

Improved Skeletal Dynamics in Adults Treated With Palopegteriparatide for Chronic Hypoparathyroidism: 214-Week Results From the Phase 2 PaTH Forward 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 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

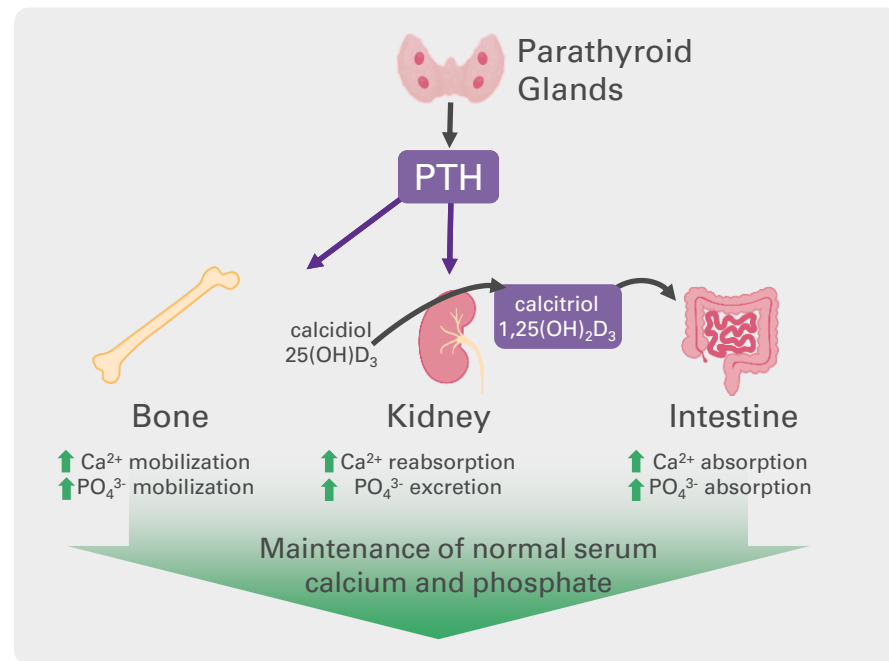
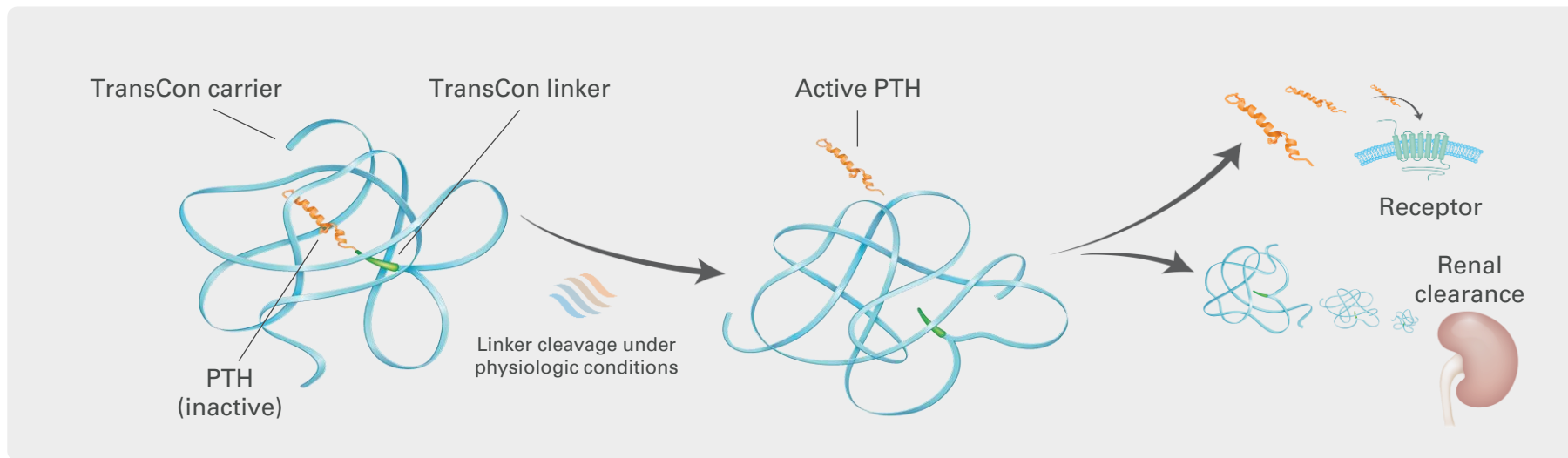


