Sustained Improvement in Renal Function With Palopegteriparatide in Adults With Chronic Hypoparathyroidism: Three-Year Results From the PaTH Forward and PaTHway Trials

Presenter: Isavella Tryfonos

Affiliation: Nephrology Department of General Hospital of Athens "Hippocratio"

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

[1]Albany Medical College and Albany VAMC, Albany, NY, USA; [2]Rigshospitalet, Copenhagen, Denmark; [3]Aarhus University Hospital, Aarhus, Denmark; [4]McMaster University, Hamilton, ON, Canada; [5]Mayo Clinic, Rochester, MN, USA; [6]University of Pisa, Department of Clinical and Experimental Medicine, Endocrine Unit, Pisa Italy; [7]NorthShore University Health System-University of Chicago Pritzker School of Medicine, Chicago, IL; [8]University of California, San Francisco and VA Medical Center, San Francisco, CA, USA; [9]Spokane Osteoporosis and Endocrinology, Arthritis Northwest Research, Spokane, WA, USA;[10]Columbia University, New York, NY, USA; [11]Fondazione Policlinico Campus Bio-medico and Unit of Endocrinology and Diabetes, Campus Bio-medico University, Rome, Italy; [12]CHU de Québec-Université Laval Research Centre and Department of Medicine, Université Laval, Quebec City, QC, Canada; [13]Technische Universität Dresden Medical Center, Dresden, Germany; [14]Ascendis Pharma Inc, Palo Alto, CA, USA.

