

Sustained Improvement in Skeletal Dynamics and Renal Function With Palopegteriparatide in Adults With Chronic Hypoparathyroidism: 2-Year Results From the Phase 3 PaTHway Trial

Lynn Kohlmeier,¹ Peter Schwarz,² Lars Rejnmark,³ Elvira Gosmanova,⁴ Aliya A. Khan,⁵ Noriko Makita,⁶ Yasuo Imanishi,⁷ Yasuhiro Takeuchi,⁸ Stuart Sprague,⁹ Dolores M. Shoback,¹⁰ Mishaela R. Rubin,¹¹ Andrea Palermo,¹² Claudia Gagnon,¹³ Elena Tsourdi,¹⁴ Aimee D. Shu¹⁵

¹Endocrinology and Spokane Osteoporosis, Spokane, WA, USA; ²Rigshospitalet, Copenhagen, Denmark; ³Aarhus University Hospital, Aarhus, Denmark; ⁴Albany Medical College, Albany, NY, USA; ⁵McMaster University, Hamilton, ON, Canada; ⁶University of Tokyo Graduate School of Medicine, Tokyo, Japan; ⁷Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; ⁸Toranomon Hospital, Tokyo, Japan and Okinaka Memorial Institute for Medical Research, Tokyo, Japan; ⁹NorthShore University Health System-University of Chicago Pritzker School of Medicine, Chicago, IL; ¹⁰University of California, San Francisco and VA Medical Center, San Francisco, CA, USA; ¹¹Columbia University, New York, NY, USA; ¹²Fondazione Policlinico Campus Bio-medico and Unit of Endocrinology and Diabetes, Campus Bio-medico University, Rome, Italy; ¹³CHU de Québec-Université Laval Research Centre and Department of Medicine, Université Laval, Quebec City, QC, Canada; ¹⁴Technische Universität Dresden Medical Center, Dresden, Germany; ¹⁵Ascendis Pharma Inc, Palo Alto, CA, USA.

MED-US-TC-PTH-2500143
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

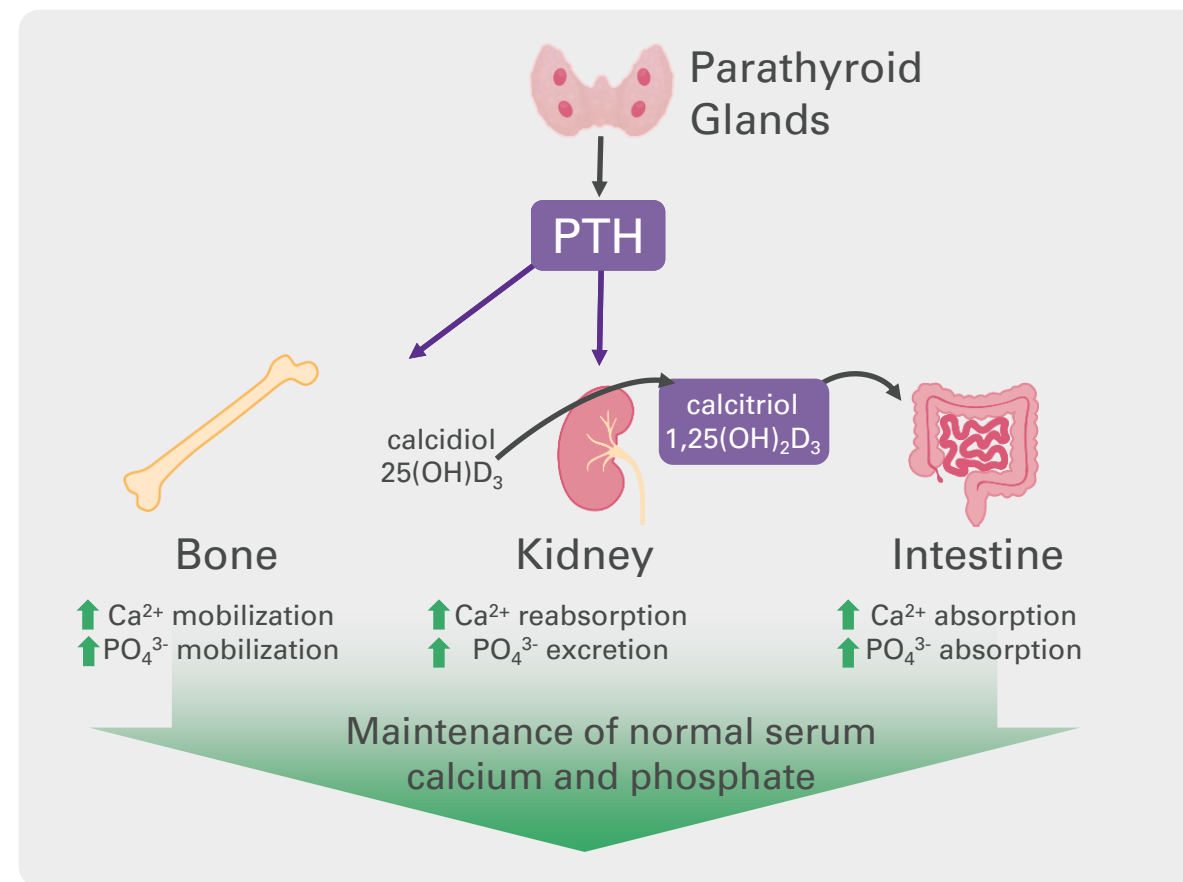
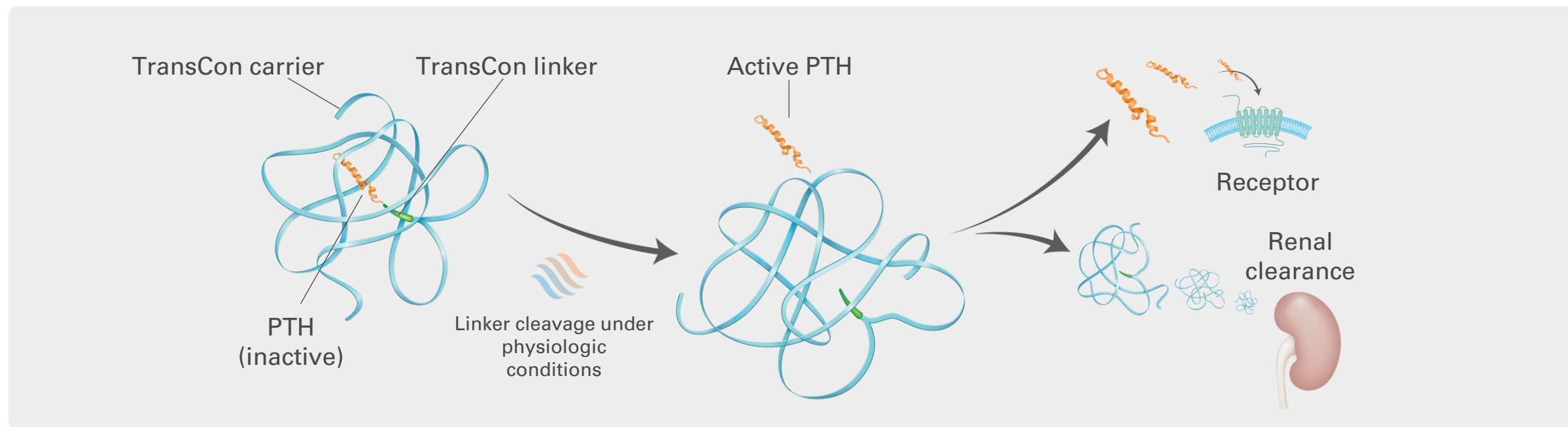


