

Clinical Research Article

PaTH Forward: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial of TransCon PTH in Adult Hypoparathyroidism

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Abbreviations: AE, adverse event; CTx, C-telopeptide; FEca, fractional excretion of calcium; HPES, Hypoparathyroidism Patient Experience Scale; P1NP, procollagen type 1 N-terminal propeptide; PEG, polyethylene glycol; PTH, parathyroid hormone; rh, recombinant human; SAE, serious adverse event; SC, subcutaneous; sCa, serum Ca; SF-36, generic 36-Item Short Form Health Survey.

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Abstract

Context: Hypoparathyroidism is characterized by insufficient levels of parathyroid hormone (PTH). TransCon PTH is an investigational long-acting prodrug of PTH(1-34) for the treatment of hypoparathyroidism.

Objective: This work aimed to investigate the safety, tolerability, and efficacy of daily TransCon PTH in adults with hypoparathyroidism.

Methods: This phase 2, randomized, double-blind, placebo-controlled 4-week trial with open-label extension enrolled 59 individuals with hypoparathyroidism. Interventions included TransCon PTH 15, 18, or 21 μg PTH(1-34)/day or placebo for 4 weeks, followed by a 22-week extension during which TransCon PTH dose was titrated (6-60 μg PTH[1-34]/day).

Results: By Week 26, 91% of participants treated with TransCon PTH achieved independence from standard of care (SoC, defined as active vitamin D = 0 μg /day and calcium [Ca] \leq 500 mg/day). Mean 24-hour urine Ca (uCa) decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 ($n = 44$) while normal serum Ca (sCa) was maintained and serum phosphate and serum calcium-phosphate product fell within the normal range. By Week 26, mean scores on the generic 36-Item Short Form Health Survey domains increased from below normal at baseline to within the normal range. The Hypoparathyroidism Patient Experience Scale symptom and impact scores improved through 26 weeks. TransCon PTH was well tolerated with no treatment-related serious or severe adverse events.

Conclusion: TransCon PTH enabled independence from oral active vitamin D and reduced Ca supplements (\leq 500 mg/day) for most participants, achieving normal sCa, serum phosphate, uCa, serum calcium-phosphate product, and demonstrating improved health-related quality of life. These results support TransCon PTH as a potential hormone replacement therapy for adults with hypoparathyroidism.

Key Words: hypoparathyroidism, prodrug, parathyroid hormone, PTH(1-34), replacement therapy, TransCon PTH

Hypoparathyroidism is a 2-hormone deficiency resulting in abnormal calcium and phosphate homeostasis, neuromuscular symptoms, and impaired health-related quality of life. Under normal conditions, the 2 hormones—parathyroid hormone (PTH) and calcitriol—act at the bone, kidney, intestines, and parathyroid glands to maintain normal serum calcium (sCa) and phosphate. Within the kidney, PTH is responsible for the 1α -hydroxylation of calcidiol to become calcitriol (also known as $1,25$ -dihydroxyvitamin D_3 , or active vitamin D), the downstream hormone to PTH (1-4).

Conventional therapy of hypoparathyroidism includes oral calcitriol (or its analogue alfacalcidol)—because its endogenous production is insufficient in the face of PTH deficiency—and oral calcium. This approach results in the increased intestinal absorption of calcitriol and calcium in an attempt to keep sCa high enough to prevent symptoms but does not mimic normal physiology. Instead, this approach increases the filtered load of calcium; increases the risk of nephrolithiasis, nephrocalcinosis, and chronic kidney disease; fails to restore normal rates of bone turnover; and fails to alleviate the burden of diminished quality of life (5, 6).

In 2015, the US Food and Drug Administration approved the once-daily subcutaneous (SC) administration of recombinant human (rh) PTH(1-84) (Natpara) as an adjunctive treatment for adult patients with chronic hypoparathyroidism who cannot be adequately controlled with active vitamin D and calcium supplements (7).

TransCon PTH is an investigational long-acting prodrug of PTH in development as a once-daily hormone replacement therapy for adult hypoparathyroidism, and is designed to replace PTH at physiologic levels over a 24-hour period (8). The prodrug consists of a parent drug, PTH(1-34), transiently bound to an inert carrier via a proprietary linker (Fig. 1) (8). The carrier blocks the parent drug from receptor binding and uptake, renal clearance, and enzymatic degradation (8). Following SC injection and on exposure to physiologic conditions, autocleavage of the linker occurs, and active PTH is released in a controlled manner (8).

The PaTH Forward phase 2 trial was designed to assess the safety, tolerability, and efficacy of TransCon PTH as a PTH replacement therapy for adults with chronic hypoparathyroidism. It was previously demonstrated in a phase 1 trial that the active PTH released from the prodrug TransCon PTH has an effective half-life of approximately 60 hours, and that active PTH levels are sustained within the physiologic range for 24 hours a day when at steady state (8, 9).

Materials and Methods

Trial Design

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 4-week clinical trial with an open-label extension period planned through week 214 (data from Weeks 4 and 26 are presented here) to

evaluate the daily administration of TransCon PTH and its effect on the need for active vitamin D and/or calcium (Fig. 2). The protocol was reviewed by the appropriate institutional review boards and independent ethics committees, with participants providing signed informed consent prior to initiation (ClinicalTrials.gov identifier: NCT04009291; EudraCT No.: 2018-004815-33).

Population

Men and nonpregnant female adults aged 18 years and older with a body mass index of 17 to 40 and postsurgical, autoimmune, genetic, or idiopathic hypoparathyroidism were enrolled. Hypoparathyroidism diagnosis was based on hypocalcemia in the setting of inappropriately low serum PTH levels of at least 26 weeks' duration. Participants were on stable doses of active vitamin D

(defined as calcitriol ≥ 0.5 $\mu\text{g}/\text{day}$, alfacalcidol ≥ 1.0 $\mu\text{g}/\text{day}$) and calcium (defined as elemental calcium ≥ 800 mg/day) for at least 12 weeks before screening and were required to have an estimated glomerular filtrate rate of at least 30 $\text{mL}/\text{min}/1.73$ m^2 . Individuals with mutations in the calcium-sensing receptor gene were excluded, as were people with pseudohypoparathyroidism, diseases other than hypoparathyroidism affecting calcium or PTH homeostasis (including hyperparathyroidism, Paget disease, hypomagnesemia, type 1 or poorly controlled type 2 diabetes mellitus, Cushing syndrome, or multiple endocrine neoplasia), or other significant comorbidities. Individuals taking certain medications (loop or thiazide diuretics, phosphate binders, bisphosphonates, PTH-like or other drugs known to influence calcium and bone metabolism except for calcium supplements and active vitamin D analogs) were also excluded.

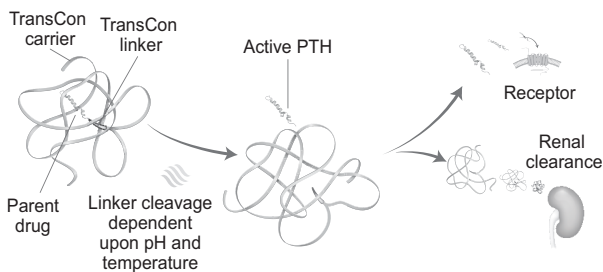


Figure 1. Transient conjugation. TransCon parathyroid hormone (PTH), a sustained-release prodrug consists of a parent drug, PTH(1-34), transiently bound to a carrier via a linker that is autocleaved on exposure to physiologic conditions, releasing active PTH.