Presenter’s Disclosure

- Nothing to declare

Background

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

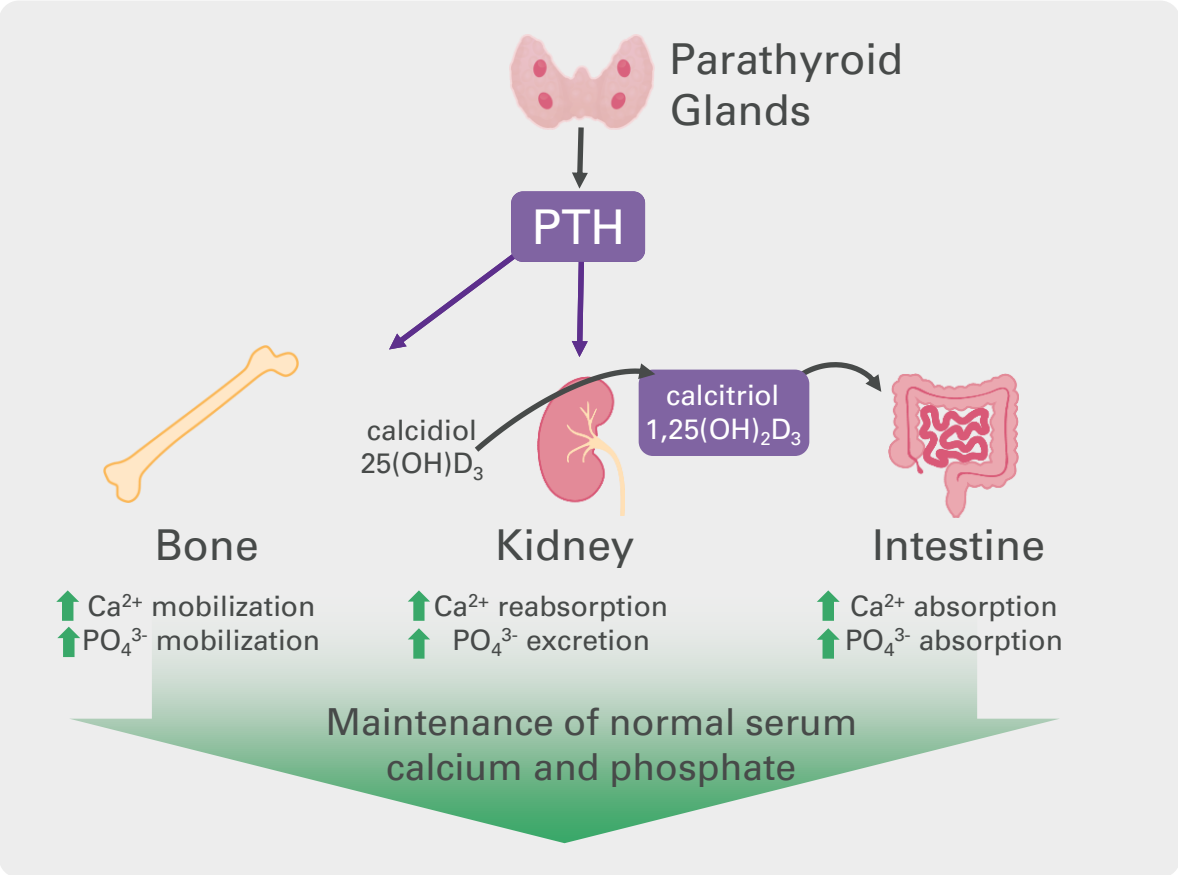
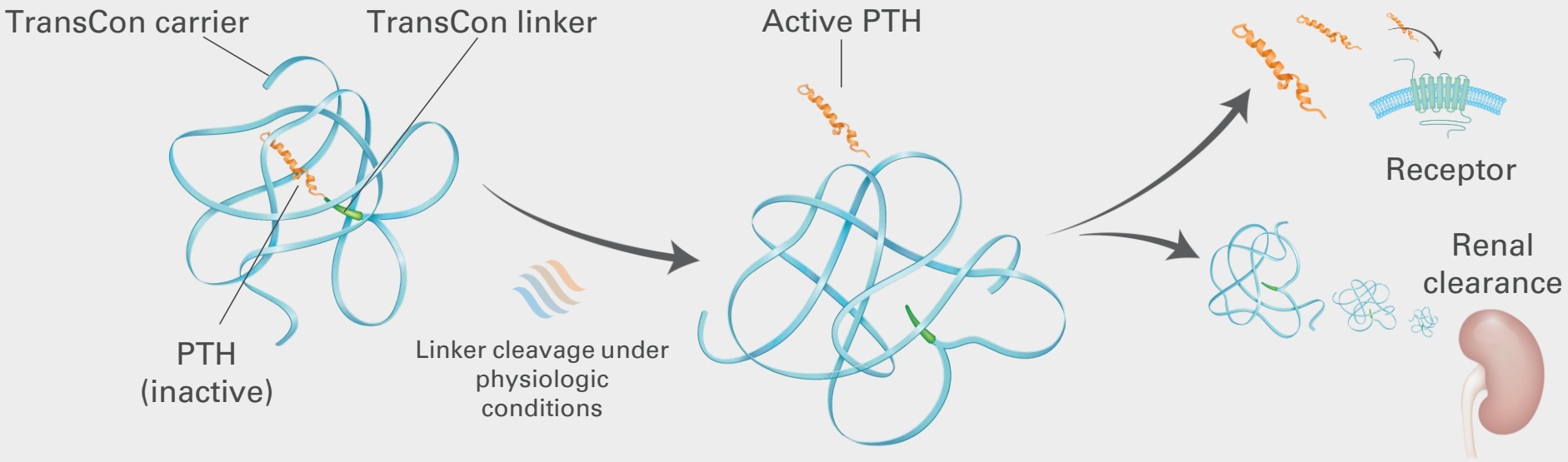


Figure adapted from Shoback D. *N Engl J Med.* 2008;359:391-403.[7]

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. 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



