

Efficacy and Safety of Palopegteriparatide Treatment in Adults With Hypoparathyroidism: 3-Year Results From the Phase 3 PaTHway Trial

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Endocrine Society Annual Meeting (ENDO) 2025, San Francisco, California

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MED-US-TC-PTH-2500141
November 2025

PTH Therapy for Hypoparathyroidism

- 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 physiology⁶
- 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

PTH, parathyroid hormone

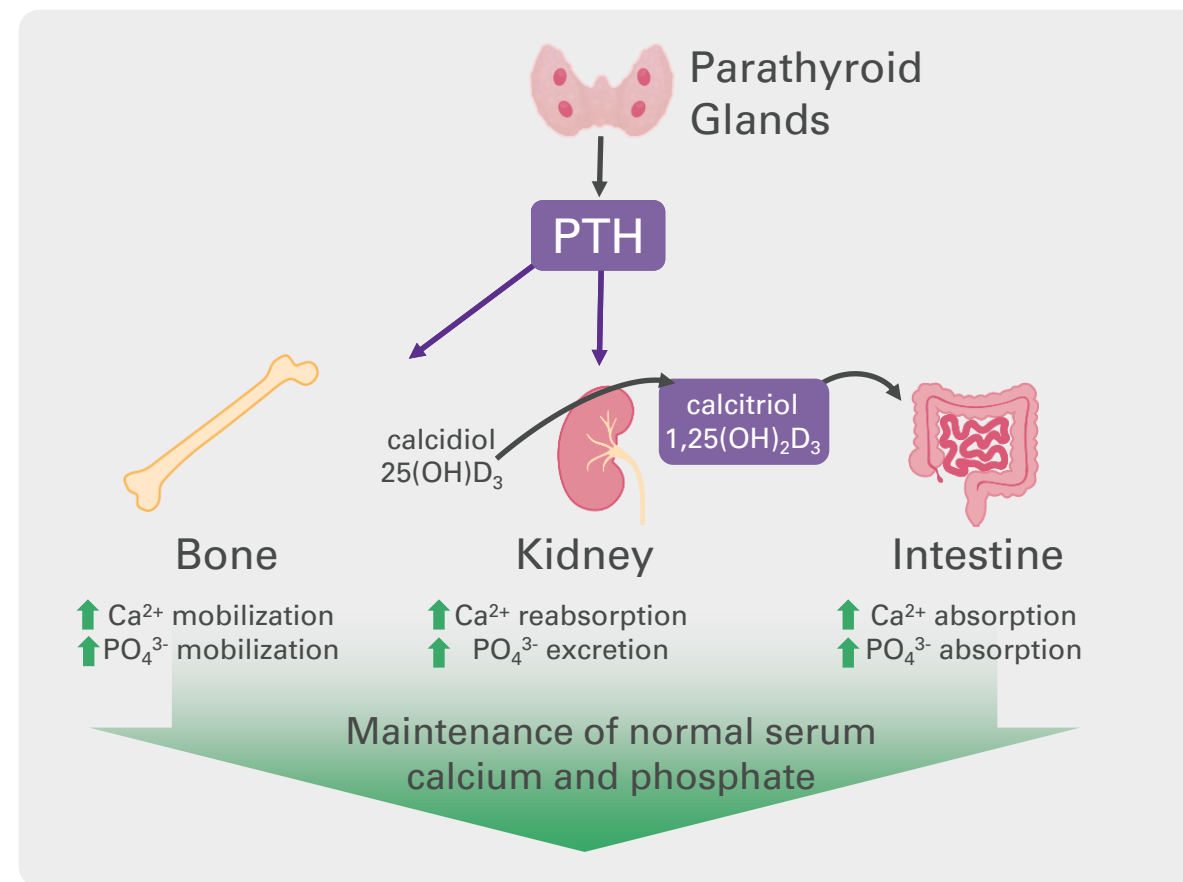
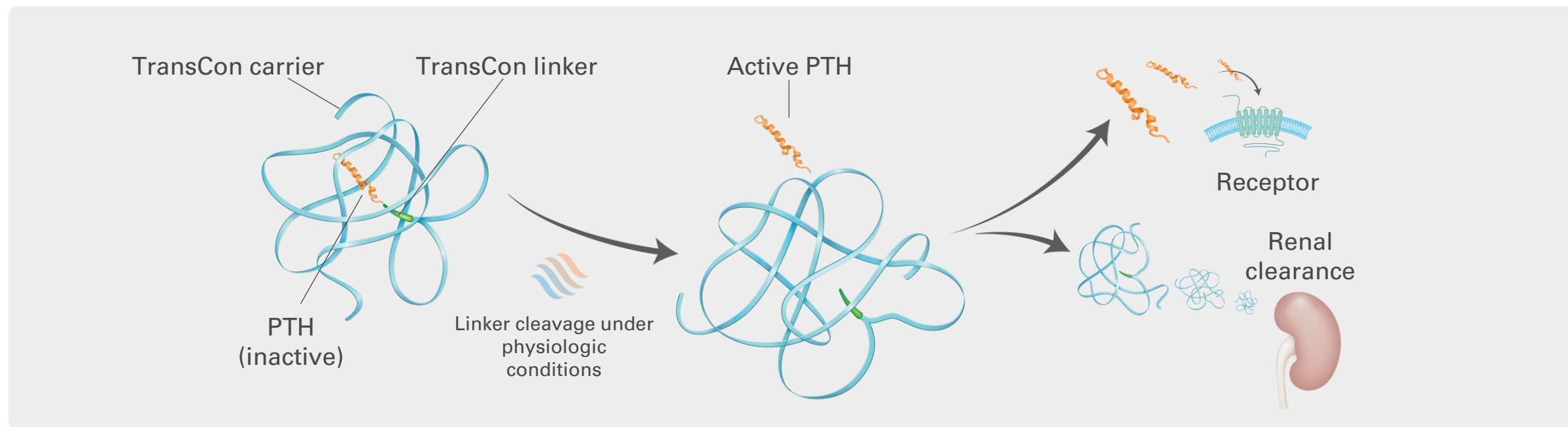