Trial Protocol

During the screening period and before randomization, active vitamin D and calcium supplementation was optimized to achieve a 25-hydroxyvitamin D level between 30 and 70 ng/mL , normal serum magnesium, and an albumin-adjusted (or ionized) sCa level in the lower half of normal. For the purpose of this trial, the normal range for albumin-adjusted sCa was 8.3 to 10.6 mg/dL (2.07-2.64 mmol/L) and the normal range for ionized sCa was 1.16-1.32 mmol/L . Participants were then randomly assigned to receive daily TransCon PTH 15, 18,

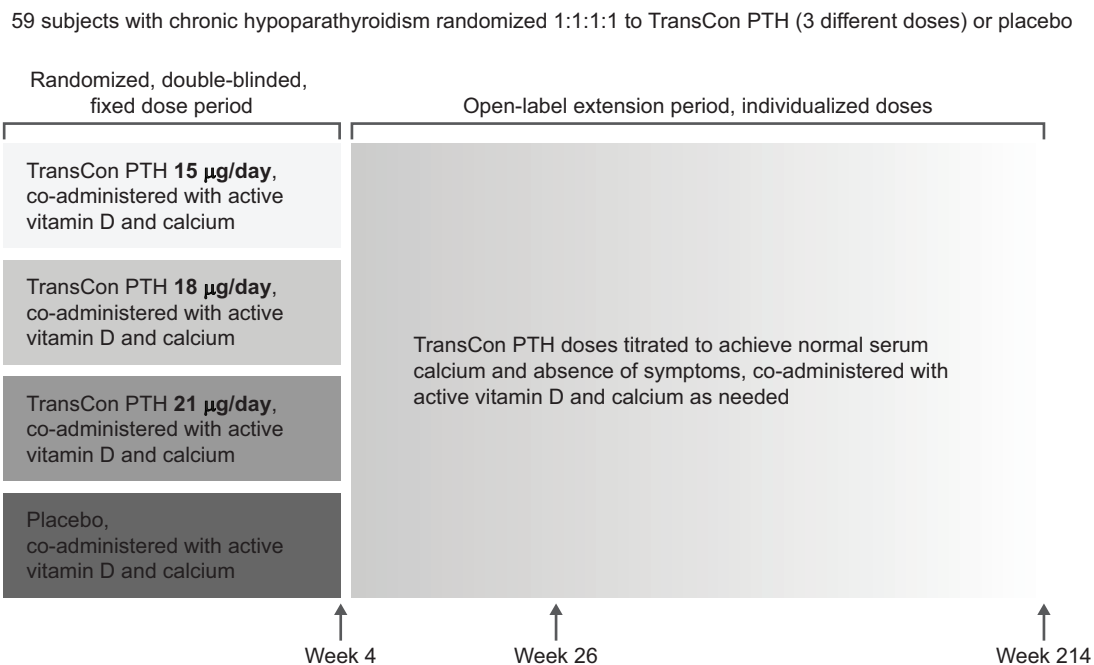


Figure 2. PaTH Forward trial design.

or 21 µg PTH(1-34)/day, or placebo (subrandomized into 3 groups of 1:1:1 to mimic the 3 TransCon PTH cohorts). The drug was administered by SC injection via Ypsomed Uno prefilled pens with a 31-gauge needle. Participants were maintained at the same dose throughout the 4-week blinded period. When sCa was within the normal range at predefined visits, active vitamin D was decreased by increments of 33% to 50% (ie, by skipping the second of 2 daily doses or skipping the third of 3 daily doses) until discontinued. Calcium was subsequently decreased and ultimately discontinued according to a predefined protocol. In the event of laboratory results or clinical symptoms indicating hypocalcemia, rescue doses of active vitamin D and/or calcium were permitted.

For the open-label extension period, participants were assigned to treatment groups based on the continued need for active vitamin D. Individuals no longer requiring active vitamin D were continued on the same dose of TransCon PTH as previously. Those still receiving active vitamin D were started on a TransCon PTH dose of 15 µg/day with the titration of active vitamin D and calcium as per the initial 4-week period protocol. At follow-up visits, TransCon PTH was either increased by 3 µg/day (if persistently hypocalcemic or if sCa was below the lower limit of normal), maintained at the same dose, or decreased by 3 µg/day (if persistently hypercalcemic and no longer taking active vitamin D or calcium). Doses for the extension period ranged from TransCon PTH 6-60 µg/day, with rescue doses of active vitamin D and/or calcium allowed throughout.

Safety Assessments

At predefined intervals, the following were assessed: use of concomitant medications, serum chemistries, hematology, 25-hydroxyvitamin D, anti-PTH and antipolyethylene glycol (anti-PEG) antibodies, and urine chemistries including random “spot” and 24-hour samples. Adverse events (AEs) were collected and assessed by site staff at clinic visits and on review of subject diaries. Urgent care, emergency room, or hospital visits for hypercalcemia or hypocalcemia as well as progression of vascular calcification, nephrocalcinosis, and nephrolithiasis were recorded.

Efficacy Assessments

Efficacy was determined by a composite end point at the end of the 4-week blinded period based on serum calcium within normal range, fractional excretion of calcium (FE_{Ca}) from a spot morning urine sample either within normal range (ie, ≤ 2%) or reduced by 50% or more, discontinuation of all active vitamin D supplements, and a

reduction of calcium supplementation to less than or equal to 1000 mg/day (primary end point) or less than or equal to 500 mg/day (secondary end point). FE_{Ca} was calculated as follows:

$$\text{FE}_{\text{Ca}} = [\text{urinary calcium (mg)} \times \text{serum creatinine}] / (\text{mean albumin-adjusted serum calcium (mg/dL)} \times \text{urinary creatinine})$$

Efficacy was similarly defined at Week 26 except that urine calcium was assessed by a 24-hour sample rather than a spot FE_{Ca}. Other secondary efficacy end points included absolute doses of active vitamin D and calcium, sCa, serum phosphate, FE_{Ca}, and serum calcium-phosphate product. Exploratory endpoints included markers of bone turnover ie, serum procollagen type 1 N-terminal propeptide (P1NP) and C-telopeptide (CTx).

Patient-Reported Outcomes

Patient-reported outcomes were assessed by the generic 36-Item Short Form Health Survey (SF-36, version 2), a 36-item, self-reported, health questionnaire that assesses 8 health dimensions. The SF-36 was administered at baseline and Week 4 to compare differences in health status between TransCon PTH- and placebo-treated individuals and again at Week 26 to determine whether any effect was maintained in the TransCon PTH-treated participants (10). Each question was scored from 0 to 100 with lower scores corresponding to greater disability (11). The SF-36 has 2 component summary scores for physical and mental health, which are expressed relative to the mean of the general US population (12). Similarly, scores for each of the 8 subscales, including general and mental health, physical functioning, role limitations associated with emotional and physical problems, vitality, and pain, were averaged to create norm-based domain scores.

