Sustained Improvement in Renal Function With Palopegteriparatide in Adults With Chronic Hypoparathyroidism: Three-Year Results From the PaTH Forward and PaTHway Trials

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TH-PO0227

Conclusion

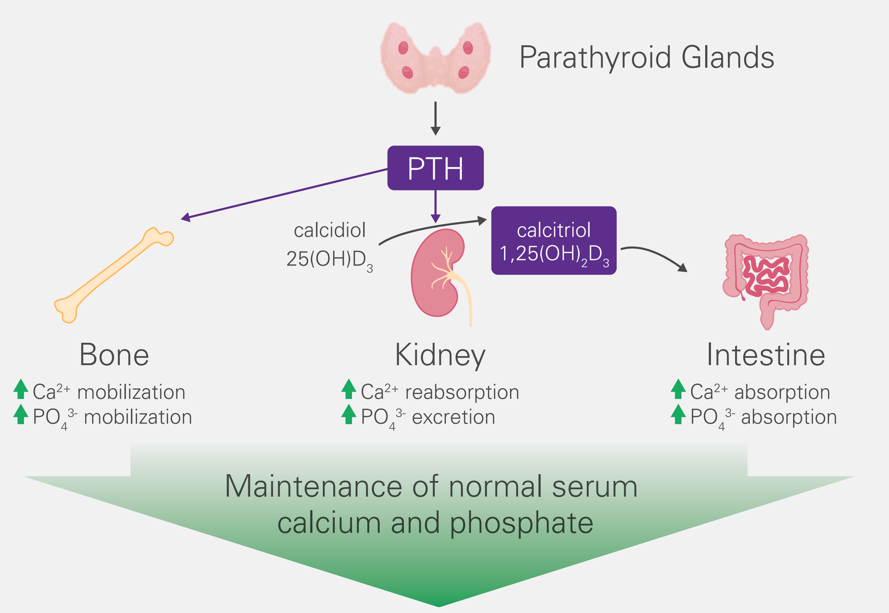
Clinically meaningful early improvements in eGFR with palopegteriparatide observed in PaTH Forward and PaTHway were sustained through Year 3.

- The greatest increases in eGFR were observed in the first 6 months, with a continued upward trend thereafter.
- Reductions in 24-hour urinary calcium excretion were observed and maintained within the normal range through Year 3.
- Palopegteriparatide for the treatment of hypoparathyroidism maintained safety and efficacy through Year 3.

Background

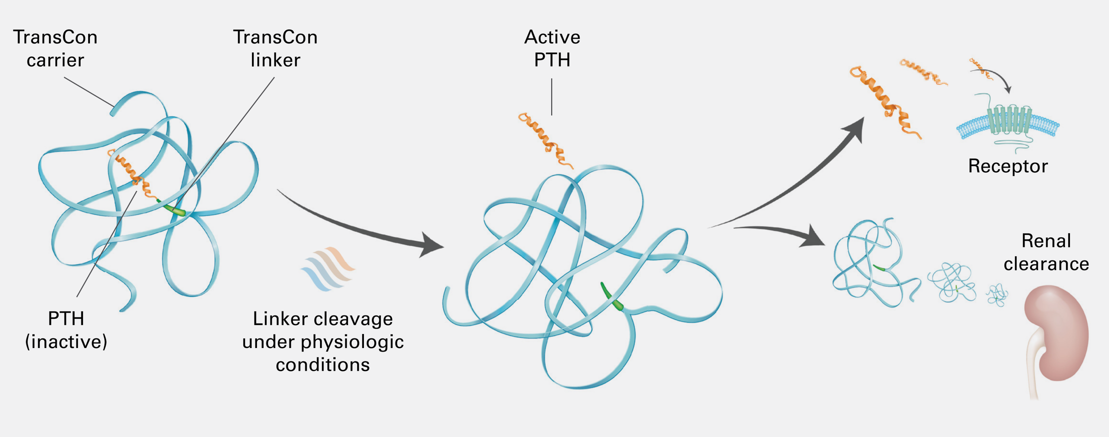
- An intact PTH axis maintains normal serum and urine calcium and phosphate homeostasis[1,2,3]
- PTH is the primary regulator of calcium/phosphate balance, acting directly on bone and kidney, and indirectly on the intestine[4,5]
- Conventional therapy for hypoparathyroidism (active vitamin D (calcitriol) and oral calcium) aims to alleviate hypocalcemic symptoms but fails to restore normal PTH physiology[6]
- PTH replacement therapy for hypoparathyroidism should provide PTH levels within the physiological range and restore downstream calcitriol, promoting independence from conventional therapy and normalizing:
 - Serum and urine calcium and phosphate
 - Skeletal health
 - Quality of life

