Sustained Improvement in Renal Function With Palopegteriparatide in Adults With Chronic Hypoparathyroidism: 2-Year Results From the Phase 3 PaTHway Trial

Peter Schwarz,[1] Lars Rejnmark,[2] Elvira Gosmanova,[3] Aliya A. Khan,[4] Noriko Makita,[5] Yasuhiro Takeuchi,[6] Yasuo Imanishi,[7] Stuart Sprague,[8] Dolores M. Shoback,[9] Lynn Kohlmeier,[10] Mishaela R. Rubin,[11] Andrea Palermo,[12] Claudia Gagnon,[13] Elena Tsourdi,[14] Carol Zhao,[15] Michael A. Makara,[15] Michael Ominsky,[15] Bryant Lai,[15] Jenny Ukena,[15] Christopher T. Sibley,[15] Aimee D. Shu[15]

[1]Rigshospitalet, Copenhagen, Denmark; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Albany Medical College, Albany, NY, USA; [4]McMaster University, Hamilton, ON, Canada; [5]The University of Tokyo Graduate School of Medicine, Tokyo, Japan; [6] Toranomon Hospital and Okinaka Memorial Institute for Medical Research, Tokyo, Japan; [7]Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; [8]NorthShore University Health System-University of Chicago Pritzker School of Medicine, Chicago, IL; [9]University of California, San Francisco and VA Medical Center, San Francisco, CA, USA; [10]Endocrinology and Spokane Osteoporosis, Spokane, WA, USA; [11]Columbia University, New York, NY, USA; [12]Fondazione Policlinico Campus Bio-medico and Unit of Endocrinology and Diabetes, Campus Bio-medico University, Rome, Italy; [13]CHU de Québec-Université Laval Research Centre and Department of Medicine, Université Laval, Quebec City, QC, Canada; [14]Technische Universität Dresden Medical Center, Dresden, Germany; [15]Ascendis Pharma Inc, Palo Alto, CA, USA.

MED-US-TC-PTH-2500140

November 2025

European Society of Endocrinology

CONFLICT OF INTEREST

Peter Schwarz

☒ **I have the following potential conflicts of interest to report**:

- ☐ Research Contracts
- ☐ Consulting
- ☐ Employment in the Industry
- ☒ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☐ **I declare that I have no potential conflict of interest.**