In addition, patient-reported outcomes were assessed at Weeks 4 and 26 by the disease-specific, participant-completed Hypoparathyroid Patient Experience Scale (HPES). The HPES has been psychometrically validated to include a symptom and an impact measure (13) and is under review by the US Food and Drug Administration. The HPES symptom measure assesses key hypoparathyroidism-related physical and cognitive symptoms (“domains”), whereas the HPES impact measure assesses impacts of the disease on functioning and well-being, all from the patient’s perspective. Physical symptoms included muscle cramping, spasms, twitching, and weakness, tingling (with or without numbness), pain, sensitivity to heat, tiredness, difficulty sleeping, heart problems (eg, beating strongly or irregularly), and low energy. Cognitive symptoms included “remembering,” “finding the right words,” “concentrating,” “understanding information,” and “thinking

clearly.” Participants were asked to rate the frequency of each symptom as never (0%), occasionally (1%-25%), sometimes, (26%-50%), often (51%-75%), or very often/always (76%-100%), with answers scored 0 to 4, respectively. For questions within a domain, answers were averaged to create a domain-level score. Domain-level scores were then averaged to create a total score. Finally, domain-level and total scores were both transformed into a 0 to 100 scale for ease of understanding, with lower scores indicating improvement.

Statistical Analyses

Sample size was targeted for 40 total participants (10 in each of the 4 arms), assuming a response rate of 80% in treated and 1% in placebo; for a power of 94.7% at α equal to 0.05. Clinical and safety assessments were reported by summary statistics. Numerical variables were summarized by mean, median, SD, and SE while categorical variables were summarized by absolute numbers and proportions. At 4 weeks, a comparison between each TransCon PTH group and the pooled placebo was conducted for the primary and key secondary endpoints using Fisher exact test based on the intention-to-treat participants, with significance defined as P less than .05 (2-sided). A sensitivity analysis, redefining 2 of 4 components of the composite end point, was performed on the week 26 data. Calcium intake of 500 mg/

day or less was considered to represent independence from therapeutic dosing. Given that urine calcium exists on a continuum and therapeutic benefits may be observed following reduction, even for those who fail to reach normal range, 24-hour urine calcium was further defined as a 50% or greater reduction from baseline. For the HPES symptoms and impact scales as well as the SF-36 component summary and subscale score analyses at week 4, an analysis of covariance model was used, with baseline as a covariate and treatment as a fixed factor.

Results

Participant Disposition and Demographics

A total of 104 individuals were screened, of whom 59 were randomly assigned (Fig. 3). Post hoc, it was determined that 2 participants in the placebo group were taking less than the required minimum threshold of calcitriol at baseline and thus the analysis population was redefined as a modified full analysis set. The primary end point at week 4 was evaluated using this population. A second modified full analysis set, which excluded 1 additional person from each of the TransCon PTH 15 and 21 μg cohorts because of insufficient calcium intake, was also defined and used for the sensitivity analysis of the primary end point for the week 4 data. One individual withdrew

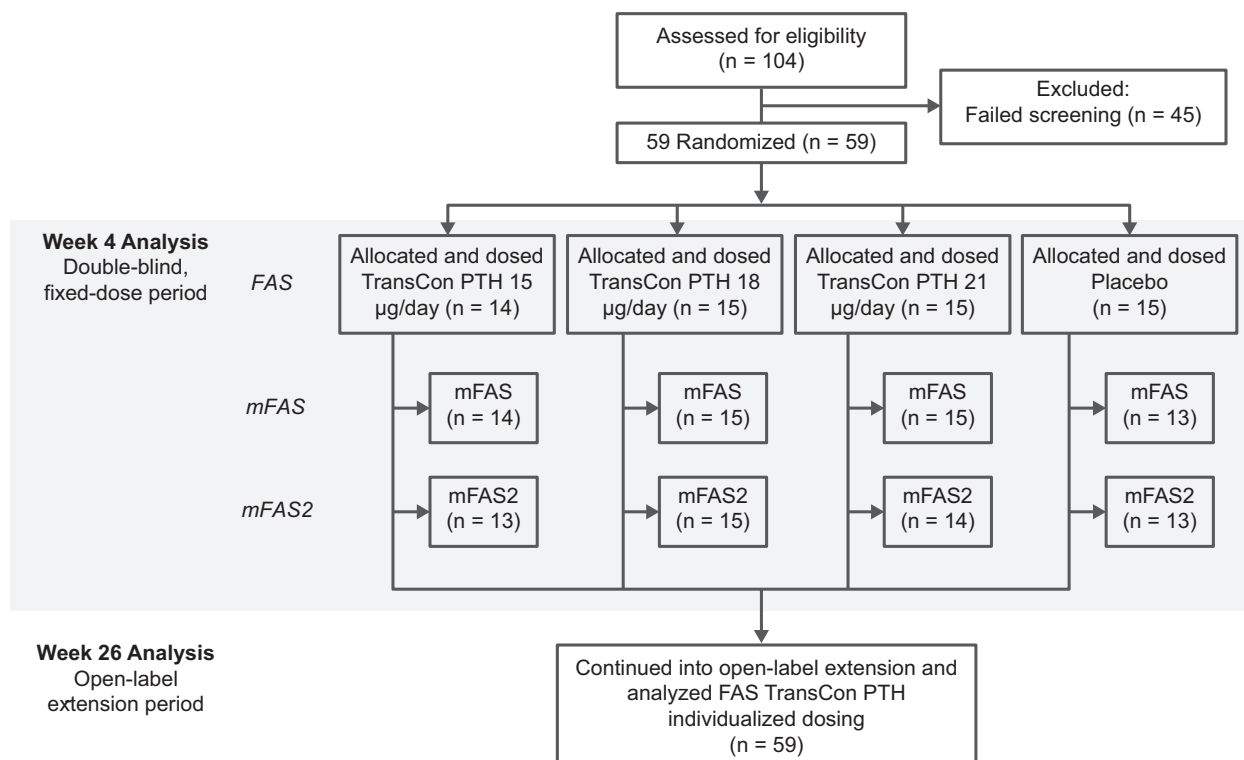


Figure 3. Participant disposition. FAS, full analysis set; mFAS, modified full analysis set.

after 5 weeks of participation for personal reasons, resulting in 58 participants completing the trial through week 26. Given that all participants were transitioned to TransCon PTH during the open-label extension, the 4 people with insufficient calcitriol and calcium intakes at baseline, respectively, were included in the safety analysis at week 26 (N = 59), which did not change the results in a meaningful way.

Table 1 includes participant demographic information as well as hormonal status, etiology, and duration of hypoparathyroidism diagnosis, medical history, and conventional and PTH therapy at baseline. The cohorts were balanced with respect to sex, race, age, and baseline hypoparathyroidism characteristics.

