Long-Term Efficacy and Safety of Palopegteriparatide Treatment in Adults With Chronic Hypoparathyroidism: 4-Year Results From the Phase 2 PaTH Forward Trial

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MED-US-TC-PTH-2500139

November 2025

European Congress of Endocrinology (ECE) 2025, Copenhagen, Denmark

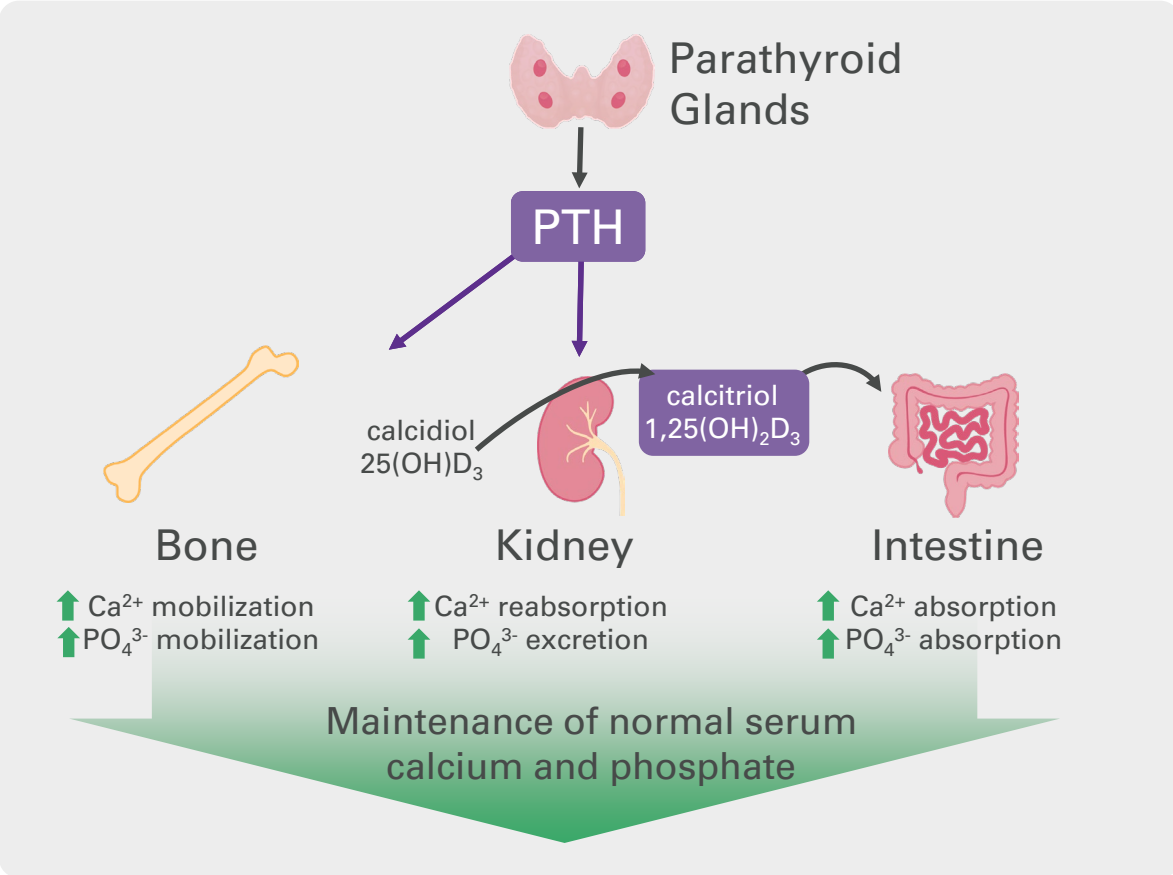
Final Abstract Code: OC7.9

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.
- Financial arrangements of the authors with companies whose products may be related to this presentation are listed as declared by the authors:
  AP reports having a consultant role for Theramex, Bruno Farmaceutici, Amgen; research funding from Amgen, Shire, Ascendis; speakers bureau UCB, Amgen; industry grant from Amgen. **AAK** reports having an advisory/consulting role for Alexion, Amgen, Amolyt Pharma, and Ascendis Pharma; honoraria from Alexion, Amgen, and Ascendis; research funding from Amolyt Pharma and Ascendis Pharma; travel, accommodations, expenses from Amgen and Ascendis; serving on speaker's bureau for Amgen. **MRR** reports having a consulting role for MBX Biosciences; honoraria from Ascendis Pharma; and serving on speaker's bureau for Ascendis Pharma. **PS** reports stock/ownership of Aventis Pharma, Genmab, and Novo Nordisk. **BC** Research funding and industry grants from Ascendis and Takeda; advisory board member, consultant, honoraria from Ascendis, Takeda, Entera-Bio, Extend-Bio, Amolyt. **UP** reports having an advisory role for Havas Life Italy and Novo Nordisk, and UVET; research funding from Amolyt Pharma, Ascendis Pharma, Eli Lilly, Neurocrine, and Novo