

Palopegteriparatide Treatment in Adults With Hypoparathyroidism: Final Results of 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 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

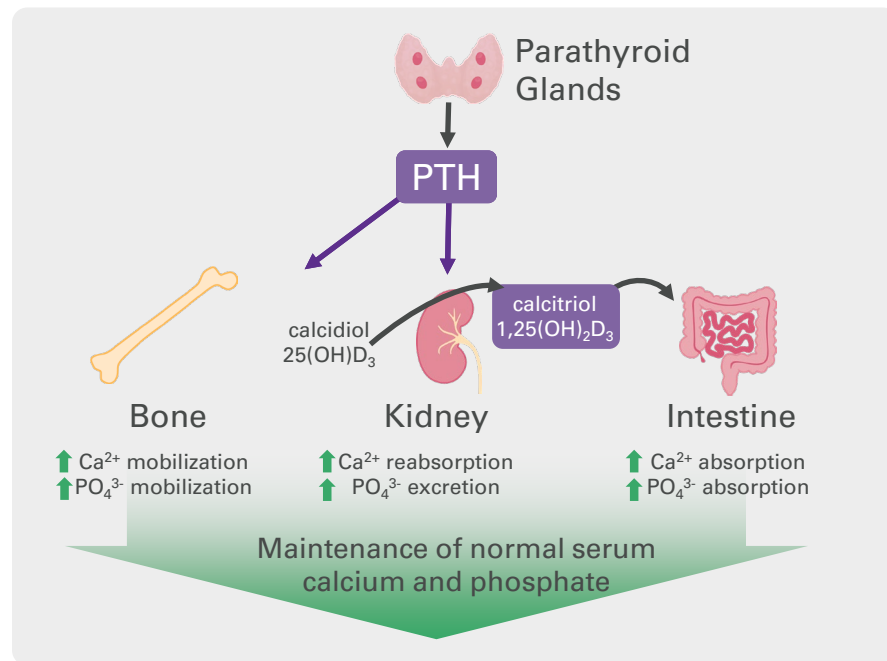
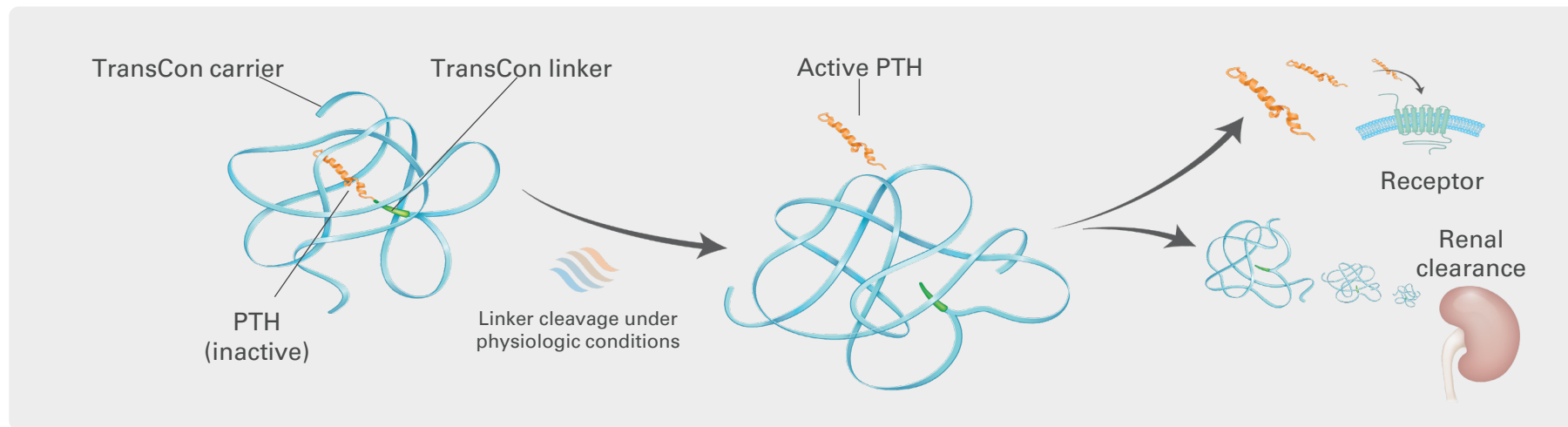


