The Design of a Long-acting PTH (TransCon™ PTH) Phase 2 Trial in Patients With Hypoparathyroidism, Based on Phase 1 Results in Healthy Subjects

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BACKGROUND

PTH deficiency in hypoparathyroidism (HP) leads to hypocalcemia, hyperphosphatemia, hypercalcuria, low bone turnover, and overly mineralized bone. Standard of Care (SoC) with large doses of active Vitamin D and calcium raises serum Ca (iCa) and phosphate (Pi), and can increase the burden of illness on patients by worsening both hypercalcuria and the Ca x Pi product, increasing the risk of nephrocalcinosis, nephrolithiasis, end-stage renal disease, ectopic calcifications in the kidneys, vascular system, lens of the eye, basal ganglia and parathyromatous hypercalcemia. Recent approval of short-acting PTH(1-84)-N-Ter (n = 3 hrs) can raise serum calcium and allow partial withdrawal of SoC, but did not control urinary calcium excretion or symptomatic hypercalcemia.1,2,3 NIH-sponsored studies in children and adults with HP have shown that in terms of normalizing iCa, Pi, urinary calcium (iCa), serum magnesium (iMg), and bone turnover:

- Daily PTH(1-34) injections are superior to SoC
- Twice daily PTH(1-34) injections are superior to SoC or once daily injections
- Continuous PTH(1-34) infusion via an insulin pump is superior to SoC

Ascendis Pharma is developing TransCon PTH, a long-acting produg, as a true replacement therapy for HP designed to maintain a continuous iCa infusion of PTH(1-34) to an iCa level of iCa levels of 10.0 mg/dL. In its initial produg form, PTH(1-34) is transiently conjugated (“TransCon”) to the inert TransCon carrier via the TransCon linker. Through autocleavage at physiological pH and temperature, active PTH is sustainably released with a half-life of ~60 hours, and is designed to provide stable PTH levels with a flat, infusion-like profile in the physiological range for 24 hours a day at steady-state.

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 132 healthy adults. SAD and MAD cohorts consisted of 10 subjects each (8 active, 2 placebo) who received up to 7 SAD or 6 MADs (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 Free PTH [PTH(1-34)] and PTH(1-33)] and TransCon PTH levels. The primary PD endpoints included sCa, sP, sMg, intact PTH(1-84), PTH(1-33), and bone turnover markers (BTM).

In the 7 SAD cohorts, Free PTH demonstrated a dose-dependent response with a half-life of ~60 hours, shown for cohorts 4-7 administered TransCon PTH 48, 72, 100, and 124 µg, respectively.

RESULTS

In the SAD TransCon PTH 124 µg cohort (n=8), albumin-adjusted sCa increased to 10.40 mg/dL – 12.08 mg/dL (mean ± SE, 10.97 ± 0.20) over 16 days, shown for cohorts 4-7 administered TransCon PTH 12, 16, 20, and 24 µg/day, with full suppression at doses of ≥16 µg/day.

The MAD cohorts demonstrated a dose-dependent suppression of endogenous PTH(1-84) (intact PTH), shown for cohorts 3-6 administered TransCon PTH at 12, 16, 20, and 24 µg/day, respectively.

The MAD cohorts demonstrated a sustained, dose-dependent increase in albumin-adjusted sCa that was maximal 48 hours post-dose, shown for cohorts 3-7 administered TransCon PTH at 32, 48, 72, 100, and 124 µg, respectively.

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TransCon PTH was generally well tolerated, with no drug-related serious or severe adverse events (AEs). The highest single dose of 124 µg was not associated with dose-limiting toxicity (DLT). The top multiple dose of 24 µg did show mild DLT for the MAD, the maximum tolerated dose (MTD) was TransCon PTH 20 µg/day. Five of 7 female MAD cohort participants who received TransCon PTH 24 µg/day (2 with both female placebo-treated subjects had orthostatic hypotension, tachycardia, and/or palpitations, and 1 had syncope). Two male subjects had asymptomatic hypercalcemia; no males experienced vasodilatory symptoms. Observed AEs leading to the MTD reflected known PTH pharmacology. Minor non-renal injection site reactions, consisting primarily of erythema (without pain or pruritus), were observed, likely reflecting the known vasodilatory effects of PTH. 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.

CONCLUSION

The phase 2 trial is designed to support the TransCon PTH target profile as a true PTH replacement therapy while confirming both the starting dose and the optimal down titration of SoC (active vitamin D and calcium) in the planned pivotal global phase 3 trial.

REFERENCES


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