Long-Term Efficacy and Safety of TransCon™ PTH in Adults with Hypoparathyroidism: 52-Week Results From the Open-Label Extension of the Phase 3 PaTHway Trial

Presented at ENDO 2023
June 17, 2023

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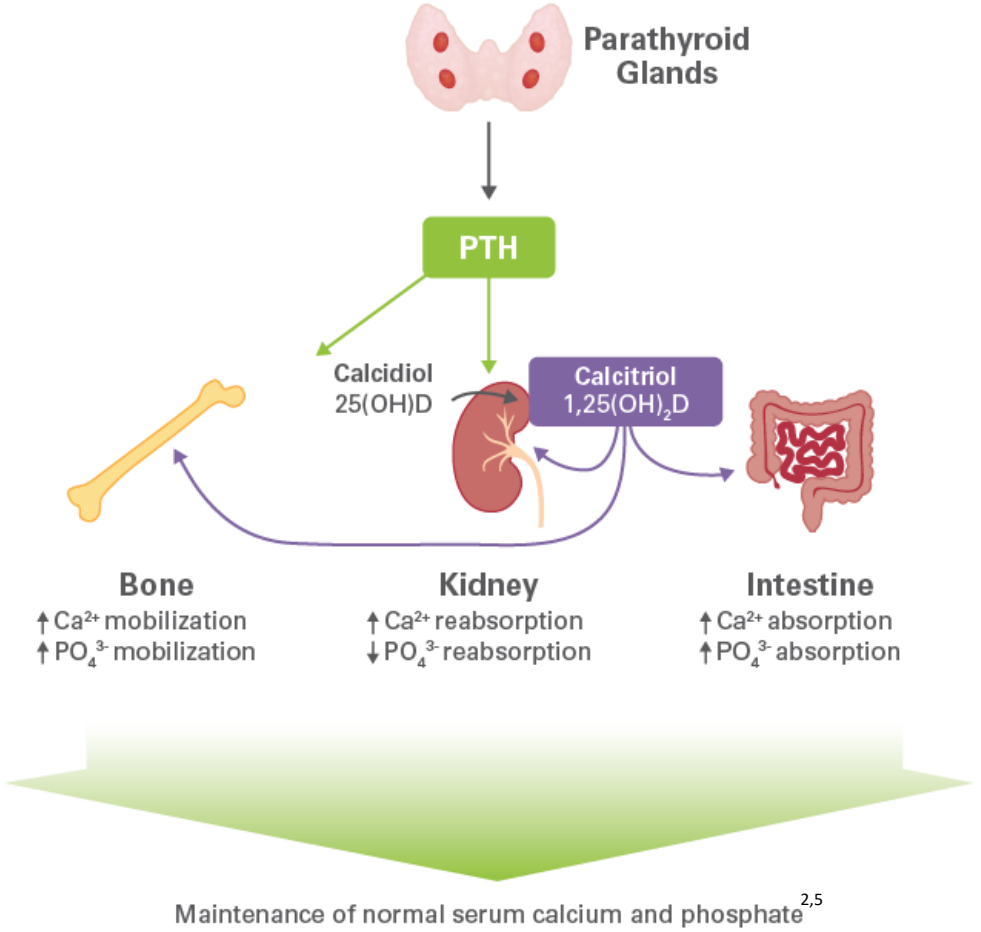
PTH Therapy for Hypoparathyroidism

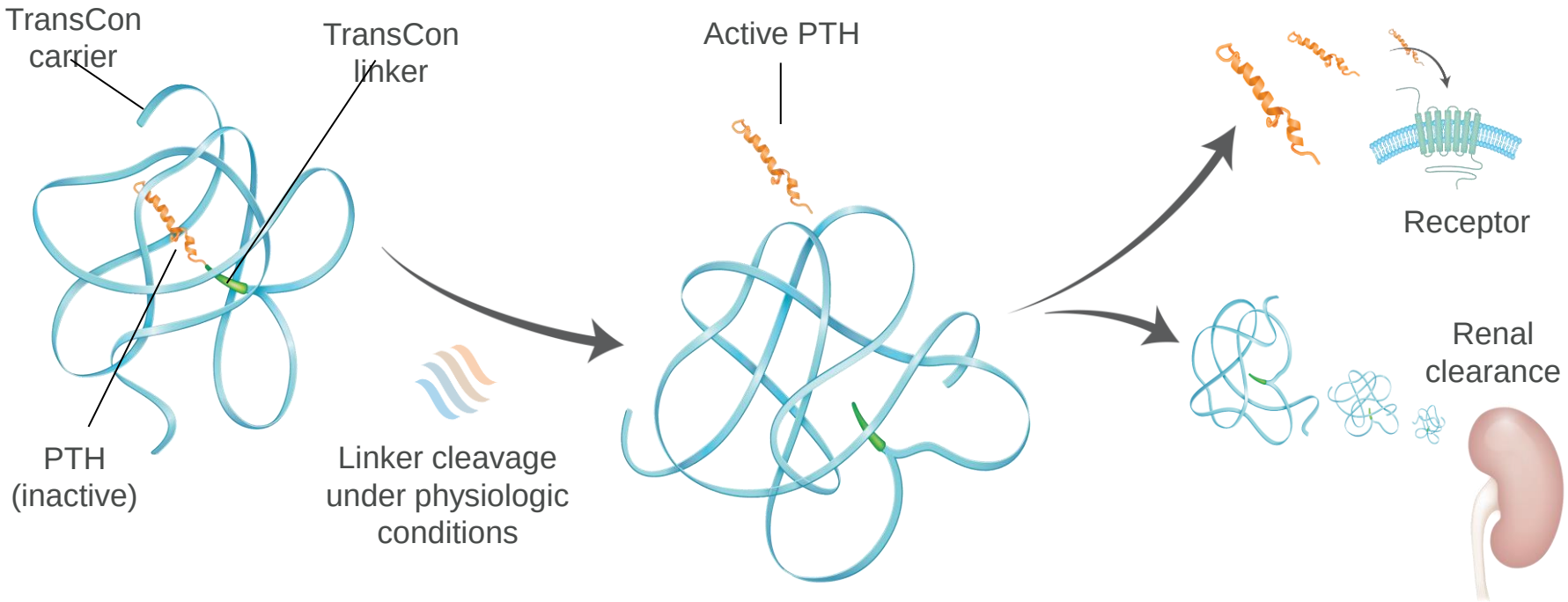
- An **intact PTH axis** maintains normal serum calcium and phosphate homeostasis[1,2]
  - PTH acts on bone, kidney, and indirectly, intestine[1,3]
  - Promotes normal nerve and muscle function[4]
- Conventional therapy for hypoparathyroidism (active vitamin D [e.g., calcitriol, alfacalcidol], calcium) aims to alleviate hypocalcemic symptoms but fails to restore normal PTH physiology
- PTH 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 biochemistries
  - Skeletal health
  - Quality of life



PTH, parathyroid hormone

1. Brandi ML, et al. J Clin Endocrinol Metab. 2016;101(6):2273-2283. 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. Vetter T, et al. Curr Opin Nephrol and Hypertens. 2002;11:403-410.

