Pharmacokinetics of TransCon PTH, a Sustained-Release PTH Prodrug for Hypoparathyroidism, in Rat and Cynomolgus Monkey

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Background

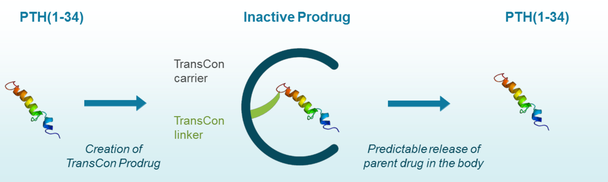
Hypoparathyroidism (HP) is a condition of parathyroid hormone (PTH) deficiency that leads to abnormal calcium metabolism.

The mainstay of therapy, vitamin D and calcium, as well as adjunct Natpara [PTH(1-84)] with a half-life of only 3 hours, incompletely control urinary calcium.[1,2]

NIH-sponsored studies of HP patients have shown that continuous PTH(1-34) infusions in the physiological range normalize serum calcium (sCa), urinary calcium, and bone turnover.[3]

Ascendis Pharma is developing TransCon PTH, a sustained-release prodrug of PTH(1-34) for the treatment of HP. In its prodrug form, PTH is transiently bound to the TransCon carrier via the TransCon linker.

Through auto-hydrolysis, fully active, unmodified PTH is released, providing free PTH with a low peak-to-trough ratio and within the physiological range over 24 hours.



Methods

TransCon PTH Single Dose Studies

TransCon PTH was administered subcutaneously (SC) to cynomolgus monkeys and rats in single doses of 1 or 5 µg/kg and 10 or 30 µg/kg, respectively, with pharmacokinetic (PK) sampling for 168 hours. The TransCon PTH half-life was also calculated. Based on these results, a PK model was constructed simulating the release of PTH after chronic daily dosing of TransCon PTH.

TransCon PTH Multiple Dose Studies

Repeated daily doses of TransCon PTH were administered to cynomolgus monkeys and rats (0, 0.2, 0.5, or 1.5 µg/kg/day and 0, 10, 30, or 60 µg/kg/day, respectively) over 28 days. Blood was collected on Day 28 for PK assessments at 3, 6, 8, 12, 18 and 24 hours post-dose. PK was evaluated using non-compartmental analysis, including peak-to-trough ratios at steady state (day 28).

Results

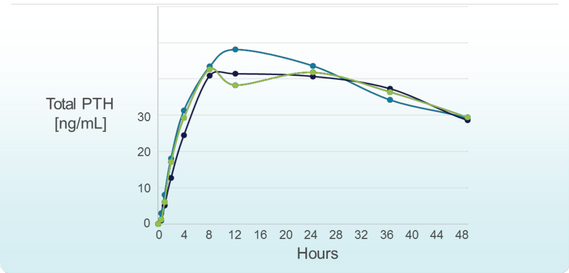
TransCon PTH Single Dose Studies

After a single dose of TransCon PTH 1 and 5 µg/kg in monkeys (n=3/group), the individual PK profiles demonstrated a mean half-life of 34 hours.

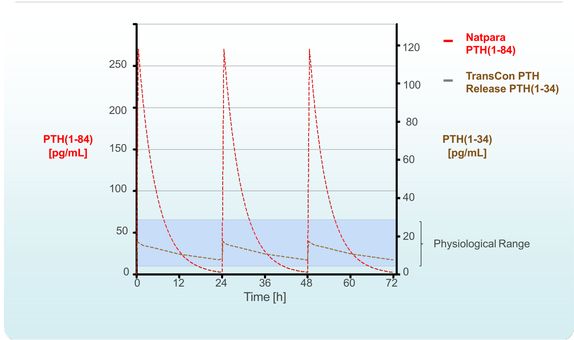
After a single dose of TransCon PTH 10 and 30 µg/kg in rats (n=3/sampling time point), the individual PK profiles demonstrated a half-life of 28 hours, thus illustrating that following once-daily administration, TransCon PTH would support an infusion-like profile.

Results

Monkeys dosed with TransCon PTH 5 µg/kg (n=3):



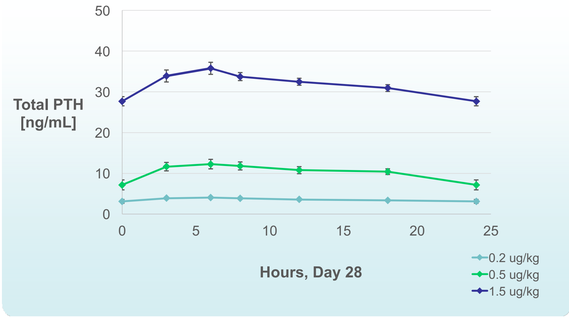
These results allowed modeling of chronic daily TransCon PTH dosing at steady state, suggesting that physiological PTH replacement can be achieved with once-daily dosing.



TransCon PTH Multiple Dose Studies

Daily dosing in monkeys (n=6 to 10/group) demonstrated dose-dependency and an infusion-like PK profile similar to modeling of continuous infusion PTH(1-34).

Results



The TransCon PTH peak-to-trough ratios following 28 day dosing was approximately 1.3 to 1.6 in monkeys (n=6 to 10/group) and 1.1-1.3 in rats (n=6/sampling time point).

Conclusions

TransCon PTH is being developed for HP as once-daily SC administration of PTH(1-34).

It is designed to maintain a steady PTH blood concentration within the normal range, thus addressing fundamental limitations of currently available therapies.

Studies in monkeys and rats demonstrated that TransCon PTH provided physiological levels of PTH with an infusion-like profile following once-daily administration.

References:
1. Natpara Product Label
2. JCEM 101(6):2273-2283, 2015
3. J Clin Endocrinol Metab 97: 391–399, 2012