Efficacy

Of 57 participants included in the week 4 analysis, 50% (22/44) treated with TransCon PTH at 15, 18, or 21 µg PTH/day achieved the primary composite end point compared to 15% (2/13) of placebo-treated individuals ($P < .03$) despite being restricted to a fixed (rather than titrated and optimized) dose (Table 2). By week 4, 82% (36/44) of TransCon PTH-treated participants were able to stop oral active vitamin D and reduce calcium supplementation to 500 mg/day or less compared with 15% (2/13) of individuals on placebo ($P < .0001$). In addition, 50% (22/44) of TransCon PTH-treated participants achieved complete independence from conventional therapy (ie, oral

Table 1. Demographics, past medical history, hypoparathyroidism characteristics, and treatment

	TransCon PTH 15 µg/d (n = 14)	TransCon PTH 18 µg/d (n = 15)	TransCon PTH 21 µg/d (n = 15)	All TransCon PTH (n = 44)	Placebo (n = 15)
Mean age, y (SD)	47 (13)	47 (11)	54 (11)	49 (12)	52 (12)
Female, No. (%)	12 (86)	12 (80)	12 (80)	36 (82)	12 (80)
Premenopausal	8 (67)	8 (67)	7 (58)	23 (64)	8 (67)
Postmenopausal	4 (33)	4 (33)	5 (42)	13 (36)	4 (33)
Race, %					
Asian	0	0	13	5	0
White	100	80	87	89	100
Other	0	20	0	7	0
Geographic region, %					
North America	50	80	67	66	60
Europe	50	20	33	34	40
Mean weight, kg (SD)	77 (22)	80 (11)	72 (19)	76 (18)	76 (14)
Past medical history, No. (%)					
Renal insufficiency	1 (7)	3 (20)	1 (7)	5 (11)	0
Nephrolithiasis	2 (14)	1 (7)	1 (7)	4 (9)	4 (27)
Ectopic calcifications	0	0	1 (7)	1 (2)	0
Vascular calcifications	0	0	0	0	0
Brain calcifications	0	0	0	0	0
Cataracts	0	0	0	0	0
Seizures	1 (7)	0	0	1 (2)	1 (7)
Median hypoparathyroidism duration, y	9	7	10	9	13
Etiology of hypoparathyroidism, No. (%)					
Neck surgery	10 (71)	12 (80)	12 (80)	34 (77)	13 (87)
Autoimmune disease	1 (7)	0	0	1 (2)	0
Intrinsic genetic defects of parathyroid glands	0	0	0	0	0
Idiopathic disease	3 (21)	3 (20)	3 (20)	9 (21)	2 (13)
Conventional therapy at baseline ^a					
Median elemental calcium, mg/d	1200	1316	2699	1550	1200
Median calcitriol, µg/d	0.63	0.75	0.50	0.63	0.50
Median alfacalcidol, µg/d	2.5	2.0	2.0	2.5	2.5
PTH ^b therapy within 6 mo of screening, No. (%)	3 (21)	3 (20)	3 (20)	9 (21)	3 (20)

Abbreviation: PTH, parathyroid hormone.

^aBaseline data available for elemental calcium (n = 53), calcitriol, or alfacalcidol (n = 57).

^bIncludes PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein.

Table 2. Composite end points with respective components for weeks 4 and 26

	Week 4					Week 26
	TransCon PTH 15 µg/d	TransCon PTH 18 µg/d	TransCon PTH 21 µg/d	All TransCon PTH	Placebo	All TransCon PTH
Participants with data for all criteria at wk 4 or 26						49 ^d
Full analysis (N = 59)	14	15	15	44	15	
Modified full analysis 1 (N = 57)	14	15	15	44	13	
Modified full analysis 2 (N = 55)	13	15	14	42	13	
Participants meeting primary composite end point, No. (%)	7 (50)	6 (40)	9 (60)	22 (50)	4 (27)	35 (71)
(95% CI)	7 (50) 6 (46) (23-77)	6 (40) 6 (40) (16-68)	9 (60) 9 (64) (32-84)	22 (50) 21 (50) (35-65)	4 (27) 2 (15) (8-55)	(57-83)
<i>P</i> ^a	0.26 0.10 0.20	0.70 0.22 0.22	0.14 0.02 0.02	0.14 0.03 0.05	(2-45) (2-45)	
Participants meeting each component of end point, No. (%)						
Serum calcium within normal range ^b	12 (86)	12 (80)	14 (93)	38 (86)	14 (93)	45 (92)
Active vitamin D = 0 µg/d	14 (100)	14 (93)	15 (100)	43 (98)	6 (40)	49 (100)
Calcium ≤ 1000 mg/d	13 (93)	13 (87)	15 (100)	41 (93)	8 (53)	46 (94)
FECa (spot morning urine) within normal range (≤ 2%) or ≥ 50% reduction from baseline	10 (71)	8 (53)	9 (60)	27 (61)	7 (54)	
24-h urine calcium within normal range ^c	9 (69)	8 (53)	9 (64)	26 (62)	5 (38)	41 (84)

Abbreviations: FECa, fractional excretion of calcium; PTH, parathyroid hormone.

^aFisher exact test used to compare differences in proportions with placebo.

^bNormal range for albumin-adjusted serum calcium is 8.3 to 10.6 mg/dL (2.07-2.64 mmol/L); normal range for ionized serum calcium is 1.16 to 1.32 mmol/L.

^cNormal range for 24-hour urine calcium is defined as less than or equal to 250 mg/24 h (≤ 6.25 mmol/24 h) for women, and less than or equal to 300 mg/24 h (≤ 7.5 mmol/24 h) for men.

^dPercentages are based on 49 individuals with available data for all criteria at 26 weeks.

active vitamin D = 0 µg and reduce calcium supplementation to ≤ 500 mg/day compared with 0% (0/13) of placebo recipients.

After week 4, dose titration of TransCon PTH was guided by sCa. By week 26, participants were using all available dosage strengths, with TransCon PTH 18 µg representing both the mean and median dose. At week 26, 10 individuals were missing 1 or more data points required to evaluate the composite end point and were thus excluded from the analysis. Reasons for missing data included trial withdrawal (n = 1), urine sample collected outside the allowable time window (n = 7), and urine sample lost in transit (n = 2).

By week 26, of those with full data, 71% (35/49) of participants achieved the primary extension end point (Table 2). Furthermore, 91% (53/58) of participants were able to

stop oral active vitamin D and reduce calcium supplementation to 500 mg/day or less, while 76% (44/58) of individuals eliminated active vitamin D and calcium entirely. Data from the sensitivity analysis were identical to that of the primary extension except 90% (44/49) and 86% (42/49) of participants achieved the individual components of calcium intake (≤ 500 mg/day) and 24-hour urine calcium (normal or ≥ 50% reduction from baseline), respectively.

Mean serum 25-hydroxyvitamin D decreased slightly from baseline through week 26 (45 ng/mL to 39 ng/mL, respectively), possibly reflecting both exposure to PTH therapy and to changes in cholecalciferol taken as part of combination calcium-cholecalciferol preparations.

On average, sCa, phosphate, and calcium-phosphate products were maintained within the normal range for

individuals with available data throughout week 26, with sCa excursions occurring less frequently than at baseline (Table 3). Similarly, renal reabsorption of filtered calcium was restored to normal, as evidenced by a decrease in the mean 24-hour urine calcium excretion from 415 mg/24 hours to 178 mg/24 hours (Fig. 4).

