Sustained Improvement in Skeletal Dynamics and Renal Function With Palopegteriparatide in Adults With Chronic Hypoparathyroidism: 2-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

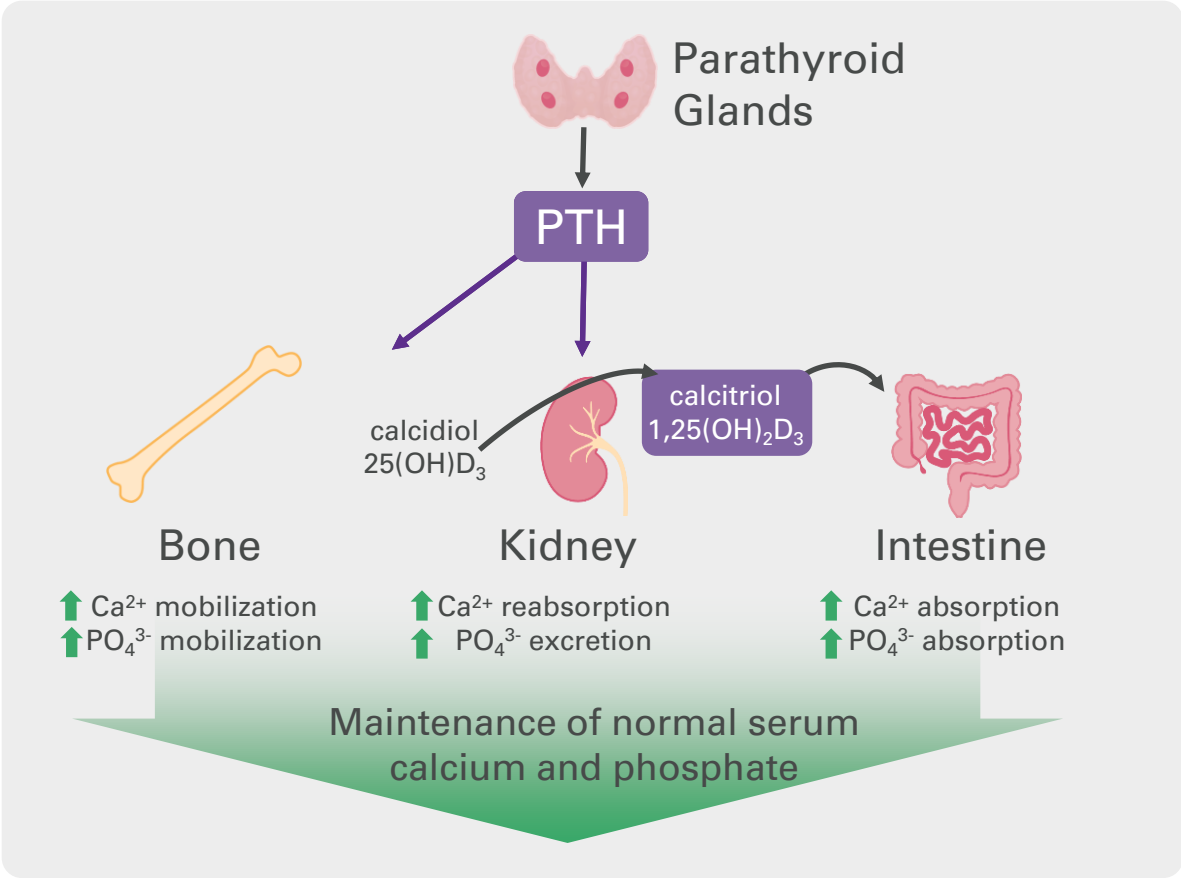
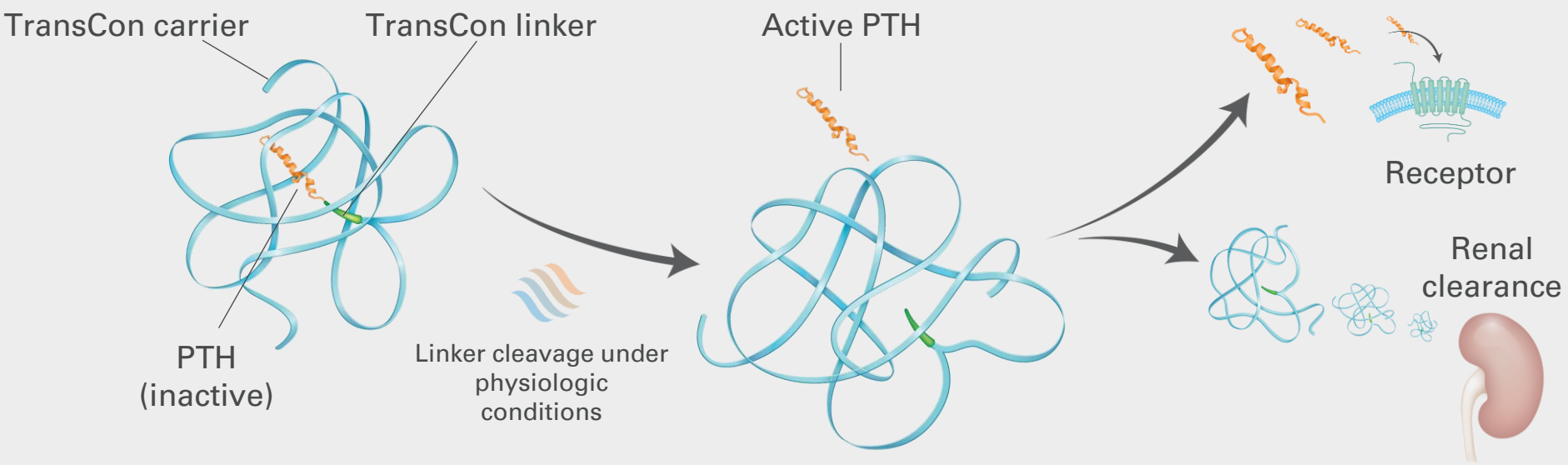