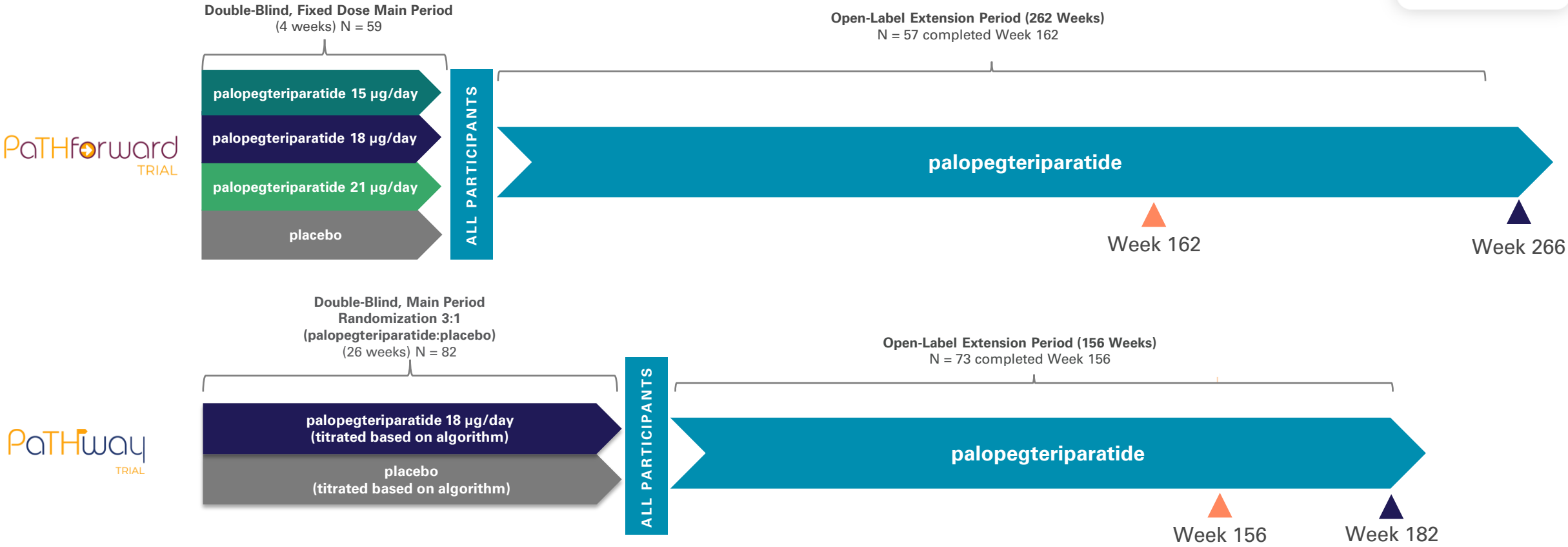
- Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, that provides active PTH within the physiological range for 24 hours per day[1,2]
- Palopegteriparatide has received regulatory approval in the EU[a], US[b] and several other countries[3-6]

[a]Indicated for the treatment of adults with chronic hypoparathyroidism. [b] Indicated for the treatment of hypoparathyroidism in adults.
PTH, parathyroid hormone; TransCon, transient conjugation

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. 3. YORVIPATH® [package insert]. Princeton, NJ: Ascendis Pharma Endocrinology, Inc.; 2024; 4. YORVIPATH® [summary of product characteristics]. Hellerup, Denmark: Ascendis Pharma Bone Diseases A/S; 2024; 5. Yorvipath (palopegteriparatide). Summary of Product Characteristics (SPC). electronic Medicines Compendium (emc); 2025. Available from emc (UK); 6. Yorvipath (palopegteriparatide). Australian Product Information (PI). 2025. Available from Therapeutic Goods Administration (TGA)

Methods

Schematics of Trial Designs Used in Combined Analysis



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

Combined Renal Analysis Study

- Changes in eGFR from baseline
- Proportion of participants with increase in eGFR ≥5 mL/min/1.73 m^2
- Levels of 24-hour urinary calcium

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; eGFR, estimated glomerular filtration rate
Analyses include only participants who received at least one dose of palopegteriparatide. Analyses were performed by time since the first dose of active drug.
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Baseline Demographics and Disease Characteristics