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.⁷

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

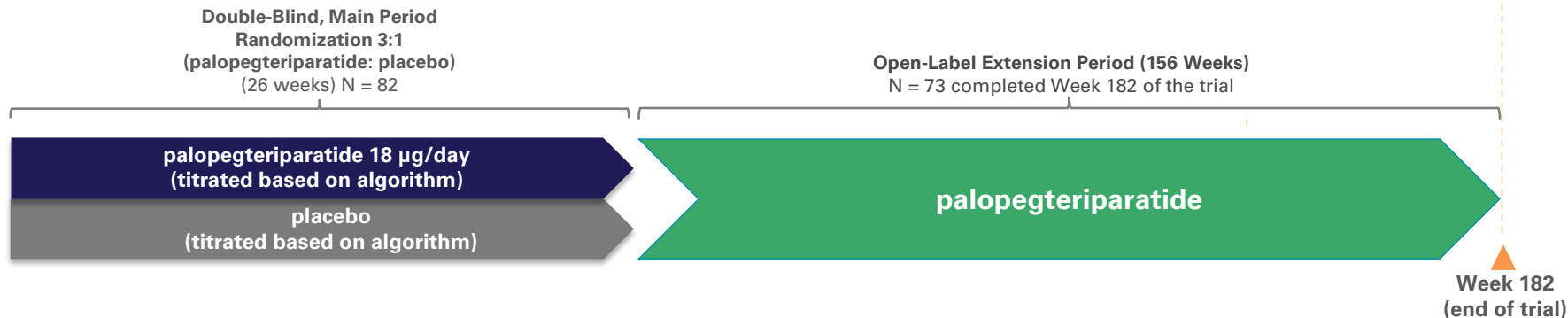
PTH, parathyroid hormone; TransCon, transient conjugation.

^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 3 PaTHway trial design (NCT04701203)

82 adults with hypoparathyroidism receiving conventional therapy (active vitamin D + calcium)



Key Efficacy and Safety Endpoints

- Levels of serum calcium (normocalcemia)
- Independence from conventional therapy (defined as taking no active vitamin D and ≤ 600 mg/day elemental calcium)
- Incidence of AEs, SAEs, TEAEs

Renal, Skeletal, and HRQoL Assessments

- Estimated glomerular filtration rate (eGFR)^a: post hoc analysis
- BMD T- and Z-scores
- HPES-Symptom physical and cognitive domain scores and HPES-Impact physical functioning and daily life domain scores

^aCalculated according to the Modified Diet in Renal Disease Equation (MDRD): $eGFR (mL/min/1.73 m^2) = 175 \times (\text{serum creatinine mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ [if female] $\times 1.212$ [if Black]
BMD, bone mineral density; HPES, Hypoparathyroidism Patient Experience Scales; HRQoL, health-related quality of life.

Baseline demographics and disease characteristics

	Palopegteriparatide (N=61)	Placebo (N = 21)
Age (years), mean (SD)	49 (13)	47 (11)
Sex, n (%) female	46 (75)	18 (86)
Postmenopausal, n (%)	19 (41)	3 (17)
Race, n (%) White	57 (93)	19 (90)
Geographic region, n (%)		
North America	39 (64)	12 (57)
Europe	22 (36)	9 (43)
Cause of hypoparathyroidism, n (%)		
Acquired from neck surgery	52 (85)	18 (86)
Genetic causes*	5 (8)	1 (5)
Primary idiopathic disease	4 (7)	2 (10)
Duration of hypoparathyroidism (years), mean (SD)	12 (11.4)	11.1 (8.5)
Conventional therapy, mean TDD (SD)		
Calcium (mg)	1748 (904)	2105 (1383)
Calcitriol (µg)	0.76 (0.34), n=53	0.69 (0.33), n=17
Alfacalcidol (µg)	2.5 (0.9), n=8	2.0 (0.4), n=4

SD, standard deviation; TDD, total daily dose.