Figure adapted from Shoback D. *N Engl J Med*. 2008;359:391-403.⁷

1. Khan AA, et al. *J Bone Miner Res*. 2022;37:2568-2585. 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;359:391-403.

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

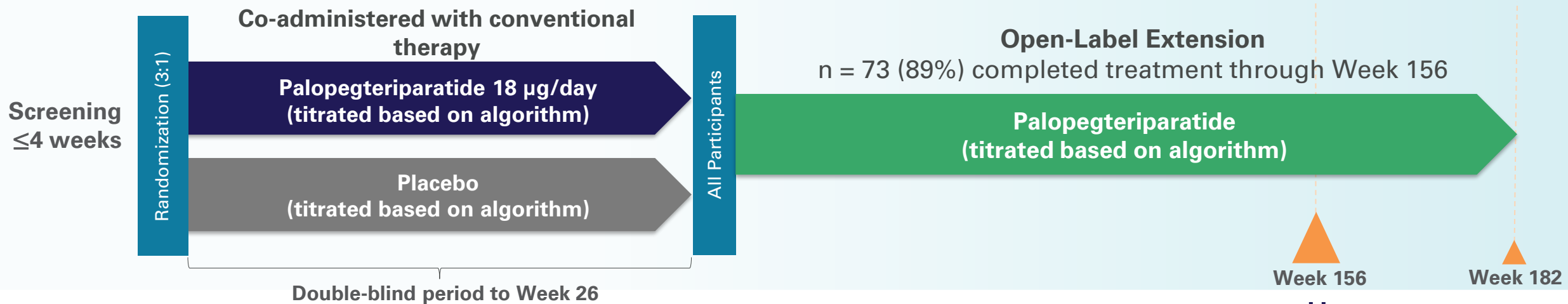
PTH, parathyroid hormone; TransCon, transient conjugation.

^aIndicated for the treatment of adults with chronic hypoparathyroidism. ^bIndicated 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.

Palopegteriparatide Phase 3 PaTHway Trial Design (NCT04701203)

82 adults with hypoparathyroidism receiving conventional therapy (active vitamin D + calcium)



Efficacy Endpoints

- Independence from active vitamin D^a
- Independence from therapeutic doses of calcium^b
- Serum calcium levels within the normal range

Renal and PRO Endpoints

- Estimated glomerular filtration rate (eGFR)^c: post hoc analysis
- HPES-Symptom physical and cognitive domain scores and HPES-Impact physical functioning and daily life domain scores

Safety and Tolerability Endpoints

- 24-hour urine calcium
- Incidence of Adverse Events, Serious Adverse Events, and Treatment-Related Adverse Events

^aIndependence from active vitamin D is defined as a standing dose of active vitamin D equal to zero on the day prior to the week 156 visit

^bIndependence from therapeutic doses of calcium is defined as a standing dose of elemental calcium ≤600 mg on the day prior to the week 156 visit

^cCalculated according to the Modified Diet in Renal Disease Equation (MDRD): $eGFR (mL/min/1.73 m^2) = 175 \times (\text{serum creatinine mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 [\text{if female}] \times 1.212 [\text{if Black}]$

PRO, patient-reported outcomes; HPES, Hypoparathyroidism Patient Experience Scales