	Baseline GFR < 60 mL/min/1.73 m² (N=41)	Baseline GFR ≥ 60 mL/min/1.73 m² (N=98)	All participants (N = 139)
Mean age, years (SD)	52 (12)	48 (12)	49 (12)
Female, n (%)	33 (80)	78 (80)	111 (80)
Postmenopausal, n (%)	13 (39)	26 (33)	39 (35)
Race, n (%) White	39 (95)	89 (91)	128 (92)
Geographic region, n (%)			
North America	28 (68)	60 (61)	88 (63)
Europe	13 (32)	38 (39)	51 (37)
Mean eGFR*, mL/min/1.73 m² (SD)	51 (8)	76 (13)	69 (17)
Cause of hypoparathyroidism, n (%)			
Acquired from neck surgery	33 (80)	83 (85)	116 (84)
Autoimmune disease	0 (0)	2 (2)	2 (1)
Idiopathic disease	6 (15)	11(11)	17(12)
Intrinsic genetic defects of parathyroid glands	1 (2)	2 (2)	3 (2)
Other	1 (2)	0 (0)	1 (1)
Median duration of hypoparathyroidism, years (range)	13 (1-56)	8 (1-39)	9 (1-56)
Baseline hypoparathyroidism supplements, mean TDD			
Elemental calcium (mg)	2091.9 (n=38)	1769.8 (n=96)	1861.2 (n=134)
Calcitriol (µg)	0.8 (n=33)	0.8 (n=81)	0.8 (n=114)
Alfacalcidol (µg)[a]	2.4 (n=8)	2.4 (n=17)	2.4 (n=25)
Cholecalciferol/vitamin D3 (µg)	67.3 (n=20)	64.2 (n=59)	65.0 (n=79)
Magnesium (mg)	666.4 (n=13)	587.6 (n=37)	608.1 (n=50)