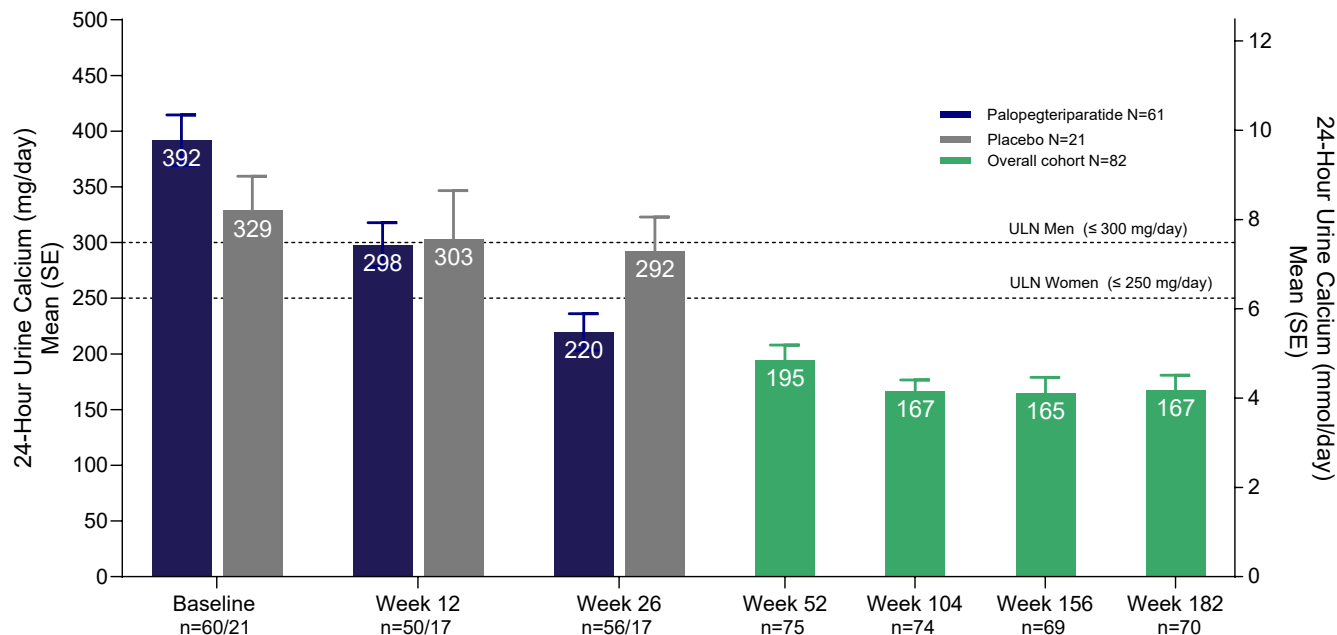
* One participant in each arm had hypoparathyroidism, sensorineural deafness, and renal disease (HDR syndrome). In the palopegteriparatide arm, 2 participants had autoimmune polyglandular syndrome type 1 (APS-1), 1 participant had autosomal dominant hypocalcemia type 1 (ADH1), and 1 participant had DiGeorge syndrome. One participant previously reported as having idiopathic hypoparathyroidism was subsequently confirmed to have HDR syndrome. Percentages were calculated based on ITT population; the percentage of postmenopausal participants based on number of female patients

96% of participants were independent from conventional therapy at Week 182

	All Participants
Number of participants who completed Week 182	73
○ Normal albumin-adjusted serum calcium, n (%)	65 (89%)
○ Independence from conventional therapy, n (%) ^a	70 (96%)
• Independence from active vitamin D, n (%)	73 (100%)
• Independence from therapeutic doses of calcium, n (%)	70 (96%)

^aIndependence defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤ 600 mg on the day prior to the Week 182 visit
Percentages are calculated based on participants who had data on all criteria.

