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 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

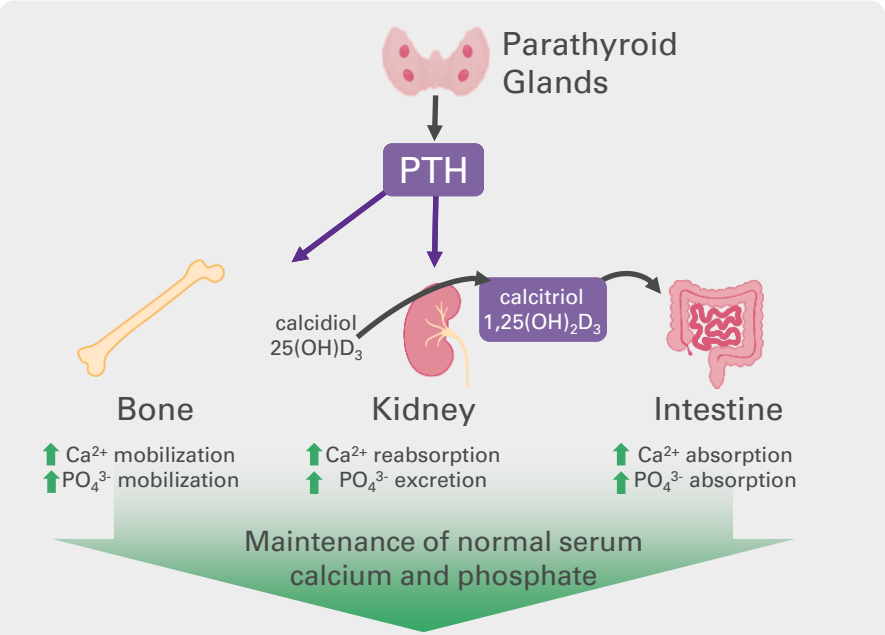
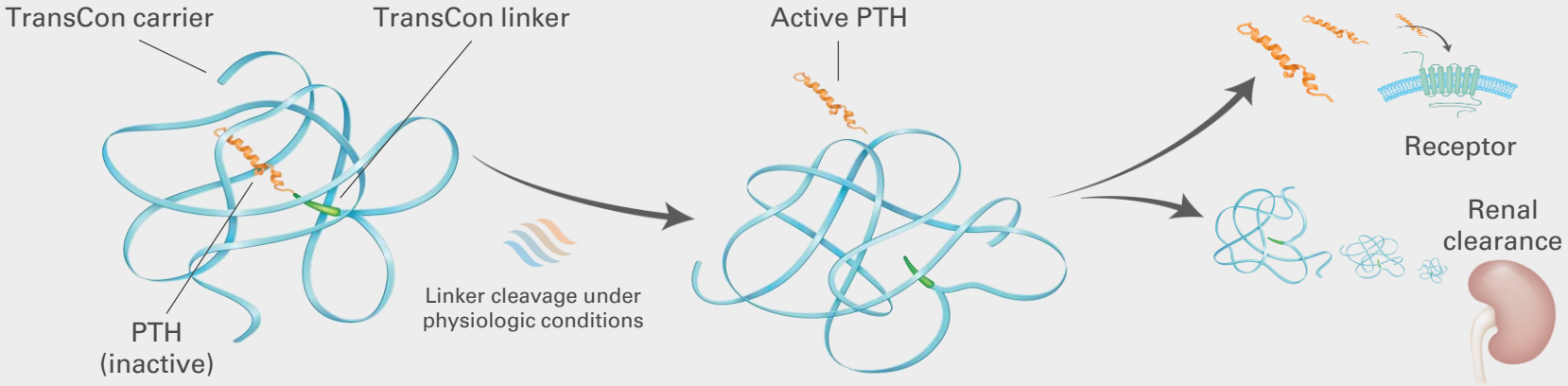


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.[7]