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.[7]

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

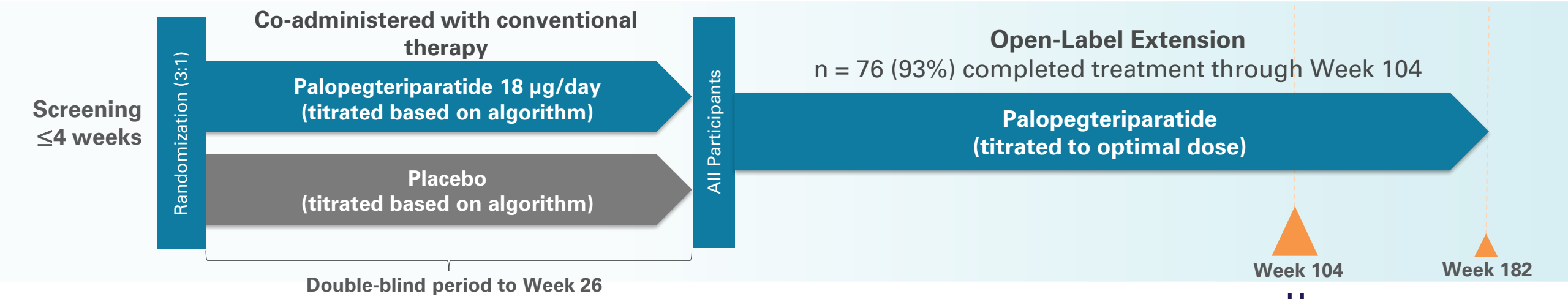


- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[1,2]
- Palopegteriparatide has received regulatory approval in the EU[a], US[b] and several other countries

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

Skeletal and Renal Endpoints

- Bone turnover markers (P1NP and CTx) and bone mineral density (BMD) by dual x-ray absorptiometry (DXA)
- Estimated glomerular filtration rate (eGFR)[c]: post hoc analysis

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 104 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 104 visit
[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]
P1NP, procollagen type 1 N-terminal propeptide; CTx, C-terminal telopeptide of type 1 collagen.

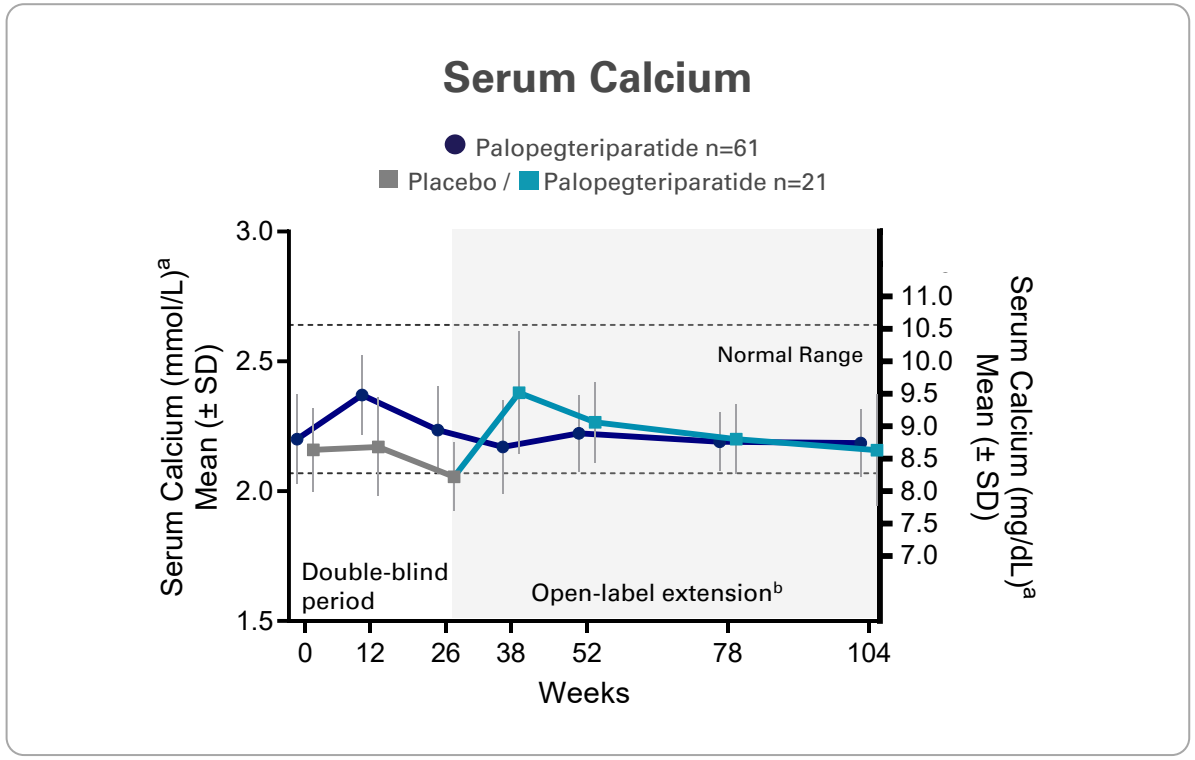
Independence From Conventional Therapy Observed in 97% of Participants at Week 104