Disclosures and Funding

Ascendis Pharma and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

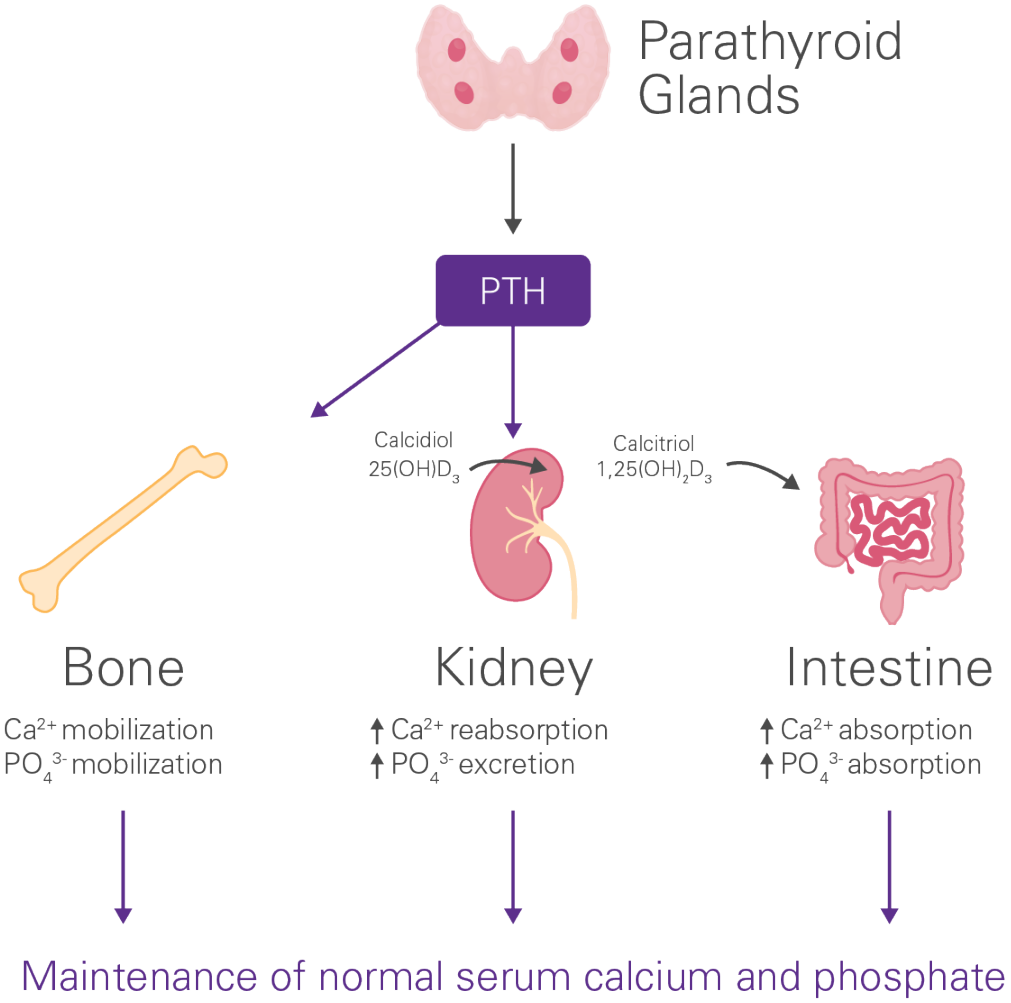
Ascendis Pharma Bone Diseases A/S funded this trial and participated in the trial design, research, analysis, data collection, interpretation of the data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Kristin Hirahatake, PhD 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: **Peter Schwarz**: Stock ownership Novo Nordisk, Ascendis Pharma. **Lars Rejnmark**: Research funding from Takeda, Kyowa Kirin International, Ascendis Pharma, and Calcilytix; honoraria from Calcilytix Therapeutics; advisory board for Takeda and Amolyt. **Elvira Gosmanova**: Honoraria from Novo Nordisk and Takeda; advisory board role for Ascendis Pharma and Takeda; travel, accommodations, and expenses from Ascendis Pharma; industry-sponsored grants from AstraZeneca, AbbVie, and Kowa Research Institute. **Aliya Khan**: 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. **Noriko Makita**: Research funding from Kyowa Kirin. **Yasuhiro Takeuchi**: Honoraria from Chugai Pharmaceutical Co. Ltd; consulting fee from Teijin Pharma; speakers bureau for Amgen Japan. **Yasuo Imanishi**: speakers bureau for Kyowa Kirin Co., Ltd and Daiichi Sankyo Co., Ltd. **Stuart Sprague**: Research funding from Amgen, Amylot, Ascendis Pharma, Ardelyx, Frensinius, and OPKO and consultant Amgen, Ardelyx, Bayer, Fresenius, Horizon, OPKO, and Shire. **Dolores Shoback**: Research/salary funding from Bone Health Tech; research funding from Ascendis Pharma. **Lynn Kohlmeier**: Research funding from Amolyt and Ascendis Pharma; speakers bureau, honoraria from Amgen, Radius, and Ascendis Pharma; advisory board, consultant for Radius, Alexion, and Ascendis Pharma. **Mishaela Rubin**: Study investigator for Takeda, Ascendis Pharma, Amolyt, and Calcilytix; advisory board for Ascendis, speakers bureau for Ascendis; consulting for MBX. **Andrea Palermo**: Consultant for Theramex, Bruno Farmaceutici, Amgen; research funding from Amgen, Shire, Ascendis; speakers bureau UCB, Amgen; industry grant from Amgen. **Claudia Gagnon**: Advisory board member for Novo Nordisk; honoraria from Amgen; industry grants from Ascendis Pharma, Shire, and Takeda. **Elena Tsourdi**: Honoraria from Amgen, UCB, Takeda, Kyowa Kirin, and Ascendis Pharma; advisory board member for Amgen and UCB. **Carol Zhao**, **Michael A. Makara**, **Michael Ominsky**, **Bryant Lai**, **Jenny Ukena**, **Christopher Sibley**, and **Aimee Shu** are full-time employees of Ascendis Pharma.