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 (TransCon® PTH) Design

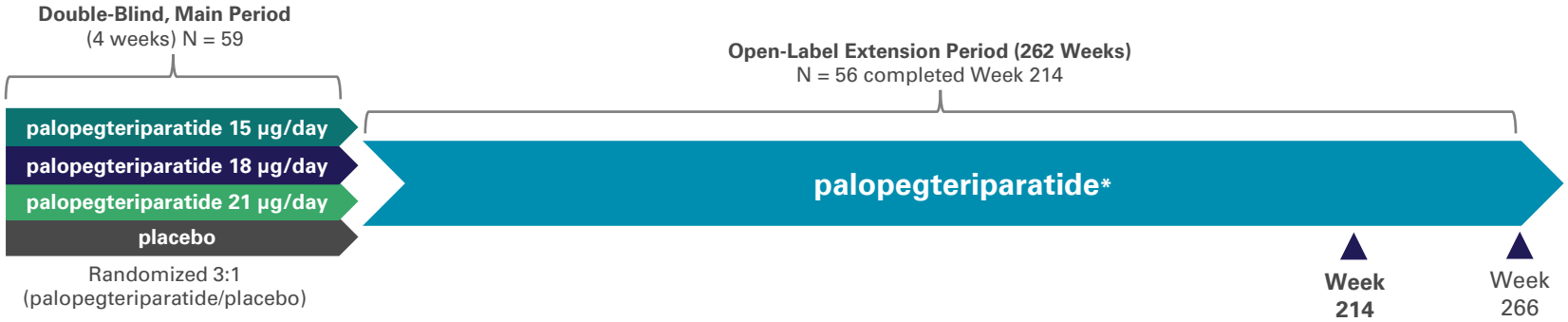


- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[1,2]
- Palopegteriparatide has received regulatory approval in the US[a], EU[b], and several other countries

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 ug/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.
[a]n = 46 (78%) participants used calcitriol at baseline. [b]n = 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%)

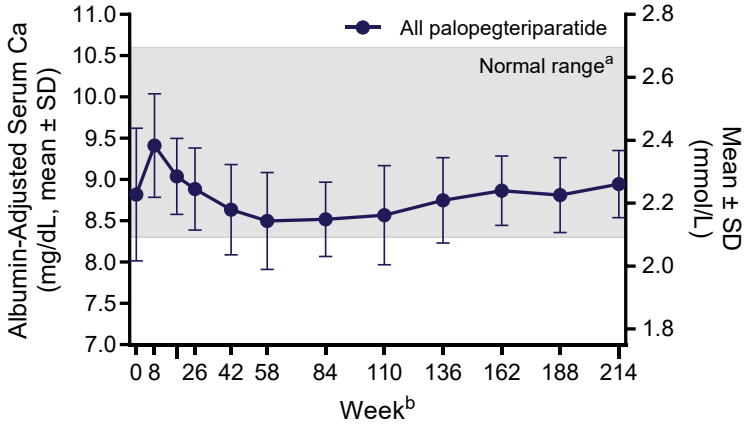
91% achieved normocalcemia and independence from conventional therapy at Week 214[a]

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

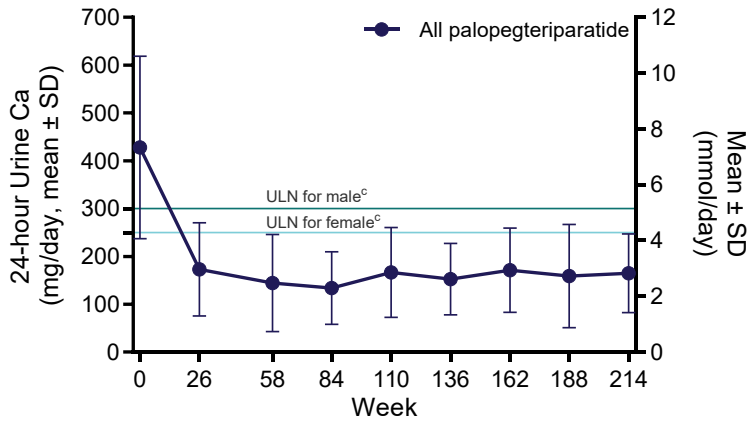
Mean Serum Calcium and 24-Hour Urine Calcium Remained in the Normal Range Through Week 214