Figure 1: **PTH Therapy for Hypoparathyroidism[7]**


Parathyroid Glands
PTH
calcidiol
25(OH)D3
calcitriol
1,25(OH)2D3
Bone
Ca2+ mobilization
PO43- mobilization
Kidney
Ca2+ reabsorption
PO43- excretion
Intestine
Ca2+ absorption
PO43- absorption
Maintenance of normal serum calcium and phosphate

Background

Figure 2: **Palopegteriparatide (TransCon® PTH) Design**

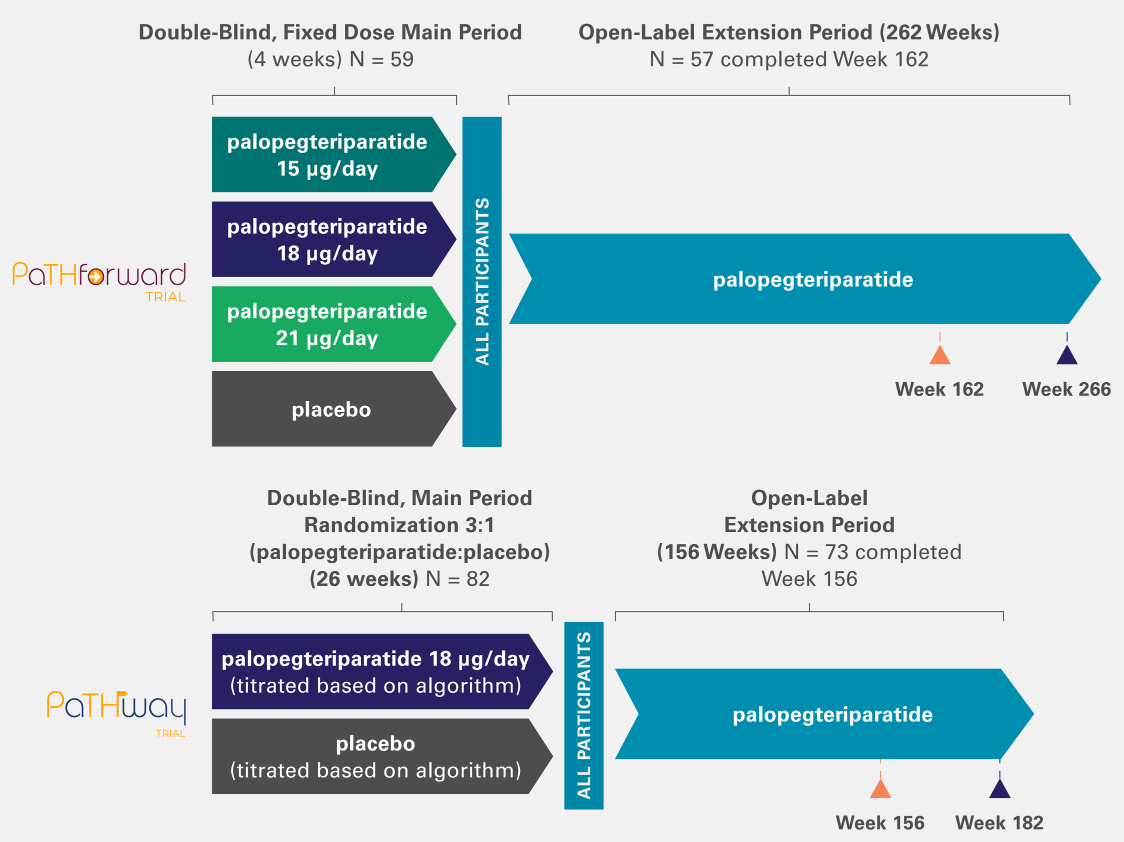

TransCon carrier
TransCon linker
Active PTH
Receptor
Renal clearance
PTH (inactive)
Linker cleavage under physiologic conditions

- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[8,9]
- Palopegteriparatide has received regulatory approval in the US, EU, and several other countries[a,b]

[a]Indicated for the treatment of hypoparathyroidism in adults.
[b]Indicated for the treatment of adults with chronic hypoparathyroidism.

