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

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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 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

PTH, parathyroid hormone

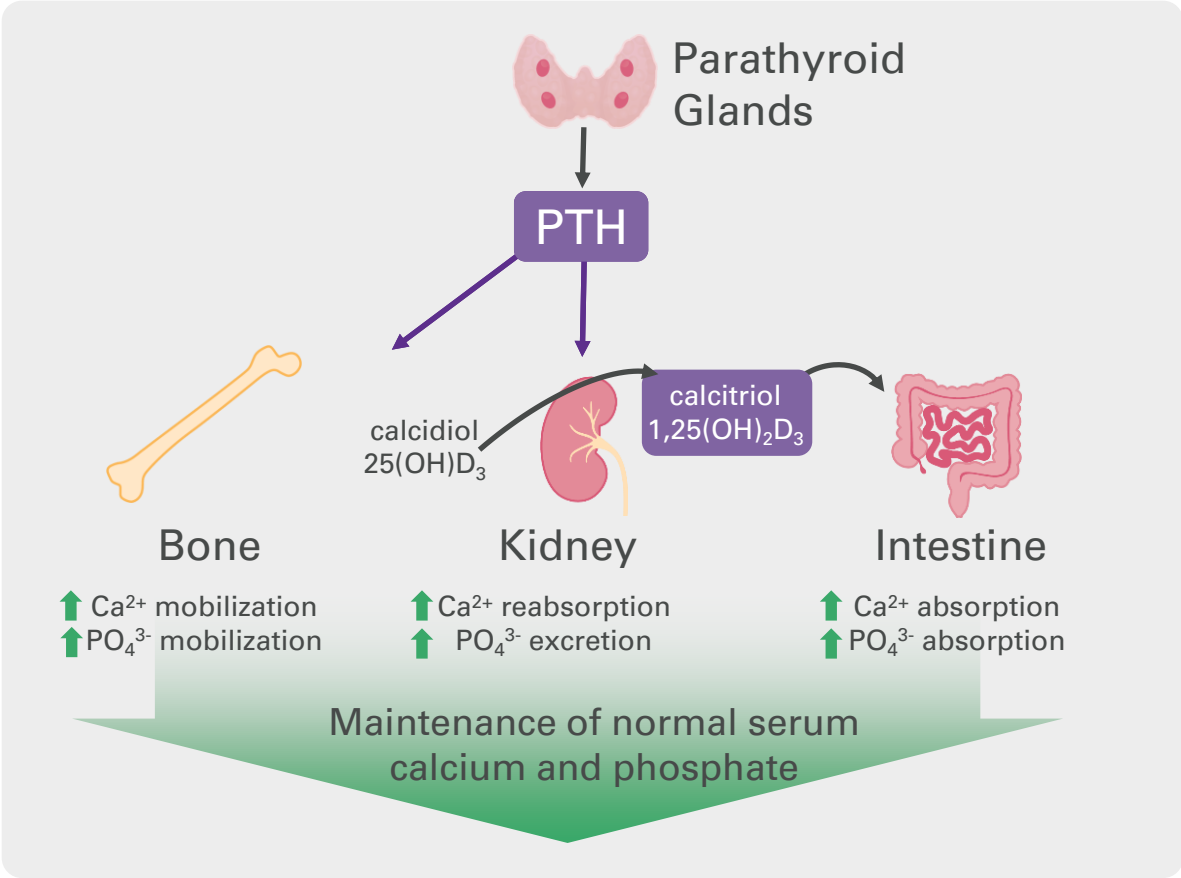
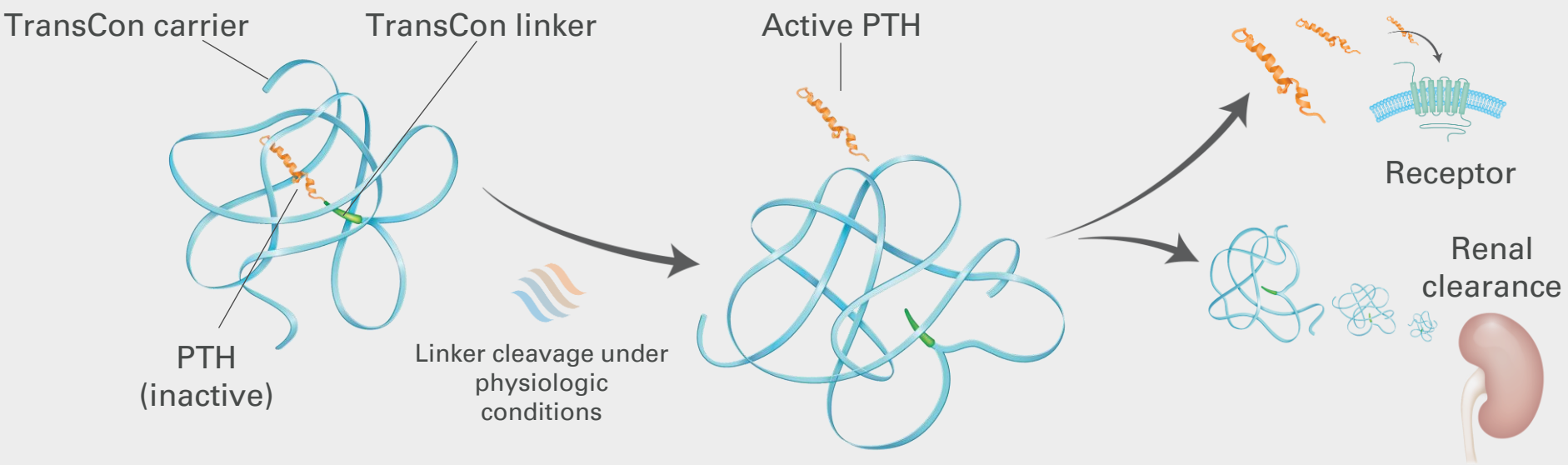