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.⁷

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 (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 US^a, EU^b, and several other countries

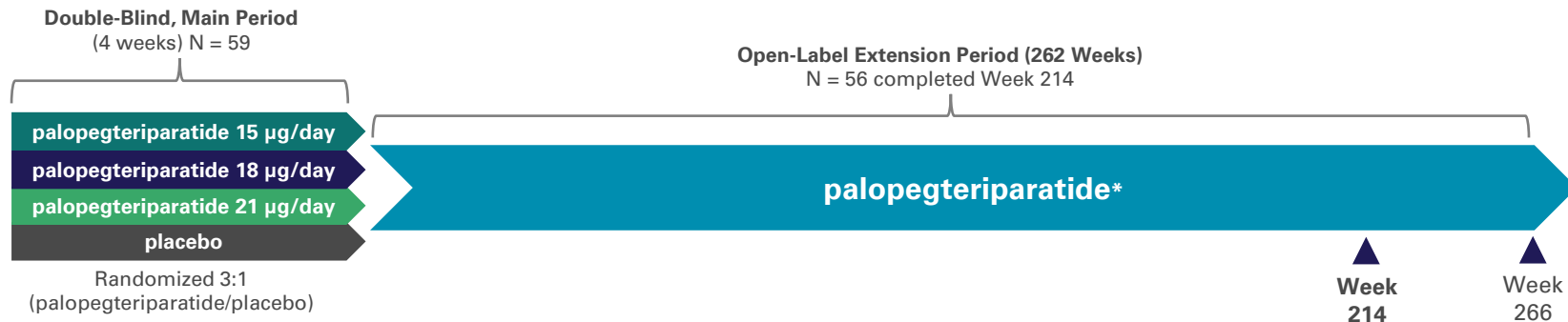
PTH, parathyroid hormone; TransCon, transient conjugation.

^a Indicated for the treatment of hypoparathyroidism in adults. ^b Indicated for the treatment of adults with chronic hypoparathyroidism.

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.

Phase 2 PaTH Forward (NCT04009291)

Randomized, double-blind, placebo-controlled trial followed by an open-label extension period in adults with chronic hypoparathyroidism



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.* Palopegteriparatide 6-60 µg/day titrated per algorithm.

Baseline Demographics and Disease Characteristics

	All participants (N = 59)
Age (years), mean (SD)	50 (12)
Sex, n (%) female	48 (81)
Postmenopausal, n (%)	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)
Duration of hypoparathyroidism (years), median (range)	9 (1 to 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.

^an = 46 (78%) participants used calcitriol at baseline. ^bn = 13 (22%) participants used alfacalcidol at baseline.

Sustained Independence From Conventional Therapy Observed in High Proportion of Participants

	All palopegteriparatide
Number of participants continuing through Week 214	56
Met multi-component efficacy endpoint criteria, ^a n (%)	51 (91%)
• Normal albumin-adjusted serum calcium, ^a n (%)	55 (98%)
• Independence from active vitamin D, ^b n (%)	53 (95%)
• Independence from therapeutic doses of calcium, ^b n (%)	53 (95%)

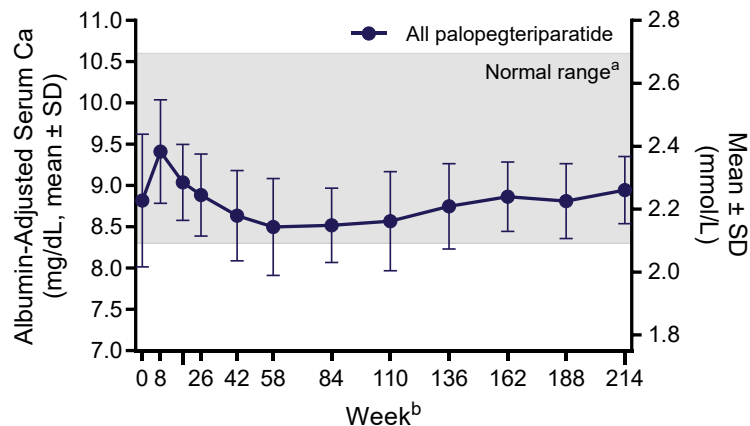
91% achieved normocalcemia and independence from conventional therapy at Week 214^a

^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 214 visit. Percentages are calculated based on participants who had data on all criteria.