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.⁷

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

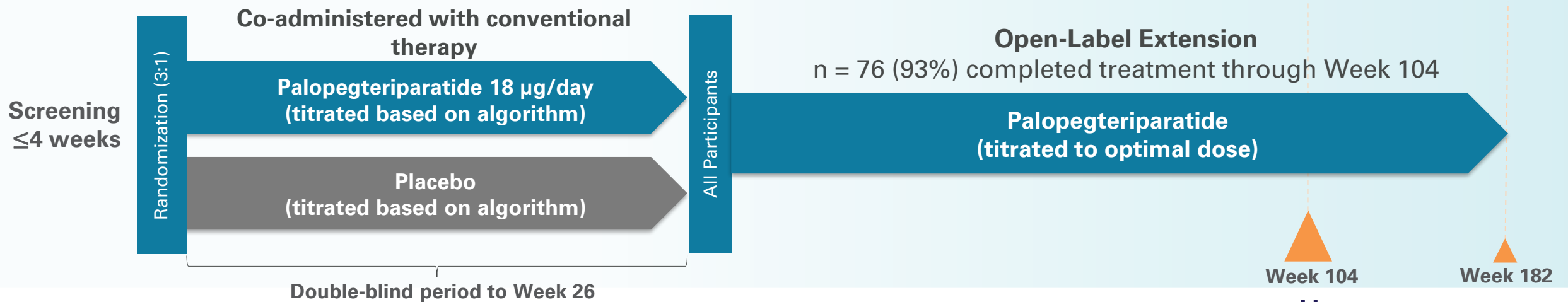
PTH, parathyroid hormone; TransCon, transient conjugation.

^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

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

^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 104 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 104 visit