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.[7]

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

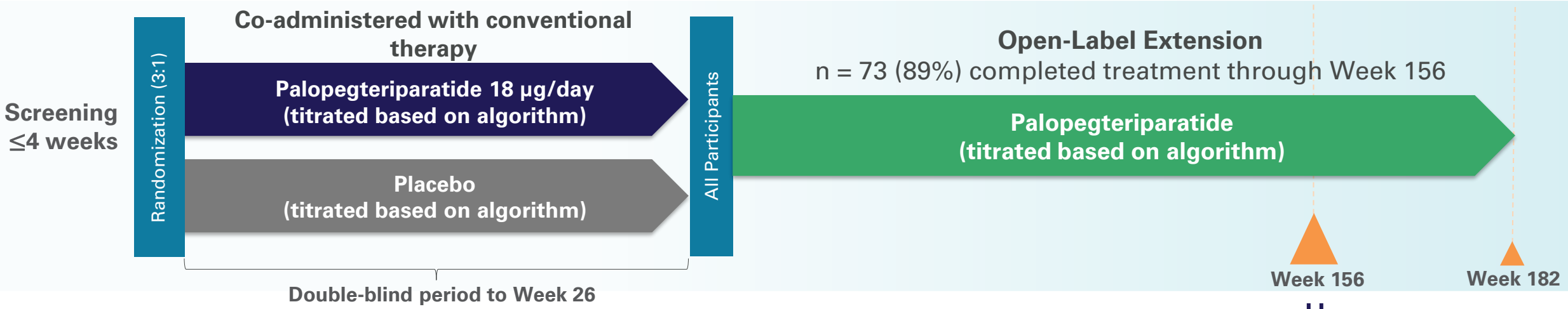


- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[1,2]
- Palopegteriparatide has received regulatory approval in the EU[a], US[b] and several other countries

PTH, parathyroid hormone; TransCon, transient conjugation.
[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.