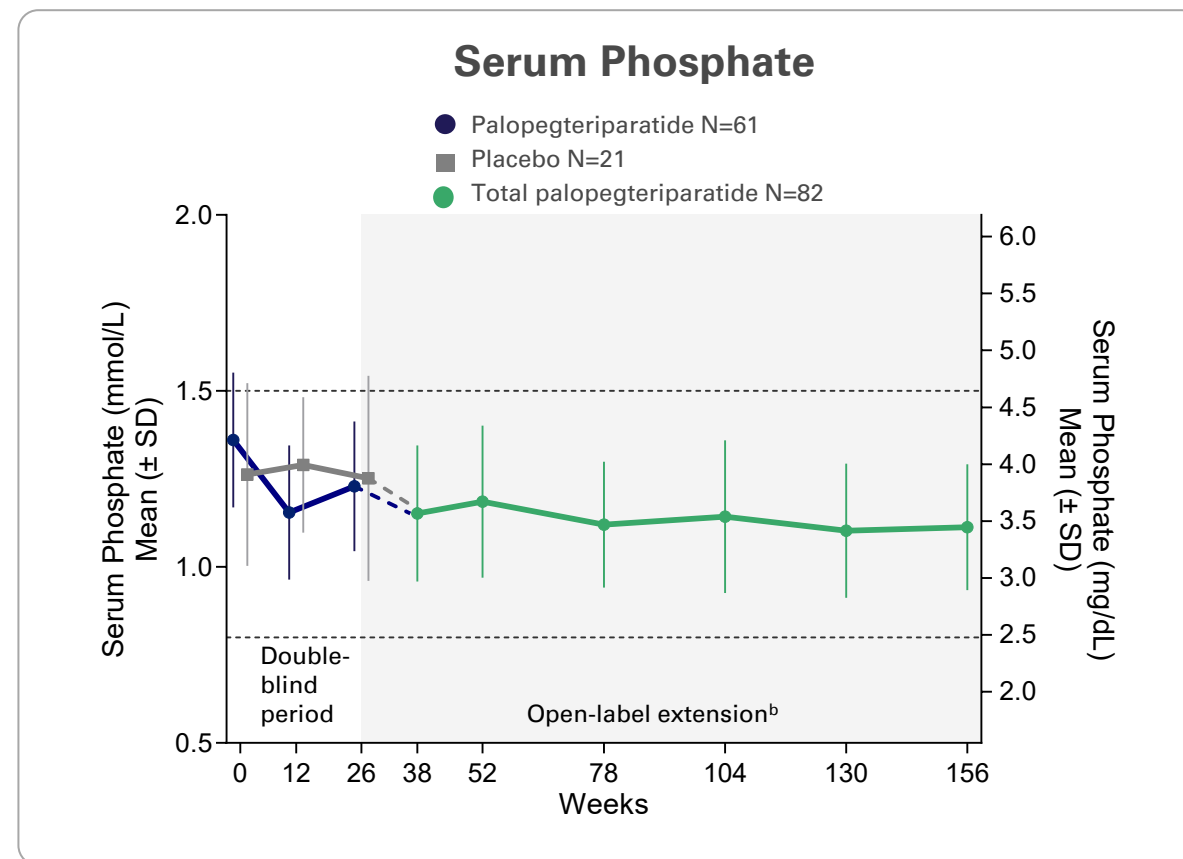
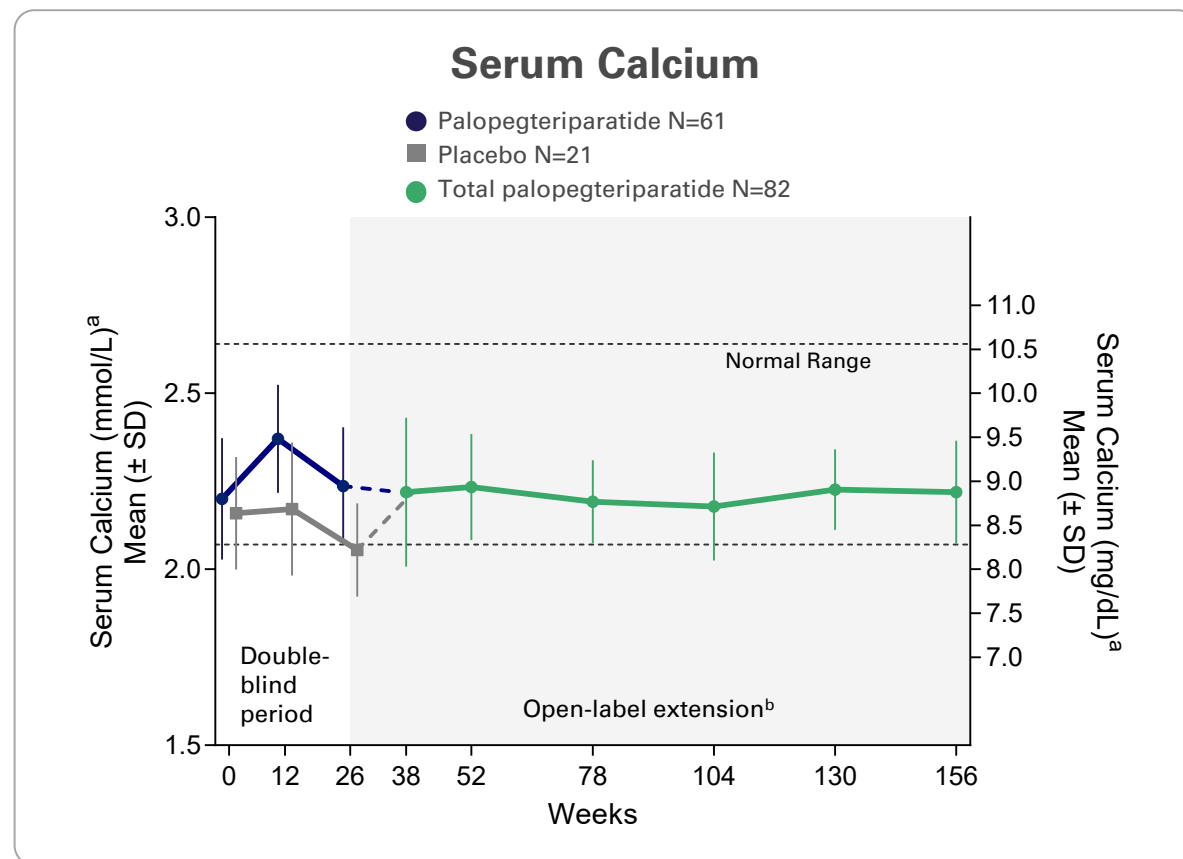
96% of Participants Independent From Conventional Therapy at Week 156