Nordisk; serving on speaker's bureau for AstraZeneca, Bruno Farmaceutici, Medinfar, and Novo Nordisk; and grants (industry sponsored) from AstraZeneca, Therascience, and Mundipharma. **ET** reports having an advisory role for Ascendis Pharma and Kyowa Kirin; honoraria from Alexion, Ascendis, KKI, Takeda and UCB. **FC** has nothing to declare. **RJ** reports having a consulting role for Ascendis; research funding from Amgen Foundation. **CZ, MO, BL, JU, CTS**, and **ADS** are full-time employees of Ascendis Pharma. **LR** reports serving on advisory boards and receiving honoraria from Amolyt Pharma, Ascendis Pharma, BridgeBio Pharma, and Takeda; consulting role for Ascendis Pharma and BridgeBio Pharma; research funding for Amolyt Pharma, Ascendis Pharma, BridgeBio Pharma, Kyowa Kirin, and Takeda.

PTH Therapy for Hypoparathyroidism

- An **intact PTH axis** maintains normal serum 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 and 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 biochemistries
  - Skeletal health
  - Quality of life

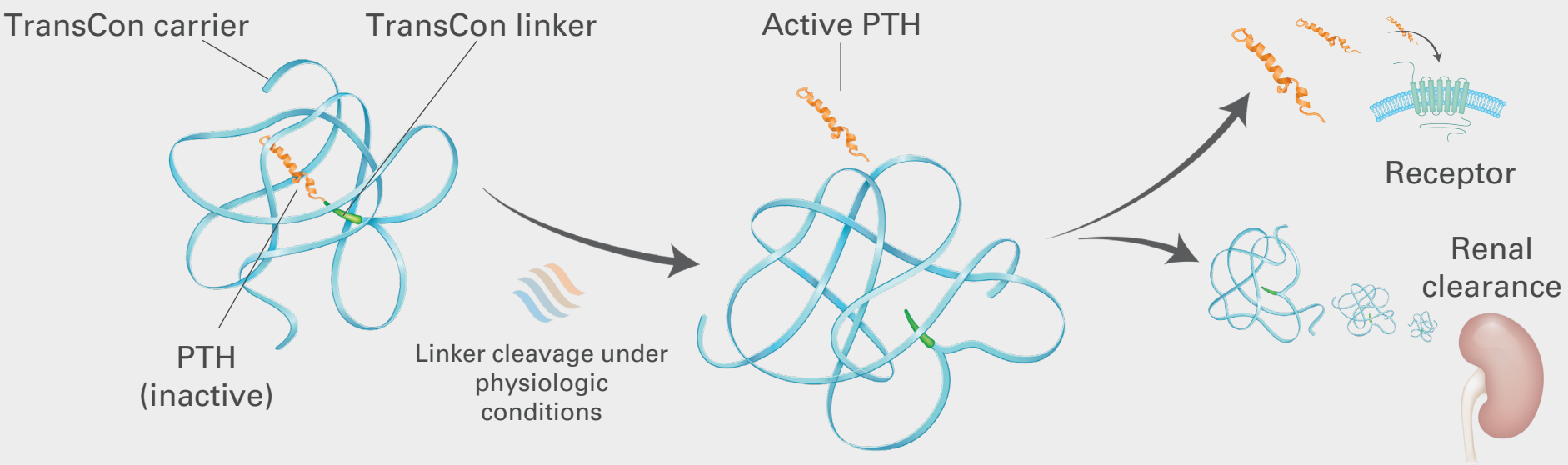


PTH, parathyroid hormone

Figure adapted from Shoback D. *N Engl J Med.* 2008;359(4):391-403.[7]

1. Khan AA, et al. *J Bone Miner Res*. 2022;37(12):2568-2585. 2. Shoback DM, et al. *J Clin Endocrinol Metab*. 2016;101(6):2300-2312. 3. Bilezikian JP, et al. *J Clin Endocrinol Metab*. 2016;101(6):2313-2324. 4. Mannstadt M, et al. *Nat Rev Dis Primers*. 2017;3:17055. 5. Brandi ML, et al. *J Clin Endocrinol Metab* 2016;101(6):2273-83. 6. Khan AA, et al. *Eur J Endocrinol*. 2019;180(3):R33-63, 7. Shoback D. *N Engl J Med*. 2008;359(4):391-403.