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

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

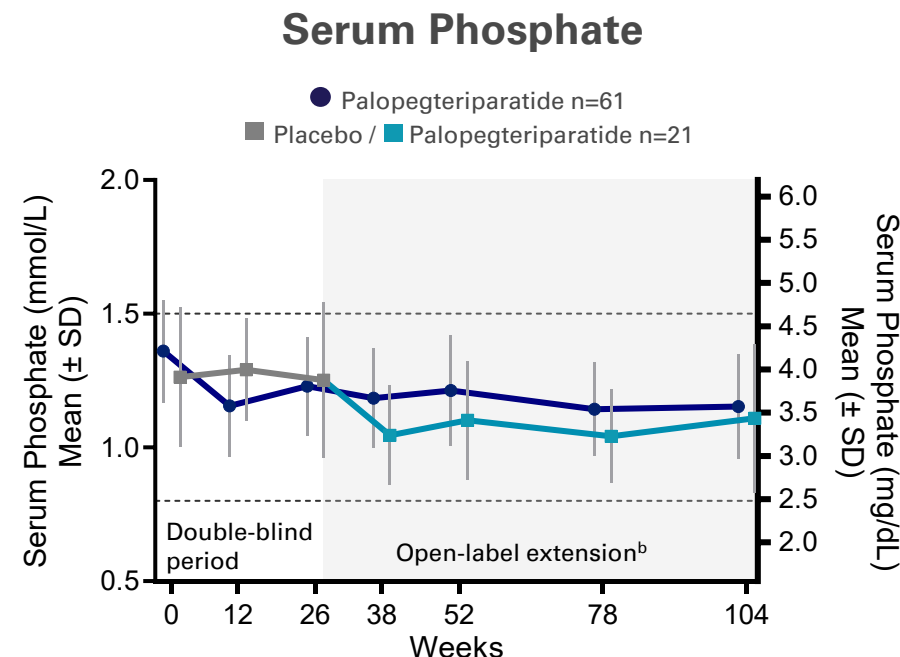
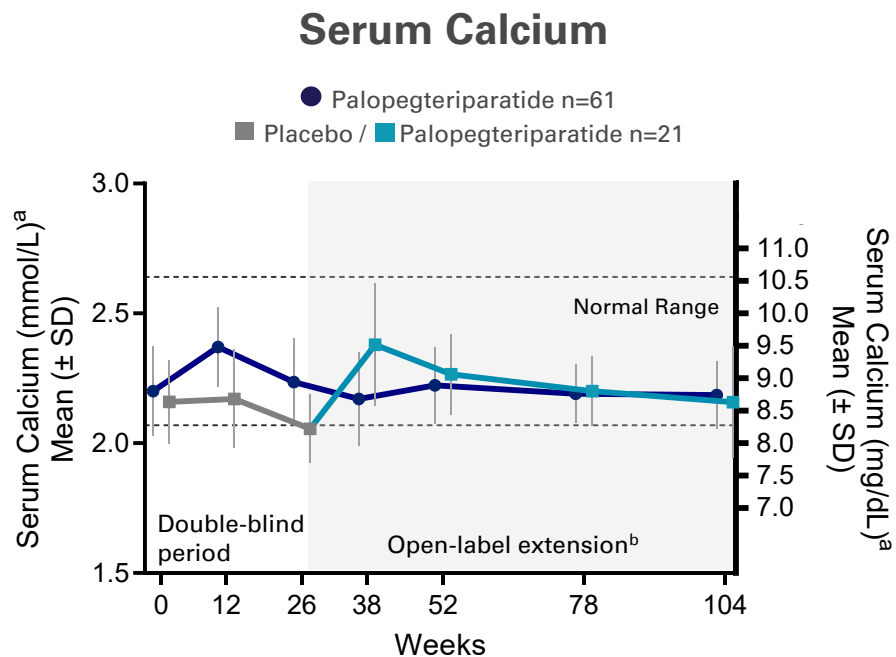
Independence From Conventional Therapy Observed in 97% of Participants at Week 104

