A Single Dose of TransCon PTH in Subjects with Impaired Renal Function: A Phase 1 Trial

Susanne Pihl[1], Eshwari Kovoor[2], Lei Xu[3], Michael Beckert[1], and Aimee D. Shu[3]

[1]Ascendis Pharma A/S, [2]Employed at Ascendis Pharma Inc at time of submission, [3]Ascendis Pharma Inc

BACKGROUND

RATIONALE AND OBJECTIVE

Rationale

- Renal impairment (RI) is one of many co-morbidities associated with chronic hypoparathyroidism and its accompanying disturbances in calcium (Ca) and phosphate metabolism. In a cohort of 120 patients with chronic hypoparathyroidism, Mitchell *et al.* found that 41% had chronic kidney disease of stage 3 or higher (estimated glomerular filtration rate [eGFR] of ≤ 60 mL/min/1.73 m^2)[1]

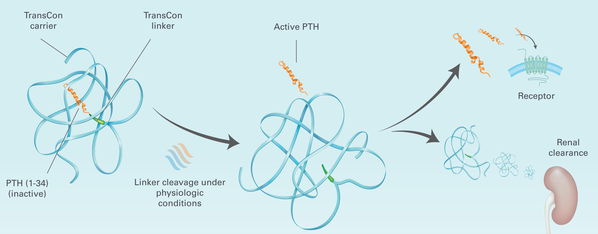
Objective

- To evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of a single dose of TransCon PTH in subjects with mild, moderate, and severe RI compared to healthy, demographically-matched subjects with normal renal function

TRANSCON PTH

- TransCon PTH is an investigational, long-acting prodrug designed to provide stable PTH levels in the physiological range for 24 hours per day[2]
- Currently in development as a once-daily subcutaneously-injected hormone replacement therapy for adult patients with hypoparathyroidism[3]
- Phase 2 and 3 trials ongoing in adults with chronic hypoparathyroidism and eGFR ≥ 30 mL/min/1.73 m^2 (NCT04009291 and NCT04701203)

Figure 1. TransCon PTH Design



The prodrug consists of a parent drug, PTH (1-34), transiently bound to an inert carrier via a proprietary linker[2,4]

- TransCon PTH is a prodrug consisting of active drug PTH(1-34) (in orange), an inert carrier (in blue) and a linker (in green)
- The sequence of PTH(1-34) is identical to the first 34 amino acids of the full length, 84-amino acid human PTH
  - PTH(1-34) displays the same receptor-mediated activity at bone and kidney as PTH(1-84)[5,6]
- In an inactive prodrug state, the carrier shields the drug and protects it from enzymatic degradation, receptor uptake, and renal clearance
- Following subcutaneous injection, under physiologic conditions, the linker auto-cleaves to release active PTH

METHODS

TRIAL DESIGN

- Male and female subjects, ages 18-75 years, who provided informed consent were eligible to enroll into one of four groups:
  - (Group 1) Normal renal function, eGFR ≥ 90 mL/min/1.73 m^2;
  - (Group 2) Mild renal impairment, eGFR ≥ 60 to < 90 mL/min/1.73 m^2;
  - (Group 3) Moderate renal impairment, eGFR ≥ 30 to < 60 mL/min/1.73 m^2;
  - (Group 4) Severe renal impairment and not on renal replacement therapy, eGFR < 30 mL/min/1.73 m^2
- All subjects received a single subcutaneous dose of TransCon PTH 50 mcg, where the dose refers to PTH(1-34) content
- Subjects were followed through 28 days with periodic assessments of physical exams, injection site reactions, adverse events (AEs), and blood and urine analytes