Palopegteriparatide (YORVIPATH®; TransCon® PTH) Design

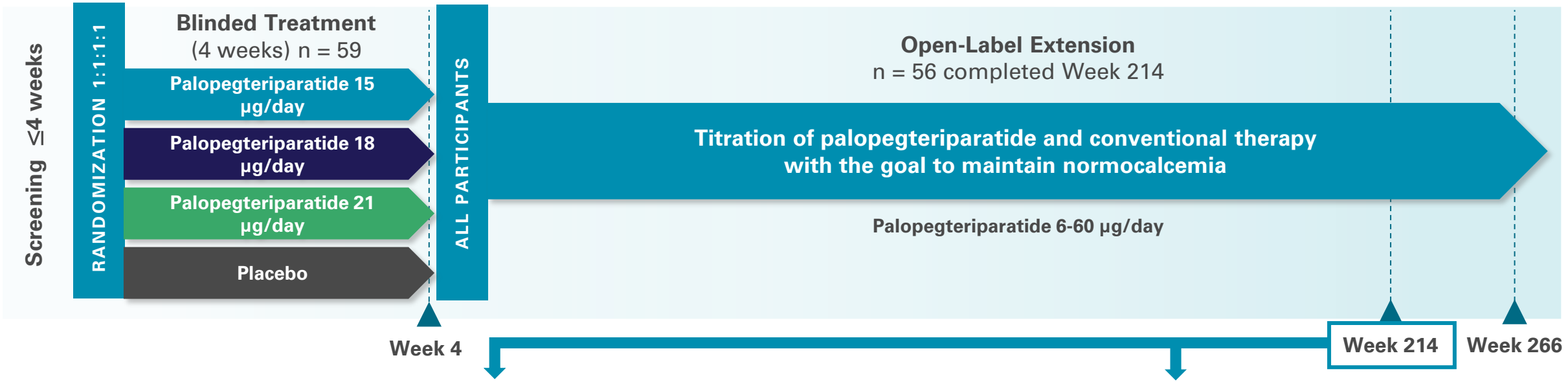


- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[1,2]
- Palopegteriparatide has received regulatory approval in the EU[a], US[b] and several other countries

PTH, parathyroid hormone; TransCon, transient conjugation.
[a] Indicated for the treatment of adults with chronic hypoparathyroidism. [b] Indicated for the treatment of hypoparathyroidism in adults.
1. Karpf DB, et al. *J Bone Miner Res*. 2020;35(8):1430-1440. 2. Holten-Andersen L, et al. *J Bone Miner Res*. 2019;34(11):2075-2086.

PaTH Forward Trial of Palopegteriparatide in Adults with Chronic Hypoparathyroidism

Phase 2 trial with a 4-week randomized, double-blind, placebo-controlled period followed by an open-label extension period through Week 266



Select Open-Label Extension Endpoints

- Levels of serum calcium (normocalcemia)
- Independence from conventional therapy (defined as taking no active vitamin D and ≤ 600 mg/day elemental calcium)
- Levels of 24-hour urinary calcium
- Incidence of AEs, SAEs, TEAEs

Skeletal Remodeling and Renal Endpoints

- Bone turnover markers (P1NP and CTx)
- Bone mineral density by DXA of the lumbar spine L1-L4, femoral neck, total hip, and distal 1/3 radius
- Renal function as assessed by eGFR

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; P1NP, procollagen type 1 N-terminal propeptide; CTx, C-terminal telopeptide of type 1 collagen; DXA, dual X-ray absorptiometry; eGFR, estimated glomerular filtration rate.

Baseline Demographics and Disease Characteristics

	All participants (N = 59)
Mean age, years (SD)	50 (12)
Sex, n (%) female	48 (81)
Menopausal status, n (%) postmenopausal	17 (35)
Race, n (%) White	54 (92)
Geographic region, n (%)	
North America	38 (64)
Europe	21 (36)
Cause of hypoparathyroidism, n (%)	
Acquired from neck surgery	47 (80)
Autoimmune disease	1 (2)
Idiopathic disease	11 (19)
Median duration of hypoparathyroidism, years (range)	9 (1-39)
Conventional therapy, mean TDD	
Calcium (mg)	1909
Calcitriol (µg)[a]	0.79
Alfacalcidol (µg)[b]	2.38

SD, standard deviation; TDD, total daily dose. Numbers may not add to 100% due to rounding.
[a]n = 46 (78%) participants used calcitriol at baseline. [b]n = 13 (22%) participants used alfacalcidol at baseline.