*Calculated according to the Modified Diet in Renal Disease Equation (MDRD): eGFR (mL/min/1.73 m²) = 175 × (serum creatinine mg/dL)-1.154 × (age)-0.203 × 0.742 [if female] × 1.212 [if Black race]
[a]The conversion from alfacalcidol to calcitriol was done using 2:1 conversion factor, as per reference Saha S, et al. *J Clin Endocrinol Metab.* 2021;106(7):2092-2102.
Numbers may not add up to 100 due to rounding effect.
SD, standard deviation; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; TDD, total daily dose
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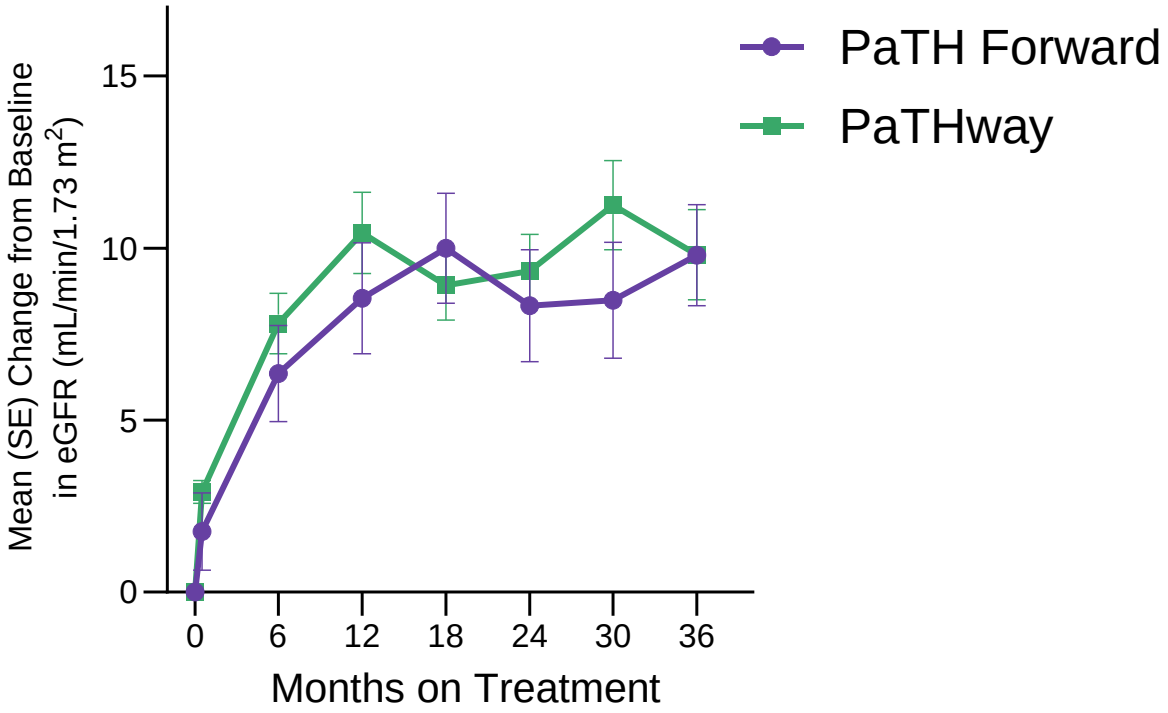
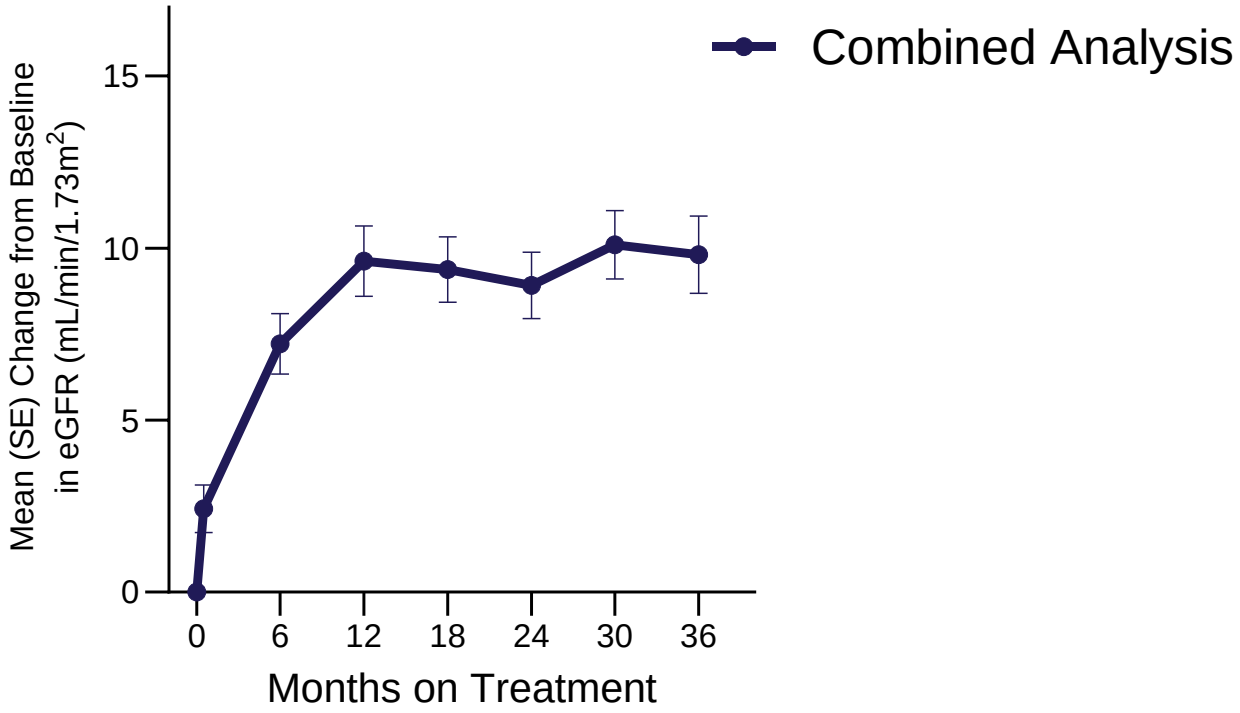
Results

Improvements in eGFR: Combined Analysis





PaTH Forward: eGFR Slope Change (mL/min/1.73 m^2/year):
0-6 Months, **12.47**; 6-36 Months, **0.99**
PaTHway: eGFR Slope Change (mL/min/1.73 m^2/year):
0-6 Months, **15.64**; 6-36 Months, **0.86**