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

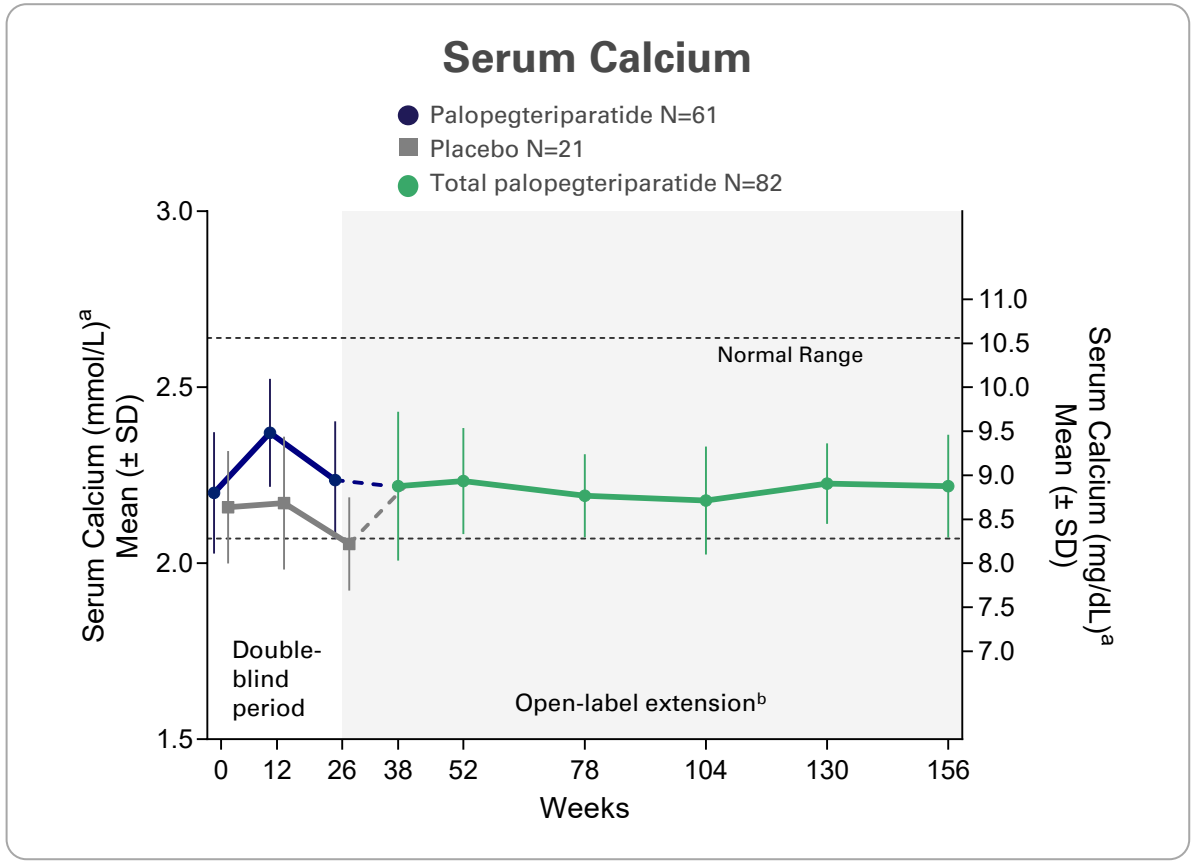
[a]Independence from active vitamin D is defined as a standing dose of active vitamin D equal to zero on the day prior to the week 156 visit
[b]Independence from therapeutic doses of calcium is defined as a standing dose of elemental calcium ≤600 mg on the day prior to the week 156 visit
[c]Calculated according to the Modified Diet in Renal Disease Equation (MDRD): eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine mg/dL)-1.154 × (age)-0.203 × 0.742 [if female] × 1.212 [if Black]
PRO, patient-reported outcomes; HPES, Hypoparathyroidism Patient Experience Scales