	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

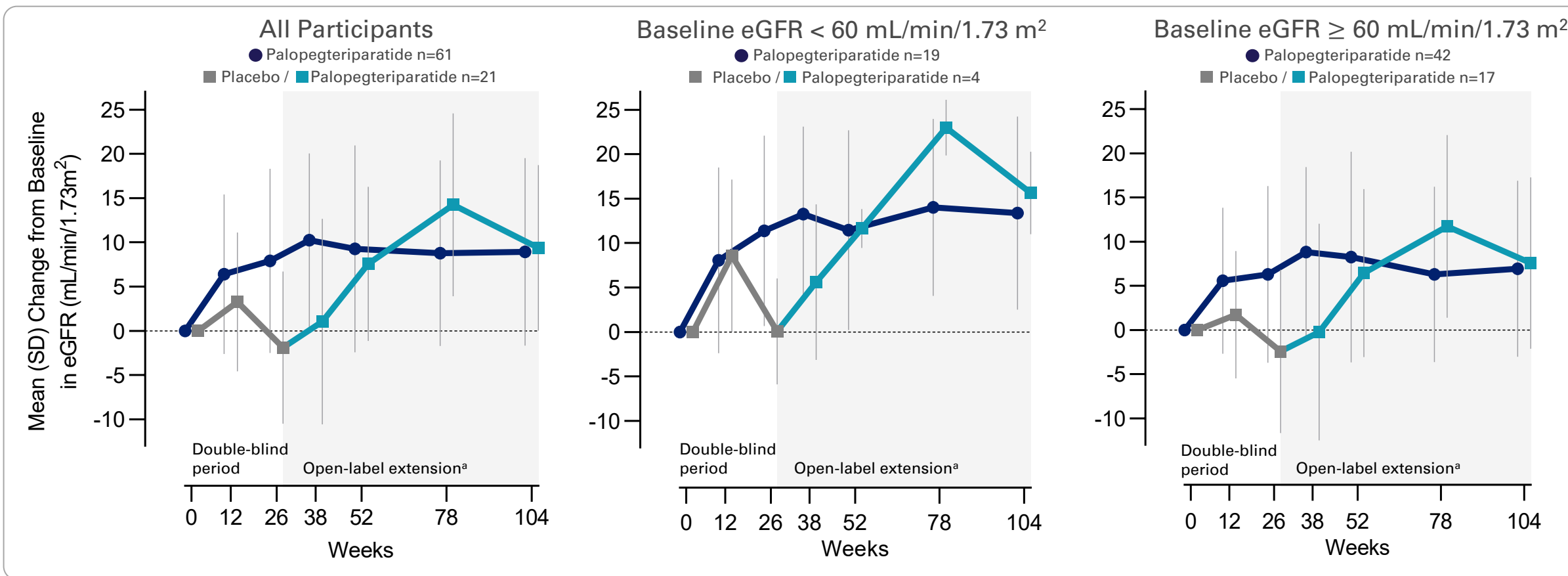


^aAlbumin-adjusted. ^bAll participants received palopegteriparatide during the open-label extension.

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)

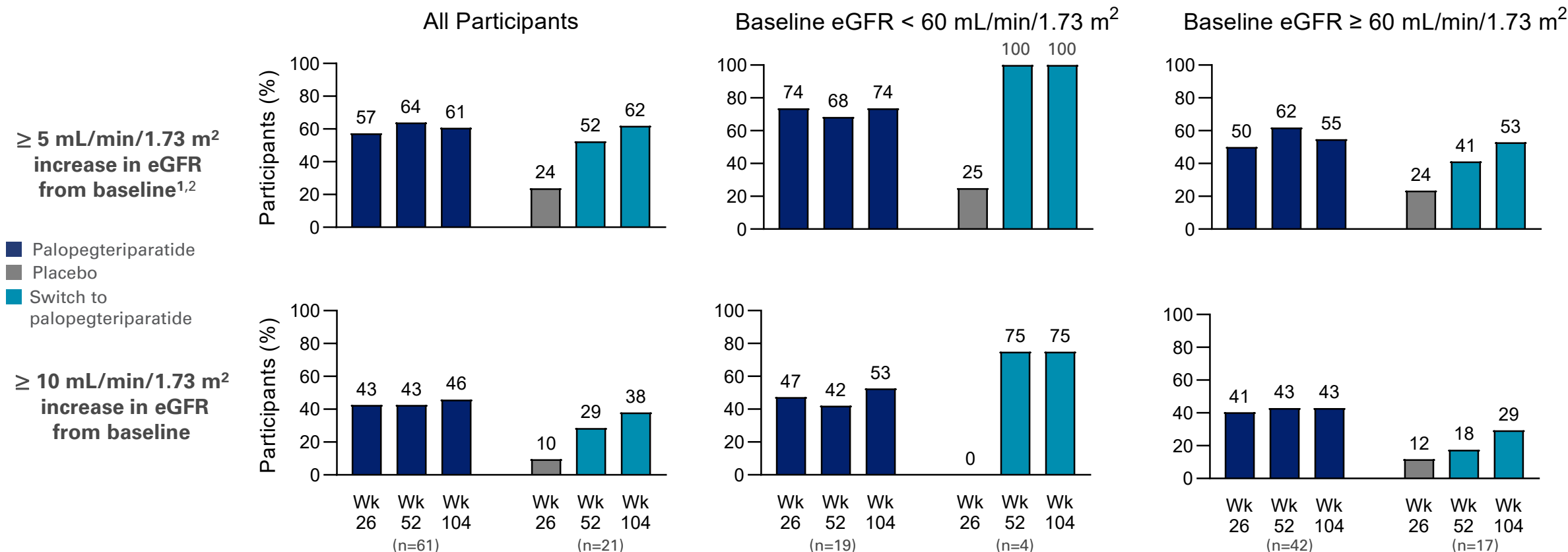
Sustained Improvements in eGFR From Baseline Through Week 104



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

^aAll 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



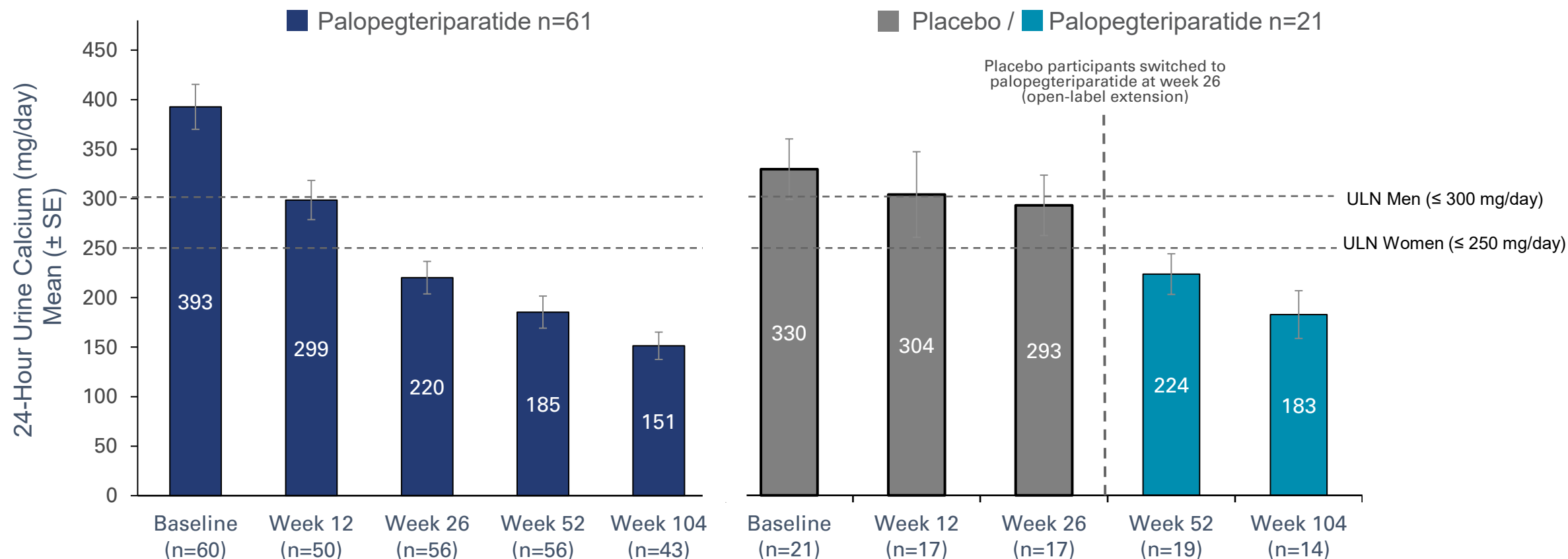
A numerically larger proportion of the lower baseline eGFR subgroup had clinically meaningful^{1,2} improvement in eGFR