PTH Therapy for Hypoparathyroidism

PaTHway TRIAL

- An **intact PTH axis** maintains normal serum calcium and phosphate homeostasis[1,2,3]
- **PTH** promotes normal nerve and muscle function[4]
- Conventional therapy for hypoparathyroidism (active vitamin D [eg, calcitriol, alfacalcidol], and oral calcium) aims to alleviate hypocalcemic symptoms but fails to restore normal PTH physiology
- 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 biochemistries
  - Skeletal health
  - Quality of life

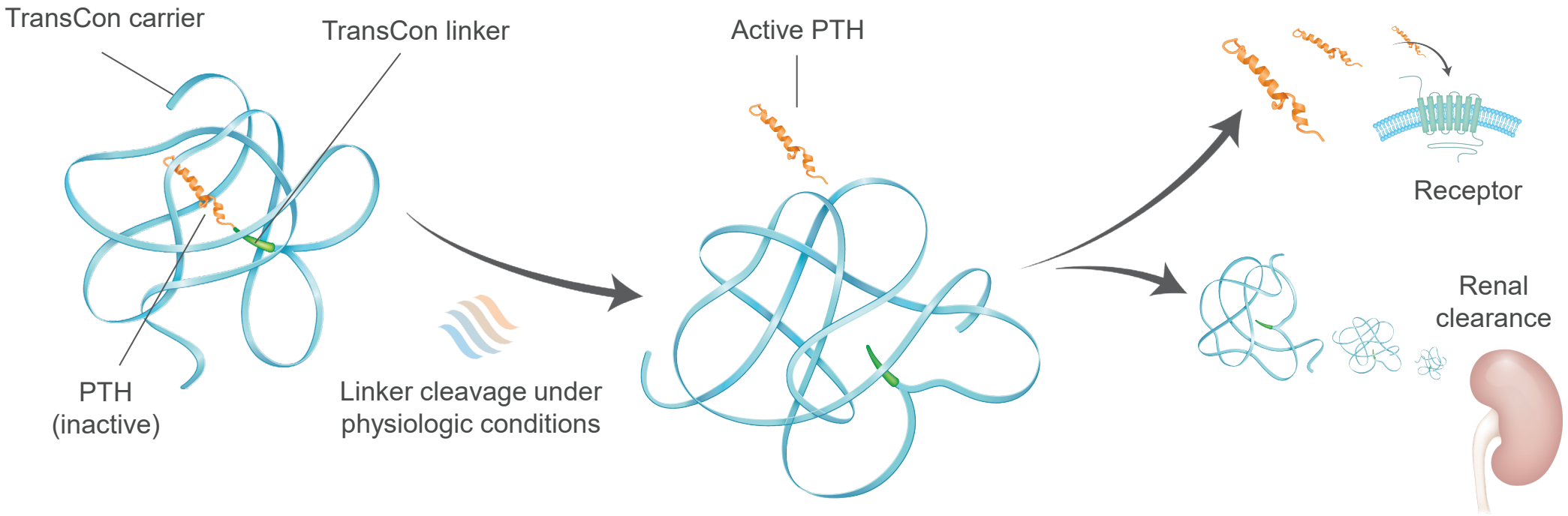


PTH, parathyroid hormone.

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.

TransCon® PTH (palopegteriparatide) Design

PaTHway TRIAL



- TransCon PTH is a prodrug of PTH (1-34), 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 approved under the brand name YORVIPATH® by the European Commission as a PTH replacement therapy for adults with chronic hypoparathyroidism