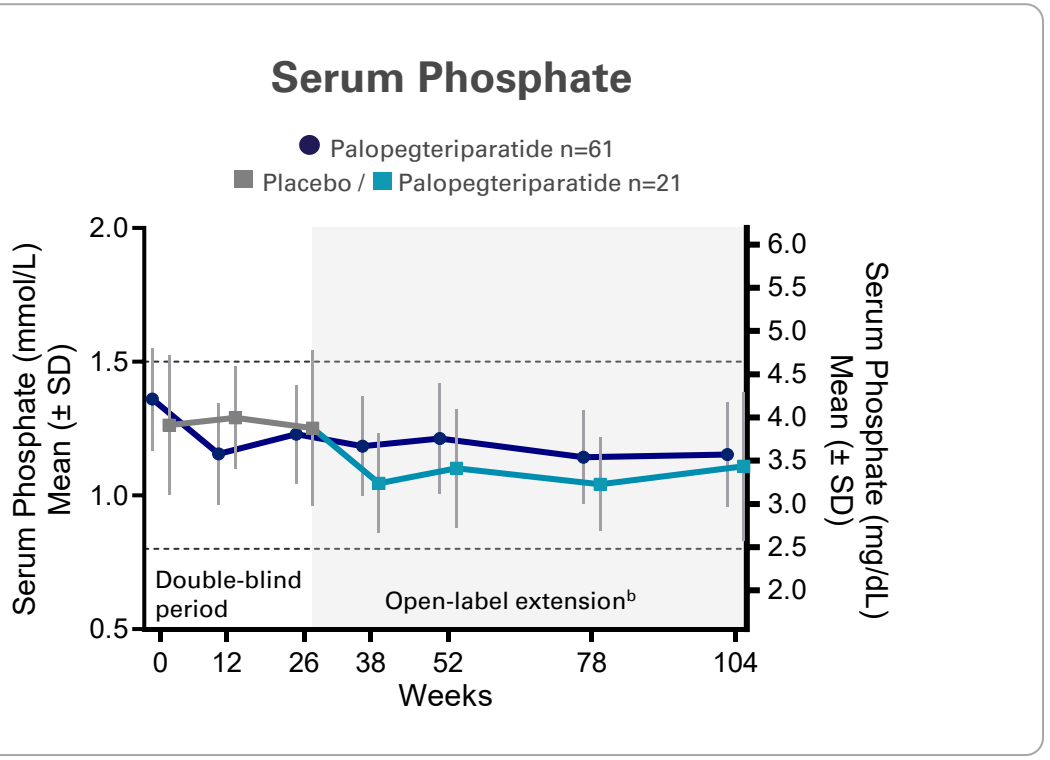
	All Participants (N=82)	Baseline eGFR < 60 mL/min/1.73 m^2 (n=23)	Baseline eGFR ≥ 60 mL/min/1.73 m^2 (n=59)
Number of participants with data at week 104	**76**	22	54
Independence from active vitamin D, n (%)	**76 (100%)**	22 (100%)	54 (100%)
Independence from therapeutic doses of calcium, n (%)	**74 (97%)**	21 (95%)	53 (98%)

Independence from conventional therapy was consistent across baseline eGFR subgroups

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 104 visit
Percentages are calculated based on participants who had data on all criteria. eGFR calculated using MDRD equation (central lab prespecified)
eGFR, estimated glomerular filtration rate

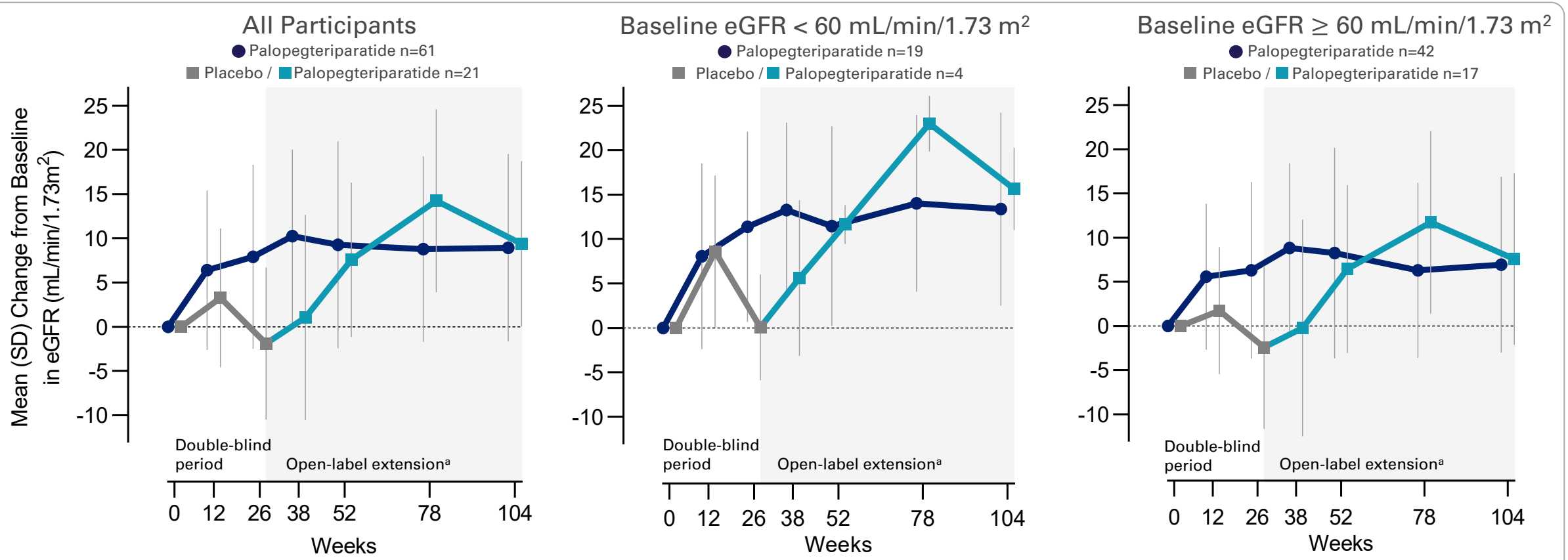
Serum Calcium and Serum Phosphate Maintained Within the Normal Range Through Week 104





[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)