PaTHforward TRIAL

Mean Serum Calcium



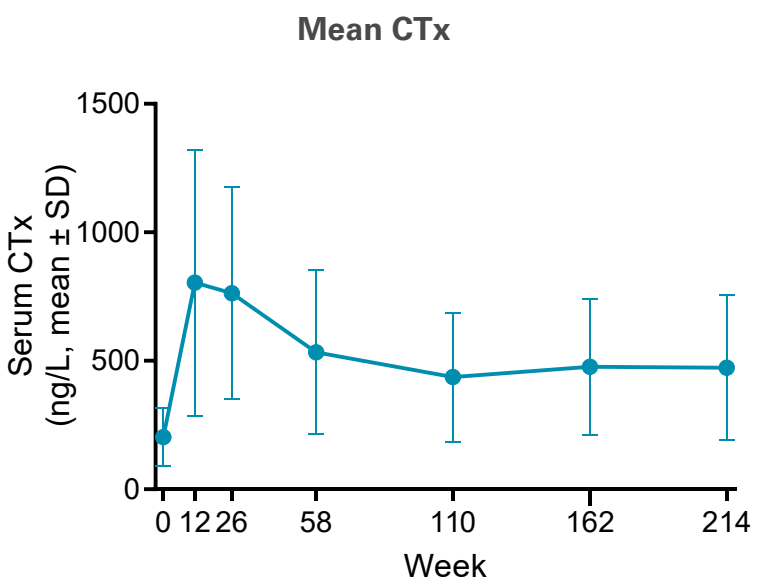
Mean 24-Hour Urine Calcium

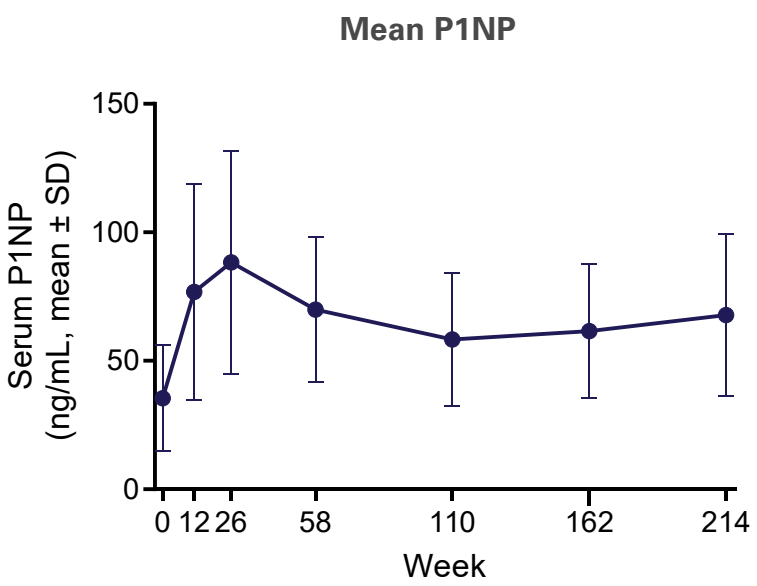


98% had normal serum calcium at Week 214; mean 24-hour urine calcium normalized within 26 weeks

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

CTx and P1NP Consistent From Week 110 to Week 214

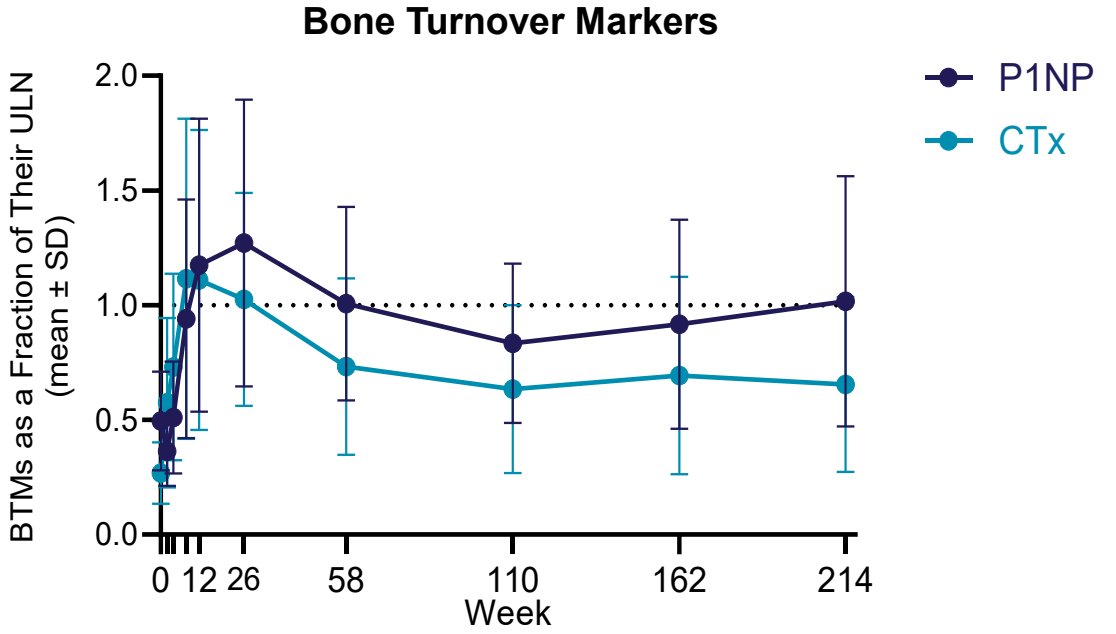




These profiles reflect a new and higher steady-state for bone remodeling achieved with palopegteriparatide

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.