Wk, week. *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.

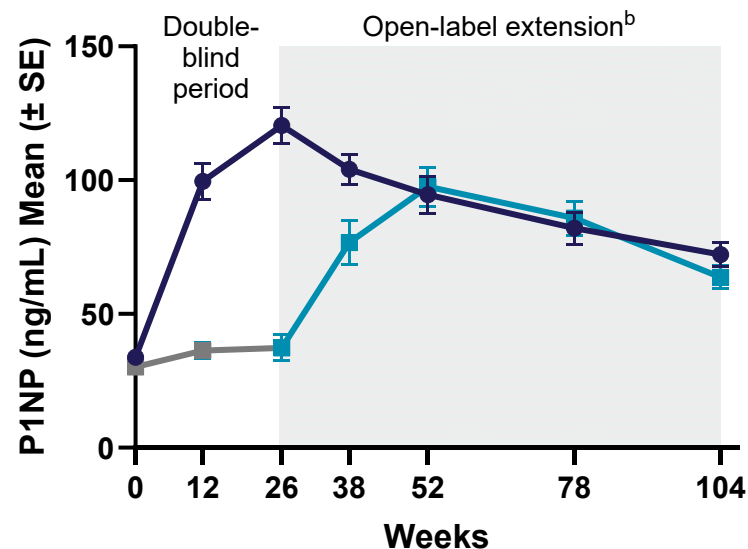
Normalization of Mean 24-Hour Urine Calcium Excretion With Continued Reductions Through Week 104



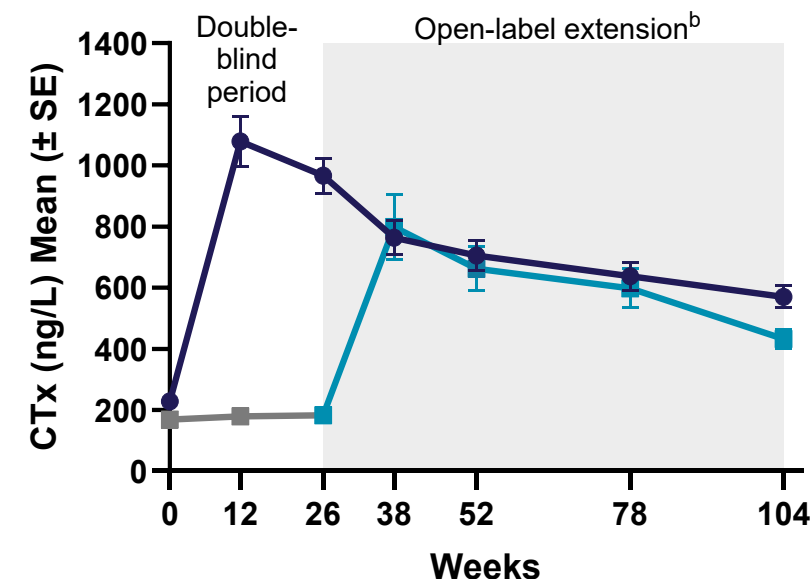
SE, standard error; ULN, upper limit of normal

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

^aNormal Ranges: P1NP (ng/mL): premenopausal women 15-59; postmenopausal women 16-74; men 14-86