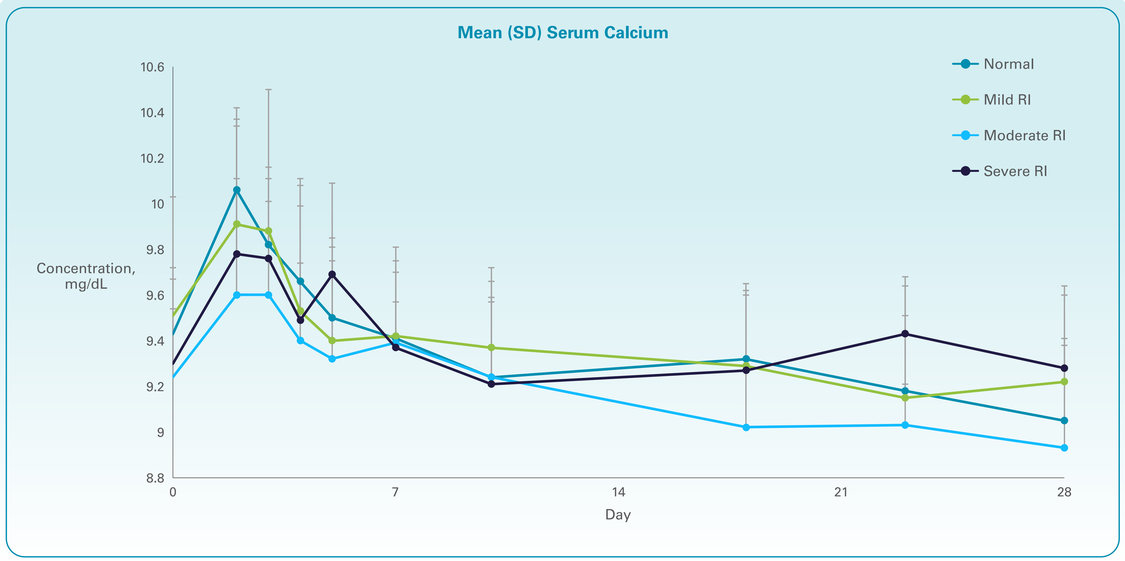
RESULTS

Table 1. Baseline Demographics

Cohort	1 (N = 13)	2 (N = 9)	3 (N = 8)	4 (N = 8)	Total (N = 38)
Renal Impairment [GFR (mL/min/1.73m^2)]	Normal (≥ 90)	Mild (60–89)	Moderate (30–59)	Severe (15–29)	
Age (year), mean	54	59	67	55	58
Gender (female:male)	7:6	5:4	3:5	4:4	19:19
Race: white	13	9	8	8	38
Medical History Related to Renal and Urinary Disorders, n (%)					
Glomerulonephritis chronic	0	0	0	3 (37.5)	3 (7.9)
Nephrolithiasis	0	1 (11.1)	0	1 (12.5)	2 (5.3)
Diabetic nephropathy	0	0	0	1 (12.5)	1 (2.6)
Renal Atrophy	0	0	0	1 (12.5)	1 (2.6)
Renal Cyst	0	0	0	1 (12.5)	1 (2.6)
Tubulointerstitial nephritis	0	0	0	1 (12.5)	1 (2.6)
Acute Kidney Injury	0	0	0	1 (12.5)	1 (2.6)
Renal Pelvis Fistula	0	1 (11.1)	0	0	1 (2.6)

- A total of 38 subjects (n = 13, 9, 8, 8, for Groups 1, 2, 3, 4, respectively) were enrolled. Mean age was 58 years and included 19 males and 19 females
- As expected in this trial of subjects with various levels of renal impairment, past medical history included chronic glomerulonephritis, nephrolithiasis, diabetic nephropathy, hypertension, and secondary hyperparathyroidism

Figure 2. Pharmacodynamics: Serum Calcium Concentration Level by RI



- An expected increase in serum calcium of similar magnitude across the four RI groups was observed after TransCon PTH administration, including in those with severe RI
- Mean baseline serum Ca (albumin-corrected) was 9.4 mg/dL, rose to 9.9 mg/dL on Day 2, and subsequently declined back to baseline
- Renal impairment did not affect the response in serum Ca after a single dose of TransCon PTH

Pharmacokinetics

- Exposure (C_{max} and AUC) to Free PTH(1-34) in the mild and moderate RI groups was similar to the normal renal function group
- In subjects with severe RI, Free PTH(1-34) C_{max} and AUC values were higher compared to subjects with normal renal function
  - Subjects with severe RI also had an elevated mean baseline intact PTH(1-84) levels in the range seen with secondary hyperparathyroidism, a common complication of chronic kidney disease[7]
  - Thus, the higher Free PTH(1-34) levels may have been related to the higher endogenous PTH(1-84) levels, combined with artifact due to sample processing
  - Despite the higher Free PTH(1-34) levels, the serum calcium response was similar to that observed in the other three groups

Table 2. Adverse Events

Treatment-Emergent Adverse (TEAE)	Normal (N = 13) N (%)	Mild (N = 9) N (%)	Moderate (N = 8) N (%)	Severe (N = 8) N (%)	Total (N = 38) N (%)
Any Events (TEAE)	0	2 (22.2)	2 (25.0)	0	4 (10.5)
Severe (TEAE)	0	0	0	0	0
Related (TEAE)	0	2 (22.2)	1 (12.5)	0	3 (7.9)
Related Adverse Event (preferred term)	—	Fatigue, Ear Discomfort	Headache	—	—
Severe Related TEAE	0	0	0	0	0
TEAE leading to Trial Discontinuation	0	0	0	0	0
Injection-site Reaction TEAE	0	0	0	0	0

- Overall, 4 subjects (10.5%; 2 subjects each in Groups 2 and 3) reported a treatment-emergent adverse event (Table 2)
  - Of these, 3 subjects (7.9%) were considered to have experienced at least one treatment-related adverse event (headache, ear discomfort, fatigue)
- There were no serious adverse events

CONCLUSIONS

- A single dose of TransCon PTH was well-tolerated across groups of subjects with normal renal function, or mild, moderate, or severe RI
- Renal impairment did not affect the response in serum Ca after a single dose of TransCon PTH
- An increase in serum Ca of similar magnitude across the four groups was observed after dosing with TransCon PTH, consistent with similar exposure to TransCon PTH across the dose groups
- Exposure (C_{max} and AUC) to Free PTH(1-34) in the mild and moderate RI groups was similar to the normal renal function group
- In subjects with severe RI, mean Free PTH(1-34) C_{max} and $AUC_{0\text{-tlast}}$ values were higher compared to that in subjects in the other three groups, likely related to their higher endogenous PTH(1-84) levels, combined with artifact due to sample processing

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