Changes in bone turnover markers are shown in Fig. 5. By week 26, mean values for both the anabolic marker P1NP and resorptive marker CTx increased within the normal range or to just above the normal range, respectively, reflecting exposure to the physiologic bone-remodeling effects of PTH. At week 26, mean (SD) P1NP increased to 88 (44) ng/mL (n = 56; see Fig. 5). Mean (SD) CTx increased to 763 (412) ng/L (n = 55), within normal range for the majority of participants.

Patient-Reported Outcomes

At week 4, health-related quality of life as measured by the SF-36 demonstrated statistically significant improvements from baseline in TransCon PTH-treated individuals compared with placebo both in the physical and mental component scores ($P < .05$; Fig. 6A). Furthermore, when compared with the general US population, the scores for TransCon PTH-treated participants at week 4 were within normal range of functioning, whereas they were below these ranges at baseline (11). These improvements continued at week 26, with both scores within the range of the US population mean (Fig. 6B).

At week 4, SF-36 scores in 7 of 8 subscales showed statistical improvement in TransCon PTH-treated patients compared with placebo ($P < .05$; Fig. 7); the general health subscale score also demonstrated improvement but did not achieve statistical significance. At week 26, the quality of life as measured by SF-36 continued to be maintained above baseline with all subscales, exceeding 50 compared with the baseline in which all scores were less than 47. Of note, there was no apparent correlation between week 4 serum calcium levels and SF-36 scores.

From baseline to week 4, the difference in mean total and domain scores for both HPES symptom and impact scales demonstrated a statistically significant improvement (ie, a decrease in score; $P < .01$) for TransCon PTH compared with placebo (Fig. 8A and 8B; Table 4). This is illustrated by radar plots in which TransCon PTH-treated participant scores at week 4 were lower and thereby covered less shaded area than at baseline, represented by the lighter gray area. In contrast, for placebo-treated individuals, the difference in dark and light gray areas was minimal, indicating a nonsignificant change from baseline to week 4. The improvement observed with TransCon PTH treatment was maintained through week 26 (Fig. 8C).

Safety

There were no serious AEs (SAEs) related to study drug and no AEs led to treatment discontinuation or death over 26 weeks. Two participants reported a total of 5 SAEs requiring hospitalizations; all SAEs were assessed as unrelated to study drug. In one individual with a history of nephrolithiasis, a screening bone density scan for the study revealed asymptomatic calcifications overlying the right abdomen, which resulted in hospitalization for percutaneous nephrolithotomy. During the nephrolithotomy, multiple

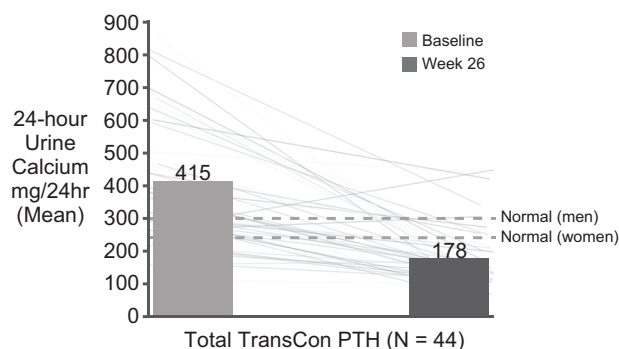


Figure 4. Mean 24-hour urine calcium at baseline and week 26. Gray lines represent individual patient data from baseline to week 26.

Table 3. Albumin-adjusted serum calcium excursions at baseline to week 26

	Serum calcium			
	< 8.3 mg/dL		> 10.6 mg/dL	
	TransCon PTH/TransCon PTH	Placebo/TransCon PTH	TransCon PTH/TransCon PTH	Placebo/TransCon PTH
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Week 0	10/44 (23)	1/15 (7)	1/44 (2)	0/15 (0)
Week 4	3/44 (7)	1/15 (7)	3/44 (7)	0/15 (0)
Week 26	4/43 (9)	1/13 (8)	0/43 (0)	0/13 (0)

Abbreviation: PTH, parathyroid hormone.

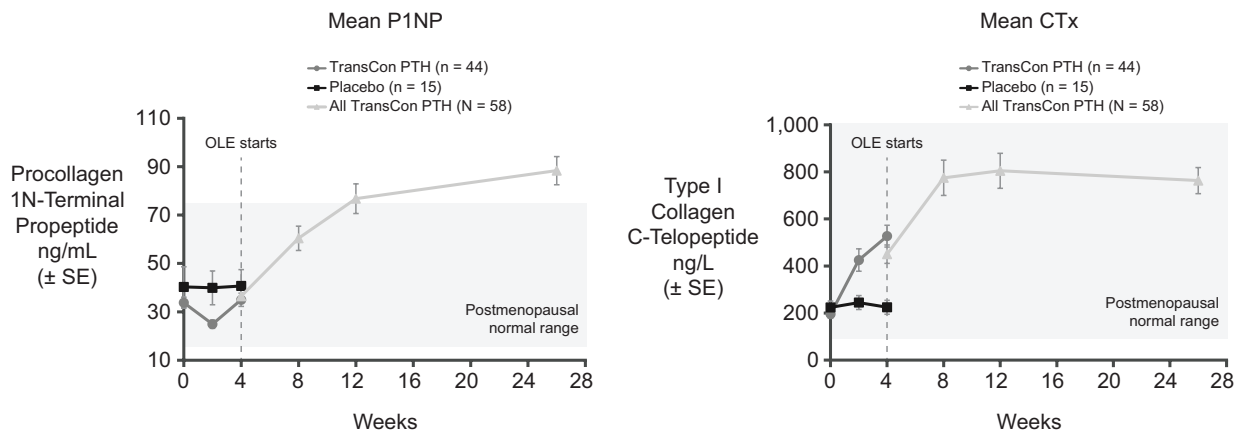


Figure 5. Bone turnover markers from baseline to week 4 and week 26.

right-sided kidney stones were removed, and calyx tumors were incidentally found and biopsied. When the biopsies revealed urothelial cancer, this individual was hospitalized again for a right-sided nephrectomy. This patient recovered and continues in the ongoing trial. Another participant was hospitalized for ethmoidectomy and sinus fenestration in the context of chronic sinusitis despite glucocorticoid therapy. This individual later had vertebral compression fractures and was hospitalized on 2 occasions for vertebroplasties. This patient recovered and continues in the ongoing trial.

AEs were reported in 37 of 59 (62.7%) individuals administered TransCon PTH, with 15 of 59 (25.4%) reporting an AE that was considered related to TransCon PTH. The most common AEs irrespective of causality were headache (16.9%), nausea (8.5%), fatigue and hypertension (each 6.8%), and arthralgia, hypocalcemia, muscle spasm, and urinary tract infection (each 5.1%). Three participants (5.1%) administered TransCon PTH reported injection site-related AEs described as localized swelling, or localized erythema, or bleeding and pain. No AEs related to hypocalcemia or hypercalcemia required urgent medical attention.

No anti-PTH antibodies were detected through week 26. No treatment-emergent anti-PEG antibodies were detected. Preexisting anti-PEG antibodies were detected in 20% (12 of 59) of participants. In 2 of the 12 participants, the anti-PEG titers increased on treatment within the first 2 to 4 weeks, with the highest titers observed after 4 to 6 weeks. The titers started to decline from week 6 and 8 and were back to baseline at or before week 26, and are therefore considered to be transient increases.