Methods

Figure 3: **Schematics of Trial Designs Used in Combined Analysis**


Double-Blind, Fixed Dose Main Period (4 weeks) N = 59
Open-Label Extension Period (262 Weeks) N = 57 completed Week 162
PaTHforward TRIAL
palopegteriparatide 15 µg/day
palopegteriparatide 18 µg/day
palopegteriparatide 21 µg/day
placebo
ALL PARTICIPANTS
palopegteriparatide
Week 162
Week 266
Double-Blind, Main Period Randomization 3:1 (palopegteriparatide:placebo) (26 weeks) N = 82
Open-Label Extension Period (156 Weeks) N = 73 completed Week 156
PaTHway TRIAL
palopegteriparatide 18 µg/day (titrated based on algorithm)
placebo (titrated based on algorithm)
ALL PARTICIPANTS
palopegteriparatide
Week 156
Week 182

Key Efficacy and Safety Endpoints
- Levels of serum calcium (normocalcemia)
- Independence from conventional therapy (defined as taking no active vitamin D and ≤ 600 mg/day elemental calcium)
- Incidence of AEs, SAEs, TEAEs

Combined Renal Analysis Study
- Changes in eGFR from baseline
- Proportion of participants with increase in eGFR ≥ 5 mL/min/1.73 m²
- Levels of 24-hour urinary calcium

Note: Analyses include only participants who received at least one dose of palopegteriparatide. Analyses were performed by time since the first dose of active drug.

Methods

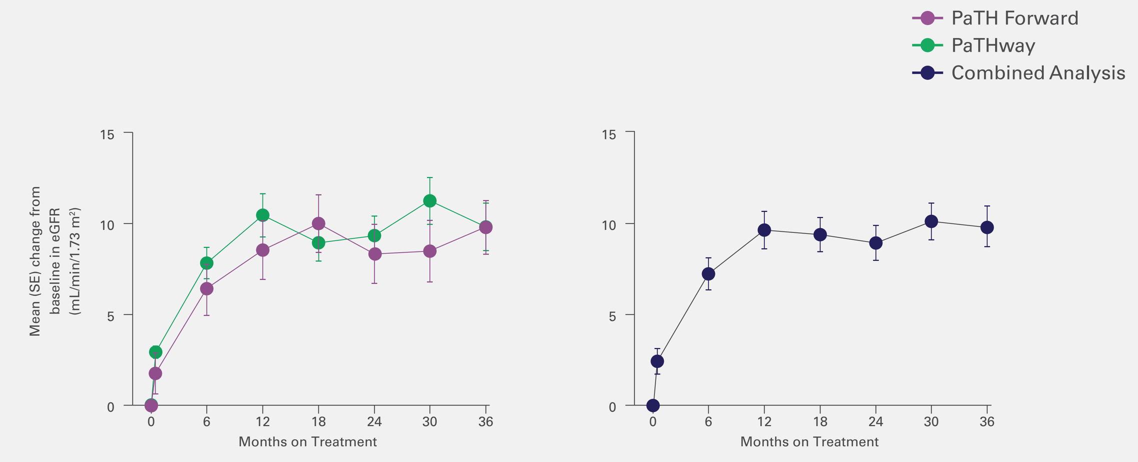
Table 1: **Baseline Demographics and Disease Characteristics**