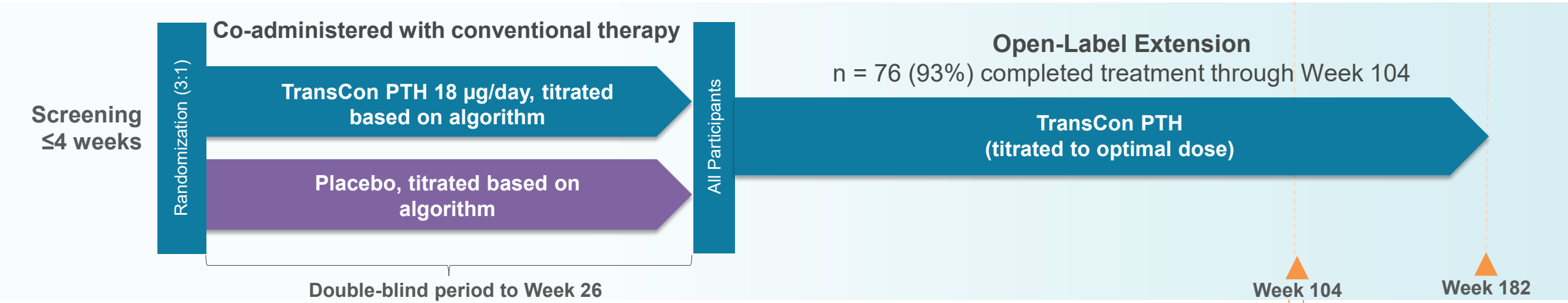
PTH, parathyroid hormone; TransCon, transient conjugation

Karpf DB, et al. *J Bone Miner Res*. 2020;35(8):1430-1440.

TransCon PTH Phase 3 PaTHway Trial Design (NCT04701203)

PaTHway TRIAL

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



Efficacy Endpoints

- Independence from active vitamin D[a]
- Independence from therapeutic doses of calcium[b]
- Serum biochemistries

Post Hoc Renal Endpoints

- Estimated glomerular filtration rate (eGFR)[c]
  - Subgroup analysis by baseline renal function < 60 mL/min/1.73 m^2 (impaired) and ≥ 60 mL/min/1.73 m^2

Safety and Tolerability Endpoints

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

[a]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
[b]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
[c]Calculated according to the Modified Diet in Renal Disease Equation (MDRD): eGFR (mL/min/1.73 m^2) = 175 × (serum creatinine mg/dL)$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 [if female] × 1.212 [if Black]

Independence From Conventional Therapy at Week 104

PaTHway TRIAL

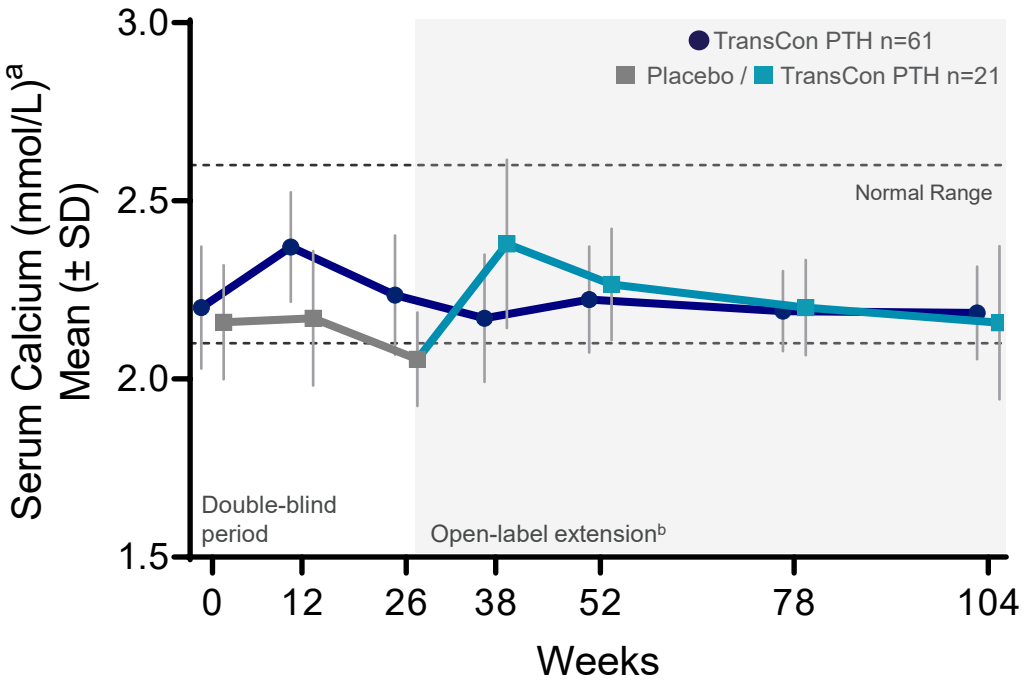
	All Participants (N=82)	Baseline eGFR < 60 mL/min/1.73 m^2 (n=23)	Baseline eGFR ≥ 60 mL/min/1.73 m^2 (n=59)
Number of participants with data at week 104	76	22	54
Independence from active vitamin D, n (%)	76 (100%)	22 (100%)	54 (100%)
Independence from therapeutic doses of calcium, n (%)	74 (97%)	21 (95%)	53 (98%)