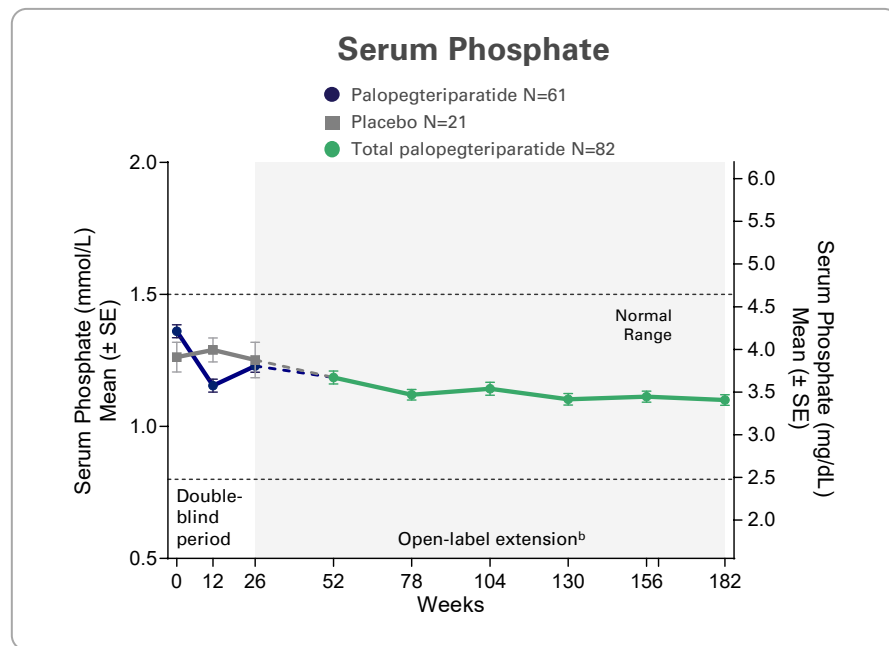
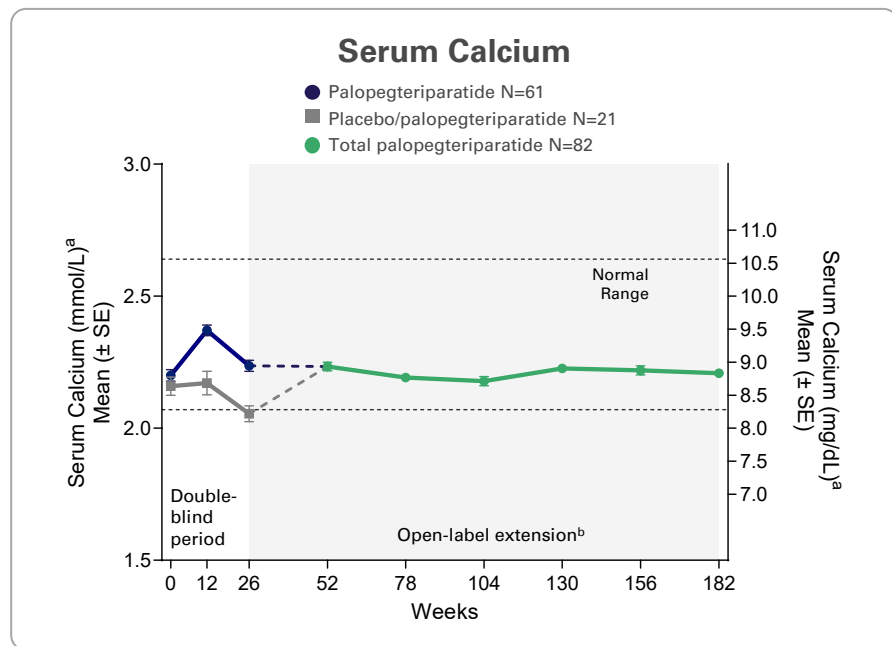
Normalized mean 24-hour urine calcium excretion was sustained through Week 182 of PaTHway



Mean 24-hour urine calcium normalized within 26 weeks of palopecteriparotide treatment and remained in the normal range through Week 182