Discussion

In this phase 2 trial of individuals with chronic hypoparathyroidism, 82% of TransCon PTH-treated participants at week 4 achieved independence from conventional therapy

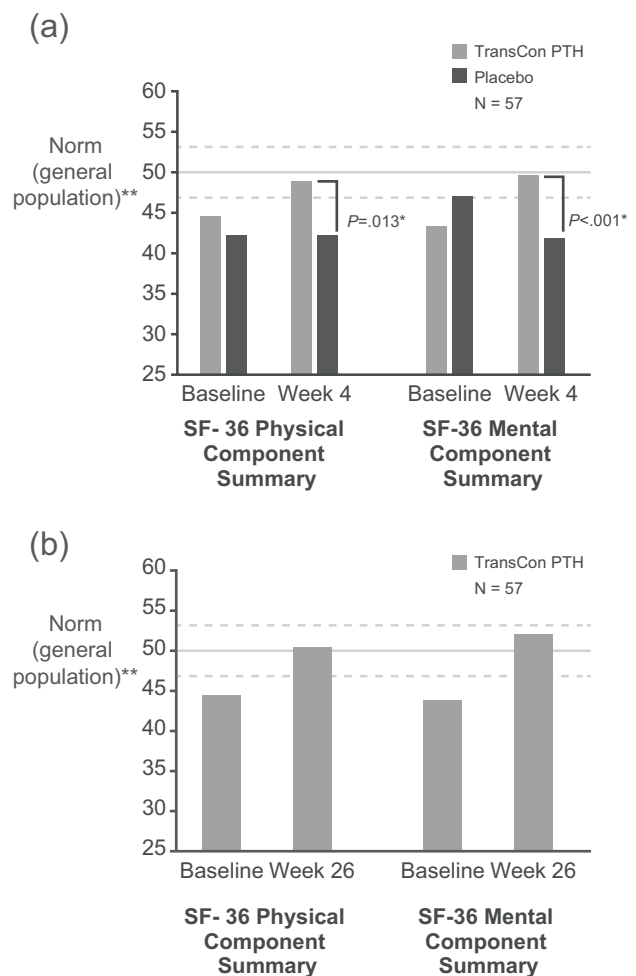


Figure 6. SF-36 Physical and Mental component summaries at A, week 4, and B, week 26. **The dashed lines (between 47 and 53) indicate the lower and upper T score bounds for the US general population's average level of functioning, with scores below 47 indicating impairment (11).

(ie, oral active vitamin D = 0 µg/day, and calcium supplements ≤ 500 mg/day) compared with only 15% of participants treated with placebo, a trend that continued through

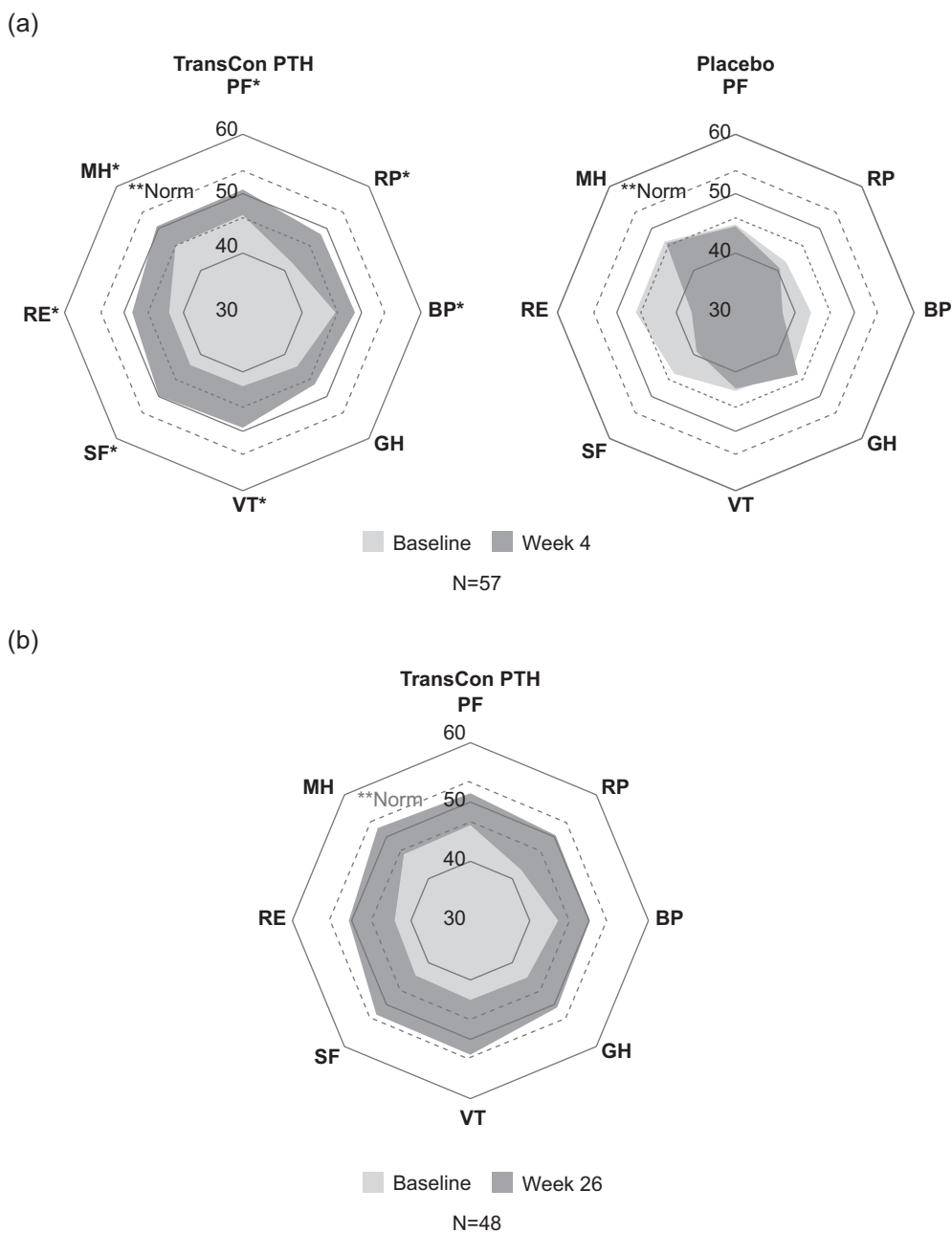


Figure 7. SF-36 domain scores at A, week 4, and B, week 26. BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; PTH, parathyroid hormone; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality. The dashed lines (between 47 and 53) indicate the lower and upper T score bounds for the US general population's average level of functioning, with below 47 indicating impairment (10). *P less than .05 compared with placebo.

week 26 when 91% of TransCon PTH-treated individuals had achieved the same supplement independence. On average, sCa was maintained within the normal range by TransCon PTH, with excursions occurring infrequently and at a lower rate than at baseline. TransCon PTH was also associated with a normalization of renal reabsorption of filtered calcium from baseline to week 26. TransCon PTH-treated individuals demonstrated a significant improvement in health-related quality of life (as measured by SF-36) compared with placebo by week 4, rising to within the normal range of the general

US population, and continuing for all participants through week 26. Similarly, the difference in mean total and domain scores for both HPES symptom and impact scales demonstrated a statistically significant improvement for TransCon PTH compared with placebo at week 4, an improvement that continued for all participants through week 26. These clinical benefits were demonstrated while maintaining a generally favorable safety profile; treatment-emergent AEs were limited and included muscle spasm, infections, and hypocalcemia, which are features of hypoparathyroidism.