Variable	Statistic or Category	Baseline GFR < 60 mL/min/1.73 m²	Baseline GFR ≥ 60 mL/min/1.73 m²	All Participants
		(N = 41)	(N = 98)	(N = 139)
Mean age, years (SD)		52 (12)	48 (12)	49 (12)
Sex, n (%)	Female	33 (80)	78 (80)	111 (80)
	Postmenopausal	13 (39)	26 (33)	39 (35)
Race, n (%)	White	39 (95)	89 (91)	128 (92)
Geographic region, n (%)	North America	28 (68)	60 (61)	88 (63)
	Europe	13 (32)	38 (39)	51 (37)
Mean eGFR, mL/min/1.73 m² (SD)*		51 (8)	76 (13)	69 (17)
Cause of hypoparathyroidism, n (%)	Acquired from neck surgery	33 (80)	83 (85)	116 (84)
	Autoimmune disease	0 (0)	2 (2)	2 (1)
	Idiopathic disease	6 (15)	11(11)	17(12)
	Intrinsic genetic defects of parathyroid glands	1 (2)	2 (2)	3 (2)
	Other	1 (2)	0 (0)	1 (1)
Median duration of hypoparathyroidism, years (range)		13 (1-56)	8 (1-39)	9 (1-56)
Baseline hypoparathyroidism supplements, mean TDD	Elemental calcium (mg)	2091.9 (n = 38)	1769.8 (n = 96)	1861.2 (n = 134)
	Calcitriol (µg)	0.8 (n = 33)	0.8 (n = 81)	0.8 (n = 114)
	Alfacalcidol (µg)	2.4 (n = 8)	2.4 (n = 17)	2.4 (n = 25)
	Cholecalciferol/ vitamin D3 (µg)	67.3 (n = 20)	64.2 (n = 59)	65.0 (n = 79)
	Magnesium (mg)	666.4 (n = 13)	587.6 (n = 37)	608.1 (n = 50)

Note: Numbers may not add to 100% due to rounding.
*Calculated according to the Modified Diet in Renal Disease Equation (MDRD): eGFR (mL/min/1.73 m²) = 175 × (serum creatinine mg/dL) -1.154 × (age) -0.203 × 0.742 [if female] × 1.212 [if Black race].

Results

Figure 4: **Improvements in eGFR: Combined Analysis**


PaTH Forward
PaTHway
Combined Analysis
Mean (SE) change from baseline in eGFR (mL/min/1.73 m²)
Months on Treatment

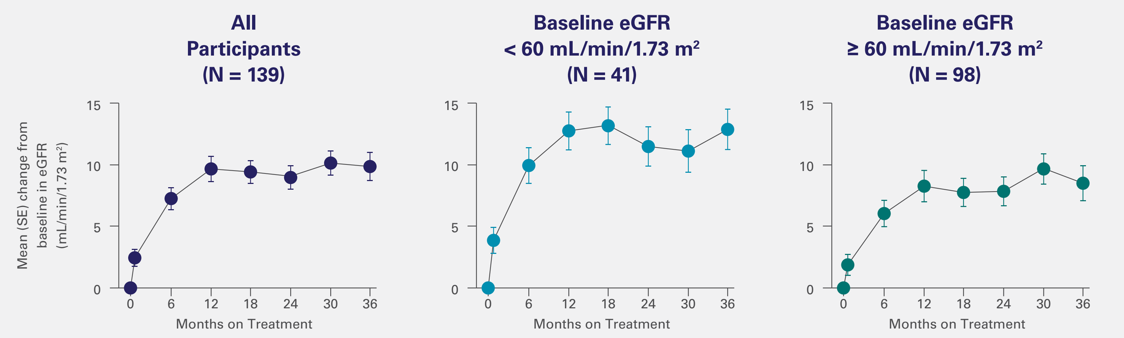
PaTH Forward
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **12.47**
- 6-36 Months: **0.99**

PaTHway
eGFR Slope Change (mL/min/1.73 m²/year)
- 0-6 Months: **15.64**
- 6-36 Months: **0.86**

Combined Analysis
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **14.33**
- 6-36 Months: **0.89**

Results

Figure 5: **Sustained Improvements in eGFR From Baseline**


All Participants (N = 139)
Baseline eGFR < 60 mL/min/1.73 m² (N = 41)
Baseline eGFR ≥ 60 mL/min/1.73 m² (N = 98)
Mean (SE) change from baseline in eGFR (mL/min/1.73 m²)
Months on Treatment