	All Participants
Number of participants who completed Week 156	73
Met multi-component efficacy endpoint criteria, n (%) ^a	61 (84%)
○ Normal albumin-adjusted serum calcium, n (%)	64 (88%)
○ Independence from conventional therapy, n (%) ^b	70 (96%)
• Independence from active vitamin D, n (%)	73 (100%)
• Independence from therapeutic doses of calcium, n (%)	70 (96%)

^aThe multi-component efficacy endpoint assessed the proportion of participants who achieved normal albumin-adjusted serum calcium levels (8.3-10.6 mg/dL) and independence from conventional therapy

^bIndependence defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg on the day prior to the week 156 visit
Percentages are calculated based on participants who had data on all criteria.

Serum Calcium and Phosphate Maintained Through Week 156

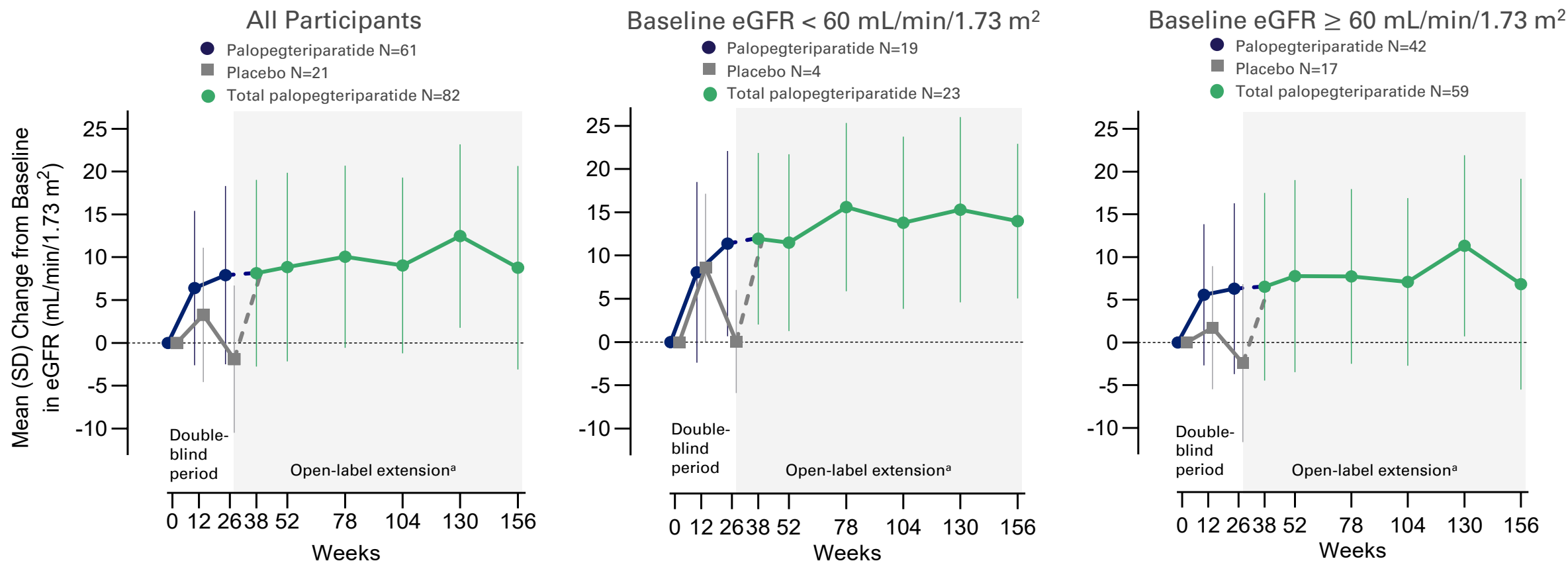


^aAlbumin-adjusted. ^bAll participants received palopegteriparatide during the open-label extension.