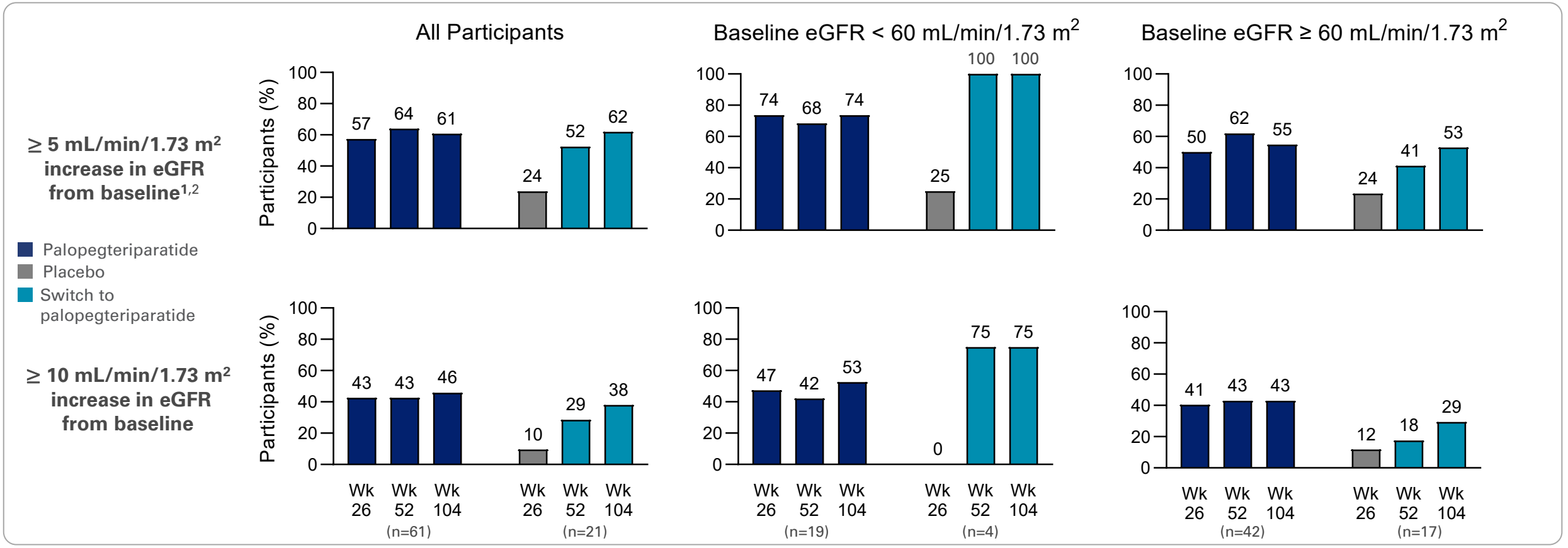
Sustained Improvements in eGFR From Baseline Through Week 104



eGFR improvements at week 104 were numerically greater in the lower baseline eGFR subgroup

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

Proportion of Participants With Clinically Meaningful Increases in eGFR Through Week 104

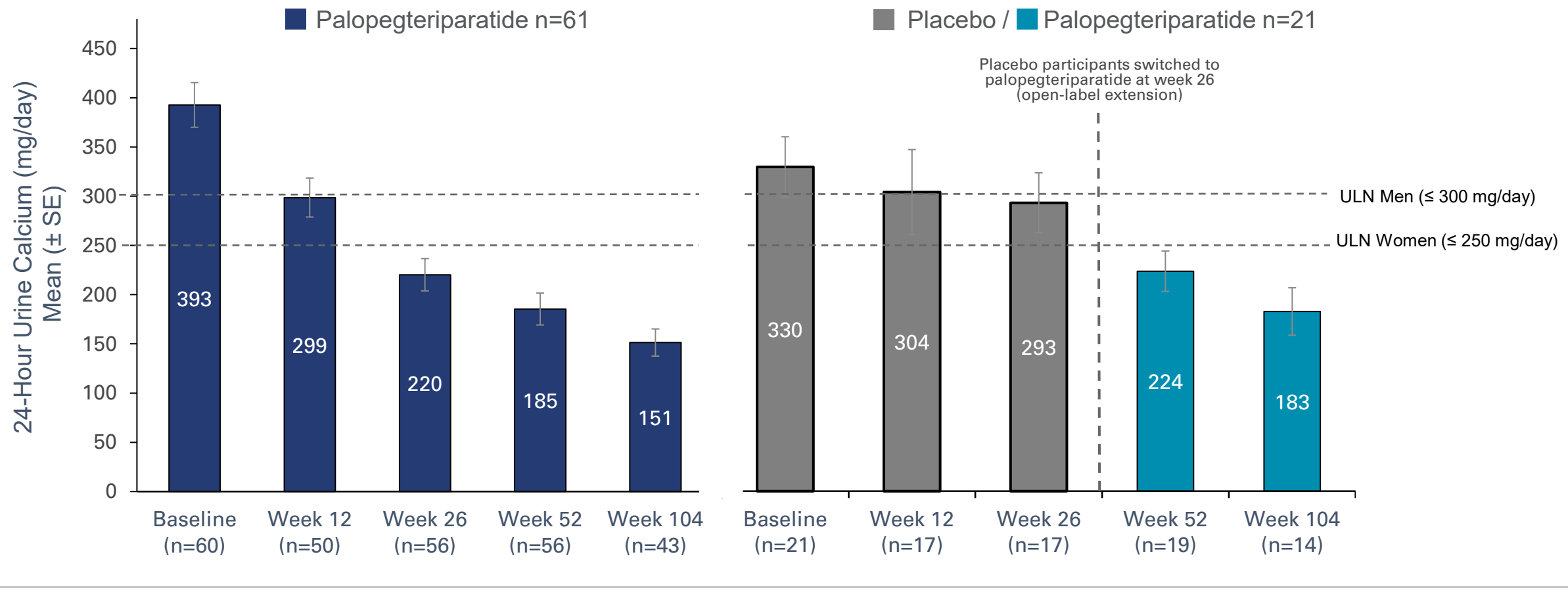


A numerically larger proportion of the lower baseline eGFR subgroup had clinically meaningful[1,2] improvement in eGFR

Wk, week. [a]Clinically meaningful increases in eGFR were those ≥ 5 mL/ min / 1.73m².

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.