High Proportion of Participants Achieved Independence From Conventional Therapy

	All palopegteriparatide
Number of participants continuing through Week 214	56
Active vitamin D = 0 µg/day, n (%)	53 (95%)
Calcium ≤ 600 mg/day, n (%)	53 (95%)
Active vitamin D = 0 µg/day ***and*** calcium ≤ 600 mg/day, n (%)	52 (93%)

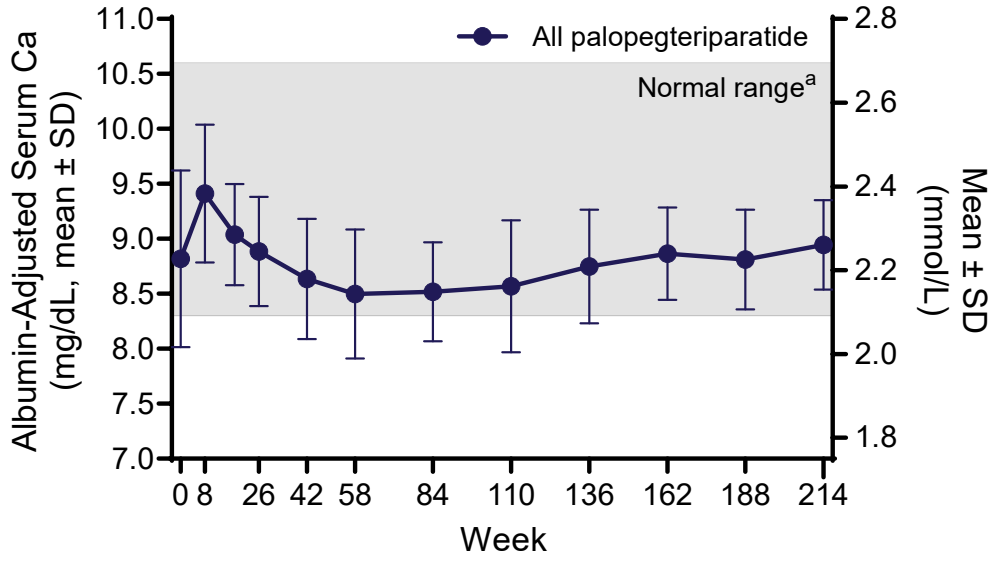
93% were independent from conventional therapy at week 214[a]

[a]Not taking active vitamin D and taking ≤ 600 mg/day of elemental calcium.

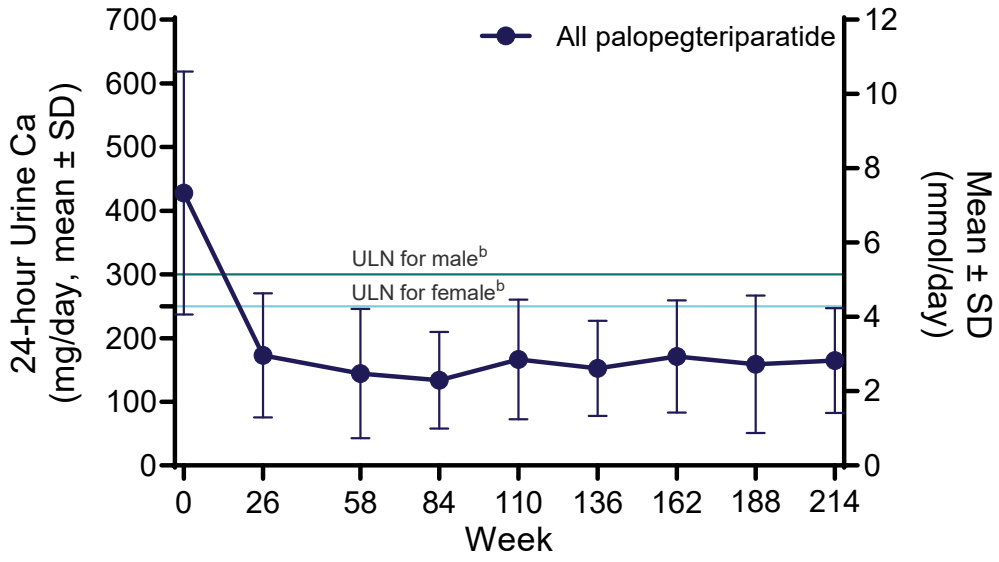
Serum and 24-Hour Urine Calcium Remained in the Normal Range Through Week 214

