

# TransCon PTH, a Sustained-Release PTH Prodrug for the Treatment of Hypoparathyroidism: Proof-of-Principle in Cynomolgus Monkeys and TPTx Rats

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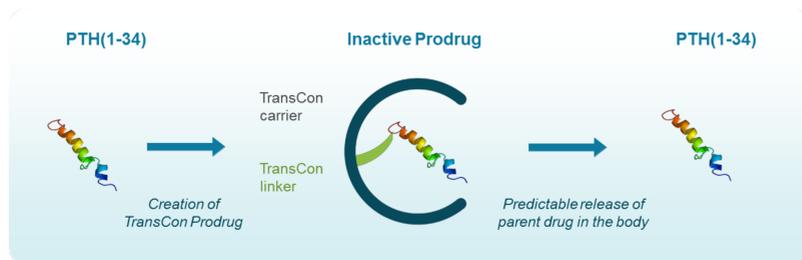


## Background

Hypoparathyroidism (HP), a condition of parathyroid hormone (PTH) deficiency that leads to abnormal calcium metabolism, is one of the few hormone disease states not treated by hormone replacement. 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.<sup>1,2</sup>

NIH-sponsored studies of HP patients have also shown that continuous PTH(1-34) infusions, which allow PTH to achieve the physiological range, simultaneously normalize serum calcium (sCa), urinary calcium, and bone turnover.<sup>2</sup>

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 Study in Monkeys

Single doses of TransCon PTH (1 and 5 µg/kg) were administered subcutaneously (SC) to cynomolgus monkeys. Serum calcium and urinary calcium was assessed over 24 hours.

## Methods

### TransCon PTH Multiple Dose Study in Rats

Female thyroparathyroidectomized rats (TPTx; i.e. rats subjected to blunt dissection of thyroid and parathyroid glands), were made euthyroid via thyroid hormone administration, leaving them functionally hypoparathyroid. The TPTx rats were used as an HP model to investigate TransCon PTH pharmacodynamic (PD) parameters.

Four groups of rats were dosed daily for 28 days:

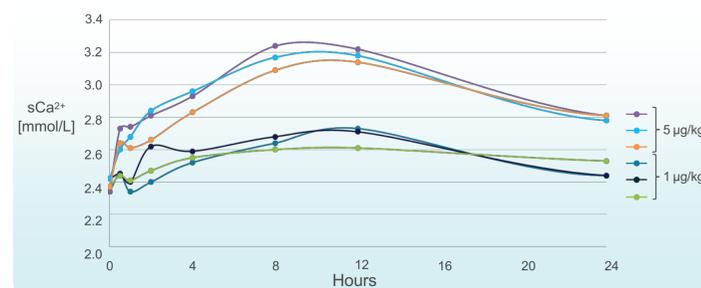
- TransCon PTH 5 µg/kg/day (TPTx rats)
- PTH(1-84) 70 µg/kg/day (TPTx rats)
- Vehicle (TPTx rats)
- Vehicle (sham-operated rats)

Serum Ca and serum phosphorous (sP) levels were assessed pre- and post-dose on days 1, 6, 12, and 27. Additionally, bone density was assessed on day 28 by pQCT.

## Results

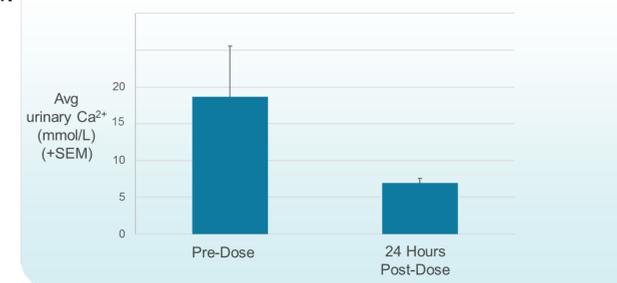
### TransCon PTH Single Dose Study in Monkeys

Following a single SC dose of TransCon PTH to monkeys (n=3/group), sCa increased in a dose-dependent manner. Inter-animal variability was low.



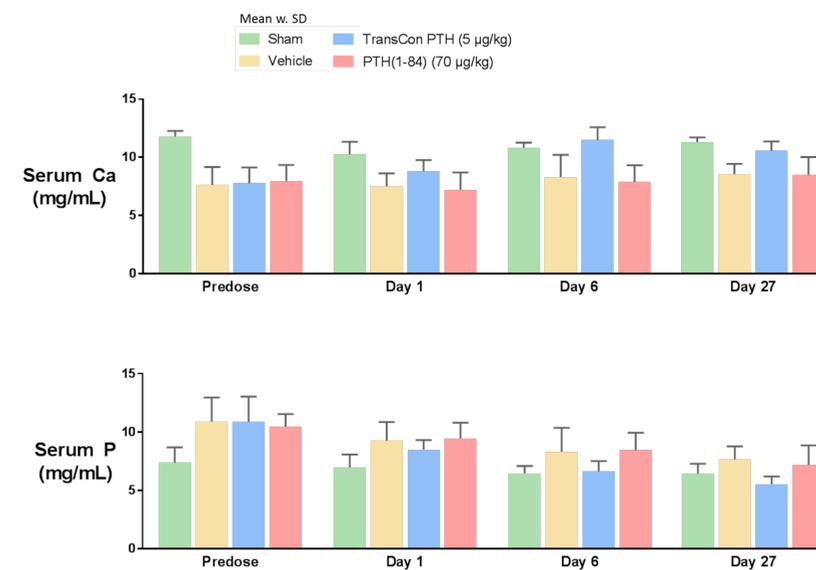
## Results

At 1 µg/kg TransCon PTH, sCa levels remained within the normal range, with a corresponding decreased urinary calcium.



### TransCon PTH Multiple Dose Study in Rats

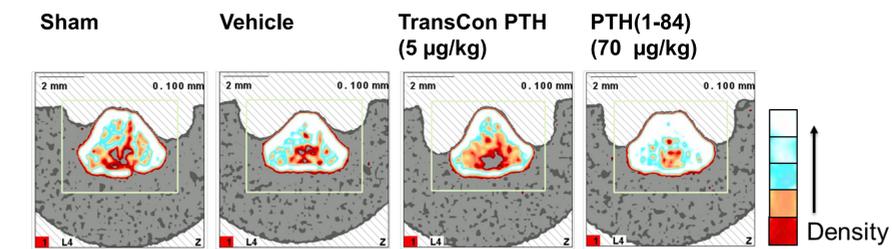
Once-daily administration of TransCon PTH at 5 µg/kg/day for 28 days to TPTx rats normalized sCa and sP levels (compared to sham) by day 6 and was maintained through day 27. In contrast, hypocalcemia was not corrected in PTH(1-84) and vehicle-dosed TPTx rats.



## Results

After 28 days, bone density measured by pQCT in TPTx rats treated with TransCon PTH appeared similar to sham-operated rats.

By comparison, vehicle-dosed TPTx rats exhibited abnormally increased bone density, and PTH(1-84)-treated TPTx rats showed further increased bone density.



## Conclusion

- Daily TransCon PTH increased sCa and reduced urinary calcium in normal monkeys.
- Daily TransCon PTH normalized sCa and sP in the TPTx rat model of HP in contrast to PTH(1-84).
- Daily TransCon PTH did not cause an abnormal increase in bone density in TPTx rats in contrast to PTH(1-84).

Based on these results, once daily TransCon PTH may address the limitations of current therapies in the treatment of hypoparathyroidism.