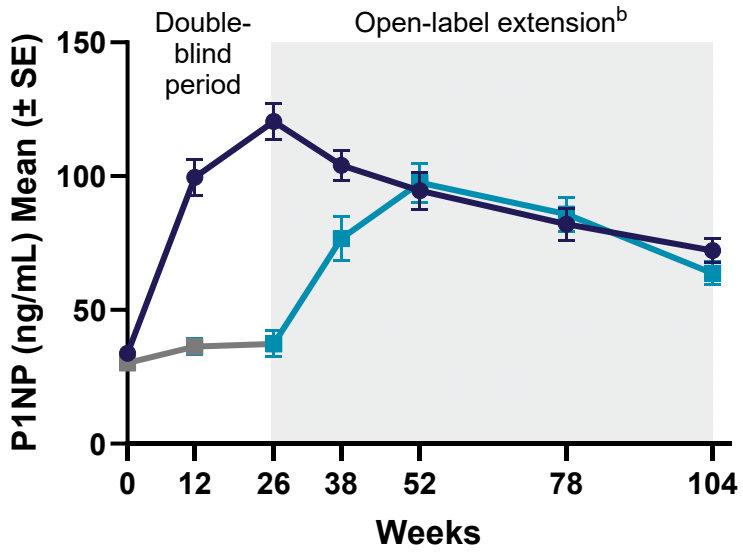
Normalization of Mean 24-Hour Urine Calcium Excretion With Continued Reductions Through Week 104



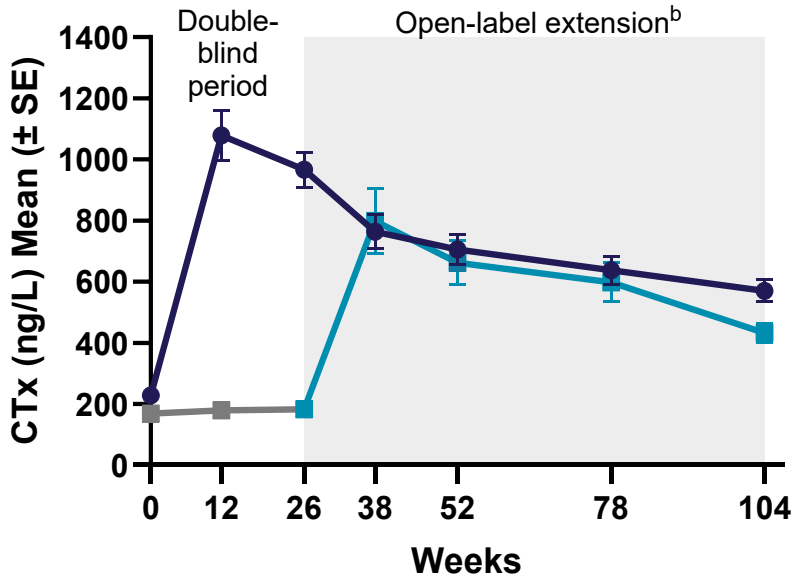
SE, standard error; ULN, upper limit of normal

Mean Bone Turnover Markers Maintained in the Normal Range[a] at Week 104

Procollagen Type 1 N-Terminal Propeptide (P1NP)



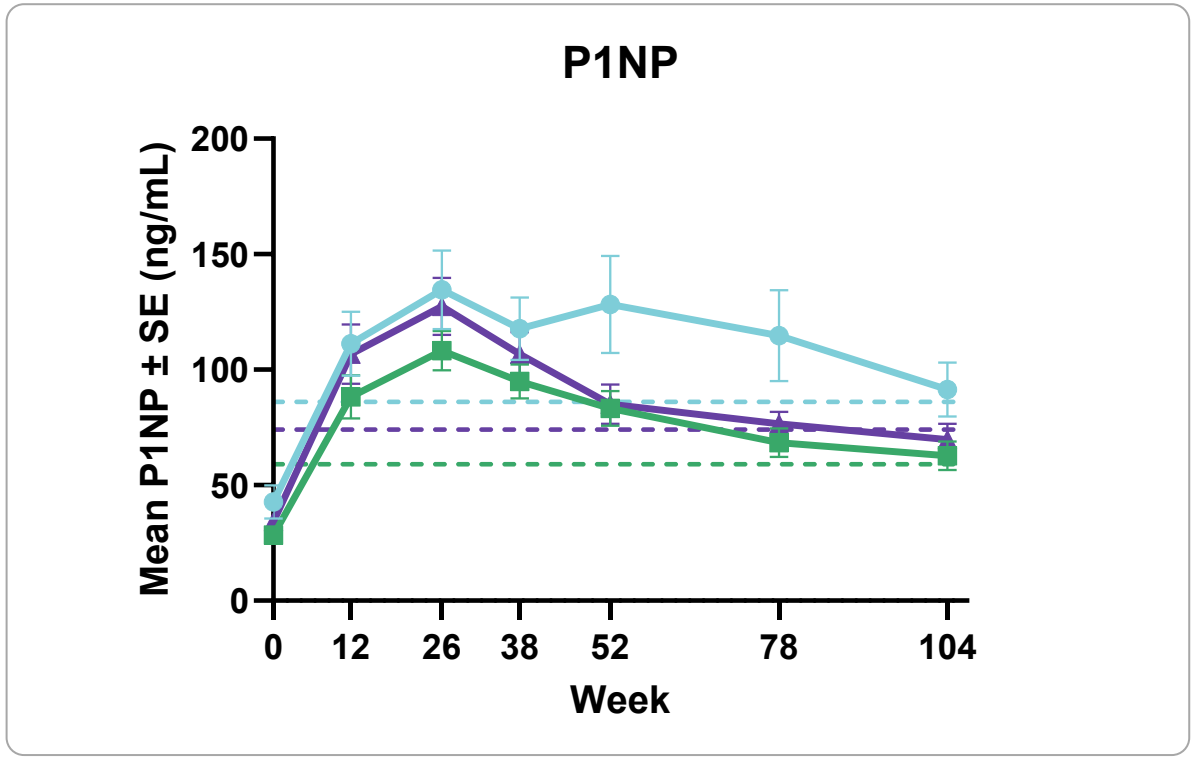
C-Terminal Telopeptide of Type 1 Collagen (CTx)

