Palopegteriparatide Enhances Work Functioning and Productivity in Employed Adults With Chronic Hypoparathyroidism: 156-Week Results From the PaTHway Trial

SUN-770

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Conclusions

Palopegteriparatide treatment was associated with early improvements in work functioning and productivity in adults with hypoparathyroidism.

- Positive changes were observed across all Work Limitations Questionnaire (WLQ)-25 domains and sustained over 3 years.
- The improvement in productivity scores may reflect increased functional capacity at work and may be economically relevant, indicating greater productivity while at work.
- These findings support the potential long-term functional and economic value of palopegteriparatide treatment for adults with hypoparathyroidism.

Background

- An intact parathyroid hormone (PTH) axis maintains normal serum and urine calcium and phosphate homeostasis.[1-3]
- 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

Figure 1. **PTH Therapy for Hypoparathyroidism[7]**

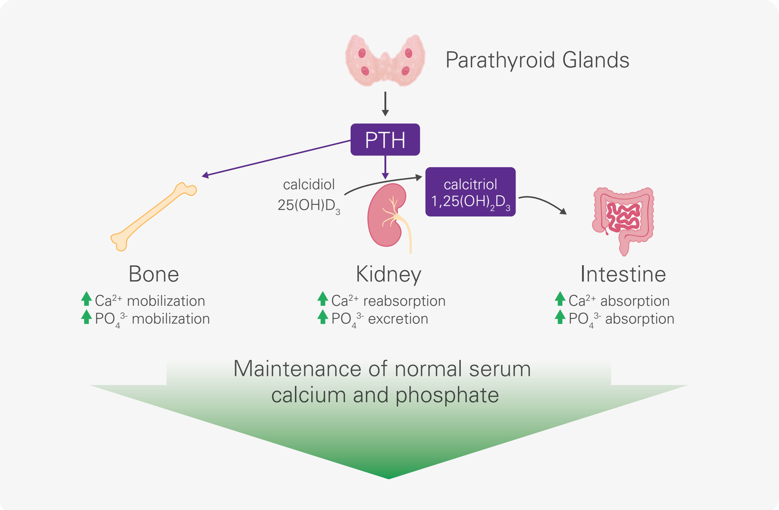
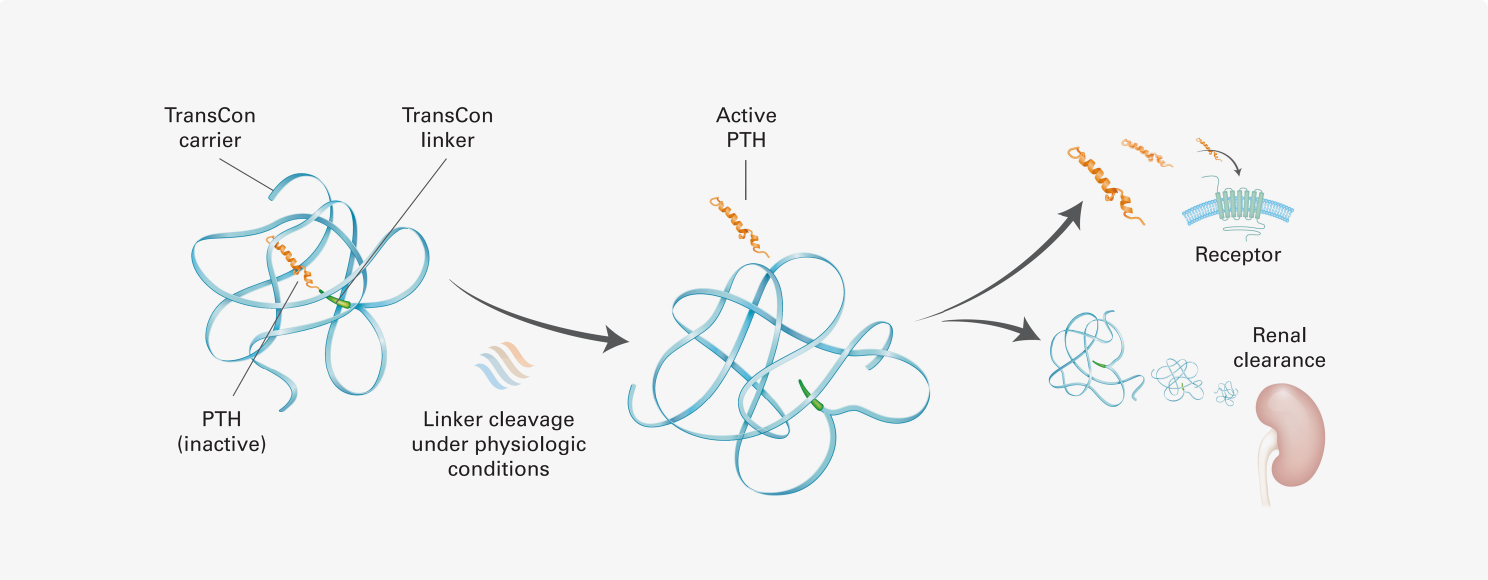