Combined Analysis: eGFR Slope Change (mL/min/1.73 m^2/year):
0-6 Months, **14.33**; 6-36 Months, **0.89**

eGFR, estimated glomerular filtration rate; SE, standard error

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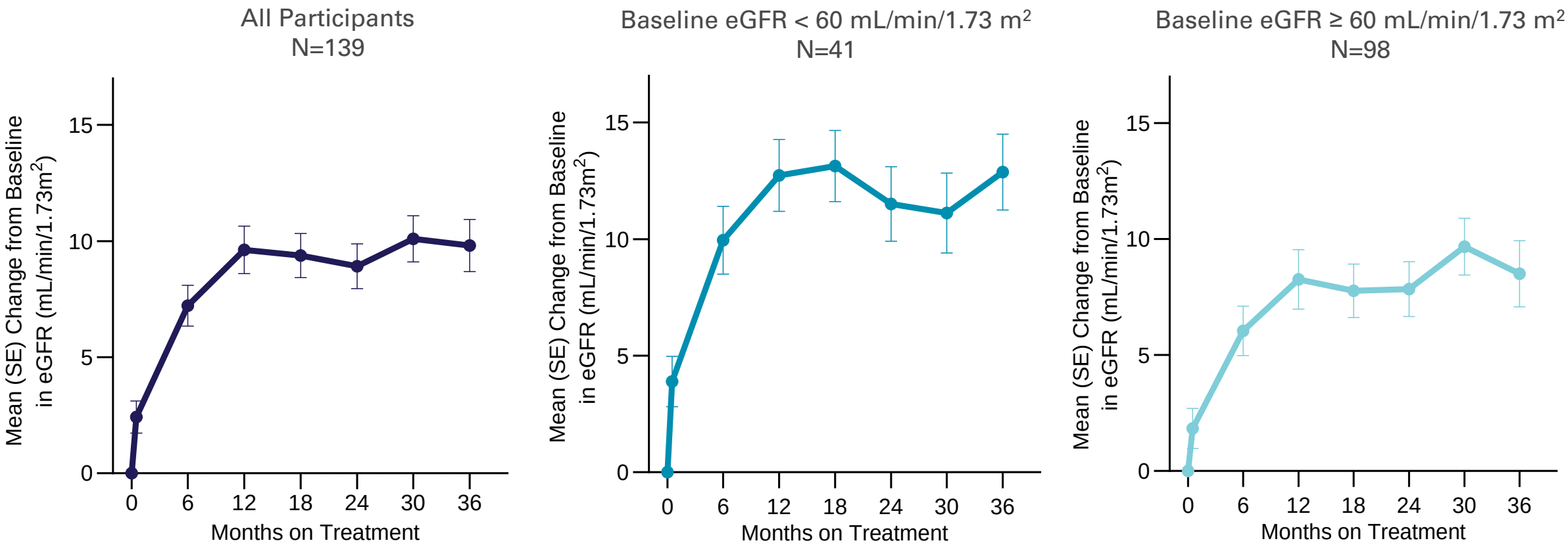
Sustained Improvements in eGFR From Baseline



A numerically greater improvement was observed in participants with lower baseline eGFR at month 36