SD, standard deviation

Normal ranges (between dashed lines): albumin-adjusted serum calcium 8.3-10.6 mg/dL (2.07-2.64 mmol/L); serum phosphate 2.5-4.6 mg/dL (0.8-1.5 mmol/L)

Sustained Improvements in eGFR From Baseline Through Week 156

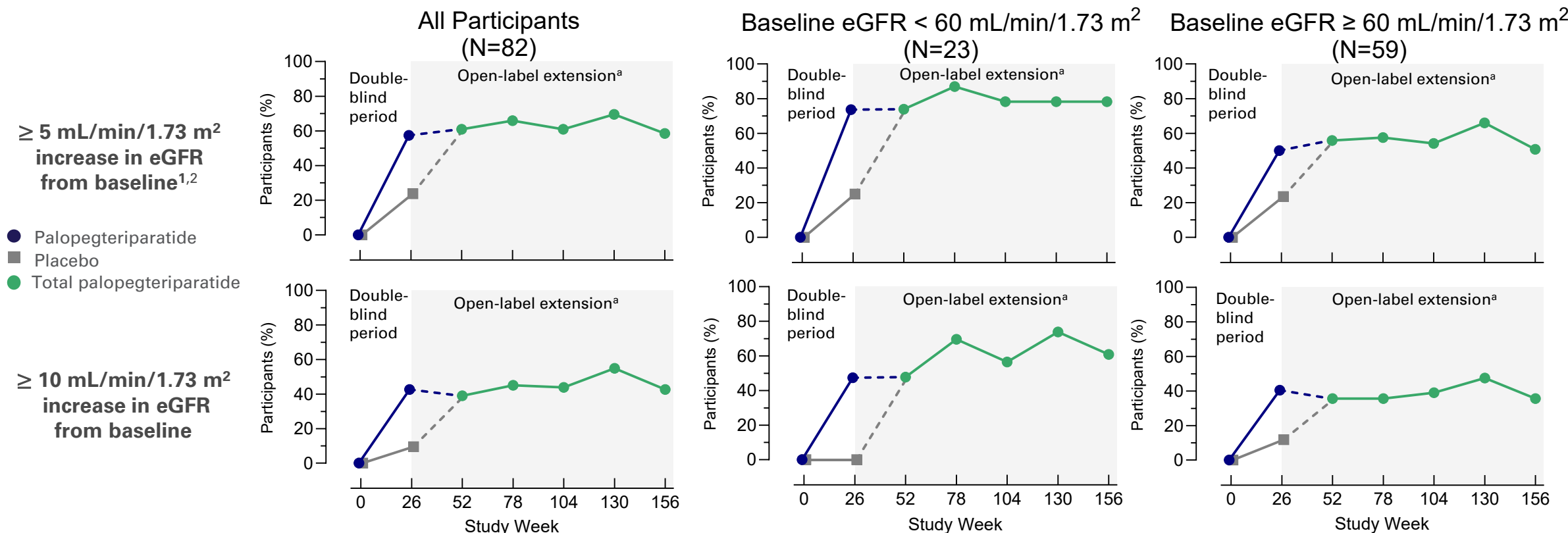


At Week 156, mean eGFR increased by 8.76 mL/min/1.73 m² across all participants and by 13.98 mL/min/1.73 m² in participants with baseline eGFR < 60

^aAll participants received palopegteriparatide during the open-label extension.
eGFR, estimated glomerular filtration rate; SD, standard deviation

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Sustained Proportion of Clinically Meaningful Increases in eGFR Through Week 156



Clinically meaningful^{1,2} ≥5 mL/min/1.73 m² improvement in eGFR observed for 59% of all participants at Week 156, with 61% of the <60 eGFR subgroup having a ≥10 mL/min/1.73 m² increase