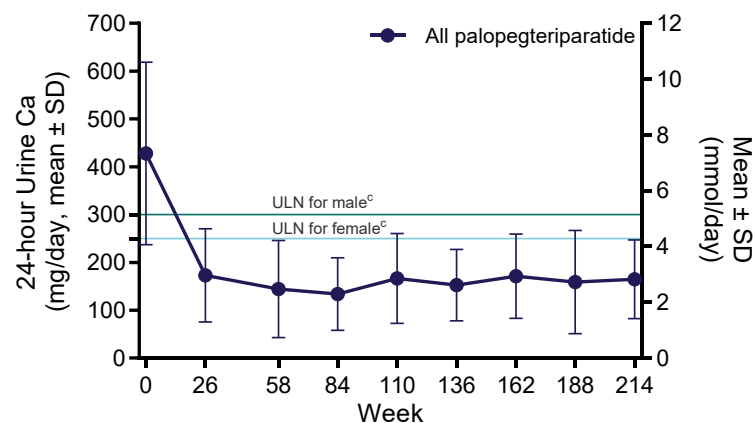
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Mean Serum Calcium and 24-Hour Urine Calcium Remained in the Normal Range Through Week 214

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

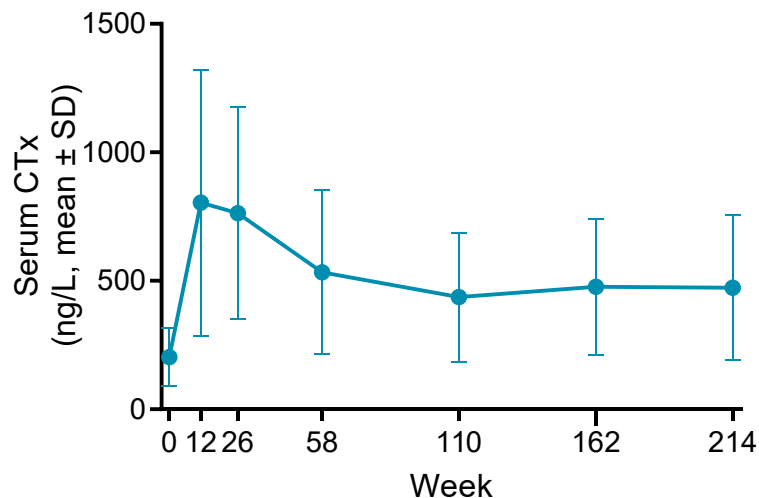
24-hour urine calcium: n=55 at week 58; n=54 at weeks 84, 110, and 214; n=53 at week 188; n=50 at week 0; n=51 at weeks 136 and 162; n=49 at week 26

Ca, calcium; SD, standard deviation; ULN, upper limit of normal.