Parathyroid Glands
PTH
calcidiol
25(OH)D3
calcitriol
1,25(OH)2D3
Bone
Ca2+ mobilization
PO43- mobilization
Kidney
Ca2+ reabsorption
PO43- excretion
Intestine
Ca2+ absorption
PO43- absorption
Maintenance of normal serum calcium and phosphate

Figure 2. **Palopegteriparatide (TransCon® PTH) Design**

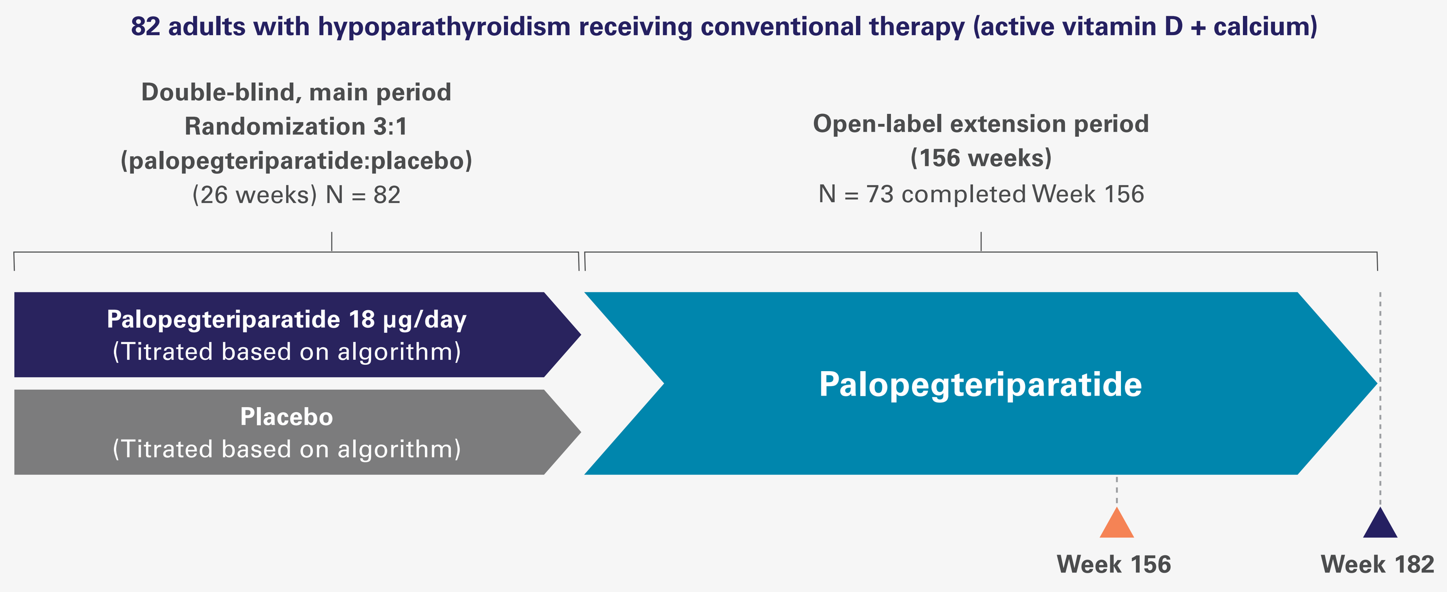

TransCon carrier
TransCon linker
Active PTH
Receptor
Renal clearance
PTH (inactive)
Linker cleavage under physiologic conditions

- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day.[8,9]
- Palopegteriparatide has received regulatory approval in the US,[a] EU,[b] Japan,[a] and several other countries based on the results of the PaTH Forward and PaTHway trials.

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

Methods

Figure 3. **Phase 3 PaTHway Trial Design (NCT04701203)**


82 adults with hypoparathyroidism receiving conventional therapy (active vitamin D + calcium)
Double-blind, main period
Randomization 3:1
(palopegteriparatide:placebo)
(26 weeks) N = 82
Open-label extension period
(156 weeks)
N = 73 completed Week 156
Palopegteriparatide 18 µg/day
(Titrated based on algorithm)
Placebo
(Titrated based on algorithm)
Palopegteriparatide
Week 156
Week 182

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

Patient-reported outcomes assessments

- HPES-Symptom physical and cognitive domain scores and HPES-Impact physical functioning and daily life domain scores
- 36-Item short form survey (SF-36) scores
- **Work Limitations Questionnaire-25**

- At Week 156, 96% of PaTHway trial participants achieved independence from conventional therapy (no active vitamin D and ≤ 600 mg/day of calcium), and 88% achieved normal albumin-adjusted serum calcium levels (8.3-10.6 mg/dL).
- Palopegteriparatide was well-tolerated in the PaTHway trial, with most treatment-related adverse events (AEs) being mild to moderate in severity.
- This analysis assessed the impact of palopegteriparatide on hypoparathyroidism-related work limitations in the PaTHway trial.

Work Limitations Questionnaire (WLQ)-25

Purpose of the WLQ

- The WLQ is a validated, self-reported instrument designed to quantify the **degree to which health problems interfere with job performance and productivity** in employed individuals.[10]
- The WLQ has strong reliability, differentiating between healthy and condition-affected employee groups.[10]
- It is widely used in clinical trials, occupational health research, and economic evaluations to assess on-the-job work functioning.[11,12]

Scoring approach[13]

- Each item is scored from **0 to 100**, where:
 - » **0** = Limited none of the time
 - » **100** = Limited all of the time
- Domain scores are calculated as the **mean of item scores** within that domain.
- **Higher scores** = greater limitation

WLQ-25 structure[14]

- The WLQ-25 consists of 25 items, grouped into 4 empirically derived domains that reflect different aspects of work functioning **(Table 1).**[10,14]

Table 1. **WLQ-25 Structure[a]**

Domain	Focus Area	Items
Time Management	Difficulties handling scheduling, being on time, staying focused	5
Physical Demands	Challenges with physical aspects of work (lifting, movement)	6
Mental-Interpersonal	Difficulty with concentration, problem-solving, social demands	9
Output Demands	Difficulties with quantity, quality, and speed of work	5

[a]Each item asks respondents to report how often, in the **past two weeks**, health problems limited their ability to meet work demands.[14]

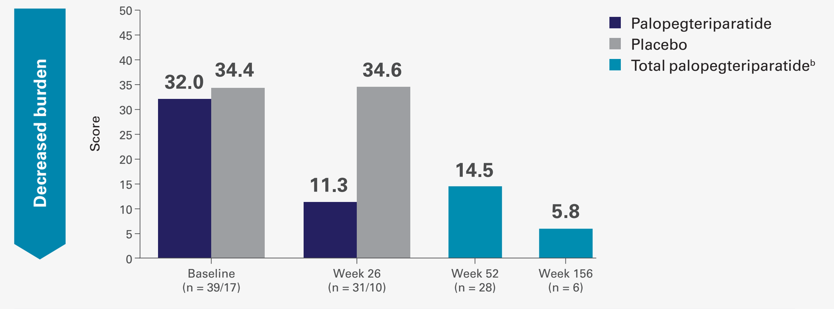
Results

Table 2. **Baseline Demographics and Disease Characteristics**

Variable		Palopegteriparatide (N = 61)	Placebo (N = 21)
Age (years), mean (SD)		49 (13)	47 (11)
Sex, n (%) female		46 (75)	18 (86)
	Postmenopausal	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[a]	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	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