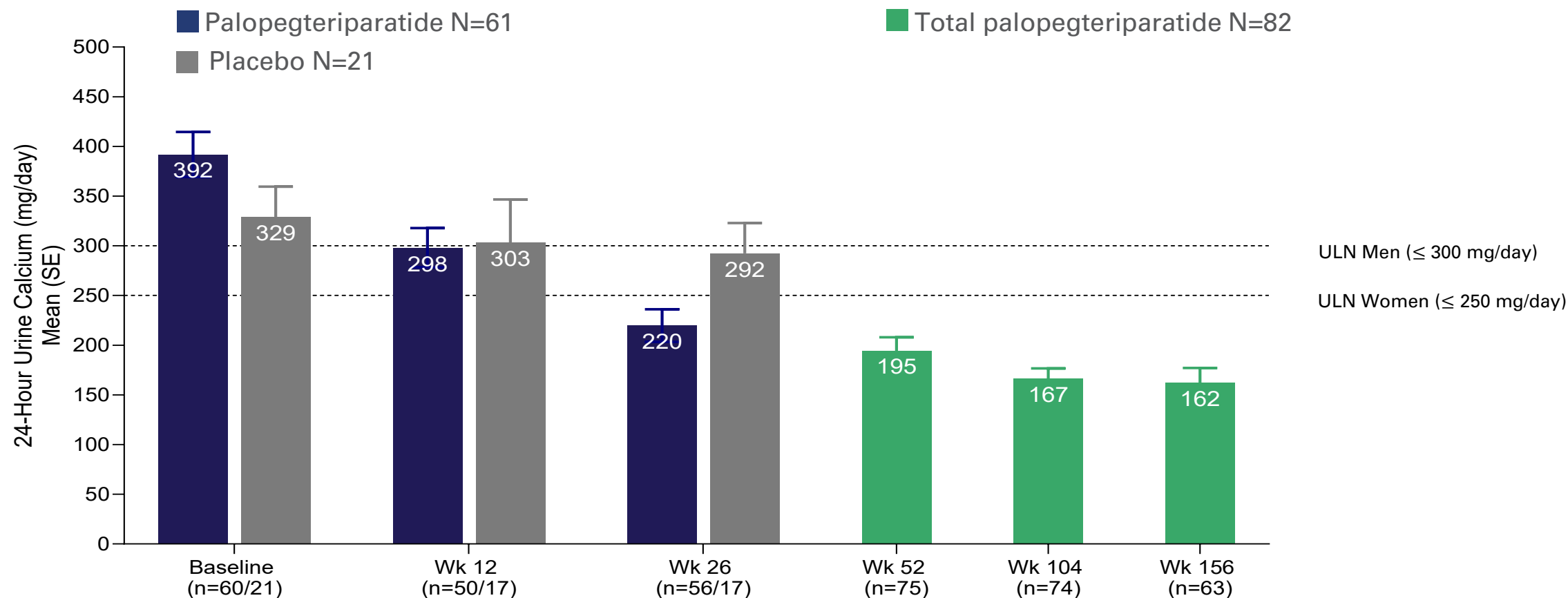
Wk, week. ^aAll participants received palopegteriparatide during the open-label extension. ^bClinically meaningful increases in eGFR were those ≥ 5 mL/min / 1.73 m².

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.

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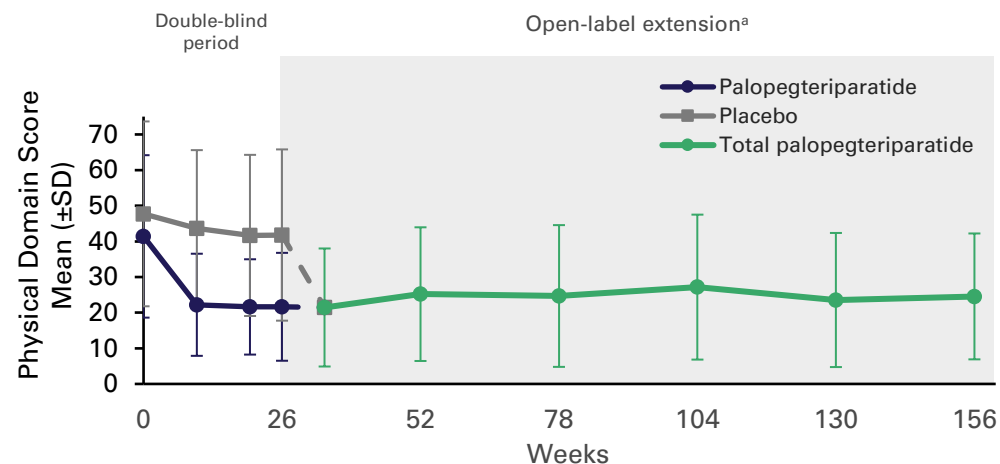
Normalization of Mean 24-Hour Urine Calcium Excretion With Continued Reductions Through Week 156