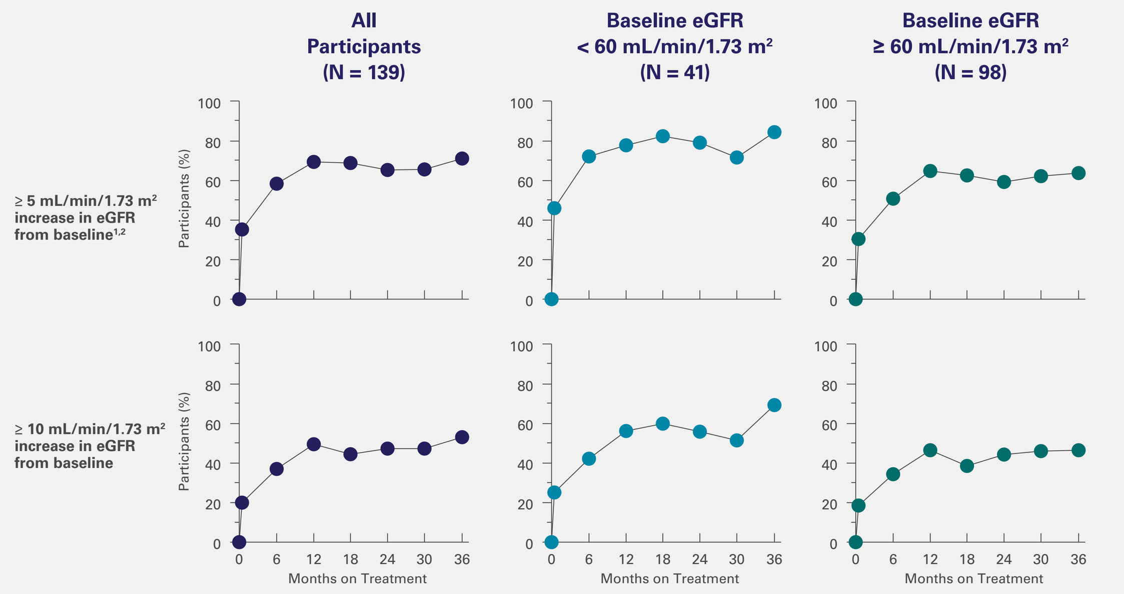
A numerically greater improvement was observed in participants with lower baseline eGFR at month 36.

All Participants
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **14.33**
- 6-36 Months: **0.89**

Baseline eGFR < 60 mL/min/1.73 m²
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **19.93**
- 6-36 Months: **0.57**

Baseline eGFR ≥ 60 mL/min/1.73 m²
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **11.98**
- 6-36 Months: **1.06**

Figure 6: **Proportion of Participants With Clinically Meaningful Increases in eGFR**


All Participants (N = 139)
Baseline eGFR < 60 mL/min/1.73 m² (N = 41)
Baseline eGFR ≥ 60 mL/min/1.73 m² (N = 98)
≥ 5 mL/min/1.73 m² increase in eGFR from baseline1,2
≥ 10 mL/min/1.73 m² increase in eGFR from baseline
Participants (%)
Months on Treatment

In 70.3% of all participants, sustained, clinically meaningful improvement in eGFR was observed at month 36.[10,11]