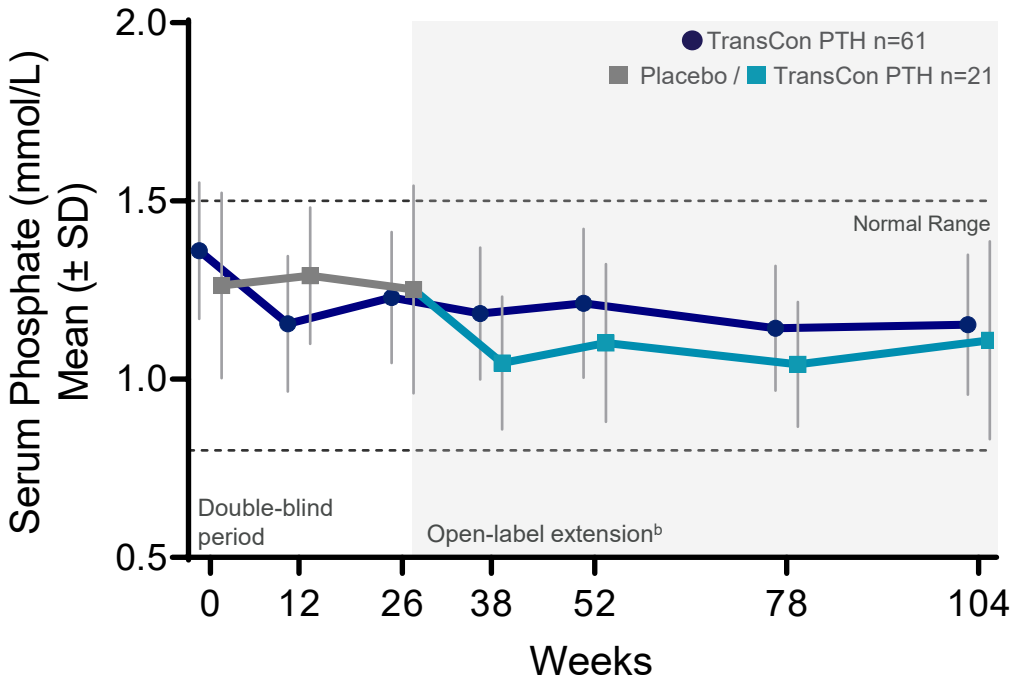
- **97%** of participants treated with TransCon PTH achieved independence from conventional therapy at Week 104 of the PaTHway trial
- Efficacy was consistent in subgroups with and without impaired renal function at baseline

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 104 visit
Percentages are calculated based on participants who had data on all criteria
eGFR, estimated glomerular filtration rate