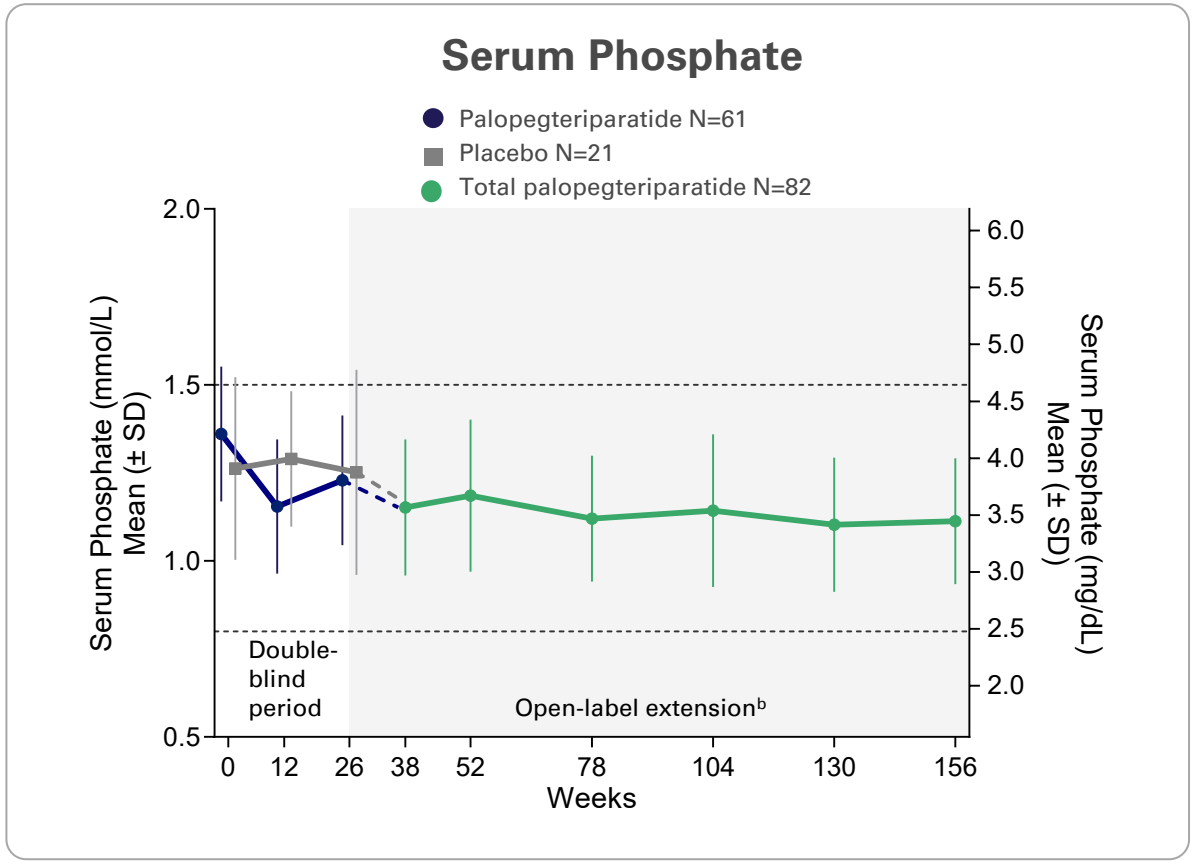
96% of Participants Independent From Conventional Therapy at Week 156

	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%)**

[a]The 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
[b]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
Percentages are calculated based on participants who had data on all criteria.