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

Biochemistries were maintained in the normal range through Week 182

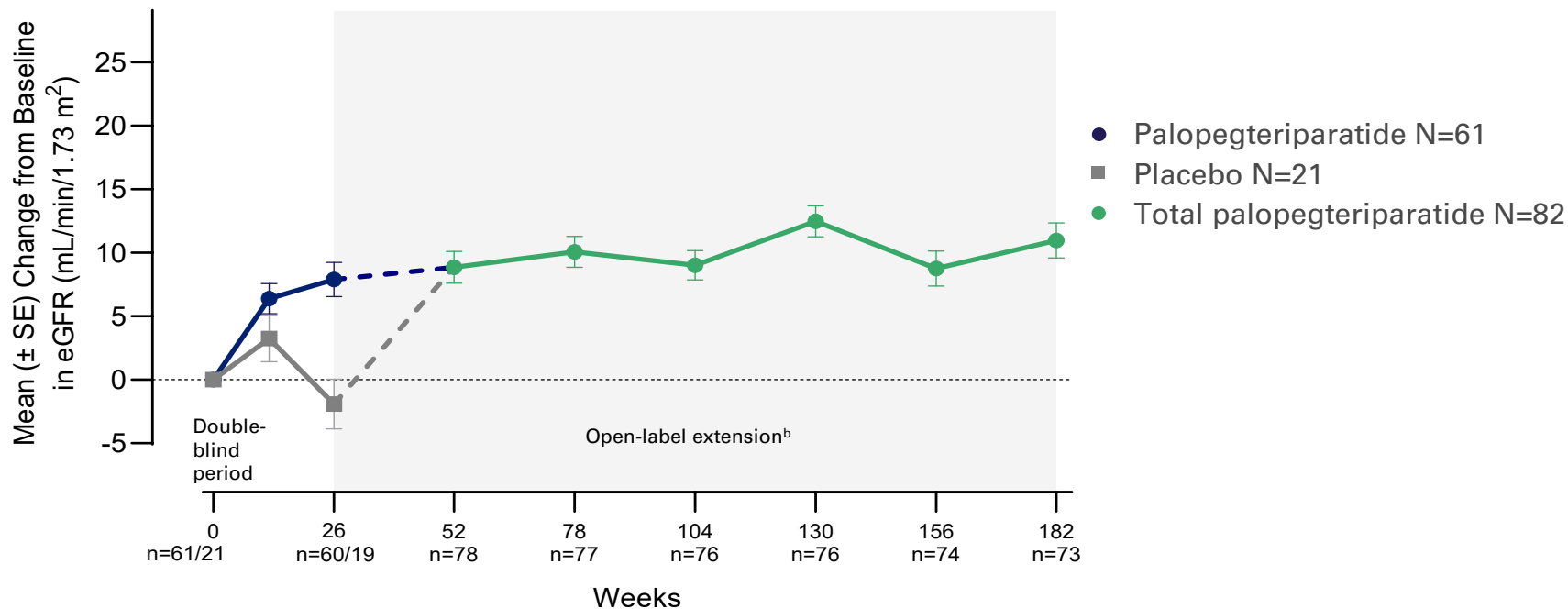


^aAlbumin-adjusted. ^bAll participants received palopegteriparatide during the open-label extension.

SE, standard error

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 clinically meaningful^a increase in eGFR through Week 182



At Week 182, mean eGFR increased from baseline by 10.97 mL/min/1.73 m²

^aClinically meaningful increases in eGFR were those ≥ 5 mL/min / 1.73 m². References: 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.

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

eGFR, estimated glomerular filtration rate; SE, standard error

Mean BMD Z-scores and T-scores demonstrated consistent trends and remained in the normal range through Week 182