PaTHforward TRIAL

Mean Serum Calcium



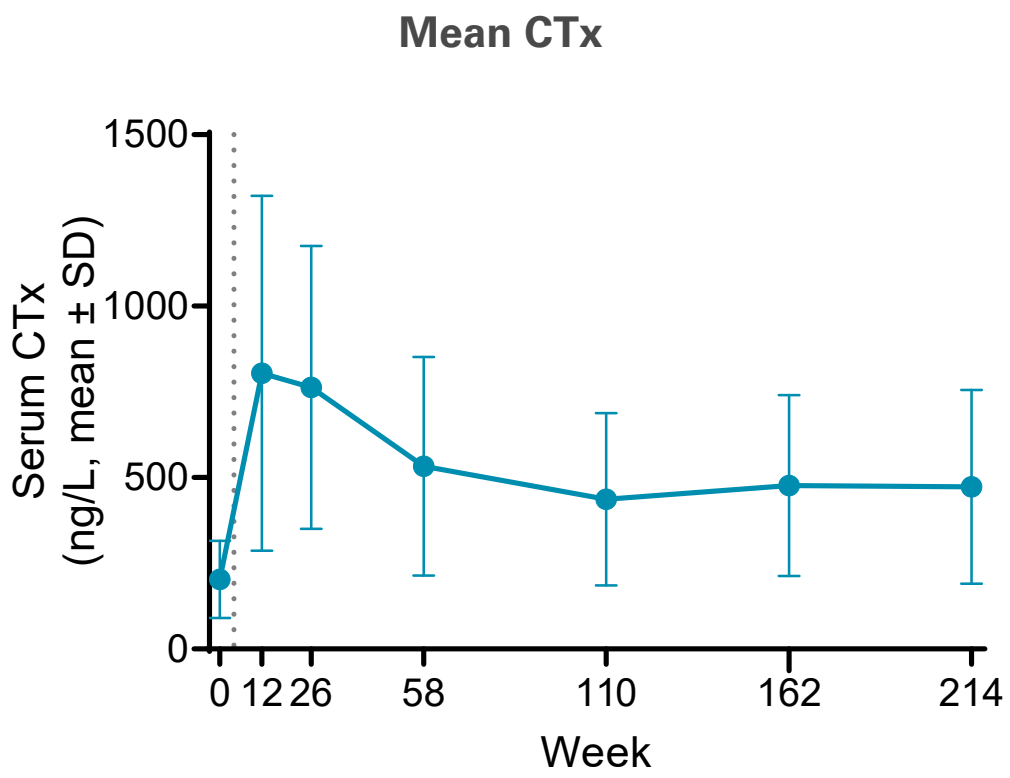
Mean 24-Hour Urine Calcium

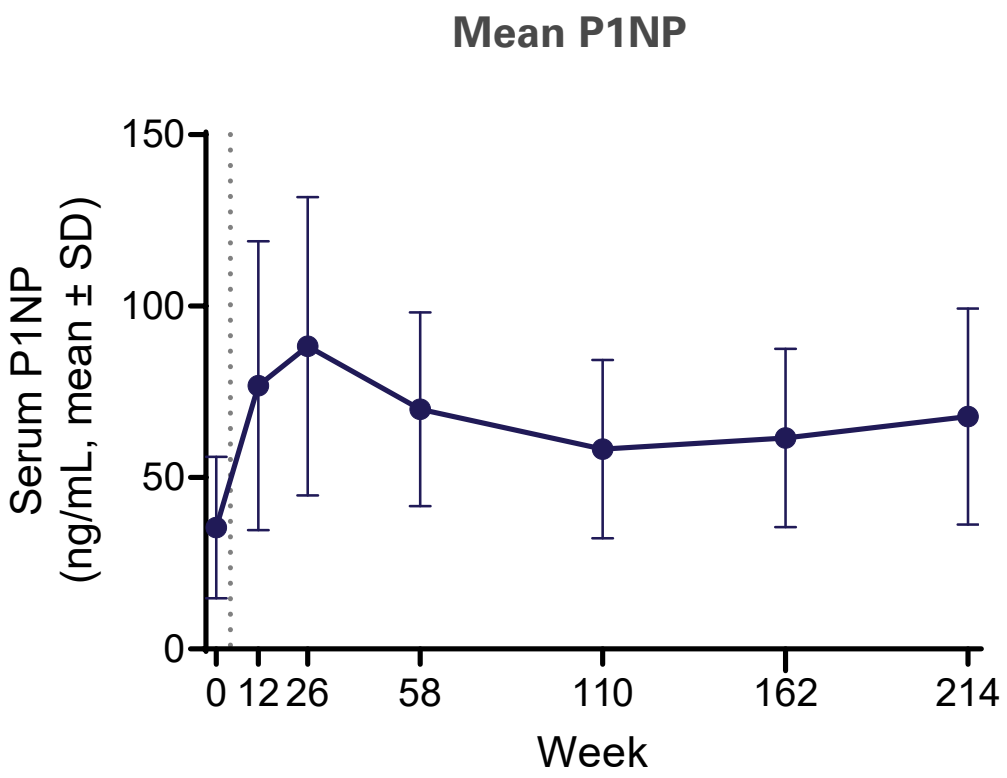


98% had normal serum calcium at week 214; mean 24-hour urine calcium normalized within 26 weeks