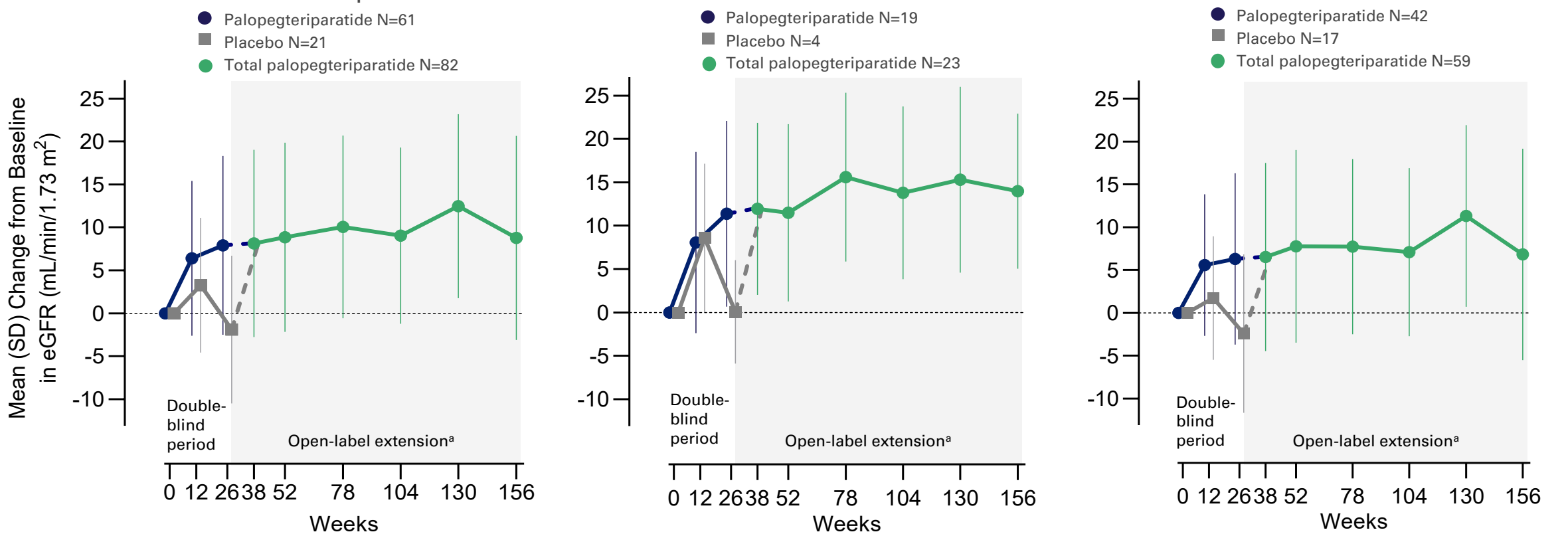
Serum Calcium and Phosphate Maintained Through Week 156





[a]Albumin-adjusted. [b]All 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)

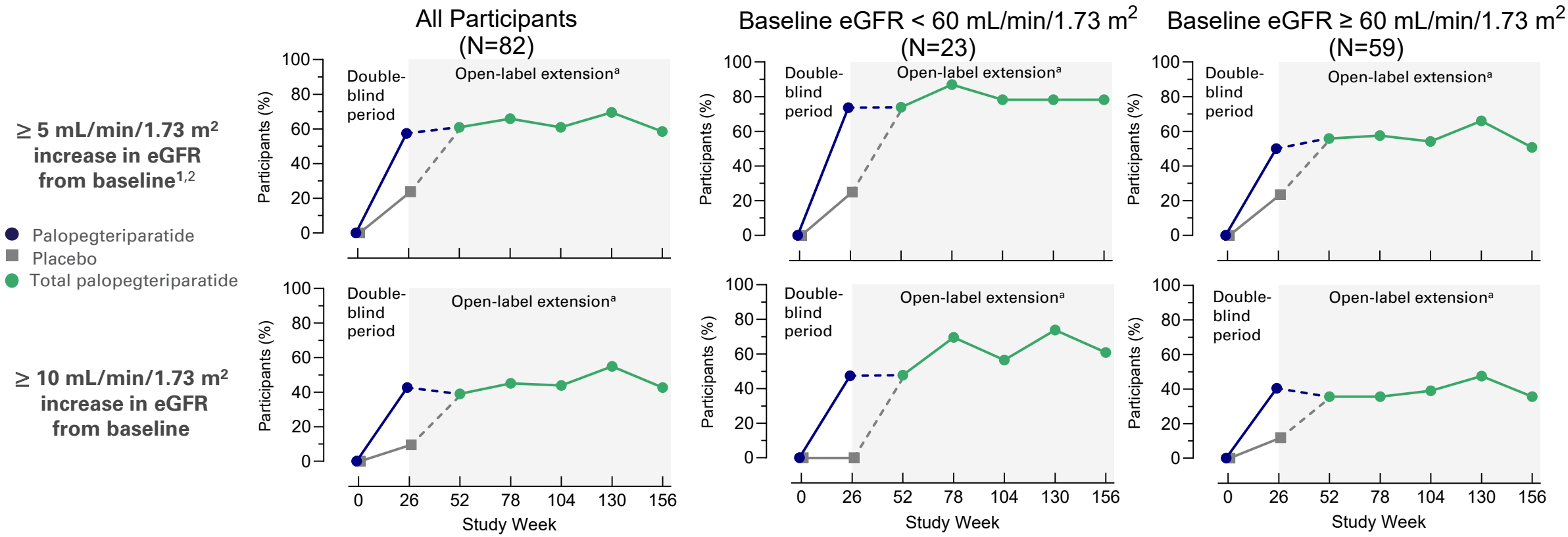
Sustained Improvements in eGFR From Baseline Through Week 156