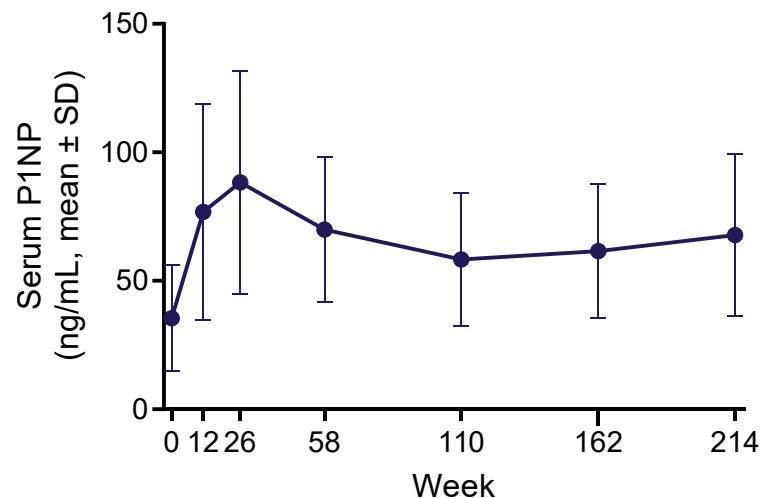
^aThe shaded area represents the normal serum calcium range of 8.3-10.6 mg/dL (2.07-2.64 mmol/L). ^bWeek 18 is captured by unlabeled x axis tick mark. ^cThe ULN for males and females are depicted by teal and light blue lines, respectively.

CTx and P1NP Consistent From Week 110 to Week 214

Mean CTx



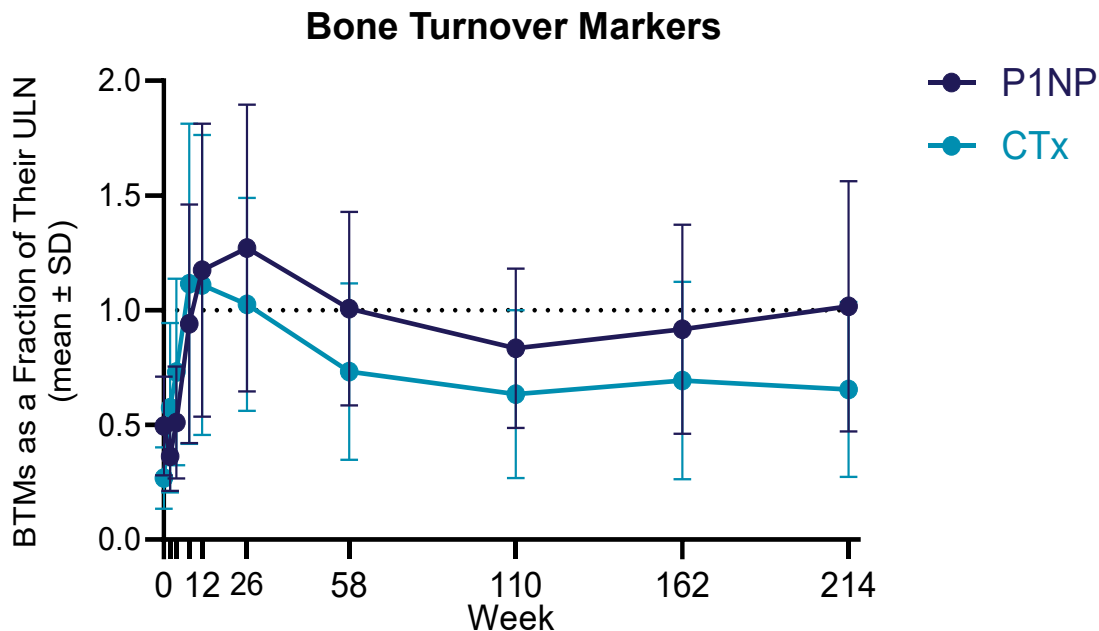
Mean P1NP



These profiles reflect a new and higher steady-state for bone remodeling achieved with palopegteriparatide

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.