[a]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.

Figure 4. **Time Management Scale[a]**


Decreased burden
Score
32.0
34.4
11.3
34.6
14.5
5.8
Baseline (n = 39/17)
Week 26 (n = 31/10)
Week 52 (n = 28)
Week 156 (n = 6)
Palopegteriparatide
Placebo
Total palopegteriparatide[b]

WLQ Time Management scores over time. Improvements observed with palopegteriparatide at Week 26 were maintained through long-term follow-up, including among participants who crossed over from placebo during the open-label extension.

[a]Greater scores correspond with more self-reported difficulties at work.
[b]Participants randomized to placebo crossed over to palopegteriparatide after Week 26.

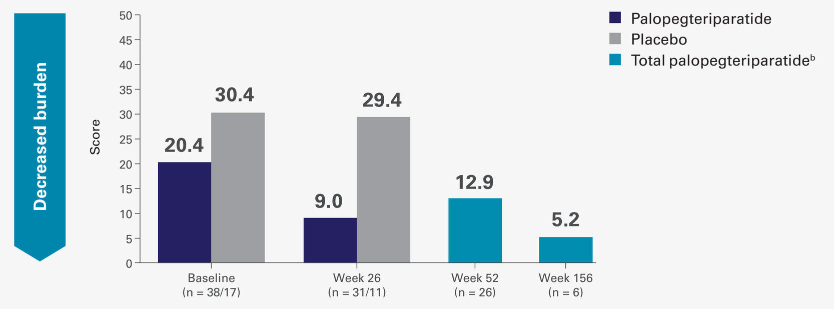
KEY INTERPRETATION

Baseline assessment
- Participants in the palopegteriparatide and placebo groups had comparable mean baseline limitation scores (32.0 and 34.4, respectively).

Double-blind period (Baseline – Week 26)
- At the end of the double-blind period (Week 26), participants receiving palopegteriparatide experienced rapid improvement, with the mean score decreasing to 11.3 (indicating reduced work limitation for Time Management).
- No improvement was observed for participants in the placebo group.
- *P* value for treatment arm comparison from Week 0 to Week 26: < 0.0001

Open-label extension (Week 26 – Week 156)
- In the open-label extension period, improvements in Time Management limitations were maintained among participants treated with palopegteriparatide through Week 156.

Figure 5. **Physical Demands Scale[a]**


Decreased burden
Score
20.4
30.4
9.0
29.4
12.9
5.2
Baseline (n = 38/17)
Week 26 (n = 31/11)
Week 52 (n = 26)
Week 156 (n = 6)
Palopegteriparatide
Placebo
Total palopegteriparatide[b]

WLQ Physical Demands scores over time. Palopegteriparatide treatment resulted in a quick improvement by Week 26 with sustained improvement through Week 156, whereas placebo showed no improvement during the double-blind period.

[a]Greater scores correspond with more self-reported difficulties at work.
[b]Participants randomized to placebo crossed over to palopegteriparatide after Week 26.