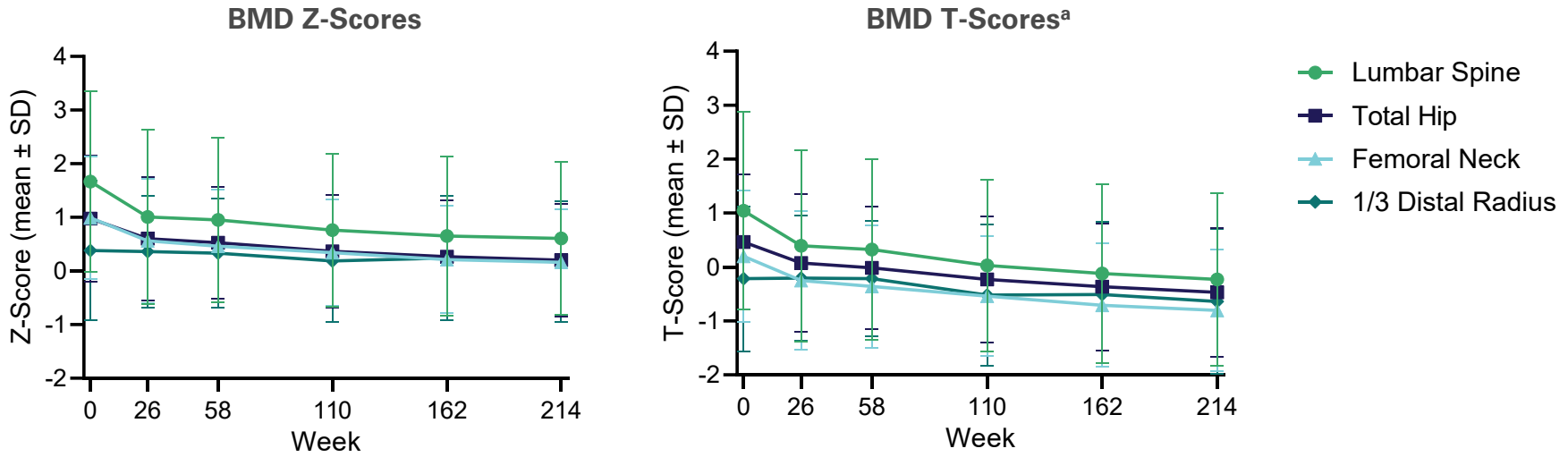
Bone Turnover Markers Consistent From Week 110 to Week 214