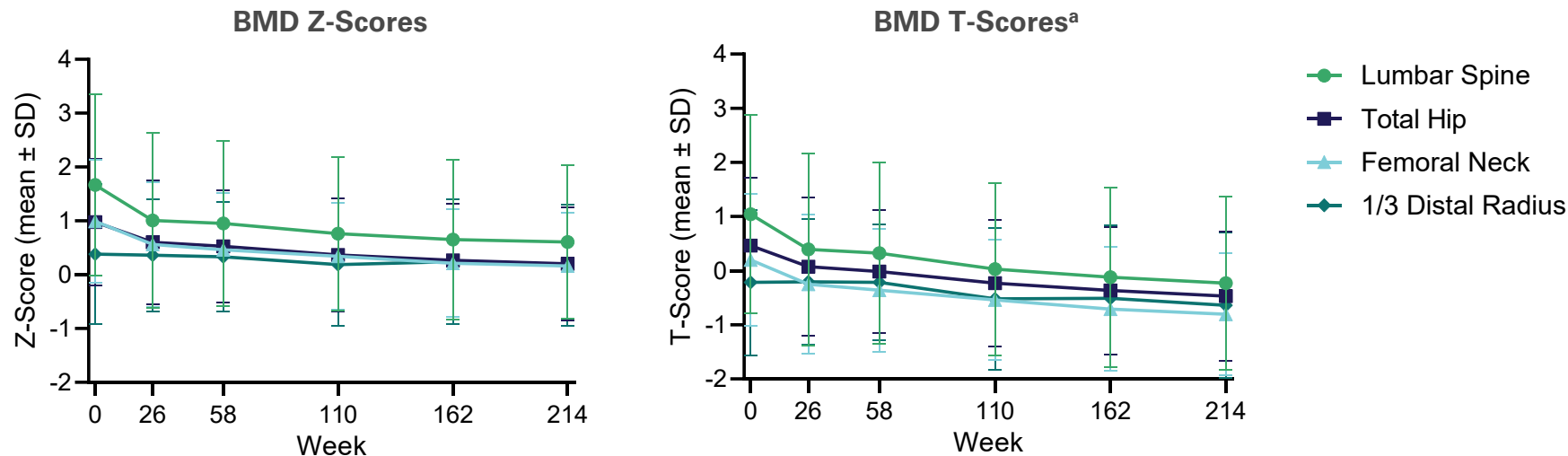
Bone Turnover Markers Consistent From Week 110 to Week 214



Mean bone turnover markers maintained at or below the ULN after week 58

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; n=40 at week 214. P1NP: n=59 at week 0; n=47 at week 12; n=56 at weeks 26, 58, 110 and 162; n=43 at week 214. BTM, bone turnover marker; CTx, C-terminal telopeptide of type 1 collagen; P1NP, procollagen type 1 N-terminal propeptide; SD, standard deviation; ULN, upper limit of normal.