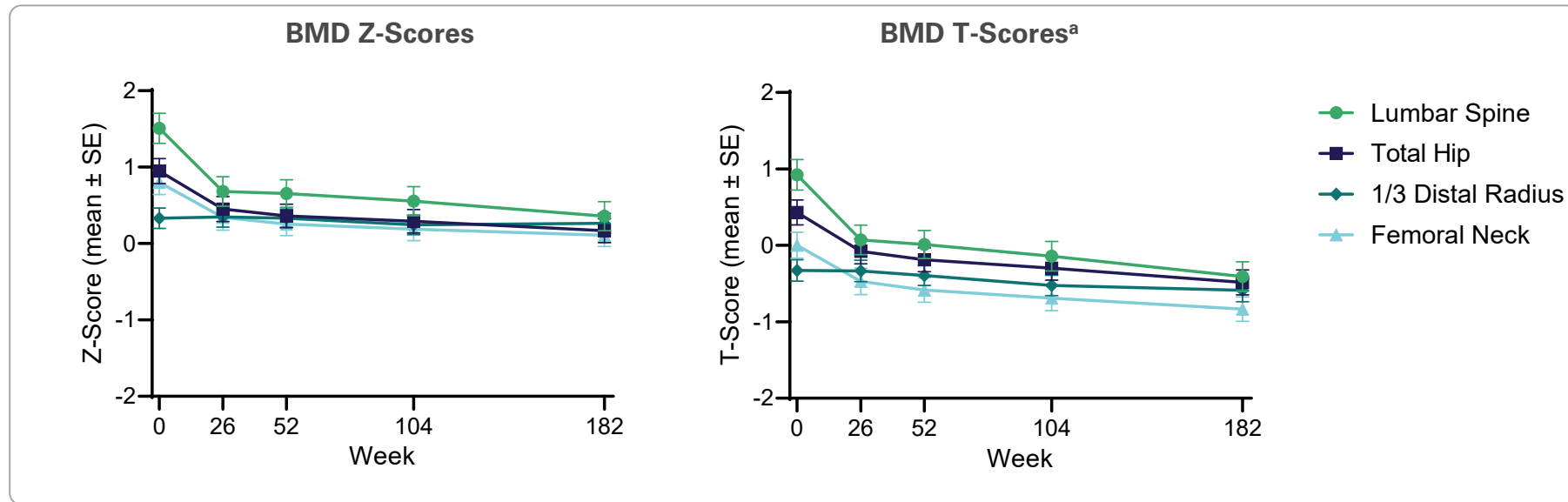


Figure shows changes over time in participants randomized to palopegteriparatide (N=61).

BMD, bone mineral density; SE, standard error

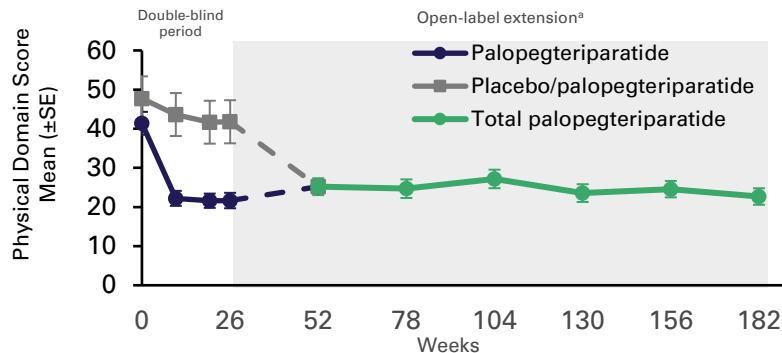
^a T-score reference point: young (30-year-old) Caucasian adult (Kanis JA. *Lancet*. 2002;359:1929–36).