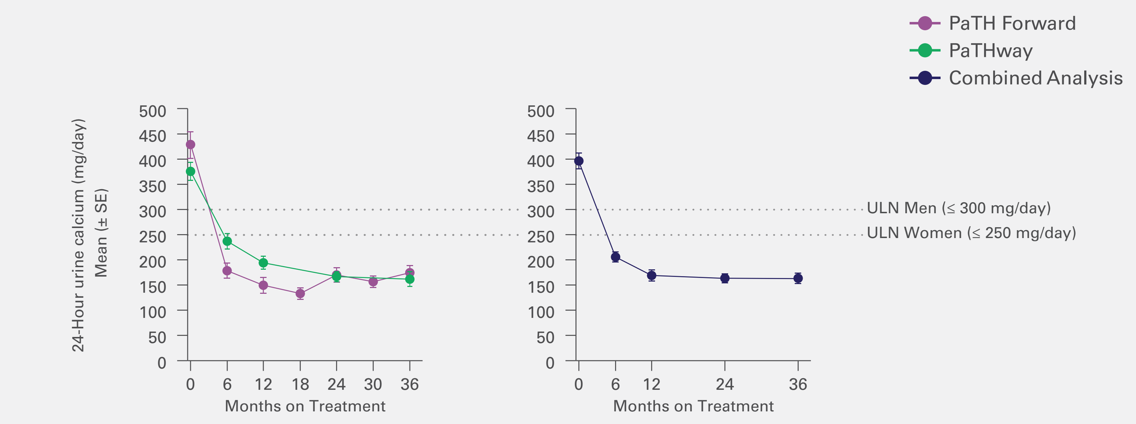
Note: Only 1 participant exceeded the decline in eGFR outcome with a reduction ≥ 30% from baseline of ≥ 2 consequent visits for at least 3 months (90 days) apart. This was secondary to nephrectomy due to malignancy.
[a]Clinically meaningful increases in eGFR were those ≥ 5 mL/ min / 1.73 m².

Table 2: **High Proportion of Participants Independent From Conventional Therapy at 3 Years**

Variable	All Participants
Number of participants with complete data at Year 3	**129**
Met multi-component efficacy endpoint criteria, n (%)	**110 (85%)**
Normal albumin-adjusted serum calcium[a]	118 (91%)
Independence from active vitamin D[b]	128 (99%)
Independence from therapeutic doses of calcium[b]	121 (94%)

[a]Normal calcium range: 8.3-10.6 mg/dL.
[b]Independence from conventional therapy defined as no active vitamin D and ≤ 600 mg/day elemental calcium.

Figure 7: **Normalization of 24-Hour Urinary Calcium Through Year 3 of PaTH Forward and PaTHway**


PaTH Forward
PaTHway
Combined Analysis
24-Hour urine calcium (mg/day) Mean (± SE)
ULN Men (≤ 300 mg/day)
ULN Women (≤ 250 mg/day)
Months on Treatment

Note: Values reflect total study population with data available from baseline and corresponding subsequent visits.

Table 3: **Summary of Adverse Events Through Year 3**

Treatment Emergent Adverse Events (TEAEs), n (%)	All Participants
	N = 139
Any TEAE	133 (95.7%)
Serious TEAE	26 (18.7%)
Related TEAE	72 (51.8%)
Serious related TEAE	2 (1.4%)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization	6 (4.3%)
TEAE leading to discontinuation of study drug[a]	3 (2.2%)
TEAE leading to discontinuation of trial[b]	1 (0.7%)
TEAE leading to death[b]	1 (0.7%)

Treatment-related TEAEs occurring at a rate of ≥ 5% among all participants (N = 139) included:
- Injection site reaction (15.1%)
- Hypercalcemia (10.8%)
- Headache (9.4%)
- Hypocalcemia (7.9%)
- Nausea (7.9%)

Most TEAEs were classified as mild or moderate.[c]

[a]Includes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (participants who received ≥1 dose of palopegteriparatide): TEAEs leading to treatment discontinuation were deemed unrelated to study drug.
[b]One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment.
[c]Classified using the World Health Organization toxicity grading scale (1=mild, 2=moderate, 3=severe, 4=life-threatening)

Abbreviations

AE = adverse event; **eGFR** = estimated glomerular filtration rate; **EU** = European Union; **MDRD** = Modified Diet in Renal Disease equation; **N** = number; **PTH** = parathyroid hormone; **SAE** = serious adverse event; **SD** = standard deviation; **SE** = standard error; **TDD** = total daily dose; **TEAE** = treatment emergent adverse event; **TransCon** = transient conjugation; **US** = United States

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Disclosures and Funding

Ascendis Pharma and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

Ascendis Pharma Bone Diseases A/S funded this trial and participated in the trial design, research, analysis, data collection, interpretation of the data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Robert Geist, MD, of Ascendis Pharma.

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MED-US-TC-PTH-2600035
March 2026