Serum calcium: n=59 at week 0; n=58 at week 58; n=57 at week 42 and 188; n=56 at weeks 26, 162, and 214; n=55 at week 136; n=54 at weeks 8 and 110; n=52 at week 18
24-hour urine calcium: n=55 at week 58; n=54 at weeks 84, 110, and 214; n=53 at week 188; n=50 at week 0; n=51 at weeks 136 and 162; n=49 at week 26
Ca, calcium; SD, standard deviation; ULN, upper limit of normal.
[a]The shaded area represents the normal serum calcium range of 8.3-10.6 mg/dL. [b]The ULN for males and females are depicted by teal and light blue lines, respectively.

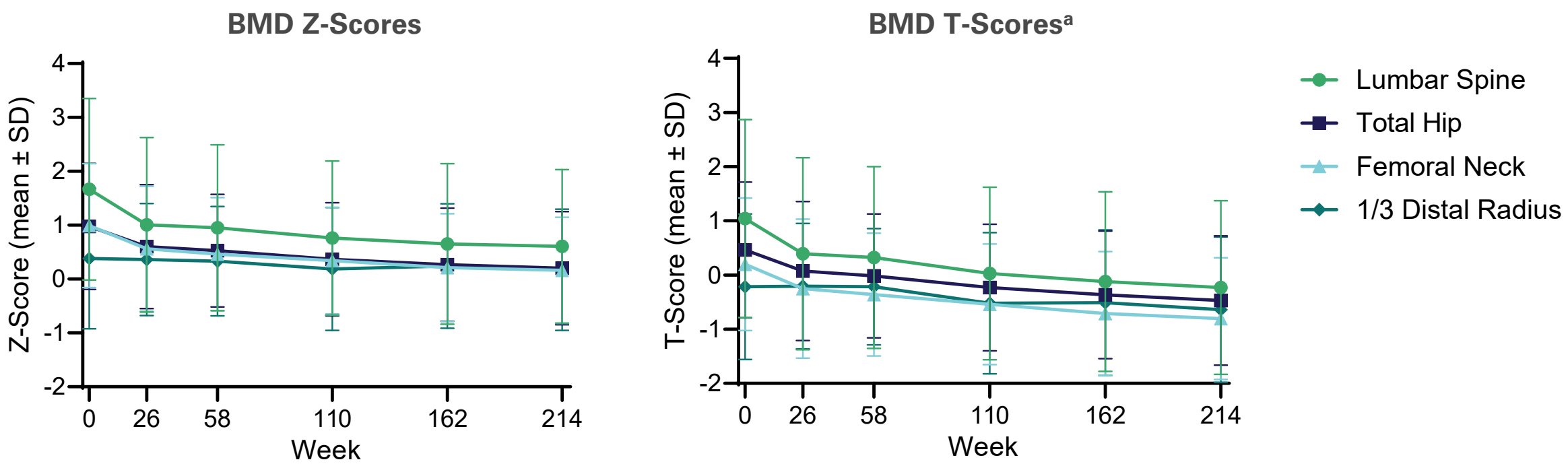
CTx and P1NP Were Consistent From Week 110 Through Week 214





CTx: n=58 at week 0; n=46 at week 12; n=55 at weeks 26 and 110; n=57 at week 58; n=54 at week 162 and 214. P1NP: n=59 at week 0, n=47 at week 12; n=56 at weeks 26, 58, 110, 162, and 214.
CTx, C-terminal telopeptide of type 1 collagen; P1NP, procollagen type 1 N-terminal propeptide; SD, standard deviation.