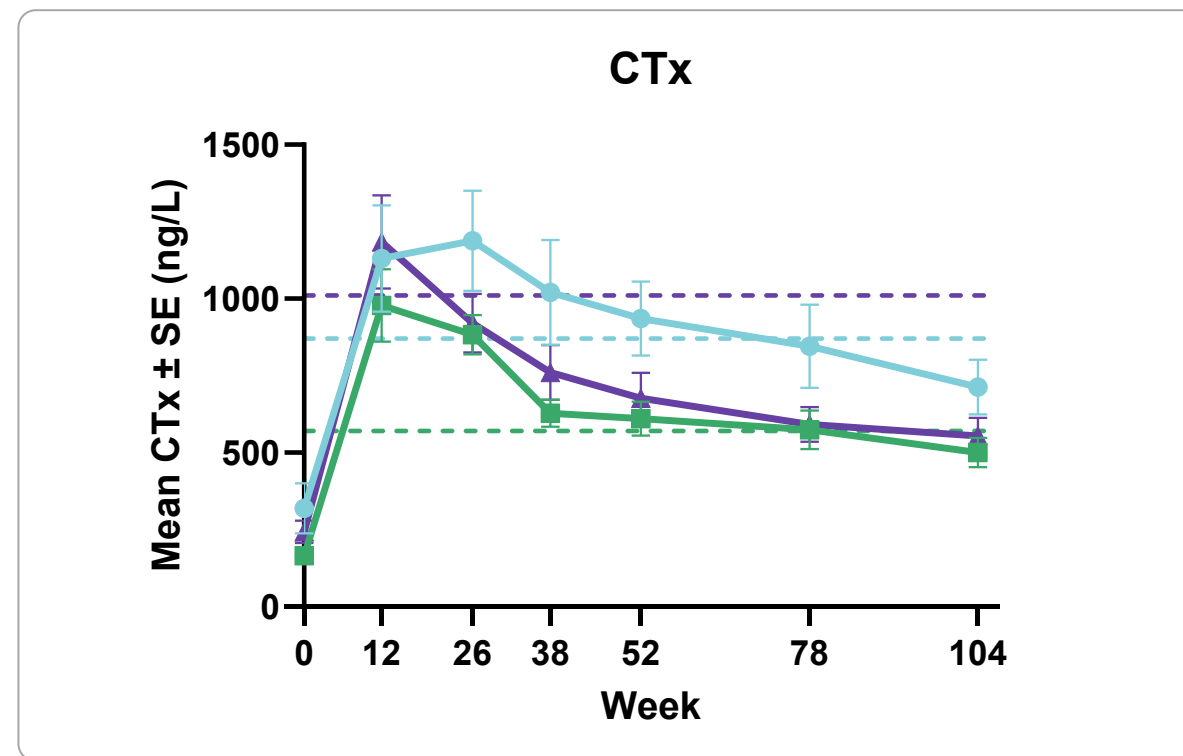
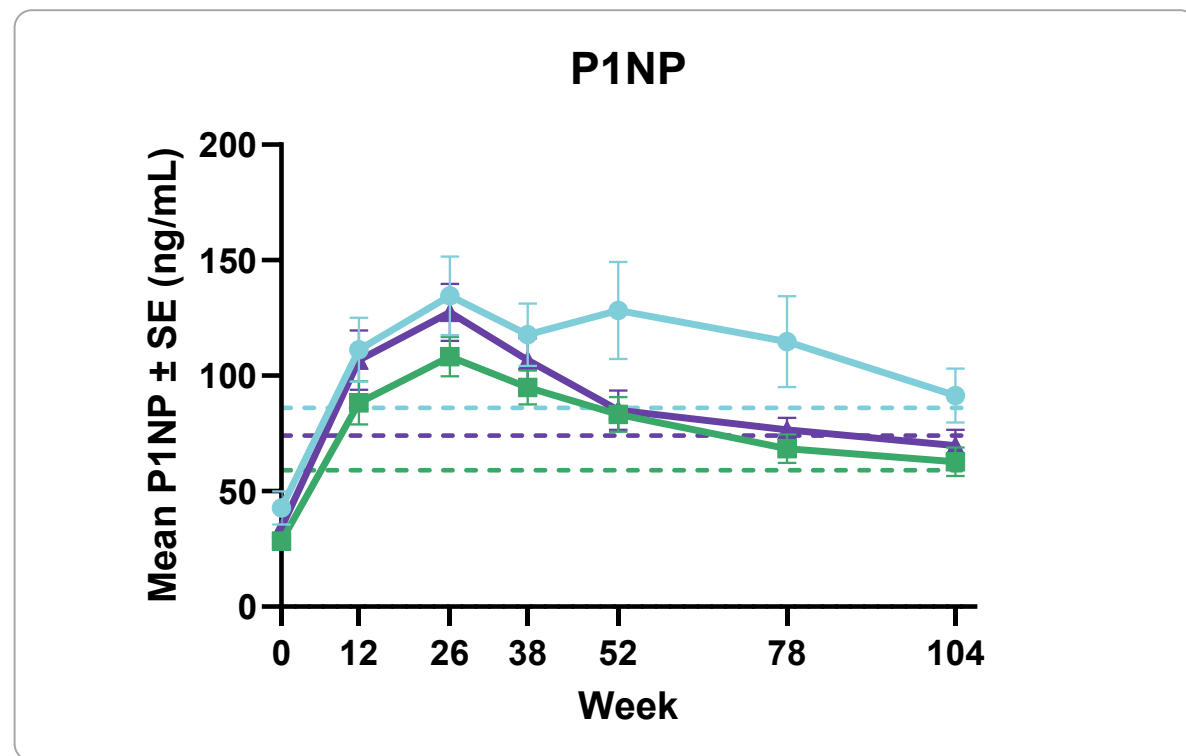
CTx (ng/L): premenopausal women 30-570; postmenopausal women 100-1010; men 18-30 yo: 160-870; men 31-50 yo: 90-630; men ≥51 yo: 40-840