TransCon PTH (palopegteriparatide) Design

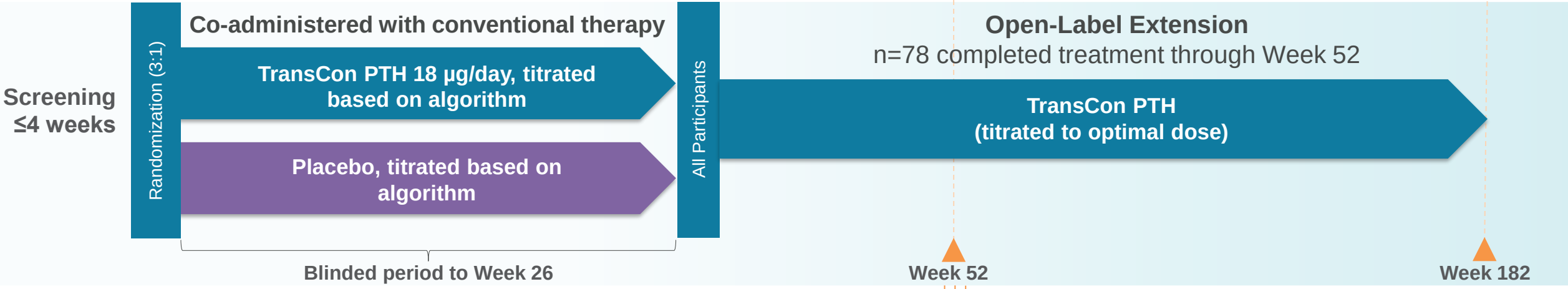


- TransCon PTH is an investigational prodrug, administered once daily, with sustained release of active PTH designed to provide PTH levels in the physiological range for 24 hours/day
- TransCon PTH is a prodrug of PTH(1-34) developed as a therapy for adults with hypoparathyroidism

PTH, parathyroid hormone; TransCon, transient conjugation
Karpf DB, et al. *J Bone Miner Res*. 2020;35(8):1430-1440.

TransCon PTH Phase 3 PaTHway Trial Design (NCT04701203)

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



Multi-Component Efficacy Endpoint

Proportion of participants with:

- Serum calcium in the normal range (8.3–10.6 mg/dL) ***and***
- Independence from therapeutic doses of calcium[a] ***and***
- Independence from active vitamin D[b]

Secondary Endpoints

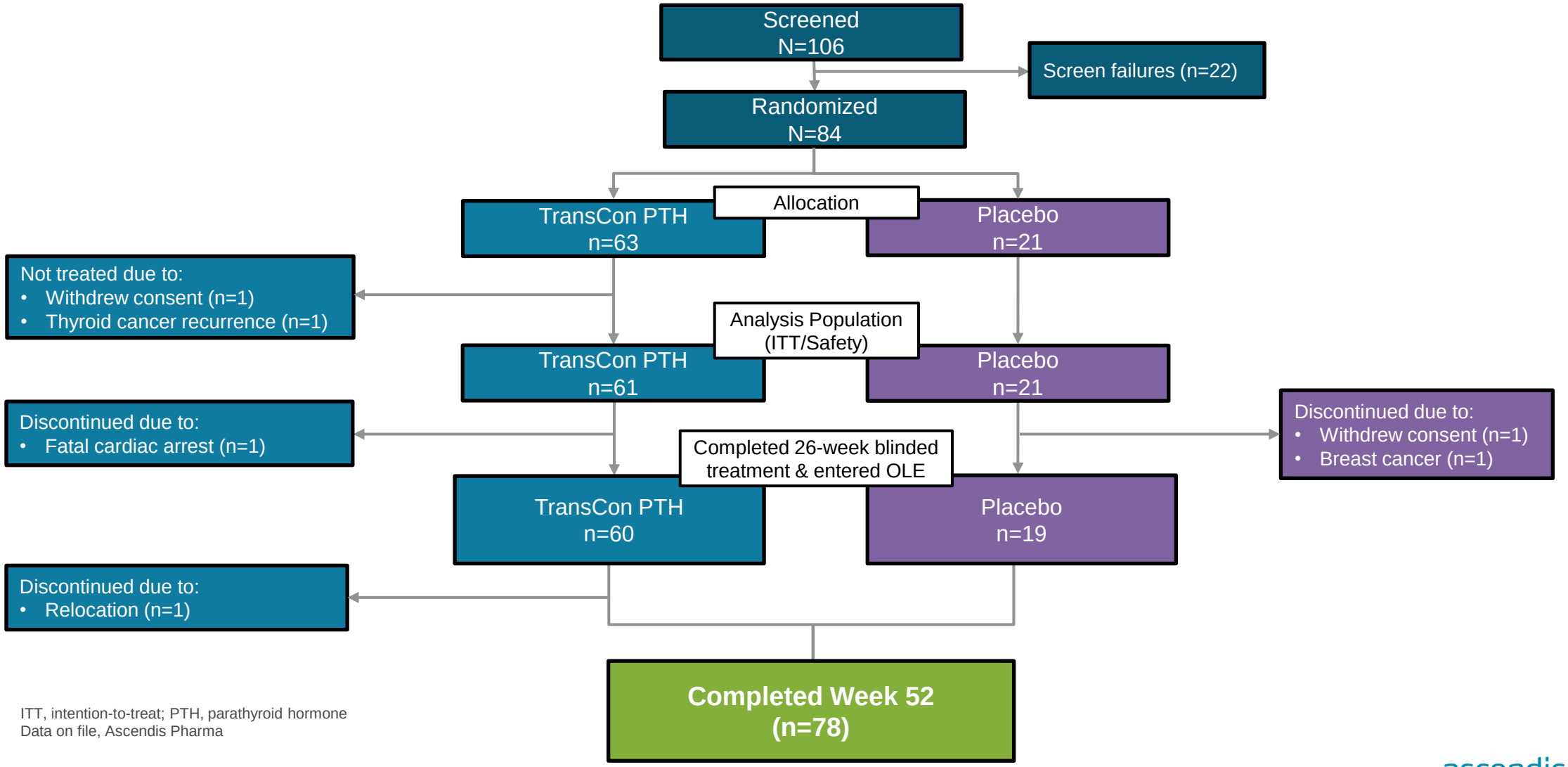
- HPES-Symptom physical and cognitive domain scores
- HPES-Impact physical functioning and daily life domain scores
- SF-36 Physical Functioning subscale score
- Bone turnover markers (P1NP, CTx) and BMD by DXA