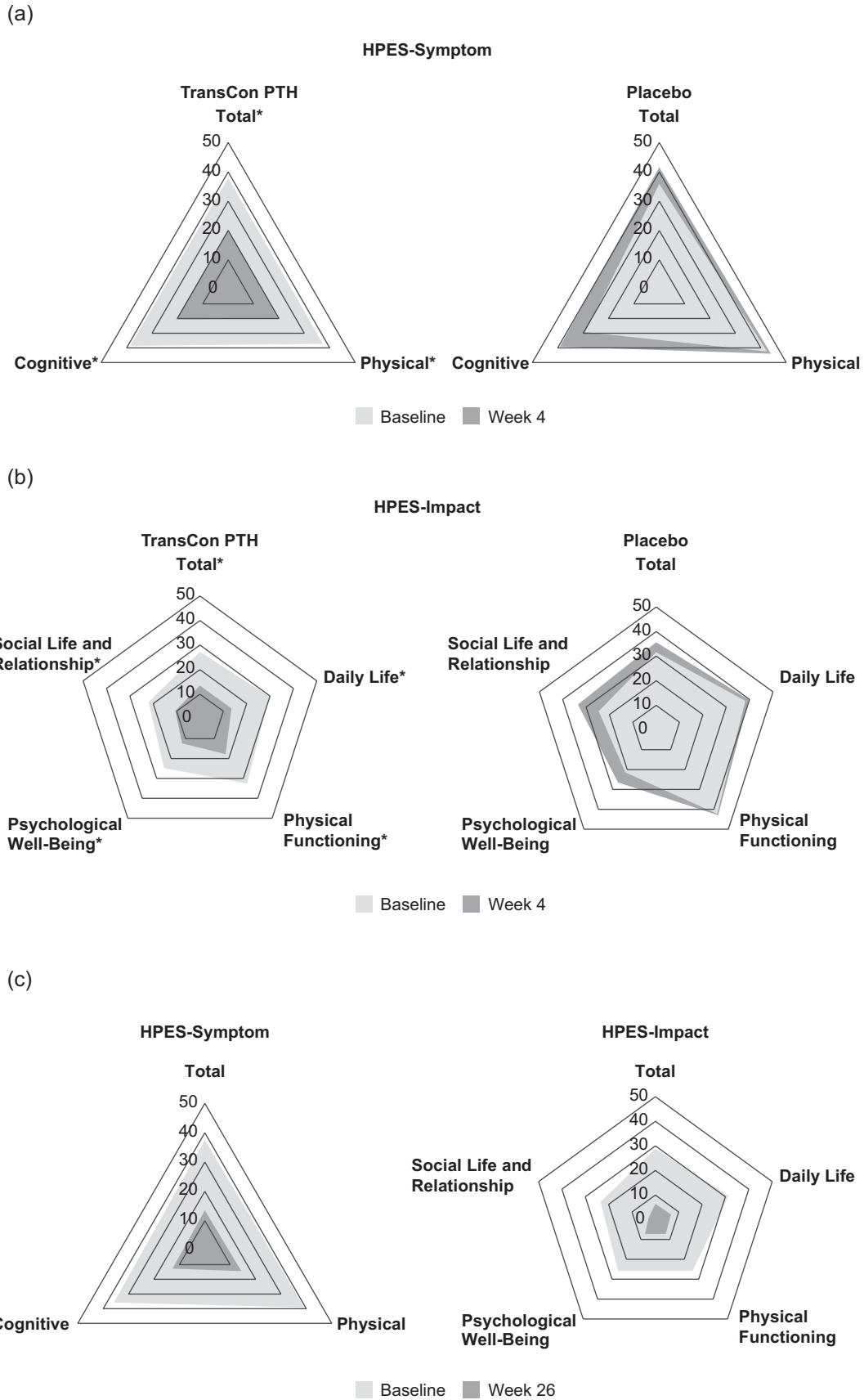


Figure 8. Symptom and impact scales for Hypoparathyroid Patient Experience Scale (HPES) total and domain-level scores at A and B, week 4, and C, at week 26. Lower scores (ie, less radar plot area) indicate less impact/symptoms. **P* less than .05 compared with placebo.

Table 4. Summary of Hypoparathyroid Patient Experience Scale impact and symptom scales for TransCon parathyroid hormone vs placebo by analysis of covariance (full analysis set; N = 59)

HPES impact scale	TransCon PTH all participants (n = 44)	Placebo (n = 15)
Daily life domain, No.	44	15
LS mean (SE)	-16.8 (2.7)	0.8 (4.6)
Difference in LS mean (SE)	-17.7 (5.3)	
P	.002	
Physical functioning domain, No.	44	15
LS mean (SE)	-15.8 (2.9)	0.3 (5.1)
Difference in LS mean (SE)	-16.1 (5.8)	
P	.008	
Psychological well-being domain, No.	44	15
LS mean (SE)	-12.5 (2.6)	0.1 (4.5)
Difference in LS mean (SE)	-12.6 (5.1)	
P	.016	
Social life and relationship domain, No.	44	15
LS mean (SE)	-11.7 (2.8)	4.9 (4.9)
Difference in LS mean (SE)	-16.6 (5.6)	
P	.005	
Total HPES impact score, No.	44	15
LS mean (SE)	-14.2 (2.5)	1.5 (4.3)
Difference in LS mean (SE)	-15.7 (5.0)	
P	.003	
HPES symptom scale		
Physical domain, No.	44	15
LS mean (SE)	-17.5 (2.3)	0.4 (4.0)
Difference in LS mean (SE)	-18.1 (4.6)	
P	< .001	
Cognitive domain, No.	44	15
LS mean (SE)	-17.6 (2.8)	3.2 (4.9)
Difference in LS mean (SE)	-20.8 (5.6)	
P	.001	
Total HPES symptom score, No.	44	15
LS mean (SE)	-17.7 (2.3)	2.3 (4.0)
Difference in LS mean (SE)	-20.0 (4.6)	
P	< .001	

Abbreviation: HPES, Hypoparathyroid Patient Experience Scale; LS, lumbar spine; PTH, parathyroid hormone.

In a previous phase 1 trial, it was shown that active PTH released from the prodrug, TransCon PTH, had an effective half-life of approximately 60 hours and that active PTH levels were sustained within the physiologic range for 24 hours per day at steady state (8, 9). The data from this phase 2 trial demonstrate that TransCon PTH can restore the physiologic effects of PTH so that exogenous supplementation of the downstream hormone calcitriol is no longer required.