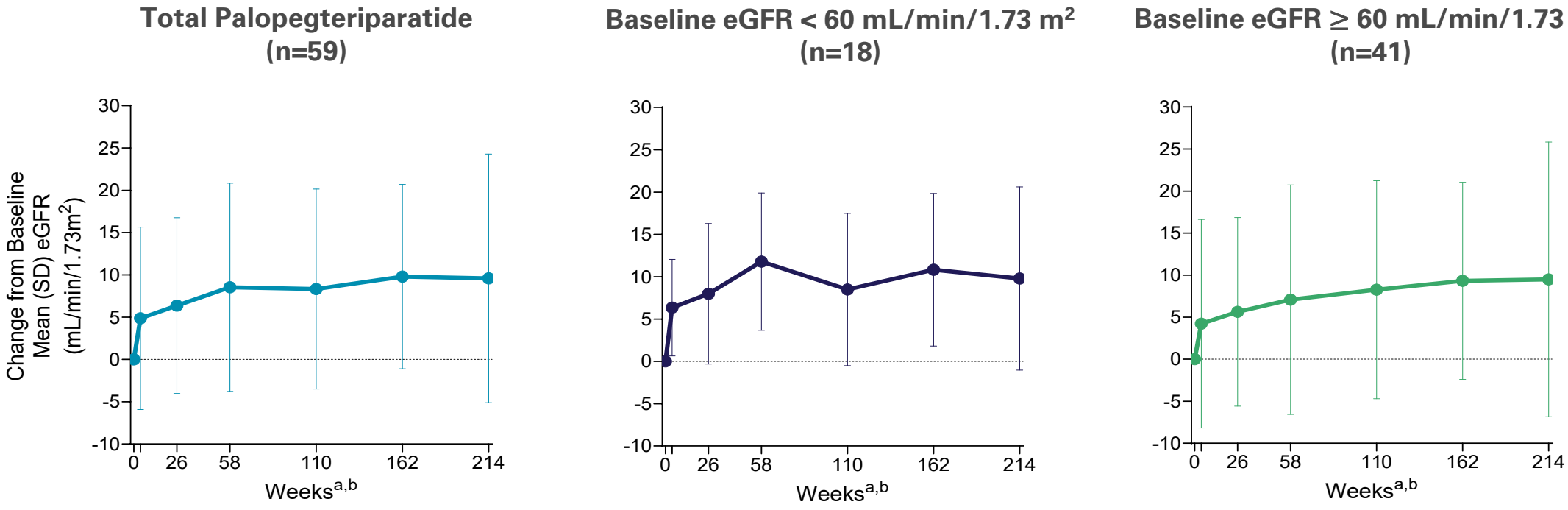
Bone Mineral Density by DXA: Consistent From Week 26 Through Week 214



Mean T- and Z-scores were elevated at baseline and remained within the normal range

Lumbar spine, total hip, and femoral neck: n=57 at week 0; n=46 at weeks 26 and 58; n=55 at weeks 110 and 162; n=54 at week 214. 1/3 distal radius: n=55 at week 0; n=43 at weeks 26and 58; n=53 at week 110; n=52 at week 162 and 214.
BMD, bone mineral density; DXA, dual X-ray absorptiometry; SD, standard deviation.
[a] T-score reference point: young (30-year-old) Caucasian adult (Kanis JA. *Lancet*. 2002;359:1929–36).

eGFR Increase With Palopegteriparatide Treatment was Sustained Through Week 214



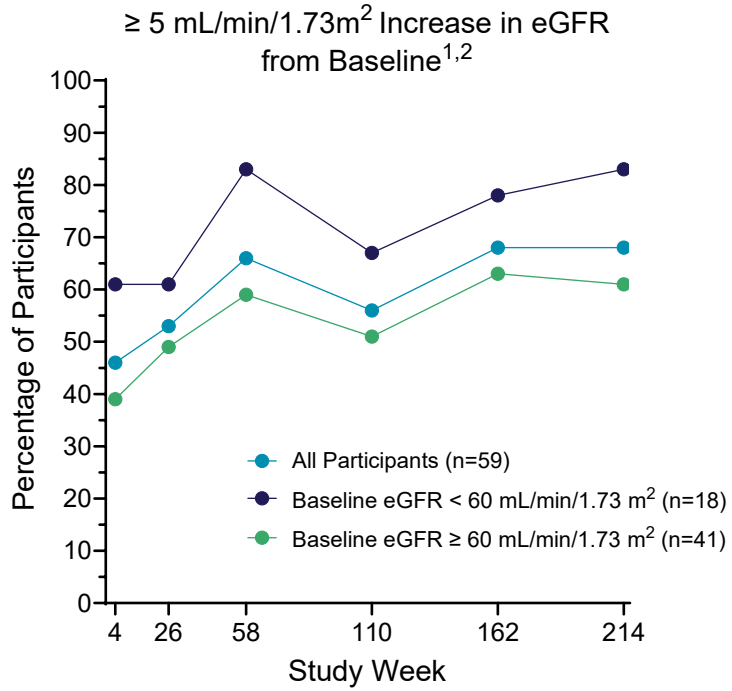
Mean (SD) eGFR for total population increased approximately 9.6 (14.7) mL/min/1.73m^2 from baseline[c]