Safety and Tolerability Endpoints

- 24-hour urine calcium
- Incidence of Adverse Events, Serious Adverse Events, and Treatment-Emergent Adverse Events

[a]Independence from therapeutic doses of calcium is defined as a standing dose of elemental calcium ≤600 mg on the day prior to the week 52 visit
[b]Independence from active vitamin D is defined as a standing dose of active vitamin D equal to zero on the day prior to the week 52 visit
BMD, bone mineral density; CTx, C-terminal telopeptide of type 1 collagen; DXA, dual x-ray absorptiometry; HPES, Hypoparathyroidism Patient Experience Scale; SF-36, 36-Item Short Form Survey; P1NP, procollagen type 1 N-terminal propeptide; PTH, Parathyroid Hormone

Participant Disposition



ITT, intention-to-treat; PTH, parathyroid hormone
Data on file, Ascendis Pharma

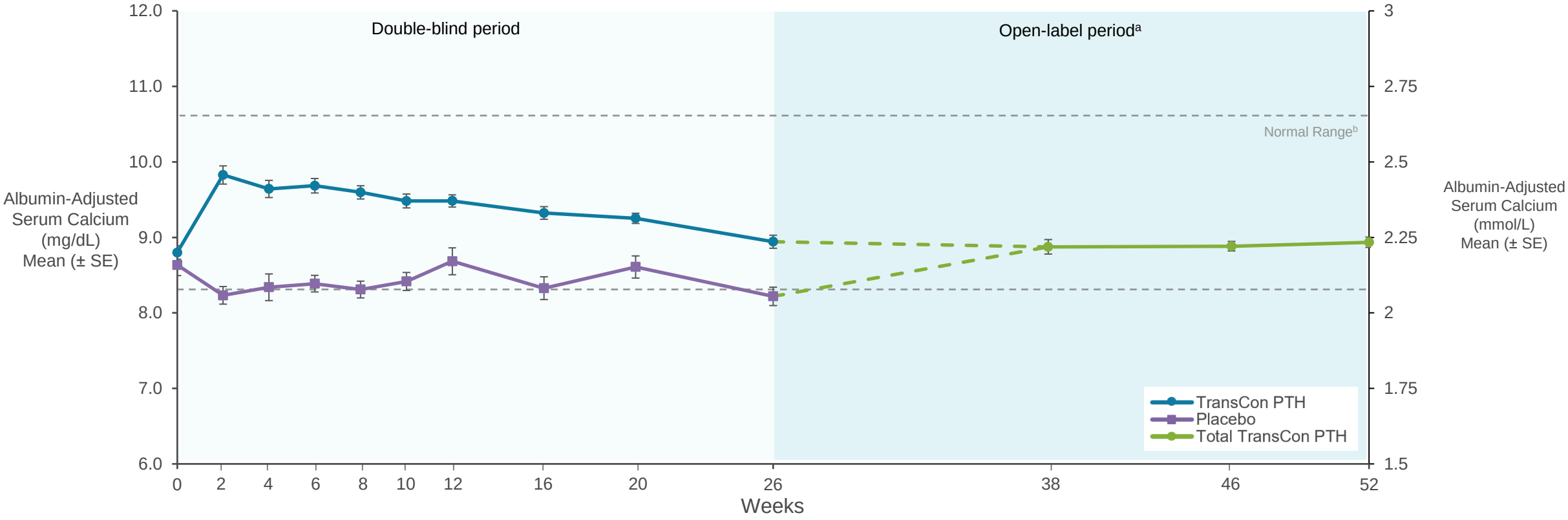
Participants Who Met the Multi-Component Endpoint Criteria at Week 52

	Total TransCon PTH (N=82)
Participants with data on all criteria at Week 52, n	78
Participants meeting the multi-component efficacy endpoint criteria at Week 52, n	63
Proportion, % (95% CI)[a]	**81** (70, 89)
Number of participants meeting each component, n (%):	
Albumin-adjusted serum calcium within the normal range[b]	67 (86)
Independence from active vitamin D	78 (100)
Independence from therapeutic doses of calcium	74 (95)

81% of participants treated with TransCon PTH met the multi-component efficacy endpoint and **95%** achieved independence[c] from conventional therapy at Week 52 of the PaTHway trial

[a]Percentages are calculated based on participants who had data on all criteria
[b]Normal range for albumin-adjusted serum calcium = 8.3-10.6 mg/dL
[c]Defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg on the day prior to the week 52 visit
Data on file, Ascendis Pharma