Serum Calcium and Serum Phosphate Through Week 104

PaTHway TRIAL



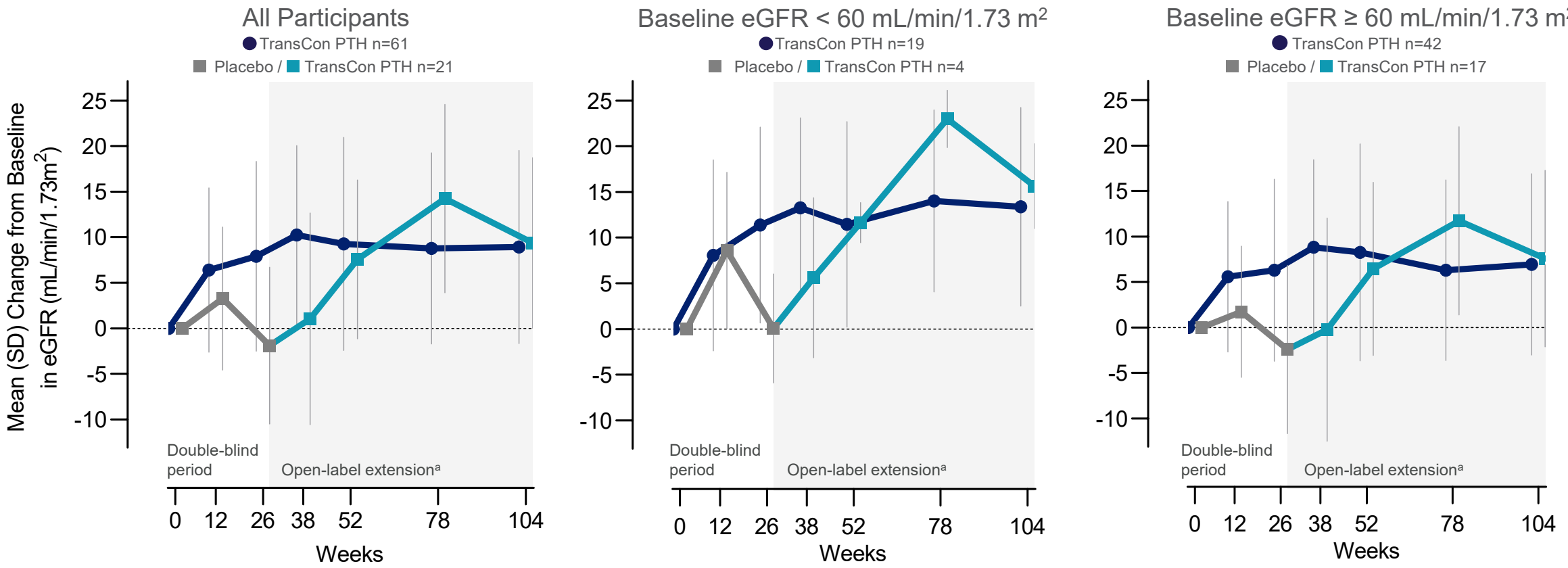


TransCon PTH treatment over 104 weeks maintained serum calcium and phosphate within normal ranges

[a]Albumin-adjusted. [b]All participants received TransCon PTH during the open-label extension SD, standard deviation
Normal ranges (shaded region): albumin-adjusted serum calcium 2.1-2.6 mmol/L; serum phosphate 0.8-1.5 mmol/L