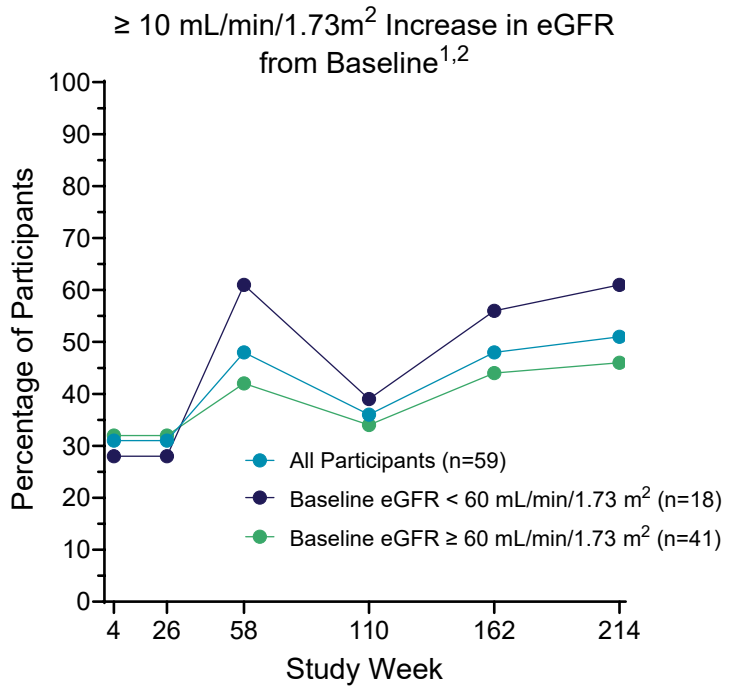
[a]All participants received TransCon PTH during the open-label extension. [b]Second (unlabeled) X-axis tick in each figure denotes 4 weeks [c]Calculated according to the Modified Diet in Renal Disease Equation (MDRD): eGFR (mL/min/1.73 m2) = 175 × (serum creatinine mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 [if female] × 1.212 [if Black].

Total palopegteriparatide: n=59 at week 4; n=58 at week 58; n=56 at week 214; n=55 at weeks 26, 162; n=53 at week 110. Baseline eGFR < 60 mL/min/1.73 m^2: n=18 at weeks 4, 58, 214; n=17 at weeks 26, 162; n=16 at week 110. Baseline eGFR ≥ 60 mL/min/1.73 m2: n=41 at week 4; n=40 at week 58; n=38 at weeks 26, 162, 214; n=37 at week 110.

eGFR, estimated glomerular filtration rate; SD, standard deviation

Proportions of Participants With ≥ 5 and ≥ 10 mL/min/1.73 m^2 Increases in eGFR





Most participants (67.8%)[a] had a clinically meaningful[1,2] ≥ 5 mL/min/1.73 m^2 increase in eGFR at week 214

[a] Percentages calculated based on ITT population.

1. Mayne TJ, et al. *Clin Transplant*. 2021;35(7):e14326.
2. Ku E, et al. *J Am Soc Nephrol*. 2016;27(7):2196-204.

Treatment-Emergent Adverse Events Summary Through Week 214

TEAEs during palopegteriparatide treatment, n (%)	All palopegteriparatide (N = 59)
Any TEAE	58 (98.3)
Serious TEAE	7 (11.9)
Serious treatment-related TEAE	0
Treatment-related TEAE	27 (45.8)
Treatment-related TEAEs occurring in ≥ 5% of participants	
Headache	7 (11.9)
Hypocalcaemia	6 (10.2)
Hypercalcaemia	4 (6.8)
Nausea	4 (6.8)
Paraesthesia	4 (6.8)
TEAE related to hypercalcaemia or hypocalcaemia leading to ED/urgent care visit and/or hospitalization	2 (3.4)
TEAE leading to discontinuation of trial or of study drug	0
TEAE leading to death	0

Most TEAEs were mild or moderate and not related to study drug; no new safety signals were identified

A minor data correction was made from the original version of this slide.
ED, emergency department; PTH, parathyroid hormone; TEAE, treatment-emergent adverse event.

Conclusions

Palopegteriparatide demonstrated sustained efficacy and safety over a 4-year period

- 93% of remaining participants were independent from conventional therapy and 98% had normal albumin-adjusted serum calcium levels at Week 214
- Mean BMD T- and Z-scores declined from elevated baseline levels and stabilized within the normal range through Week 214
- eGFR increased with palopegteriparatide treatment and was sustained through Week 214
- Palopegteriparatide was generally well tolerated, with no treatment discontinuation due to related adverse events

Thank you for your attention!

The authors and Ascendis Pharma thank the participants, study site nurses, research coordinators, and other site personnel, and the investigators who participated in this clinical trial