Albumin-Adjusted Serum Calcium Levels at Week 52

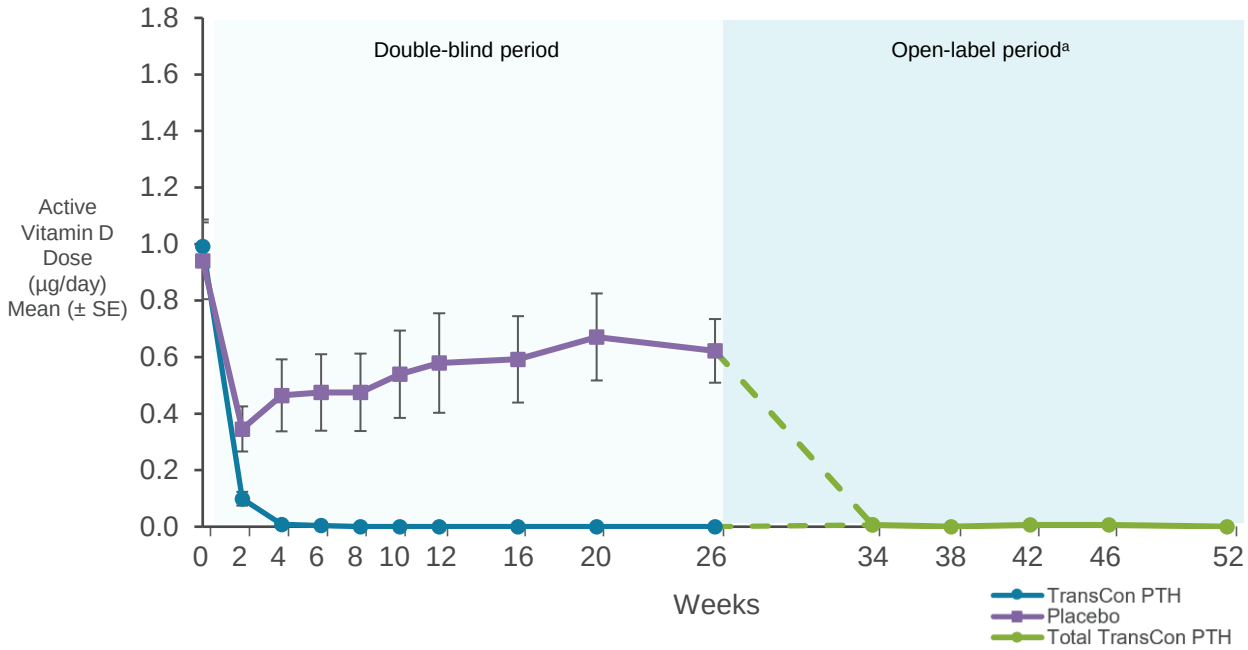


Mean albumin-adjusted serum calcium levels were maintained within the normal range with TransCon PTH treatment through Week 52 of the PaTHway Trial

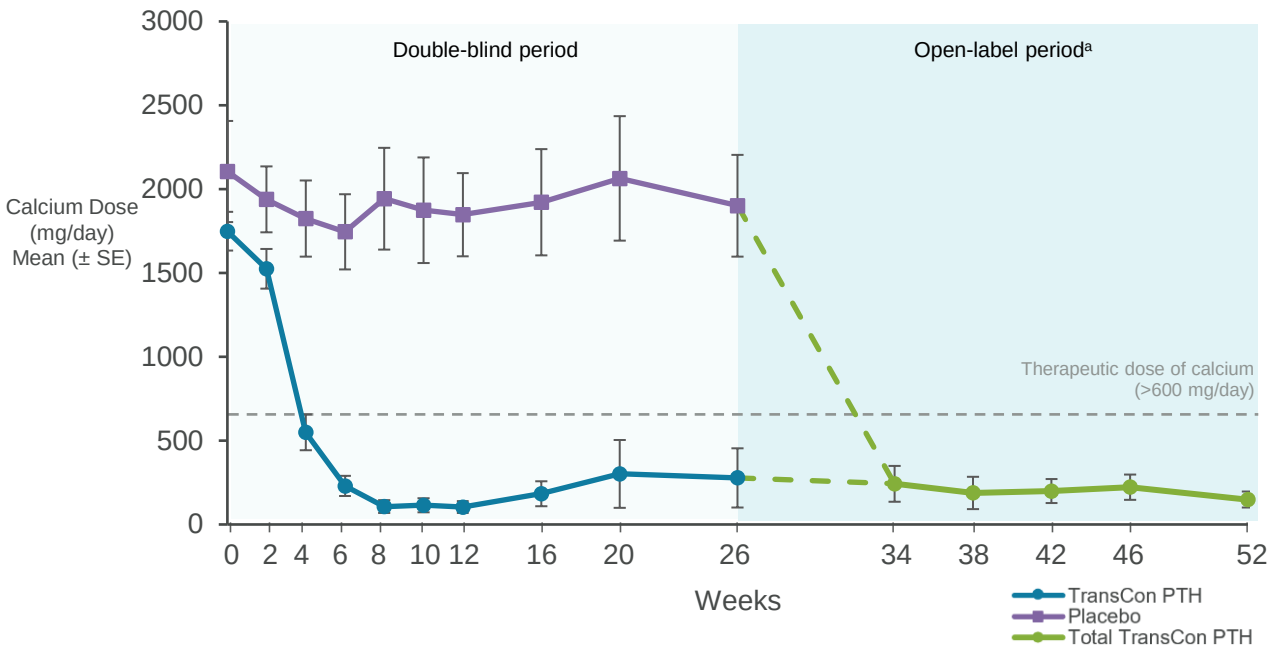
[a]All participants received TransCon PTH during the open-label period [b]Normal range 8.3-10.6 mg/dL
SE, standard error
Data on file, Ascendis Pharma

Independence from Conventional Therapy at Week 52

Active Vitamin D



Elemental Calcium

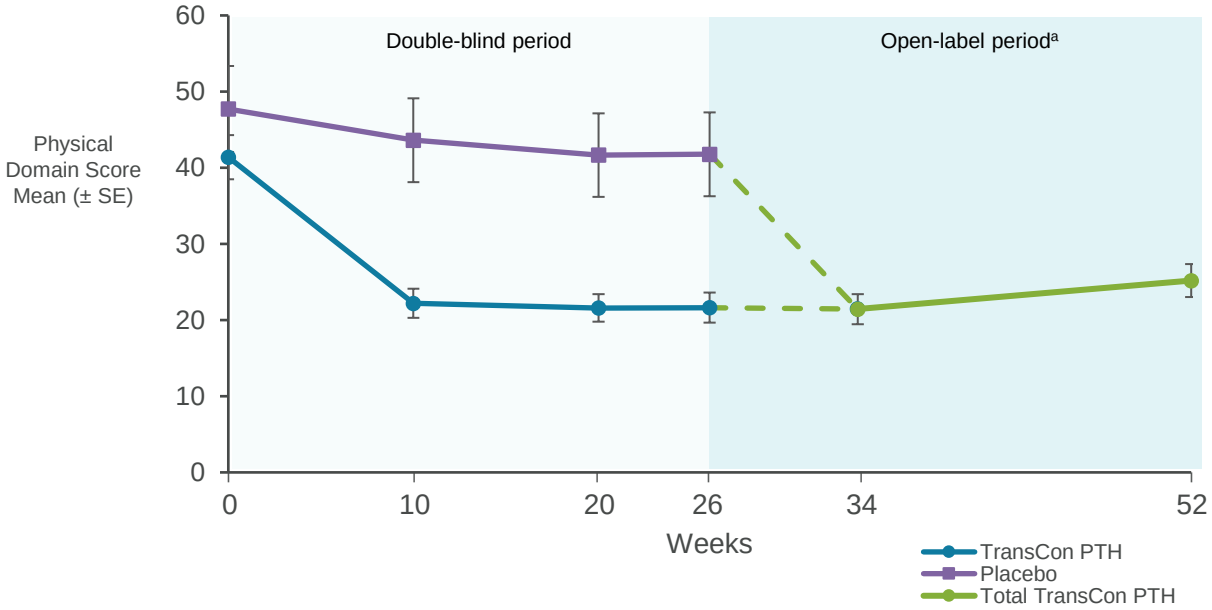


- TransCon PTH enabled rapid and sustained independence[b] from conventional therapy over 52 weeks
- Independence[b] from conventional therapy in the placebo/TransCon PTH group from Week 26 through 52 followed a trend similar to that of the active treatment group from baseline to Week 26