^bAll 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)

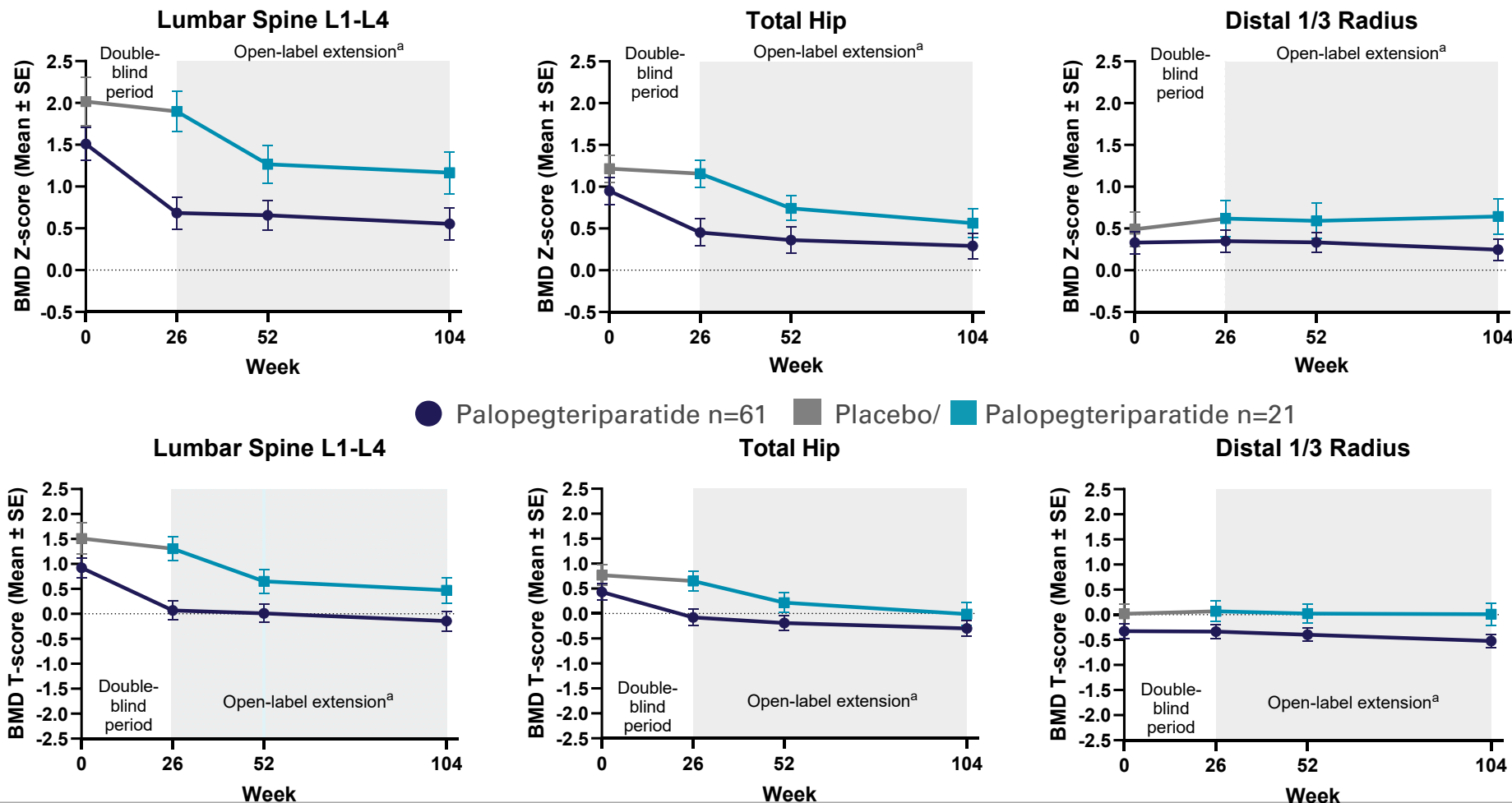
Dashed lines indicate upper limit of the normal ranges for the color-specified population based on values from Labcorp.