Early HPES score improvements maintained through Week 182

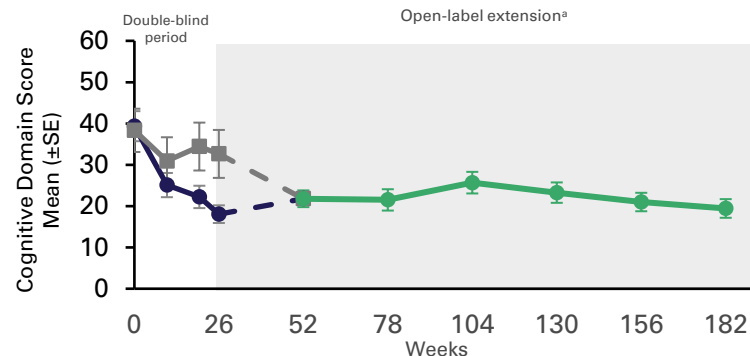
Decreased burden

Decreased burden

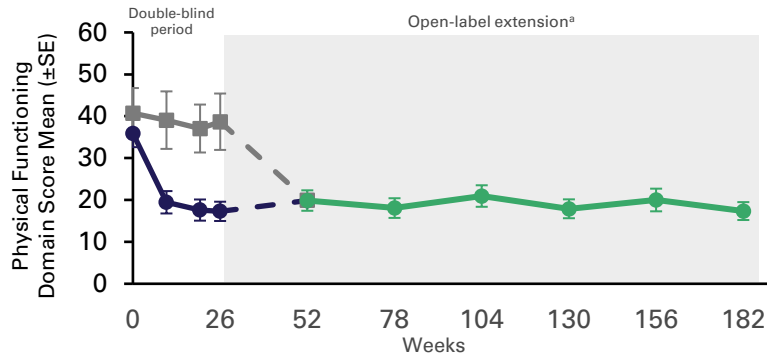
HPES-Symptom Physical Domain Score



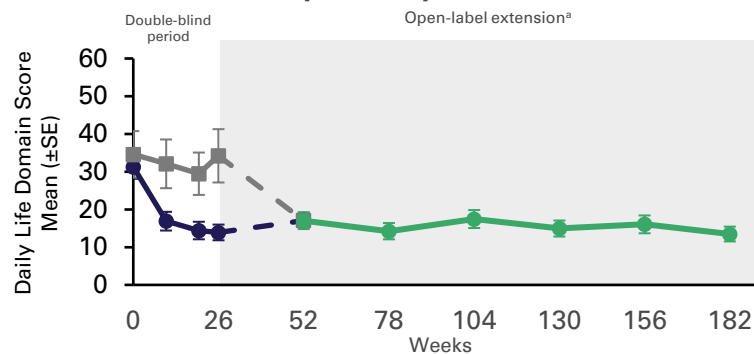
HPES-Symptom Cognitive Domain Score



HPES-Impact Physical Functioning Domain Score



HPES-Impact Daily Life Domain Score



*All participants received palopegteriparatide during the open-label period
HPES, Hypoparathyroidism Patient Experience Scale; SE, standard error

Summary of TEAEs in palopegteriparatide treated participants through Week 182

Treatment-Related TEAEs Occurring at a Rate of $\geq 5\%$, n (%)	All Participants ^a N=80
Injection site reaction	20 (25.0)
Hypercalcemia	11 (13.8)
Nausea	7 (8.8)
Headache	6 (7.5)
Hypocalcemia	5 (6.3)
Orthostatic hypotension	4 (5.0)
Postural orthostatic tachycardia syndrome	4 (5.0)

TEAEs for all participants (N=80) included:

- Serious TEAE: 20 (25.0%)
- Related TEAE: 46 (57.5%)
- 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%)

Most TEAEs were classified as mild (36.3%) or moderate (40.0%)^e with no new safety signals identified

^aIncludes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (patients who received ≥ 1 dose of palopegteriparatide); median exposure to palopegteriparatide was 182 weeks for total patient group.^bMedian time to onset of these calcium-related TEAEs was 181 days (range 8-855 days). ^cTEAEs leading to treatment discontinuation were deemed unrelated to study drug. ^dOne participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment. ^eClassified using the World Health Organization toxicity grading scale (1=mild, 2=moderate, 3=severe, 4=life-threatening)

Treatment with palopegteriparatide showed sustained efficacy and safety through the end of the 182-week PaTHway trial

- High rates of independence^a from conventional therapy (96%) and normocalcemia (89%) were achieved, consistent with those observed at earlier timepoints
- Mean 24-hour urine calcium excretion normalized by Week 26 and remained within the normal range through the end of the trial
- BMD Z- and T-scores trended towards age- and sex-appropriate norms through Week 182
- Substantial improvements in renal function and multiple HPES domains were sustained through the end of the trial
- Palopegteriparatide was generally well-tolerated, with no new safety signals identified

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^aIndependence defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤ 600 mg on the day prior to the week 182 visit

Disclosures and funding

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