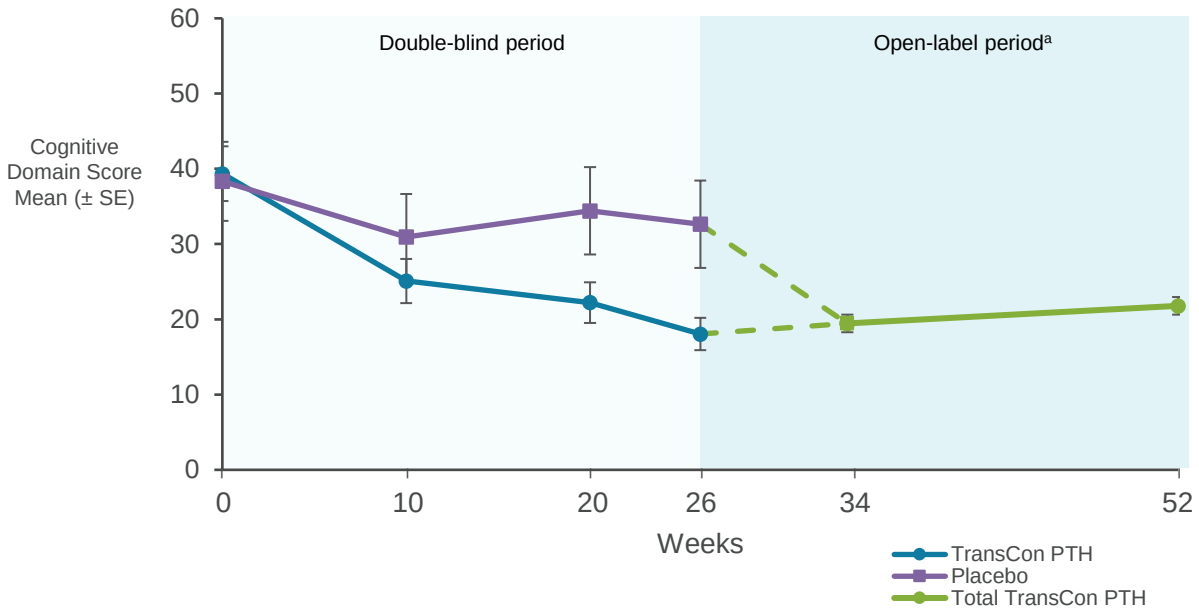
[a]All participants received TransCon PTH during the open-label period
[b]Defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg on the day prior to the week 52 visit
SE, standard error
Data on file, Ascendis Pharma 2023

HPES-Symptom Scores Through Week 52

HPES-Symptom Physical Domain Score



HPES-Symptom Cognitive Domain Score

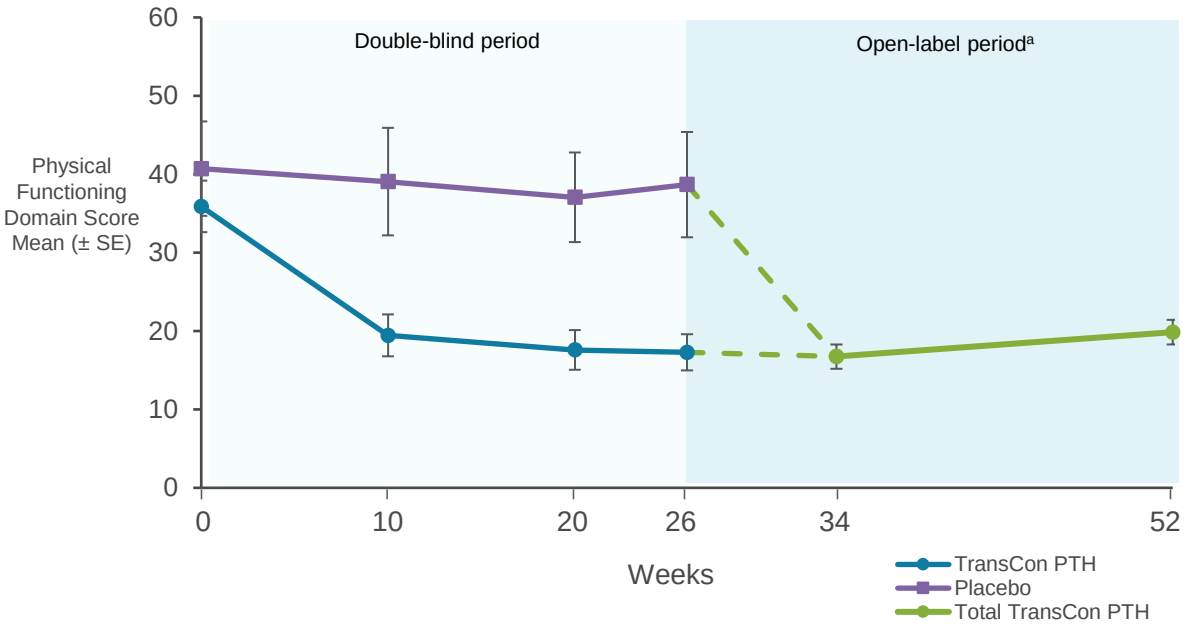


HPES-Symptom scores showed a sustained improvement in hypoparathyroidism-related physical and cognitive symptoms with TransCon PTH treatment over 52 weeks