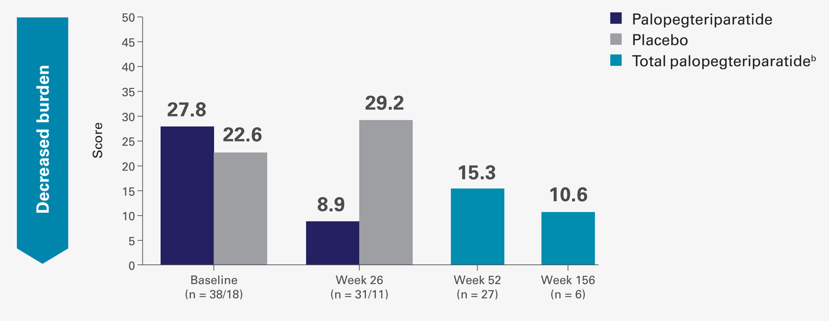
KEY INTERPRETATION

Baseline assessment
- A slight imbalance was observed at baseline, with participants randomized to placebo exhibiting greater Physical Demands limitations.

Double-blind period (Baseline – Week 26)
- Participants receiving palopegteriparatide showed rapid improvement, with scores dropping to a mean value of 9.0 at Week 26.
- Scores in the group randomized to placebo remained high with a mean value of 29.4 at Week 26
- *P* value for treatment arm comparison from Week 0 to Week 26: 0.0008

Open-label extension (Week 26 – Week 156)
- During the open-label extension, participants continued to demonstrate reduction in Physical Demands limitations, remaining substantially improved through Week 156.

Figure 6. **Mental-Interpersonal Scale[a]**


Decreased burden
Score
27.8
22.6
8.9
29.2
15.3
10.6
Baseline (n = 38/18)
Week 26 (n = 31/11)
Week 52 (n = 27)
Week 156 (n = 6)
Palopegteriparatide
Placebo
Total palopegteriparatide[b]

WLQ Mental-Interpersonal scores over time. Palopegteriparatide treatment resulted in improvement by Week 26 with continued improvement through Week 156, whereas placebo slightly worsened during the double-blind period.

[a]Greater scores correspond with more self-reported difficulties at work.
[b]Participants randomized to placebo crossed over to palopegteriparatide after Week 26.

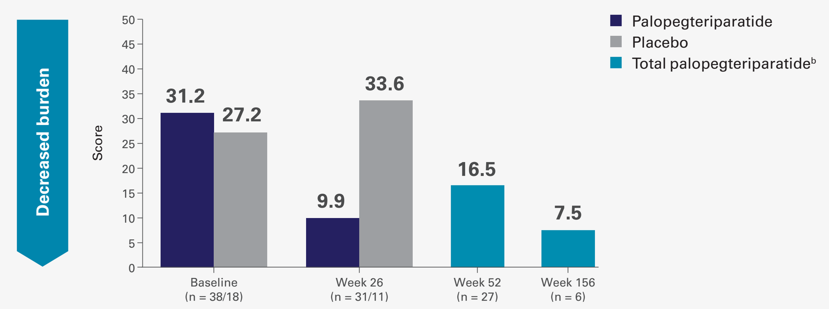
KEY INTERPRETATION

Baseline assessment
- Both groups started with Mental-Interpersonal limitations including challenges with concentration, problem-solving, and social demands.
- Participants randomized to palopegteriparatide had slightly worse baseline limitation (mean score 27.8) compared to those randomized to placebo (mean score 22.6).

Double-blind period (Baseline – Week 26)
- At the end of the double-blind period (Week 26), participants treated with palopegteriparatide showed a rapid improvement, indicating reduced mental-interpersonal work limitations.
- In contrast, participants randomized to placebo slightly worsened during the double-blind period, with the mean score increasing to 29.2.
- *P* value for treatment arm comparison from Week 0 to Week 26: < 0.0001

Open-label extension (Week 26 – Week 156)
- In the open-label extension period, participants demonstrated continued improvement in Mental-Interpersonal limitations.

Figure 7. **Output Demands Scale[a]**


Decreased burden
Score
31.2
27.2
9.9
33.6
16.5
7.5
Baseline (n = 38/18)
Week 26 (n = 31/11)
Week 52 (n = 27)
Week 156 (n = 6)
Palopegteriparatide
Placebo
Total palopegteriparatide[b]

WLQ Output Demands scores over time. Palopegteriparatide treatment resulted in improvement by Week 26 with continued improvement through Week 156, whereas participants randomized to placebo slightly worsened through the double-blind period.