Bone Mineral Density by DXA Showed Stability From Week 110 Through Week 214

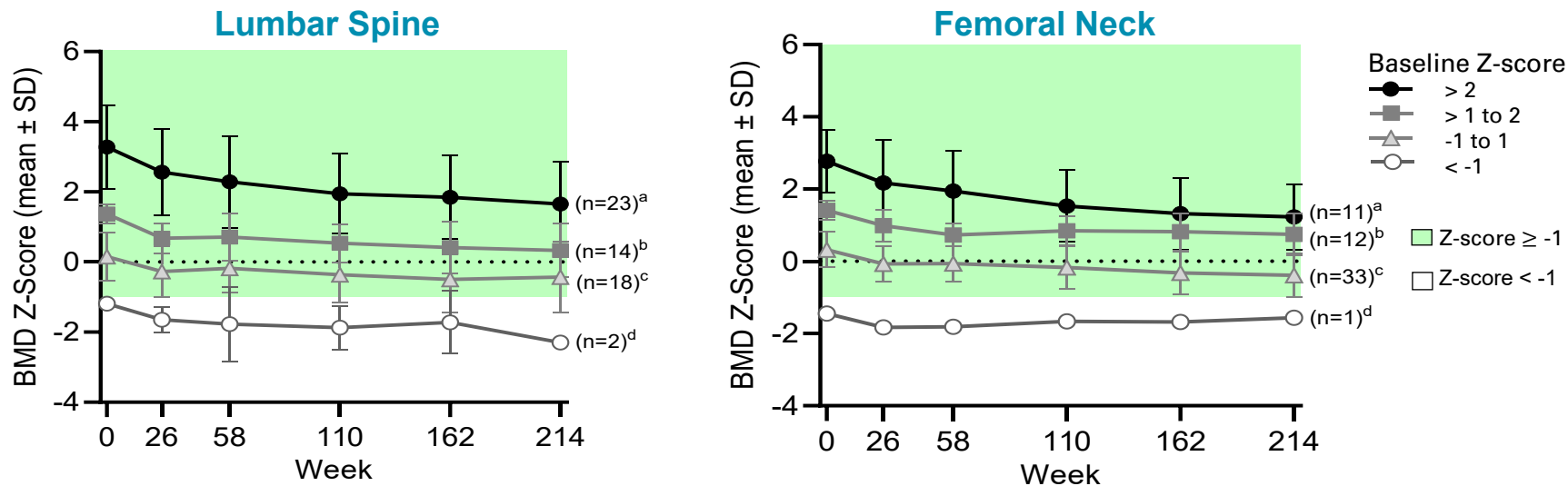


Mean BMD T- and Z-scores declined from elevated baseline levels and stayed within normal limits through Week 214

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. Lumbar spine: n=54 at week 214. Total hip, femoral neck: n=53 at week 214. 1/3 distal radius: n=55 at week 0; n=43 at weeks 26 and 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).
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Change in Mean BMD Z-Scores Varied by Baseline BMD Through Week 214



The magnitude of change in BMD Z-scores from baseline to Week 214 was generally smaller in those with lower baseline BMD and greater in those with higher baseline BMD

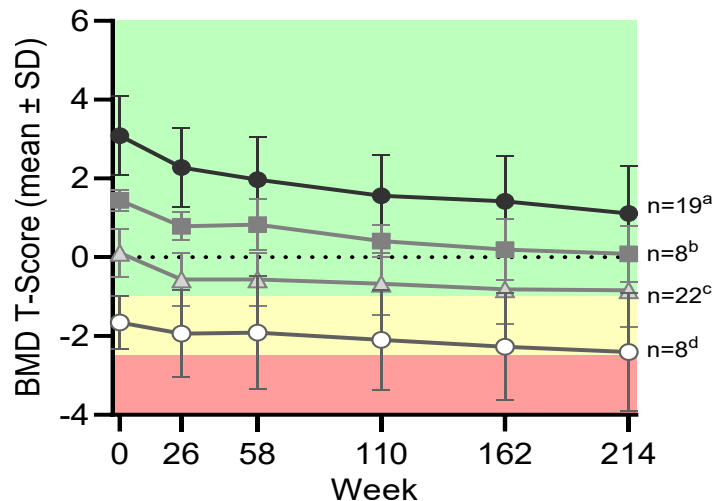
^aBaseline Z-score >2: n=2 (FN) missing at week 26, 58; n=5 (LS) missing at week 26, 58. ^bBaseline Z-score >1 to 2: n=2 (FN) missing at week 26, 58; n=3 (LS) missing at week 26; n=2 (LS) missing at week 58; n=1 (LS) missing at week 110, 162, and 214. ^cBaseline Z-score -1 to 1: n=7 (FN) missing at week 26, 58; n=3 (LS) missing at week 26; n=4 (LS) missing at week 58; n=1 (LS) missing at week 110, 162, and 214; n=1 (FN) missing at week 110, 162; n=3 (FN) missing at week 214. ^dBaseline Z-score <-1: n=0 (FN) missing; n=1 (LS) missing at week 214.

Z-score reference point: age- and sex-matched reference ranges (World Health Organization (2007) Assessment of osteoporosis at the primary health care level. Summary Report of a WHO Scientific Group, WHO, Geneva). BMD, bone mineral density. SD, standard deviation. FN, femoral neck. LS, lumbar spine.