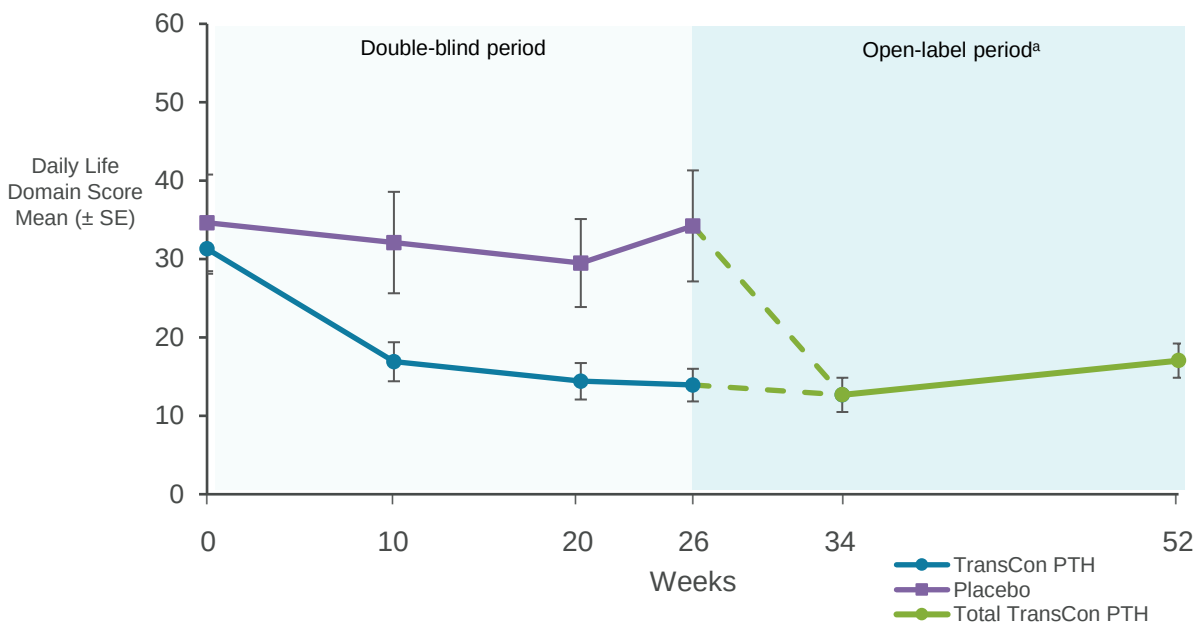
[a]All participants received TransCon PTH during the open-label period
HPES, Hypoparathyroidism Patient Experience Scale; SE, standard error
Data on file, Ascendis Pharma 2023

HPES-Impact Domain Scores Through Week 52

HPES-Impact Physical Functioning Domain Score



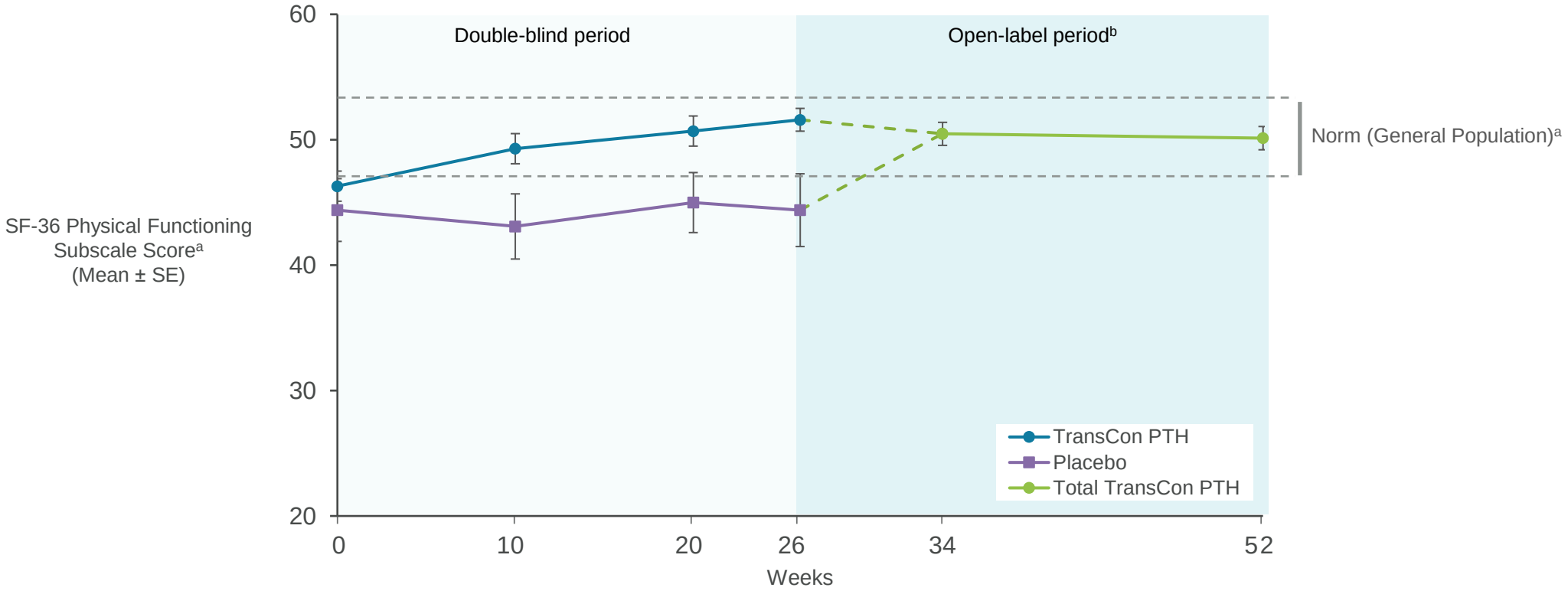
HPES-Impact Daily Life Domain Score



- HPES-Impact scores showed sustained improvement in the impact of hypoparathyroidism on physical functioning and daily life with TransCon PTH
- In participants first treated with placebo, HPES scores from weeks 26 to 52 showed the same rapid improvement seen in those treated with TransCon PTH during the blinded period

[a]All participants received TransCon PTH during the open-label period
HPES, Hypoparathyroidism Patient Experience Scale; SE, standard error
Data on file, Ascendis Pharma 2023