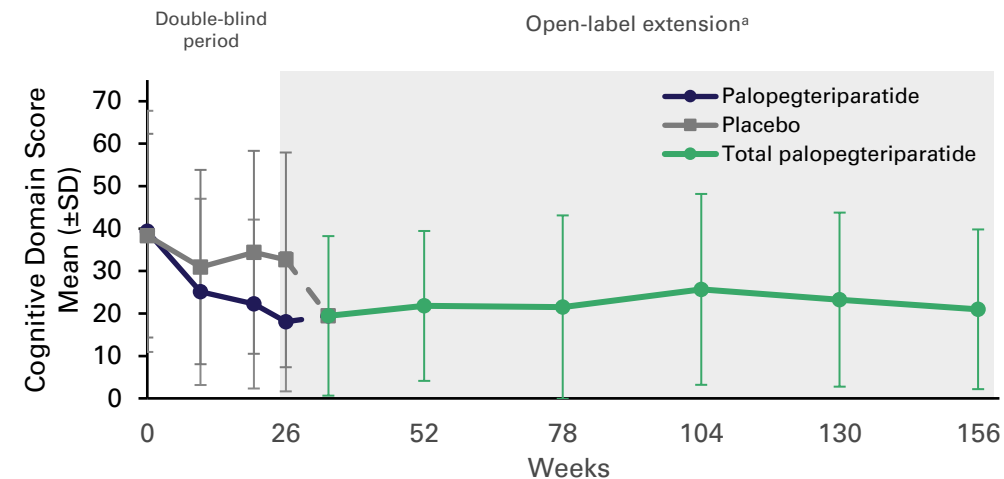
SE, standard error; ULN, upper limit of normal; Wk, week.

Hypoparathyroidism-Related Symptoms and Health-Related Quality of Life Improvements Maintained Through Week 156

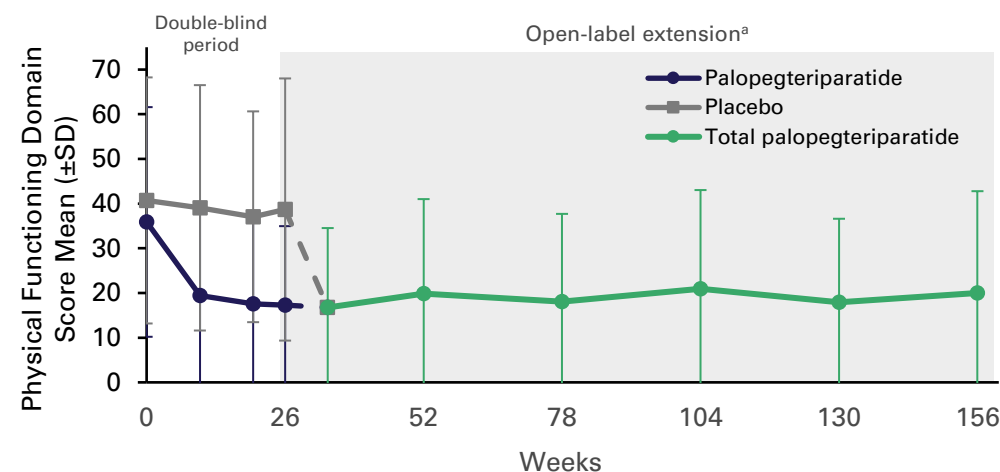
HPES-Symptom Physical Domain Score



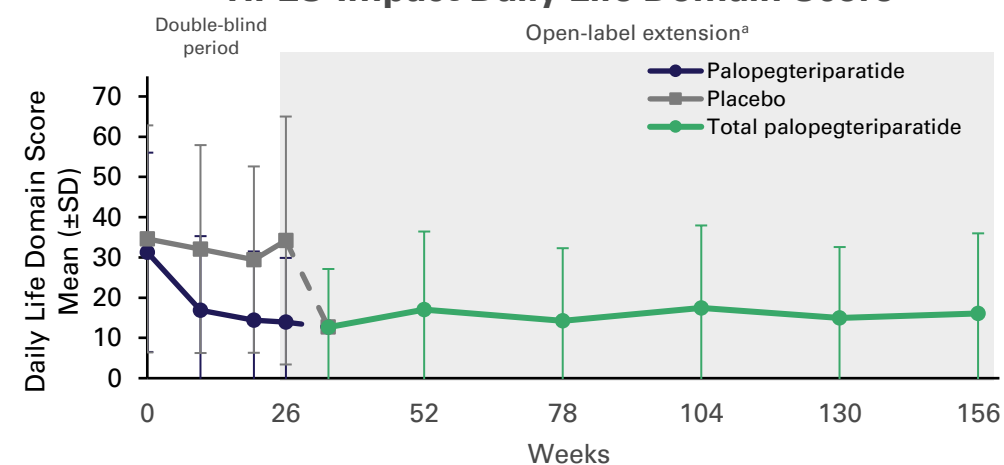
HPES-Symptom Cognitive Domain Score^b



HPES-Impact Physical Functioning Domain Score^b



HPES-Impact Daily Life Domain Score^b



^aAll participants received palopegteriparatide during the open-label period ^bStandard deviation values were truncated at 0 when values were negative.
HPES, Hypoparathyroidism Patient Experience Scale; SD, standard deviation