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



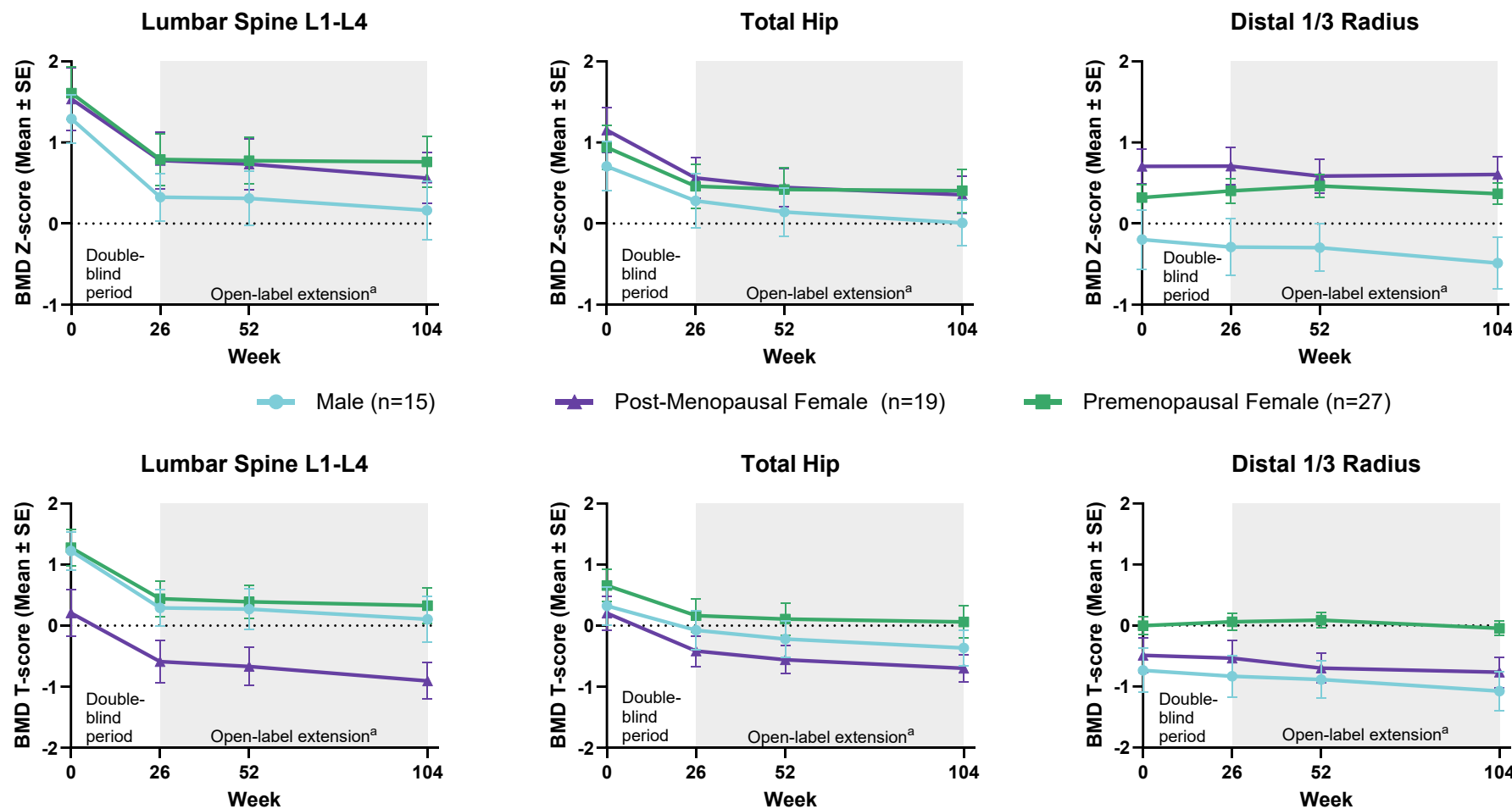
^aAll participants received palopegteriparatide during the open-label extension.

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). Palopegteriparatide: 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.

^aAll 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 m ² n=23	Baseline eGFR ≥ 60 mL/min/1.73 m ² 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

^aIncludes 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).^bMedian time to onset of these calcium-related TEAEs was 113 days (range 8-582 days). ^cOne 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!

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

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: **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. **PS**: Stock ownership Novo Nordisk, Ascendis Pharma. **LR**: Research funding from Takeda, Kyowa Kirin International, Ascendis Pharma, and Calcilytix; honoraria from Calcilytix Therapeutics; advisory board for Takeda and Amolyt. **EG**: Honoraria from Novo Nordisk and Takeda; advisory board role for Ascendis Pharma and Takeda; travel, accommodations, and expenses from Ascendis Pharma; industry-sponsored grants from AstraZeneca, AbbVie, and Kowa Research Institute. **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. **NM**: Research funding from Kyowa Kirin. **YI**: speakers bureau for Kyowa Kirin Co., Ltd and Daiichi Sankyo Co., Ltd. **YT**: Honoraria from Chugai Pharmaceutical Co. Ltd; consulting fee from Teijin Pharma; speakers bureau for Amgen Japan. **SS**: Research funding from Amgen, Amlyot, Ascendis Pharma, Ardelyx, Fresenius, and OPKO and consultant Amgen, Ardelyx, Bayer, Fresenius, Horizon, OPKO, and Shire. **DS**: Research/salary funding from Bone Health Tech; research funding from Ascendis Pharma. **MR**: Study investigator for Takeda, Ascendis Pharma, Amolyt, and Calcilytix; advisory board for Ascendis Pharma, speakers bureau for Ascendis Pharma; consulting for MBX. **AP**: Consultant for Theramex, Bruno Farmaceutici, Amgen; research funding from Amgen, Shire, Ascendis Pharma; speakers bureau UCB, Amgen; industry grant from Amgen. **CG**: Honoraria from Pendopharm; research funding from Ascendis Pharma, Amolyt, Shire, and Takeda. **ET**: Honoraria from Amgen, UCB, Takeda, Kyowa Kirin, and Ascendis Pharma; advisory board member for Amgen and UCB. **AS** is a full-time employee of Ascendis Pharma.