SF-36 Physical Functioning Subscale Scores Through Week 52

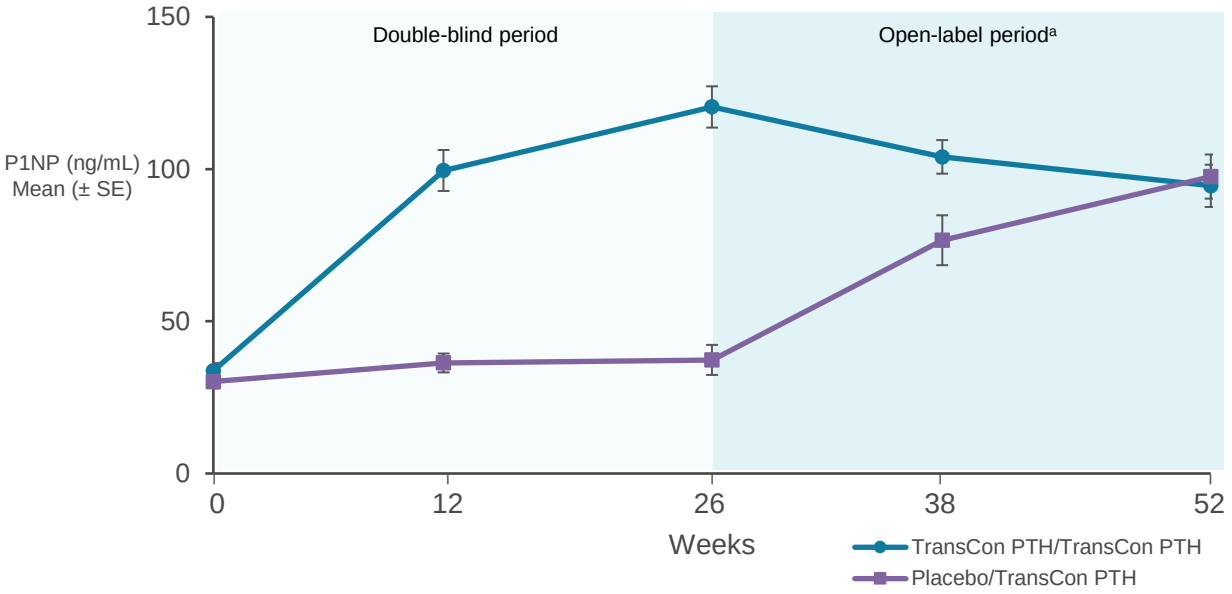


- Mean SF-36 Physical Functioning subscale scores at week 52 remained above baseline, showing sustained improvement in HRQoL with TransCon PTH
- The improvement in SF-36 Physical Functioning subscale scores with TransCon PTH in those previously treated with placebo mirrored the increase in scores in the TransCon PTH group during the blinded period

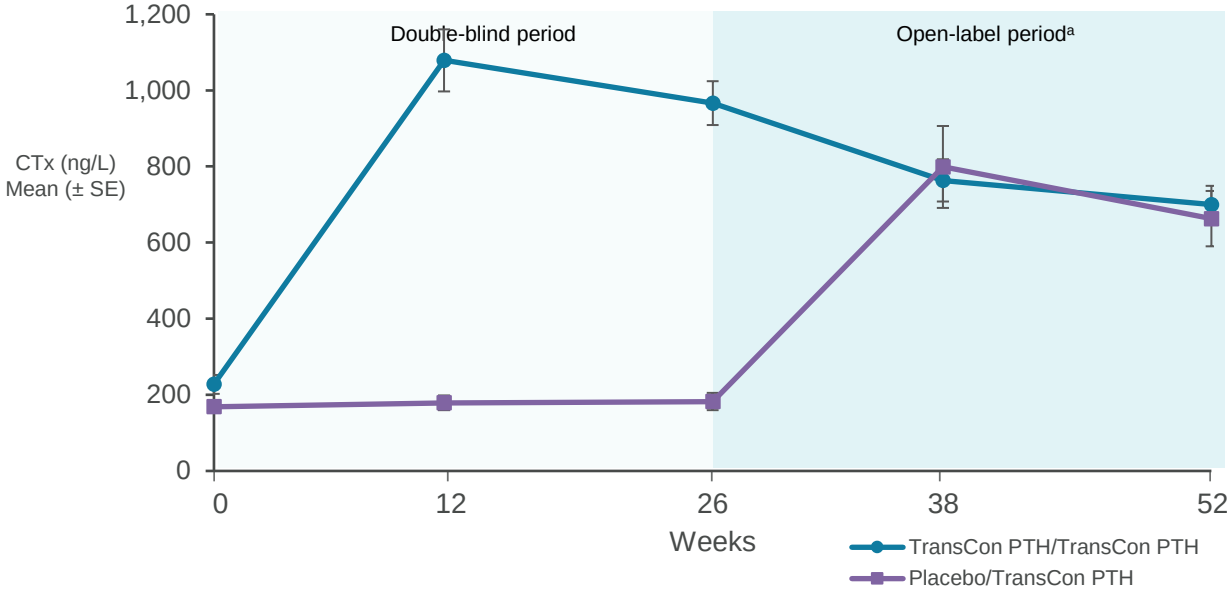
[a]The dashed lines (--) indicate the upper (53) and lower (47) bounds of T scores considered to be in the range of average functioning for the U.S. general population of group level data. Group mean scores lower than 47 indicate impairment. Source: Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). [b]All participants received TransCon PTH during the open-label period.
HRQoL, health-related quality of life; SE, standard error; SF-36, 36-Item Short Form Survey
Data on file, Ascendis Pharma 2023

Bone Turnover Markers Through Week 52

Procollagen Type 1 N-Terminal Propeptide (P1NP)



C-Terminal Telopeptide of Type 1 Collagen (CTx)



- In the TransCon PTH/TransCon PTH group, smaller incremental changes were seen in bone turnover markers between weeks 26 and 52 than baseline to week 26
- In the placebo/TransCon PTH group, trends from week 26 through 52 resembled those observed in the active treatment group from baseline to week 26

[a]All participants received TransCon PTH during the open-label period
SE, standard error
Data on file, Ascendis Pharma 2023

Bone Mineral Density by DXA in Participants Treated with TransCon PTH from Baseline Through Week 52

Mean Z-Scores

	Baseline (n=60)	Week 26 (n=59)	Week 52 (n=58)
Region			
Lumbar Spine L1-L4[a]	1.5	0.7	0.7
Femoral Neck	0.8	0.3	0.3
Total Hip	0.9	0.5	0.4
Distal 1/3 Radius[b]	0.3	0.3	0.3

BMD Z-scores trended toward age- and sex-matched norms with 52 weeks of TransCon PTH treatment

[a]n=59 (Baseline), n=58 (Week 26), n=57 (Week 52) [b]n=59 (Baseline)
Data from participants randomized to TransCon PTH at baseline only (TransCon PTH/TransCon PTH group)
BMD, bone mineral density; DXA, dual X-ray absorptiometry
Data on file, Ascendis Pharma 2023

