcium levels, it is possible that higher doses of TransCon PTH may be well tolerated and effective in patients with hypoparathyroidism.

SUMMARY

- The TransCon PTH PK profile demonstrated a dose-dependent response, with a flat, infusion-like profile within the normal range with daily administration
- The TransCon PTH PK translated into a predicted dose-dependent PD response, suggesting the ability to titrate patients with HP into the normal calcemic range, consistent with preclinical data
- TransCon PTH demonstrated a potent renal calcium reabsorption effect, predicting control of both serum and urine calcium
- TransCon PTH was generally well tolerated across the likely clinical dose range

CONCLUSION

Phase 1 data support the target product profile of TransCon PTH as a replacement therapy for HP providing physiological levels of PTH 24 hours per day. These data support advancement into phase 2 clinical development.

REFERENCES:
[1]Shire-NPS Pharmaceuticals, I., 2016. [2]Winer, K.K., JAMA, 1996. 276(8): p. 631-6. [3]Winer, K.K., J Clin Endocrinol Metab, 1998. 83(10): p. 3480-6. [4]Winer, K.K., J Clin Endocrinol Metab, 2008. 93(9): p. 3389-95. [5]Winer, K.K., J Clin Endocrinol Metab, 2003. 88(9): p. 4214-20. [6]Winer, K.K., J Clin Endocrinol Metab, 2012. 97(2): p. 391-9. [7]Winer, K.K., J Pediatr, 2014. 165(3): p. 556-63.e1. [8]Horwitz, M.J., J Bone Miner Res, 2011. 26(9): p. 2287-97.

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