Considering that TransCon PTH dosing was randomly assigned and fixed during the first 4 weeks, the proportion of individuals who were able to discontinue vitamin D and decrease calcium supplementation was high. This suggests that with titration of dose, there is the potential for TransCon PTH to restore the body's normal calcium homeostasis. Although sCa excursions did occur, these were expected and, in clinical practice, are considered a normal part of determining optimal therapeutic dosing for any patient with hypoparathyroidism. Assuming that the effects of TransCon PTH on renal calcium reabsorption are durable, the improvement in urine calcium excretion may lead to the preservation of long-term renal health and may contribute to a reduced risk of developing nephrocalcinosis, nephrolithiasis, renal insufficiency, and its associated sequelae.

Both the anabolic marker P1NP and resorptive marker CTx increased within or just above the normal range, reflecting restoration of the physiologic effects of PTH. Recognizing that bone remodeling is low in PTH deficiency, published data of intermittent exposure to PTH suggest that a temporary peak in P1NP and CTx lasting approximately 24 to 36 months may be expected during initial treatment (14-16). Eventually, a new steady state is expected to be achieved, higher than the untreated baseline but lower than the initial peak. Compared with intermittent PTH exposure, continuous infusion with a tonic level of serum PTH similar to TransCon PTH is associated with a smaller change in CTx at 3 months (17). This is consistent with a lower magnitude of increase in bone turnover with TransCon PTH than that of rhPTH (1-84), teriparatide, and abaloparatide, the latter 2 of which provide intermittent daily PTH pulses to maximize the anabolic effect (18-20).

To the best of our knowledge, this is the first double-blind, placebo-controlled trial in individuals with chronic hypoparathyroidism that has shown a study drug significantly enhanced the health-related quality of life (according to SF-36). At baseline, the validated SF-36 demonstrated scores below the average US population normative values for quality of life. Within 4 weeks, they had reached the normative range, exceeding the mean for the US population by week 26. The disease-specific HPES, which assesses patient-related symptom and impact outcome measures developed by the sponsor for chronic hypoparathyroidism, goes further. Health-related quality of life domains specifically affected by hypoparathyroidism, including physical symptoms such as muscle spasms, pain, lack of energy, as well as cognitive symptoms related to memory, thinking, and concentrating, all improved with TransCon PTH. With conventional therapy, it has been observed that emotional and cognitive symptoms persist despite restoration of normal sCa

levels. This suggests normalization of sCa levels alone is not sufficient in patients with hypoparathyroidism, and that the direct effect of PTH may be important for neurocognitive health (21-23). As such, the improvements in the patient-reported outcomes observed in this trial support TransCon PTH as a potential therapeutic advance (21, 22).

This study has some limitations. Doses of TransCon PTH were fixed during the initial 4-week period to allow for a straightforward comparison with conventional therapy, even though in the clinical setting doses may be titrated based on an individual patient's requirements. Dose adjustment was allowed in the open-label extension period and resulted in an overall increase in the proportion of patients who were able to achieve independence from conventional therapy. Treatment groups were small but were suitable for a clinical trial in a rare disease such as hypoparathyroidism.

With TransCon PTH normalization of PTH physiology and biochemistry was demonstrated, along with improved clinical outcomes and health-related quality of life. The results of this phase 2 PaTH Forward trial support TransCon PTH as a potential replacement therapy for patients with hypoparathyroidism and advancement to phase 3 clinical development.

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Data Availability: The data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

References

- DeLuca HF. The kidney as an endocrine organ for the production of 1,25-dihydroxyvitamin D₃, a calcium-mobilizing hormone. *N Engl J Med.* 1973;289(7):359-365.
- Haussler MR, McCain TA. Basic and clinical concepts related to vitamin D metabolism and action (first of two parts). *N Engl J Med.* 1977;297(18):974-983.
- Haussler MR, McCain TA. Basic and clinical concepts related to vitamin D metabolism and action (second of two parts). *N Engl J Med.* 1977;297(19):1041-1050.
- Reichel H, Koeffler HP, Norman AW. The role of the vitamin D endocrine system in health and disease. *N Engl J Med.* 1989;320(15):980-991.
- Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab.* 2012;97(12):4507-4514.
- Bilezikian JP, Brandi ML, Cusano NE, et al. Management of hypoparathyroidism: present and future. *J Clin Endocrinol Metab.* 2016;101(6):2313-2324.
- Center for Drug Evaluation and Research. Clinical pharmacology and biopharmaceutics review(s) application number 125511Orig1s000 (Natpara). 2014. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125511Orig1s000ClinPharmR.pdf. Accessed August 17, 2021.
- Karpf DB, Pihl S, Mourya S, et al. A randomized double-blind placebo-controlled first-in-human phase 1 trial of TransCon PTH in healthy adults. *J Bone Miner Res.* 2020;35(8):1430-1440.
- Holten-Andersen L, Pihl S, Rasmussen CE, et al. Design and preclinical development of TransCon PTH, an investigational sustained-release PTH replacement therapy for hypoparathyroidism. *J Bone Miner Res.* 2019;34(11):2075-2086.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
- Maruish ME. *User's manual for the SF-36v2 Health Survey.* 3rd ed. Quality Metric Incorporated; 2011.
- Vokes TJ, Mannstadt M, Levine MA, et al. Recombinant human parathyroid hormone effect on health-related quality of life in adults with chronic hypoparathyroidism. *J Clin Endocrinol Metab.* 2018;103(2):722-731.
- Brod M, McLeod L, Markova D, et al. Psychometric validation of the hypoparathyroidism patient experience scales (HPES). *J Patient Rep Outcomes.* 2021;5(1):70.

14. Mannstadt M, Clarke BL, Bilezikian JP, et al. Safety and efficacy of 5 years of treatment with recombinant human parathyroid hormone in adults with hypoparathyroidism. *J Clin Endocrinol Metab.* 2019;**104**(11):5136-5147.
15. Rubin MR, Cusano NE, Fan WW, et al. Therapy of hypoparathyroidism with PTH(1-84): a prospective six year investigation of efficacy and safety. *J Clin Endocrinol Metab.* 2016;**101**(7):2742-2750.
16. Cusano NE, Rubin MR, Irani D, Sliney J Jr, Bilezikian JP. Use of parathyroid hormone in hypoparathyroidism. *J Endocrinol Invest.* 2013;**36**(11):1121-1127.
17. Winer KK, Zhang B, Shrader JA, et al. Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. *J Clin Endocrinol Metab.* 2012;**97**(2):391-399.
18. Eastell R, Mitlak BH, Wang Y, Hu M, Fitzpatrick LA, Black DM. Bone turnover markers to explain changes in lumbar spine BMD with abaloparatide and teriparatide: results from ACTIVE. *Osteoporos Int.* 2019;**30**(3):667-673.
19. Rubin MR, Dempster DW, Sliney J Jr, et al. PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. *J Bone Miner Res.* 2011;**26**(11):2727-2736.
20. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L; Hypoparathyroid Study Group. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. *J Bone Miner Res.* 2011;**26**(10):2358-2370.
21. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL. Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. *Endocr Pract.* 2014;**20**(7):671-679.
22. Büttner M, Musholt TJ, Singer S. Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. *Endocrine.* 2017;**58**(1):14-20.
23. Cusano NE, Bilezikian JP. Signs and symptoms of hypoparathyroidism. *Endocrinol Metab Clin North Am.* 2018;**47**(4):759-770.