Summary of Adverse Events Through Week 156

Treatment Emergent Adverse Events (TEAEs), n (%)	All Participants ^a N=80
Any TEAE	76 (95.0)
Serious TEAE	19 (23.8)
Related TEAE	45 (56.3)
Serious related TEAE	2 (2.5)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization ^b	6 (7.5)
TEAE leading to discontinuation of study drug ^c	3 (3.8)
TEAE leading to discontinuation of trial ^d	1 (1.3)
TEAE leading to death ^d	1 (1.3)

Treatment-related TEAEs occurring at a rate of $\geq 5\%$ among all participants (n=80) included:

- Injection site reaction (25.0%)
- Hypercalcemia (13.8%)
- Nausea (8.8%)
- Headache (7.5%)
- Hypocalcemia (6.3%)
- Postural orthostatic tachycardia syndrome (5.0%)

Most TEAEs were classified as mild or moderate^e

^aIncludes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (patients who received ≥ 1 dose of palopegteriparatide): median exposure was 166 weeks for the Palopegteriparatide/Palopegteriparatide group (n=61) and 140 weeks of exposure for the Placebo/Palopegteriparatide group (n=19). ^bMedian time to onset of these calcium-related TEAEs was 181 days (range 8-885 days). ^cTEAEs leading to treatment discontinuation were deemed unrelated to study drug. ^dOne participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment. ^eClassified using the World Health Organization toxicity grading scale (1=mild, 2=moderate, 3=severe, 4=life-threatening)

Conclusions

Treatment with palopegteriparatide showed sustained efficacy and safety through Week 156 of the PaTHway Trial

- High rate (84%) of achievement of multi-component efficacy endpoint^a
- Normalization of 24-hour urine calcium excretion
- Clinically meaningful improvements in:
 - Renal function
 - HRQoL and symptoms
- Palopegteriparatide was generally well-tolerated with no new safety signals identified

^aThe multi-component efficacy endpoint assessed the proportion of participants who achieved normal albumin-adjusted serum calcium levels (8.3-10.6 mg/dL) and independence from conventional therapy. Independence defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤ 600 mg on the day prior to the week 156 visit

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: **AK:** Research funding and/or industry grants from Amolyt, Ascendis Pharma, Chugai, Radius, and Takeda; honoraria from and advisory board member for Amgen, Alexion, Ascendis Pharma, and Takeda; travel, accommodations, and expenses from Ascendis Pharma; consulting role for Amgen, Alexion, Amolyt, and Ascendis Pharma; speakers bureau participation for Amgen. **BC:** Research funding and industry grants from Ascendis and Takeda; advisory board member, consultant, honoraria from Ascendis, Takeda, Entera-Bio, Extend-Bio, Amolyt. **MR:** Study investigator for Takeda, Ascendis Pharma, Amolyt, and Calcilytix; advisory board for Ascendis Pharma, speakers bureau for Ascendis Pharma; consulting for MBX. **PS:** Stock ownership Novo Nordisk, Ascendis Pharma. **DS:** Research/salary funding from Bone Health Tech; research funding from Ascendis Pharma. **CG:** Honoraria from Pendopharm; research funding from Ascendis Pharma, Amolyt, Shire, and Takeda. **AP:** Consultant for Theramex, Bruno Farmaceutici, Amgen; research funding from Amgen, Shire, Ascendis Pharma; speakers bureau UCB, Amgen; industry grant from Amgen. **LA:** Advisory board member for and honoraria from Ascendis Pharma; speakers bureau for Abbott and Claurus; research funding from Ascendis, Shire/Takeda, Amolyt, Eli Lilly, and Corcept Therapeutics. **LK:** Research funding from Alexion/Amolyt and Ascendis Pharma; speakers bureau, honoraria from Amgen and Ascendis Pharma; advisory board, consultant for Alexion and Ascendis Pharma. **ET:** Advisory role for Ascendis Pharma and Kyowa Kirin; honoraria from Alexion, Ascendis Pharma, KKI, Takeda and UCB. **FC:** Study investigator for Ascendis Pharma, Amolyt, and Calcilytix. **RJ:** Consulting role for Ascendis Pharma; research funding from Amgen Foundation. **CZ, BL, MAM, JU, CTS, and ADS:** Full-time employees of Ascendis Pharma. **LR:** Research funding from Takeda, Kyowa Kirin International, Ascendis Pharma, and Calcilytix; honoraria from Calcilytix Therapeutics; advisory board for Takeda and Amolyt.