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

[a]All participants received palopegteriparatide during the open-label extension.
eGFR, estimated glomerular filtration rate; SD, standard deviation

Sustained Proportion of Clinically Meaningful Increases in eGFR Through Week 156

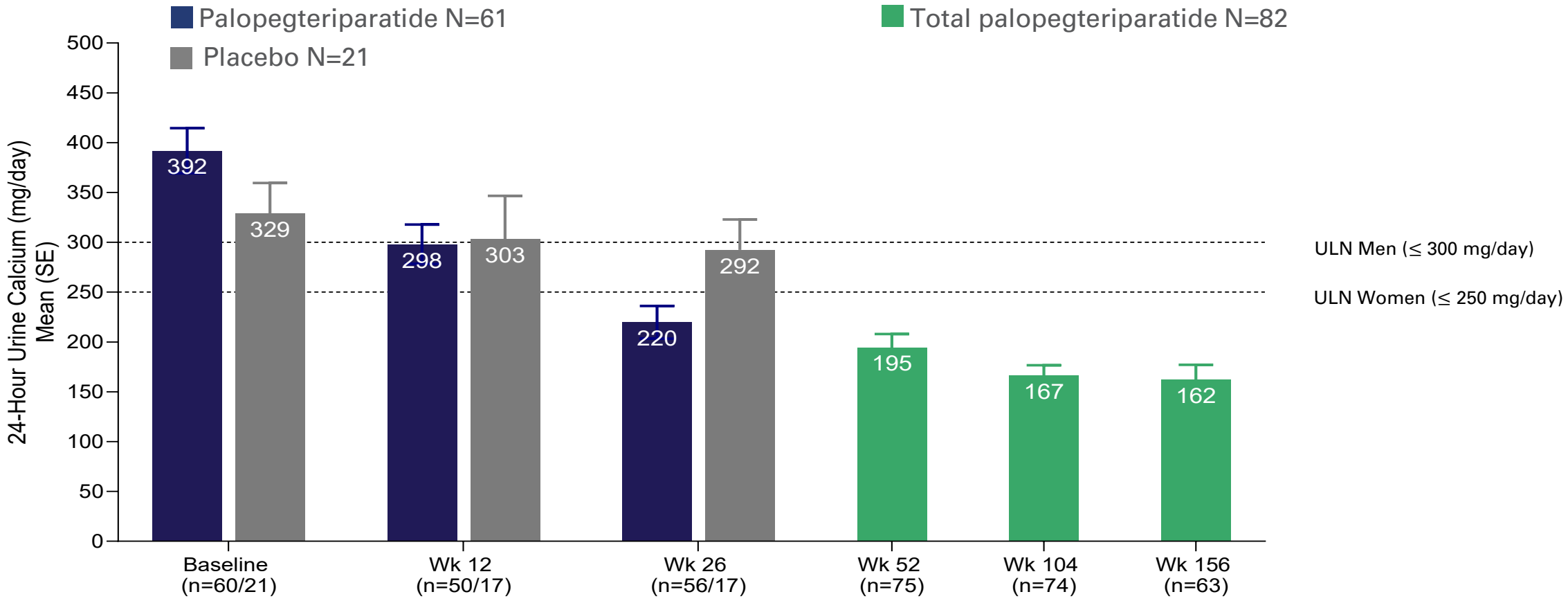


Clinically meaningful[1,2] ≥5 mL/min/1.73 m² improvement in eGFR observed for 59% of all participants at Week 156, with 61% of the <60 eGFR subgroup having a ≥10 mL/min/1.73 m² increase