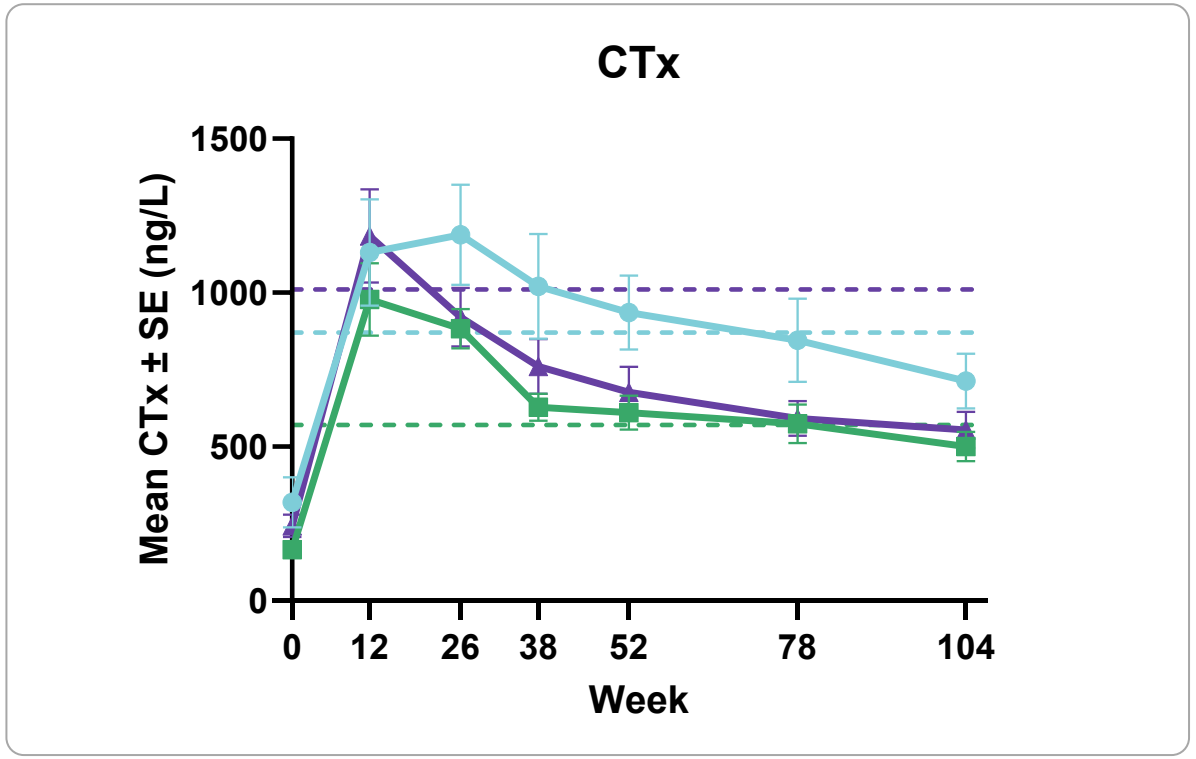


● Palopegteriparatide n=61
■ Placebo / ■ Palopegteriparatide n=21

[a]Normal Ranges: P1NP (ng/mL): premenopausal women 15-59; postmenopausal women 16-74; men 14-86
CTx (ng/L): premenopausal women 30-570; postmenopausal women 100-1010; men 18-30 yo: 160-870; men 31-50 yo: 90-630; men ≥51 yo: 40-840
[b]All participants received palopegteriparatide during the open-label extension.
Missing data were not imputed. Participants missing P1NP: n=4 at wks 12, 38, and 52, n=1 at wk 26, n=5 at wk 78; n=7 at wk 104; CTx: n=3 at wk 26, n=5 at wks 38, 52, n=6 at wk 104
PTH, parathyroid hormone; SE, standard error.

Bone Turnover Marker Responses to Palopegteriparatide Were Consistent Across Sex and Menopausal Status Through Week 104