Bone Mineral Density by DXA in Participants Treated with TransCon PTH from Baseline Through Week 52

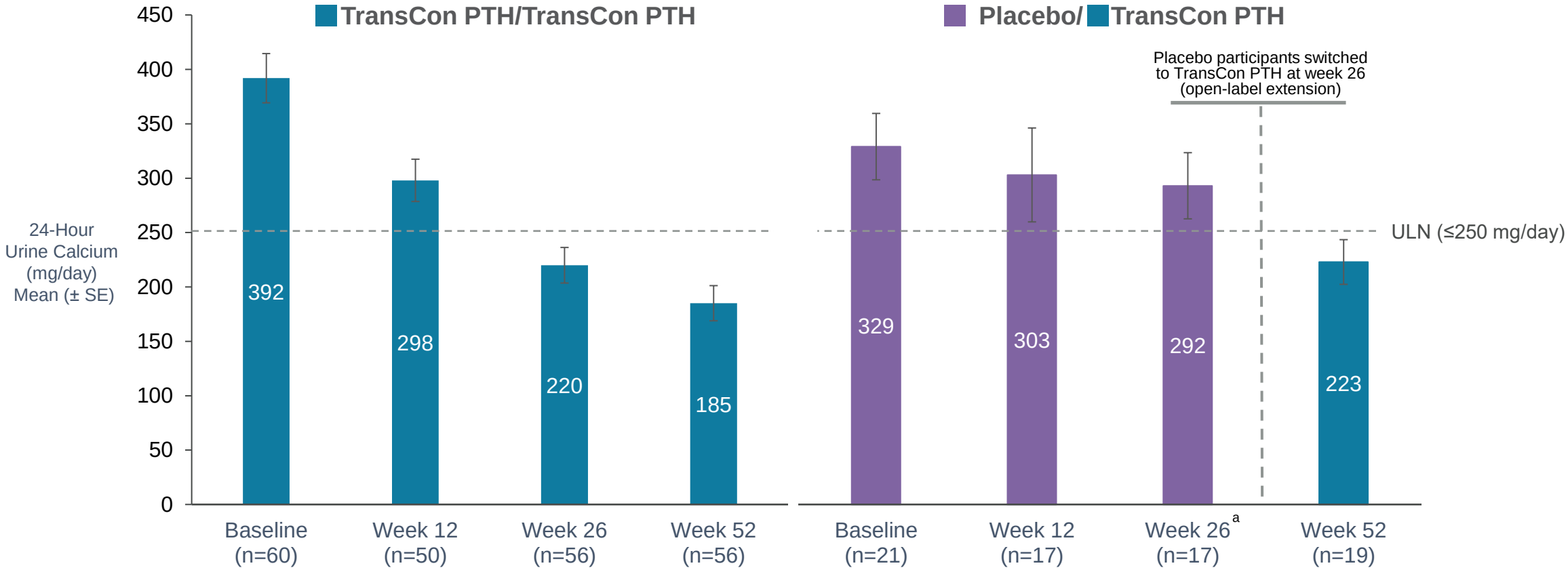
Mean T-Scores

	Baseline (n=60)	Week 26 (n=59)	Week 52 (n=58)
Region			
Lumbar Spine L1-L4[a]	0.9	0.1	0.0
Femoral Neck	0.0	-0.5	-0.6
Total Hip	0.4	-0.1	-0.2
Distal 1/3 Radius[b]	-0.3	-0.3	-0.4

T-scores remained within the normal range[c] with TransCon PTH treatment over 52 weeks

[a]n=59 (Baseline), n=58 (Week 26), n=57 (Week 52) [b]n=60 (Week 26), n=59 (Week 52) [c]T-score reference point: young (30-year-old) Caucasian adult
Data from participants randomized to TransCon PTH at baseline only (TransCon PTH/TransCon PTH group)
DXA, dual X-ray absorptiometry
Data on file, Ascendis Pharma 2023

24-Hour Urine Calcium Excretion Through Week 52



- TransCon PTH normalized mean 24-hour urine calcium excretion within 26 weeks, which was maintained through week 52
- Mean 24-hour urine calcium normalized within 26 weeks of treatment initiation in the placebo/TransCon PTH group

[a]Participants randomized to placebo at baseline initiated TransCon PTH treatment at week 26
SE, standard error; ULN, upper limit of normal
Data on file, Ascendis Pharma 2023

Summary of TEAEs in the PaTHway Trial Through Week 52

Treatment Emergent Adverse Events (TEAEs), n (%)	Total TransCon PTH[a] (N=80)
Any TEAE	72 (90.0)
Serious TEAE	8 (10.0)
Severity[b]	
Grade 1	37 (46.3)
Grade 2	27 (33.8)
Grade 3	7 (8.8)
Grade 4	1 (1.3)
Related TEAE	42 (52.5)
Serious related TEAE[c]	2 (2.5)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization	6 (7.5)
TEAE leading to discontinuation of study drug[d]	1 (1.3)
TEAE leading to death[d]	1 (1.3)

Most TEAEs were mild or moderate (grades 1-2) and none reported during the open-label extension led to discontinuation of the trial or TransCon PTH treatment

[a]Includes TEAEs occurring on or after the first dose of TransCon PTH: 52 weeks of exposure for the TransCon/TransCon group (n=61) and 26 weeks of exposure for the Placebo/TransCon group (n=19); [b]Participants are displayed for the highest severity category only; [c]Hypercalcemia (n=2); [d] One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the study drug and death during blinded treatment. Data on file, Ascendis Pharma 2023

Conclusions

In adults with hypoparathyroidism, treatment with TransCon PTH showed sustained efficacy, safety, and tolerability beyond the 26-week blinded period through Week 52 of the PaTHway Trial

- At Week 52, 81% of participants treated with TransCon PTH achieved normal serum calcium and independence[a] from conventional therapy.
  - 95% of participants achieved independence[a] from conventional therapy
- TransCon PTH resulted in improvements in symptoms and health-related quality of life within 26 weeks, demonstrated by clinical and patient-reported outcomes, whether participants were randomized to placebo at baseline or in the active treatment group during the blinded period.
- TransCon PTH normalized mean 24-hour urine calcium excretion within 26 weeks, which was maintained through Week 52.
- TransCon PTH continues to be well tolerated in the open-label extension with no new safety signals identified.

[a]Defined as a standing dose of active vitamin D equal to zero and elemental calcium ≤600 mg on the day prior to the week 52 visit

Thank you

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