Wk, week. [a]All participants received palopegteriparatide during the open-label extension. [b]Clinically 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.

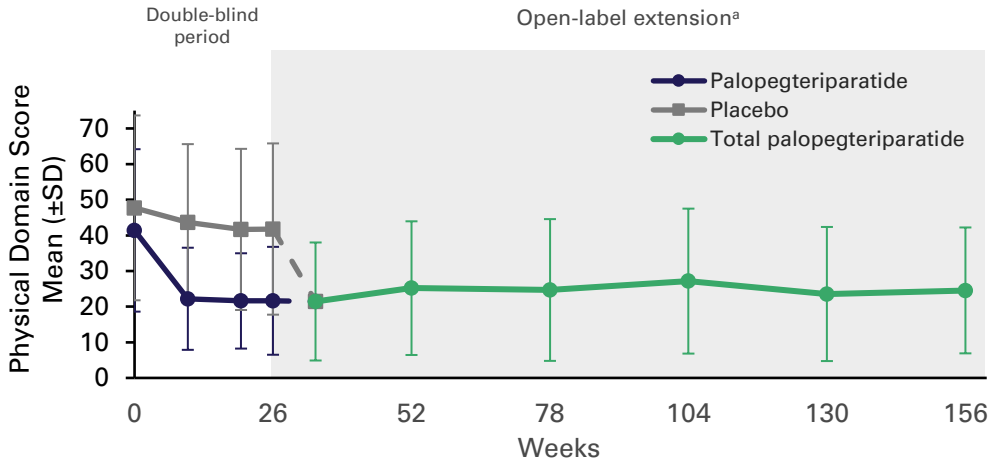
Normalization of Mean 24-Hour Urine Calcium Excretion With Continued Reductions Through Week 156



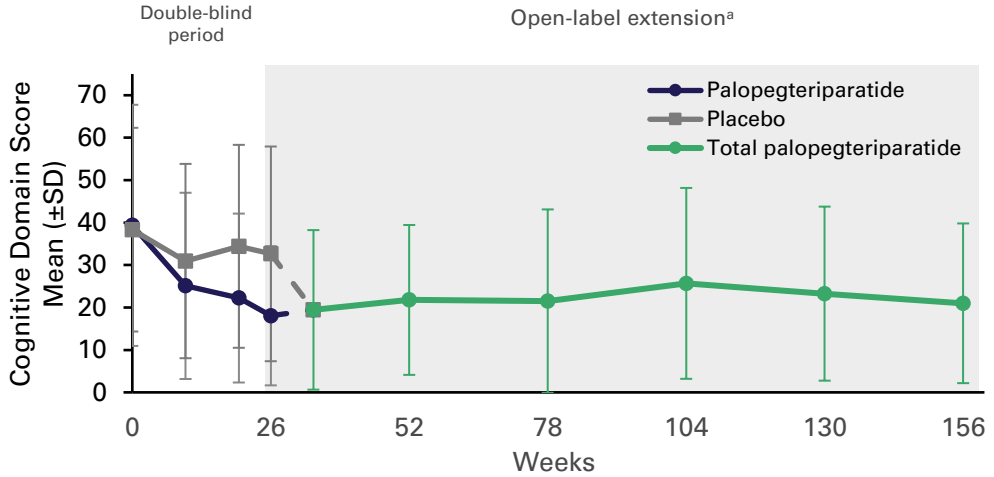
SE, standard error; ULN, upper limit of normal; Wk, week.