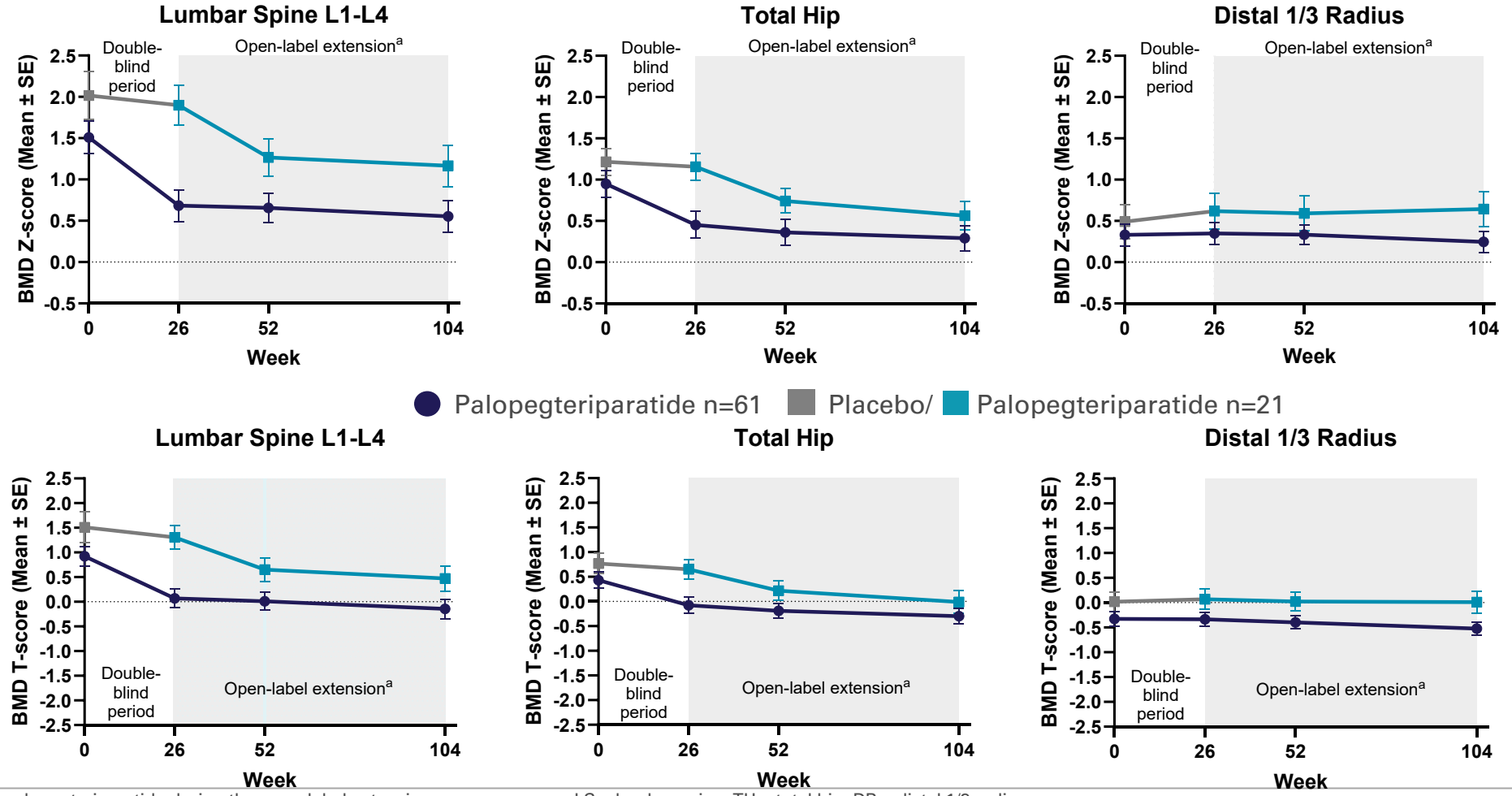




Male (n=15) Post-Menopausal Female (n=19) Premenopausal Female (n=27)

Dashed lines indicate upper limit of the normal ranges for the color-specified population based on values from Labcorp.
All means are above the lower limit of the normal range for their respective population. Data is shown for the 61 participants randomized to palopegteriparatide at baseline.
CTx, C-terminal telopeptide of type 1 collagen; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; SE, standard error.
Missing data were not imputed. Participants with missing data: males: n=1 at wks 12 (CTx), 26, 38, 52, 78 (P1NP), and 104; post-menopausal: n=1 at wk 12 (P1NP), n=2 at wk 12 (CTx); pre-menopausal: n=1 at wk 38 (CTx), 52, 78 (CTx), n=4 at wk 104 (P1NP), n=2 at wk 104 (CTx)

Mean BMD T-scores and Z-scores Remained Consistent After 26 Weeks of Treatment With Palopegteriparatide