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

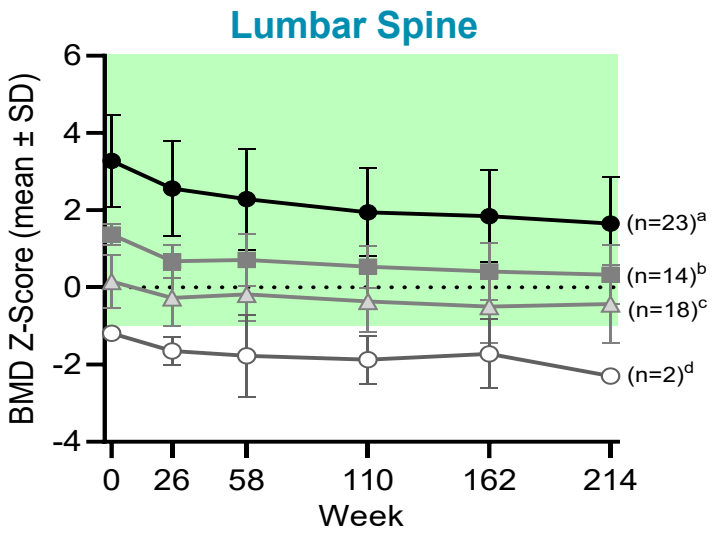


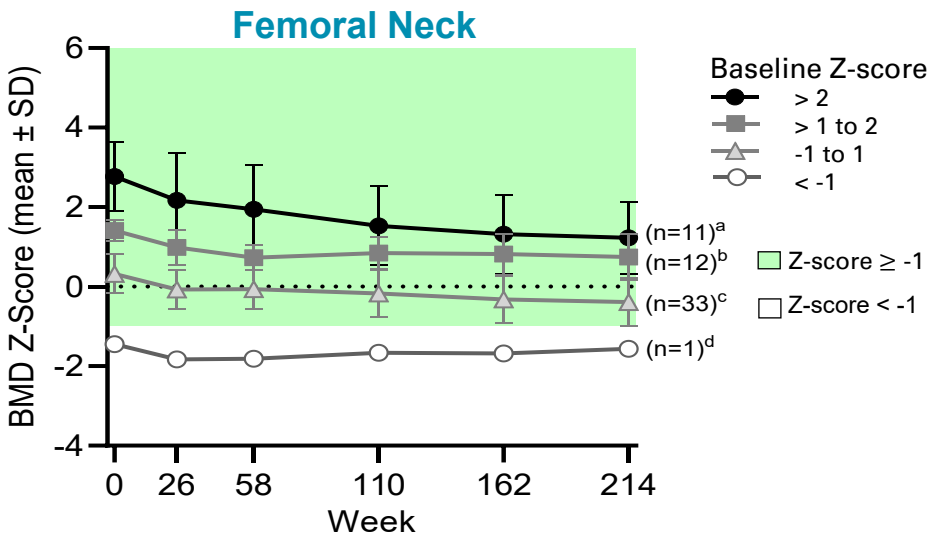
Mean BMD T- and Z-scores declined from elevated baseline levels and stayed within normal limits through Week 214

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).

Change in Mean BMD Z-Scores Varied by Baseline BMD Through Week 214



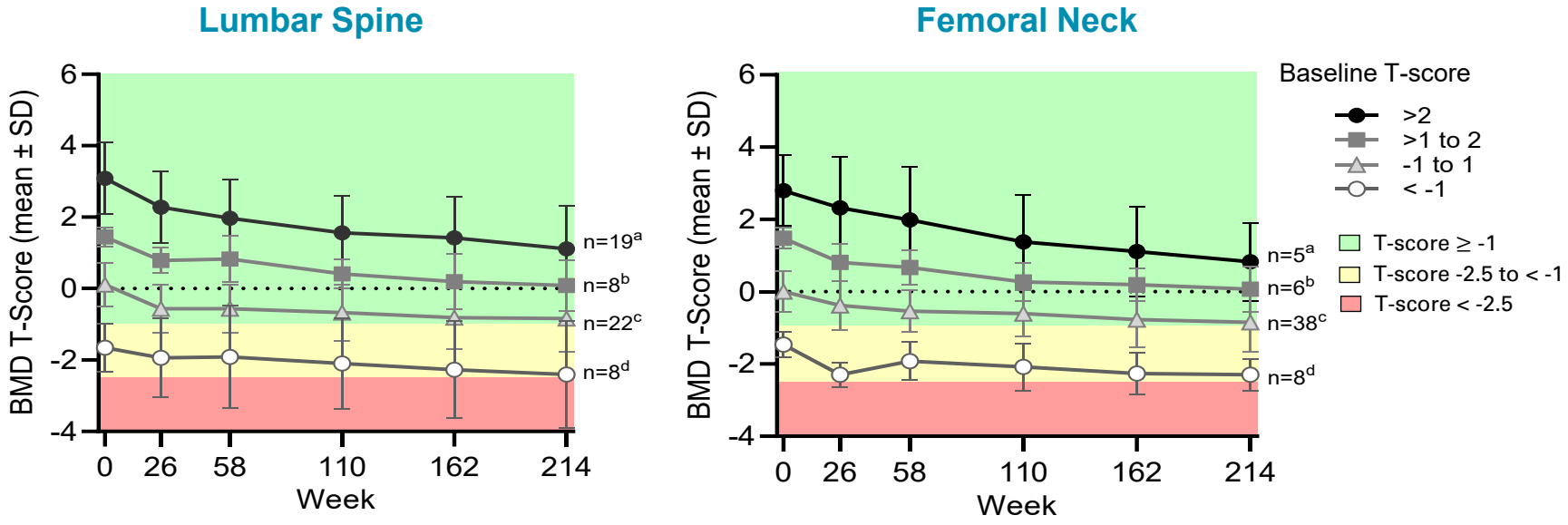


The magnitude of change in BMD Z-scores from baseline to Week 214 was generally smaller in those with lower baseline BMD and greater in those with higher baseline BMD

[a]Baseline Z-score >2: n=2 (FN) missing at week 26, 58; n=5 (LS) missing at week 26, 58. [b]Baseline 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. [c]Baseline 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. [d]Baseline 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.

Mean BMD T-Scores Through Week 214 by Baseline BMD



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

Missing values: [a]Baseline T-score >2: n=1 (FN) at week 26,58; n=3 (LS) at week 26,58. [b]Baseline 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. [c]Baseline 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. [d]Baseline 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.

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)
Treatment-related TEAEs occurring in ≥ 5% of participants	
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.

Conclusions

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