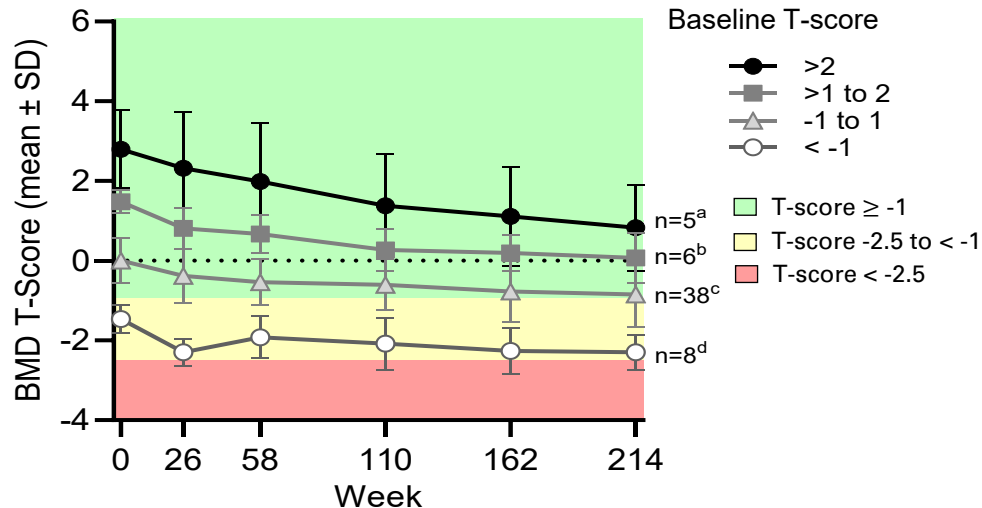
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Mean BMD T-Scores Through Week 214 by Baseline BMD

Lumbar Spine



Femoral Neck



BMD T-score responses to palopegteriparatide varied according to baseline BMD

Missing values: ^aBaseline T-score >2: n=1 (FN) at week 26,58; n=3 (LS) at week 26,58. ^bBaseline T-score >1 to 2: n=2 (FN) at week 26,58; n=2 (LS) at week 26,58; n=1 (LS) at week 110,162,214. ^cBaseline T-score -1 to 1: n=5 (FN) at week 26,58; n=5 (LS) at week 26; n=4 (LS) at week 58; n=1 (LS) at week 110,162,214; n=2 (FN) at week 110,162; n=4 (FN) at week 214. ^dBaseline T-score <-1: n=3 (FN) at week 26,58; n=1 (LS) at week 26,214; n=2 (LS) at week 58. T-score reference point: young (30-year-old) Caucasian adult (World Health Organization (2007) Assessment of osteoporosis at the primary health care level. Summary Report of a WHO Scientific Group, WHO, Geneva). BMD, bone mineral density. FN, femoral neck. LS, lumbar spine.

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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)
<i>Treatment-related TEAEs occurring in $\geq 5\%$ of participants</i>	
Headache	7 (11.9)
Hypocalcemia	6 (10.2)
Hypercalcemia	4 (6.8)
Nausea	4 (6.8)
Paresthesia	4 (6.8)
TEAE related to hypercalcemia or hypocalcemia leading to ED/urgent care visit and/or hospitalization	2 (3.4)
TEAE that led to discontinuation of trial or of study drug	0
TEAE that led to death	0

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

ED, emergency department; PTH, parathyroid hormone; TEAE, treatment-emergent adverse event.

Treatment with palopegteriparatide was associated with sustained improvement in skeletal dynamics in adults with chronic hypoparathyroidism

- Of 56 participants completing 214 weeks, 93% were independent from conventional therapy and 98% had normal albumin-adjusted serum calcium levels
- Bone turnover markers (CTx and P1NP) were consistent from Week 110 through Week 214
- Mean BMD T- and Z-scores stabilized from Week 110 through Week 214
 - Lower baseline BMD T- and Z-scores were generally associated with smaller declines in BMD over time
- Palopegteriparatide was generally well tolerated, with no treatment discontinuation due to treatment emergent adverse events

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: **MR:** Study investigator for Takeda, Ascendis Pharma, Amolyt, and Calcilytix; advisory board for Ascendis Pharma, speakers bureau for Ascendis Pharma; consulting for MBX. **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. **PS:** Stock ownership Novo Nordisk, Ascendis Pharma. **AP:** Consultant for Theramex, Bruno Farmaceutici, Amgen; research funding from Amgen, Shire, Ascendis Pharma; speakers bureau UCB, Amgen; industry grant from Amgen. **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. **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. **RJ:** Consulting role for Ascendis Pharma; research funding from Amgen Foundation. **BC:** Research funding and industry grants from Ascendis and Takeda; advisory board member, consultant, honoraria from Ascendis, Takeda, Entera-Bio, Extend-Bio, Amolyt. **CZ, MSO, BL, 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.