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

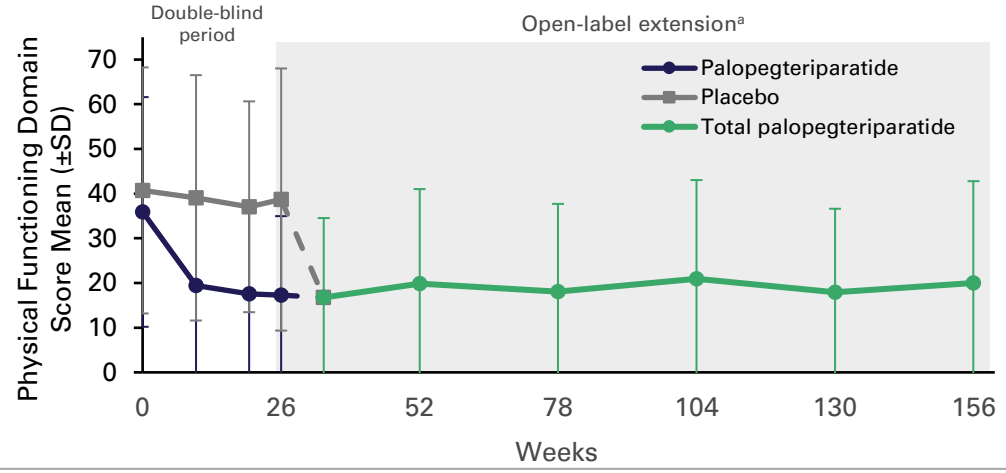
HPES-Symptom Physical Domain Score



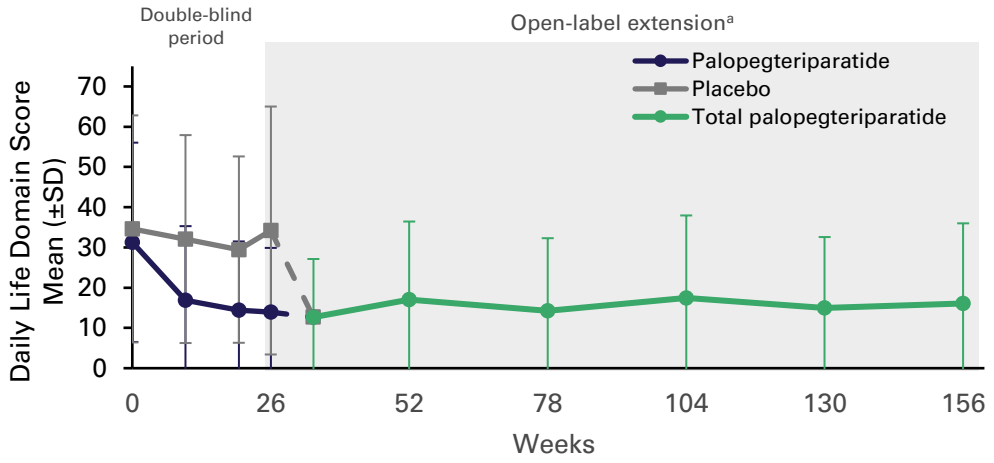
HPES-Symptom Cognitive Domain Score[b]



HPES-Impact Physical Functioning Domain Score[b]



HPES-Impact Daily Life Domain Score[b]



[a]All participants received palopegteriparatide during the open-label period [b]Standard 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 ≥ 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]

[a]Includes 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).[b]Median time to onset of these calcium-related TEAEs was 181 days (range 8-885 days). [c]TEAEs leading to treatment discontinuation were deemed unrelated to study drug. [d]One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment. [e]Classified 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

[a]The 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