[a]Greater scores correspond with more self-reported difficulties at work.
[b]Participants randomized to placebo crossed over to palopegteriparatide after Week 26.

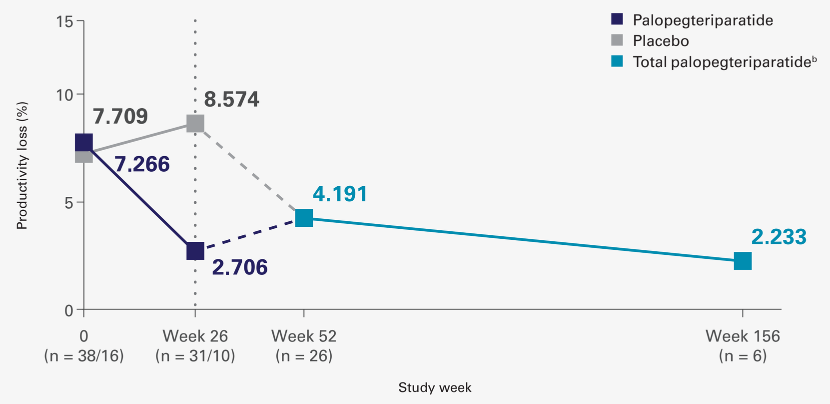
KEY INTERPRETATION

Baseline Assessment
- Participants in the groups randomized to palopegteriparatide and placebo had mean baseline scores of 31.2 and 27.2, respectively, indicating some degree of limitation in work quantity and quality.

Double-blind period (Baseline – Week 26)
- Participants randomized to palopegteriparatide showed rapid improvement, with a mean score of 9.9 by the end of the double-blind period (Week 26), whereas scores slightly worsened for participants randomized to placebo (rising to a mean value of 33.6).
- *P* value for treatment arm comparison from Week 0 to Week 26: 0.0007

Open-label extension (Week 26 – Week 156)
- By Week 156 during the open-label extension, participants showed further improvement in Output Demands.

Figure 8. **At-Work Productivity Improvement in Percentage[a]**


Productivity loss (%)
7.709
7.266
8.574
2.706
4.191
2.233
0 (n = 38/16)
Week 26 (n = 31/10)
Week 52 (n = 26)
Week 156 (n = 6)
Study week
Palopegteriparatide
Placebo
Total palopegteriparatide[b]

[a]Higher percentage corresponds with higher work productivity loss. WLQ At-Work Productivity Loss is expressed as the mean percentage of productivity loss over the past 2 weeks, derived from the four WLQ domain scores.
[b]Participants randomized to placebo crossed over to palopegteriparatide after Week 26.

KEY INTERPRETATION

Baseline assessment
- At baseline, both groups demonstrated similar levels of at-work productivity loss (approximately 7-8%).

Double-blind period (Baseline – Week 26)
- By the end of the double-blind period (Week 26), a substantial improvement was observed among participants treated with palopegteriparatide, with mean productivity loss improving to 2.7%, representing an approximately 65% reduction from baseline.
- No improvement was observed in the placebo group.
- *P* value for treatment arm comparison from Week 0 to Week 26: 0.0001

Open-label extension (Week 26 – Week 156)
- During the open-label extension, at-work productivity loss remained substantially improved among participants receiving palopegteriparatide, with the lowest levels observed at Week 156.

Abbreviations

AE = adverse event; **DBP** = double-blind period; **EU** = European Union; **HEOR** = health economics and outcomes research; **HPES** = hypoparathyroidism patient experience scales; **n** = number; **PTH** = parathyroid hormone; **SAE** = serious adverse event; **SD** = standard deviation; **SF-36** = 36-item short form survey; **TDD** = total daily dose; **TEAE** = treatment emergent adverse event; **TransCon** = transient conjugation; **US** = United States; **Wk** = week; **WLQ** = Work Limitations Questionnaire

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