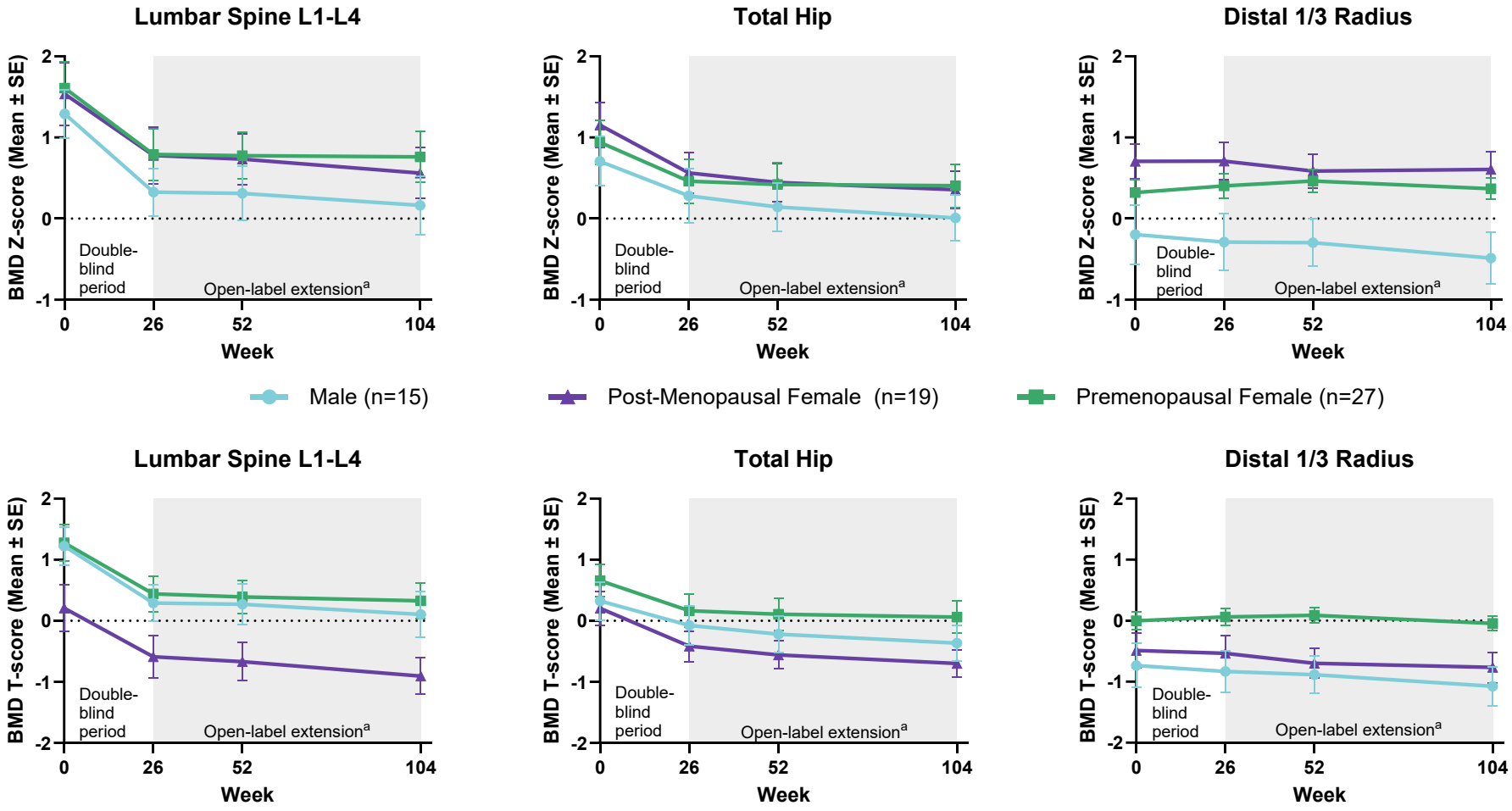


[a]All participants received palopegteriparatide during the open-label extension. LS = lumbar spine; TH = total hip; DR = distal 1/3 radius

T-score = BMD in SDs compared to young adult mean; Z-score = BMD measured in SDs compared to age- and sex-matched norms.

Missing data were not imputed. Participants with missing data: BMD Z-scores: palopegteriparatide/placebo: baseline: n=1 (LS,TH); wk 26: n=3 (LS, TH), n=2 (DR); wk 52: n=3 (LS,TH); wk 104: n=4 (LS, TH), n=3 (DR). Palopegeriparatide: baseline n=1(TH), n=2 (LS, DR); wk 26: n=3 (LS), n=2 (TH, DR); wk 52: n=4 (LS), n=3 (TH, DR); wk 104: n=4 (LS,DR), n=4 (TH). BMD T-scores: placebo/palopegteriparatide: baseline n=1 (LS, TH); wk 26: n=3 (LS,TH), n=2 (DR); wk 52: n=3 (LS, TH), n=2 (DR); wk 104: n=4 (LS, TH), n=3 (DR). Palopegteriparatide: baseline: n=2 (LS), n=1 (TH, DR); wk 26: n=3 (LS), n=2 (TH), n=1 (DR); wk 52: n=4 (LS), n=3 (TH), n=2 (DR); wk 104: n=5 (LS), n=4 (TH, DR).

BMD Responses to Palopegteriparatide Were Consistent Across Sex and Menopausal Status Through Week 104



Menopausal status determined by survey at beginning of trial. Data is shown for the 61 participants randomized to palopegteriparatide at baseline.
[a]All participants received palopegteriparatide during the open-label extension.
Missing data were not imputed. Participants with missing data: BMD Z-scores: males: baseline: n=1 (LS), n=2 (DR); wk 26: n=2 (LS,DR), n=1 (TH); wk 52: n=2 (LS, DR), n=1 (TH); wk 104: n=2 (LS, DR), n=1 (TH). Premenopausal female: baseline: n=1 (LS,TH); wk 26: n=1 (LS, TH), n=2 (DR); wk 52: n=2 (LS, TH), n=1 (DR); wk 104: n=3 (LS, TH), n=2 (DR). BMD T-scores: males: baseline: n=1 (LS); wk 26: n=2 (LS); wk 52: n=2 (LS); wk 104: n=2 (LS). Premenopausal female: baseline: n=1 (LS, TH); wk 26: n=1 (LS, TH); wk 52: n=2 (LS, TH), n=1 (DR); wk 104: n=3 (LS,TH), n=2 (DR).

Summary of Adverse Events Through Week 104

Treatment Emergent Adverse Events (TEAEs), n (%)	All Participants[a] N=80	Baseline eGFR < 60 mL/min/1.73 m² n=23	Baseline eGFR ≥ 60 mL/min/1.73 m² n=57
Any TEAE	**75 (93.8)**	22 (95.7)	53 (93.0)
Serious TEAE	**14 (17.5)**	6 (26.1)	8 (14.0)
Related TEAE	**44 (55.0)**	13 (56.5)	31 (54.4)
Serious related TEAE	**2 (2.5)**	1 (4.3)	1 (1.8)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization[b]	**6 (7.5)**	4 (17.4)	2 (3.5)
TEAE leading to discontinuation of trial[c]	**1 (1.3)**	0	1 (1.8)
TEAE leading to death[c]	**1 (1.3)**	0	1 (1.8)

Treatment-related TEAEs occurring at a rate of ≥ 5% among all participants (N=80) included:

Injection site reaction (26.2%), hypercalcemia (13.8%), nausea (8.8%), headache (7.5%), hypocalcemia (7.5%), and postural orthostatic tachycardia syndrome (5.0%)

Most TEAEs were mild or moderate and generally reported at similar rates across baseline eGFR groups

[a]Includes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (patients who received ≥1 dose of palopegteriparatide): 104 weeks of exposure for the Palopegteriparatide/Palopegteriparatide group (n=61) and 78 weeks of exposure for the Placebo/Palopegteriparatide group (n=19).[b]Median time to onset of these calcium-related TEAEs was 113 days (range 8-582 days). [c]One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment.
eGFR, estimated glomerular filtration rate.

Conclusions

Treatment with palopegteriparatide was associated with significant and sustained improvement in renal function and skeletal dynamics in adults with chronic hypoparathyroidism

- Palopegteriparatide was generally well-tolerated with no new safety signals identified
- Sustained benefits through 104 weeks:
  - Independence from conventional therapy (active vitamin D and calcium)
  - Clinically meaningful increase in eGFR
    - Numerically greater responses in participants with lower baseline eGFR
  - Mean BMD T- and Z-scores declined from elevated baseline levels and stabilized within the normal range through week 104
    - Similar impact across pre-menopausal women, post-menopausal women, and men

Thank you for your attention!

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