Change From Baseline in eGFR Through Week 104

PaTHway TRIAL

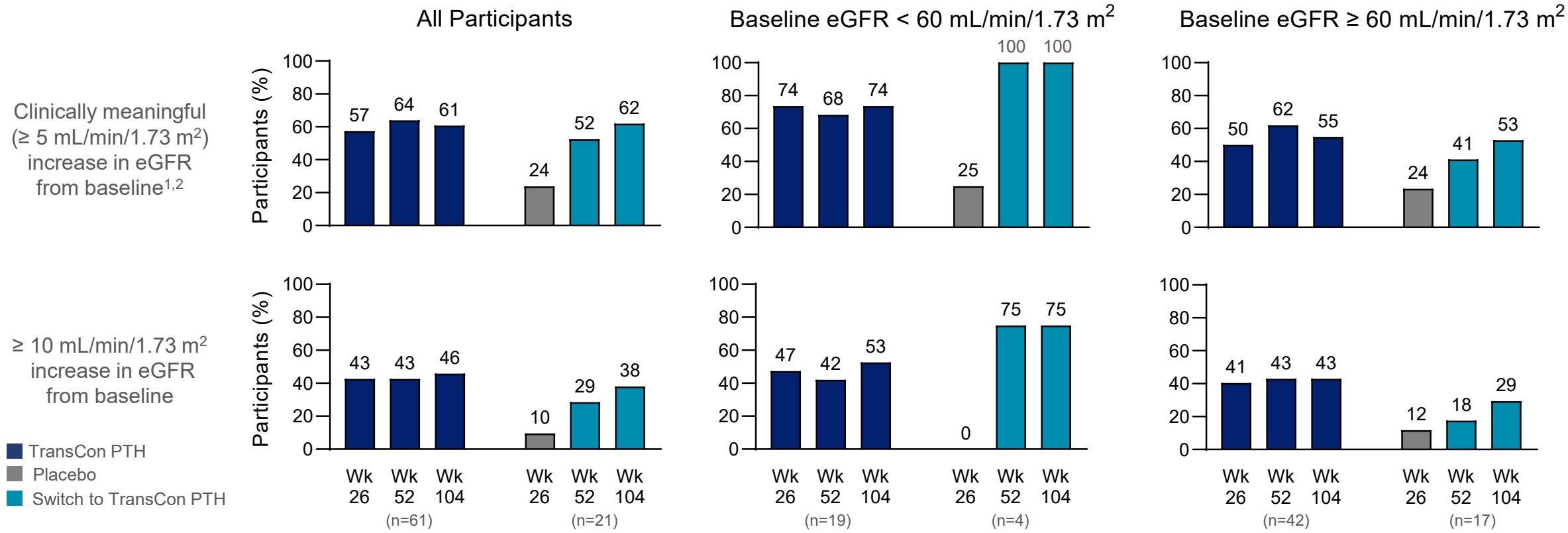


TransCon PTH treatment resulted in a mean increase in eGFR of 8.9 mL/min/1.73m^2 (P<.0001) from baseline to week 52, which was sustained through week 104 with a mean change from baseline of 9.0 mL/min/1.73m^2 (P<.0001)

[a]All participants received TransCon PTH during the open-label extension.
eGFR, estimated glomerular filtration rate; SD, standard deviation

Proportion of Participants (%) With ≥ 5 and ≥ 10 mL/min/1.73 m^2 Increases in eGFR Through Week 104

PaTHway TRIAL



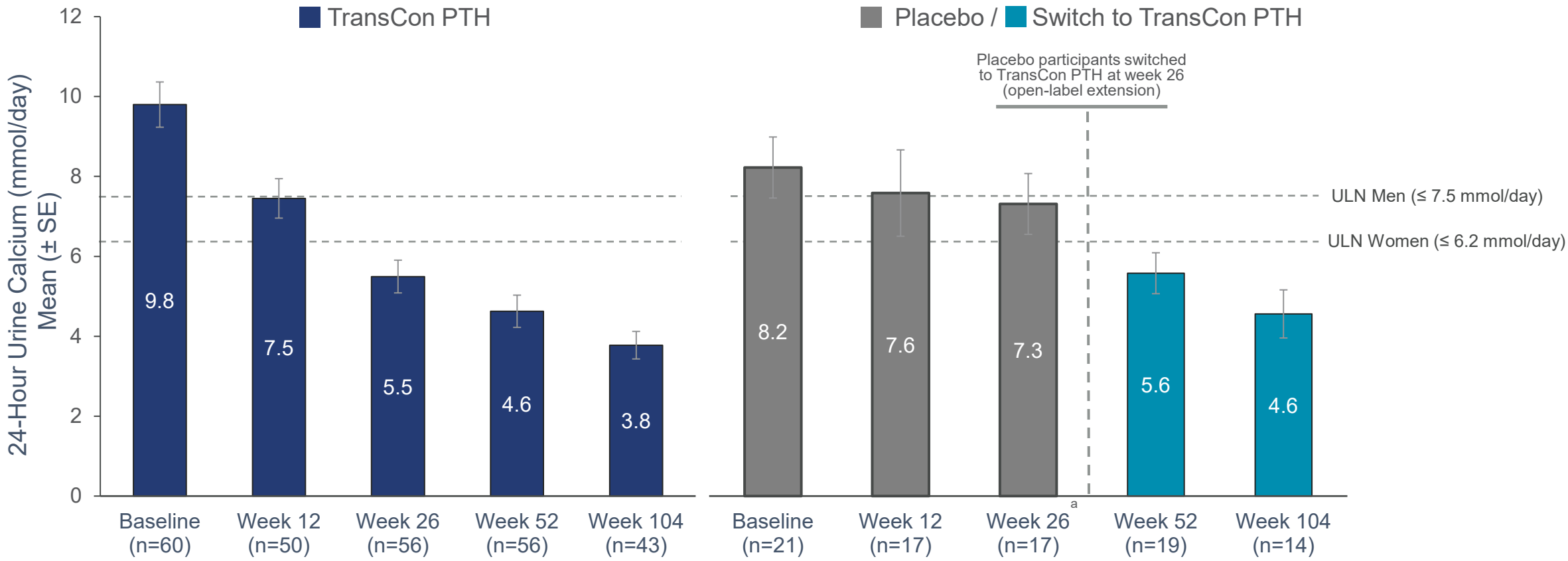
TransCon PTH treatment was associated with clinically meaningful increases ≥ 5 mL/min/1.73 m^2 in eGFR within 26 weeks that were sustained through week 104 of the PaTHway trial

Wk, week.

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

24-Hour Urine Calcium Excretion Through Week 104

PaTHway TRIAL



Mean 24-hour urine calcium excretion normalized within 26 weeks and was maintained within the normal range through week 104 with TransCon PTH treatment

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

Summary of Adverse Events Through Week 104

PaTHway TRIAL

Treatment Emergent Adverse Events (TEAEs), n (%)	All Participants[a] N=80	Baseline eGFR < 60 mL/min/1.73 m^2 n=23	Baseline eGFR ≥ 60 mL/min/1.73 m^2 n=57
Any TEAE	75 (93.8)	22 (95.7)	53 (93.0)
Serious TEAE	14 (17.5)	6 (26.1)	8 (14.0)
Severity[b, c]			
Grade 1	36 (45.0)	9 (39.1)	27 (47.4)
Grade 2	29 (36.3)	10 (43.5)	19 (33.3)
Grade 3	9 (11.3)	3 (13.0)	6 (10.5)
Grade 4	1 (1.3)	0	1 (1.8)
Related TEAE	44 (55.0)	13 (56.5)	31 (54.4)
Serious related TEAE	2 (2.5)	1 (4.3)	1 (1.8)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization	6 (7.5)	4 (17.4)	2 (3.5)
TEAE leading to discontinuation of trial[d]	1 (1.3)	0	1 (1.8)
TEAE leading to death[d]	1 (1.3)	0	1 (1.8)

- Most TEAEs were mild or moderate (grades 1-2) and were reported at similar rates across baseline eGFR levels
- No cases of nephrolithiasis were reported with TransCon PTH treatment

[a]Includes TEAEs occurring on or after the first dose of TransCon PTH in the Safety Analysis Population (pts who received ≥1 dose of TransCon PTH): 104 weeks of exposure for the TransCon/TransCon group (n=61) and 78 weeks of exposure for the Placebo/TransCon group (n=19); [b]Participants are displayed for the highest severity category only; [c]Grade 1 = mild, Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening. [d]One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment.

Conclusions

PaTHway TRIAL

Treatment with TransCon PTH was associated with significant and sustained improvement in renal function, as measured by eGFR, in adults with chronic hypoparathyroidism

- This post hoc analysis of the phase 3 PaTHway trial through week 104 suggests that PTH replacement therapy with TransCon PTH and independence from conventional therapy (active vitamin D and calcium) may not only preserve but improve renal function in adults with hypoparathyroidism
- Clinically meaningful increases in eGFR ≥ 5 mL/min/1.73m^2 were observed in 61% of participants and 44% of participants had an increase in eGFR ≥ 10 mL/min/1.73m^2 at week 104
- Participants with baseline eGFR < 60 mL/min/1.73m^2 had numerically higher increases in eGFR, suggesting that TransCon PTH treatment may be particularly beneficial to adults with chronic hypoparathyroidism who have impaired renal function
- No cases of nephrolithiasis were reported with TransCon PTH treatment and no new safety signals were identified
- Investigation of proteinuria and other biochemical parameters is warranted to further understand the potential mechanisms of the observed results