eGFR, estimated glomerular filtration rate; SE, standard error
All Participants: eGFR Slope Change (mL/min/1.73 m²/year): 0-6 Months, **14.33**; 6-36 Months, **0.89**
Baseline eGFR < 60 mL/min/1.73 m²: eGFR Slope Change (mL/min/1.73 m²/year): 0-6 Months, **19.93**; 6-36 Months, **0.57**
Baseline eGFR ≥ 60 mL/min/1.73 m²: eGFR Slope Change (mL/min/1.73 m²/year): 0-6 Months, **11.98**; 6-36 Months, **1.06**
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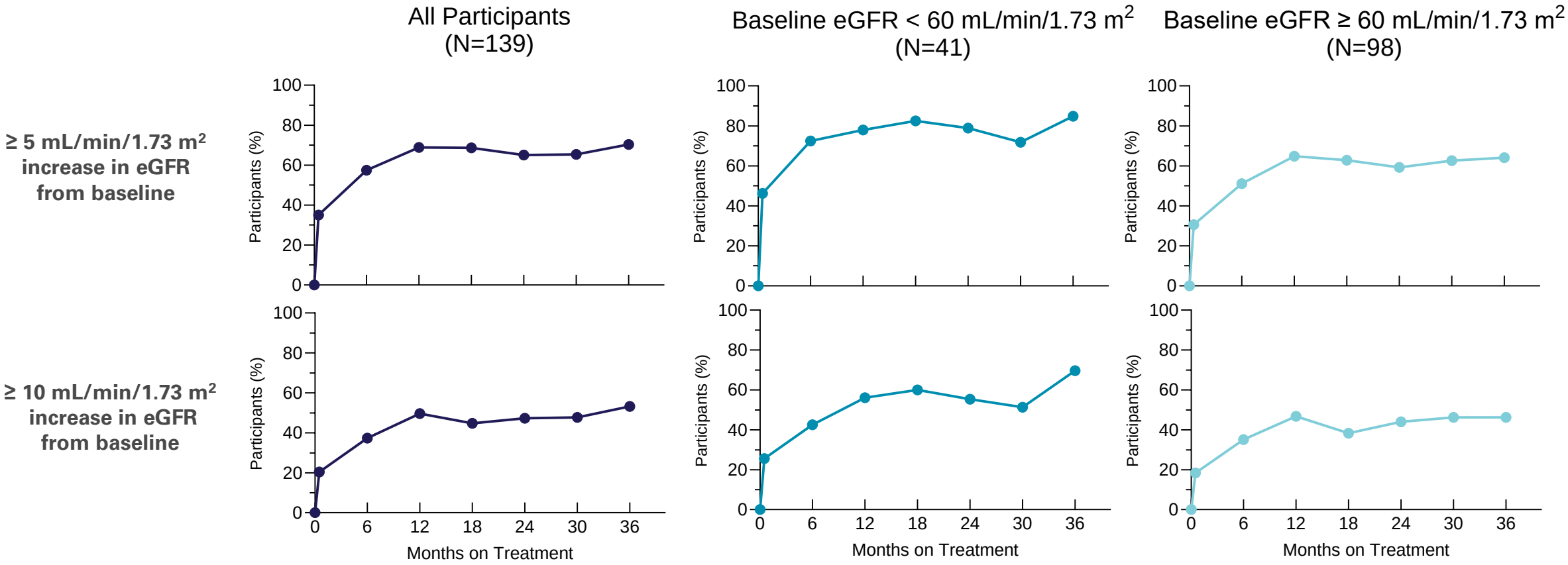
Proportion of Participants With Clinically Meaningful Increases in eGFR



In 70.3% of all participants, sustained, clinically meaningful improvement in eGFR was observed at month 36[1,2]

eGFR, estimated glomerular filtration rate

Only 1 participant exceeded the decline in eGFR outcome with a reduction ≥ 30% from baseline of ≥ 2 consequent visits for at least 3 months (90 days) apart. This was secondary to nephrectomy due to malignancy.

[a]Clinically meaningful increases in eGFR were those ≥ 5 mL/ min / 1.73 m^2.

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. 3. Gosmanova E, et al. Presented at: American Society of Nephrology (ASN) 2025: November 5-9: Houston, TX.

High Proportion of Participants Independent From Conventional Therapy at 3 Years

	All Participants
Number of participants with complete data at Year 3	**129**
Met multi-component efficacy endpoint criteria, n (%)	**110 (85%)**
•Normal albumin-adjusted serum calcium, n (%)[a]	**118 (91%)**
•Independence from active vitamin D, n (%)[b]	**128 (99%)**
•Independence from therapeutic doses of calcium, n (%)[b]	**121 (94%)**

[a]Normal calcium range: 8.3-10.6 mg/dL. [b]Independence from conventional therapy defined as no active vitamin D and ≤600 mg/day elemental calcium.
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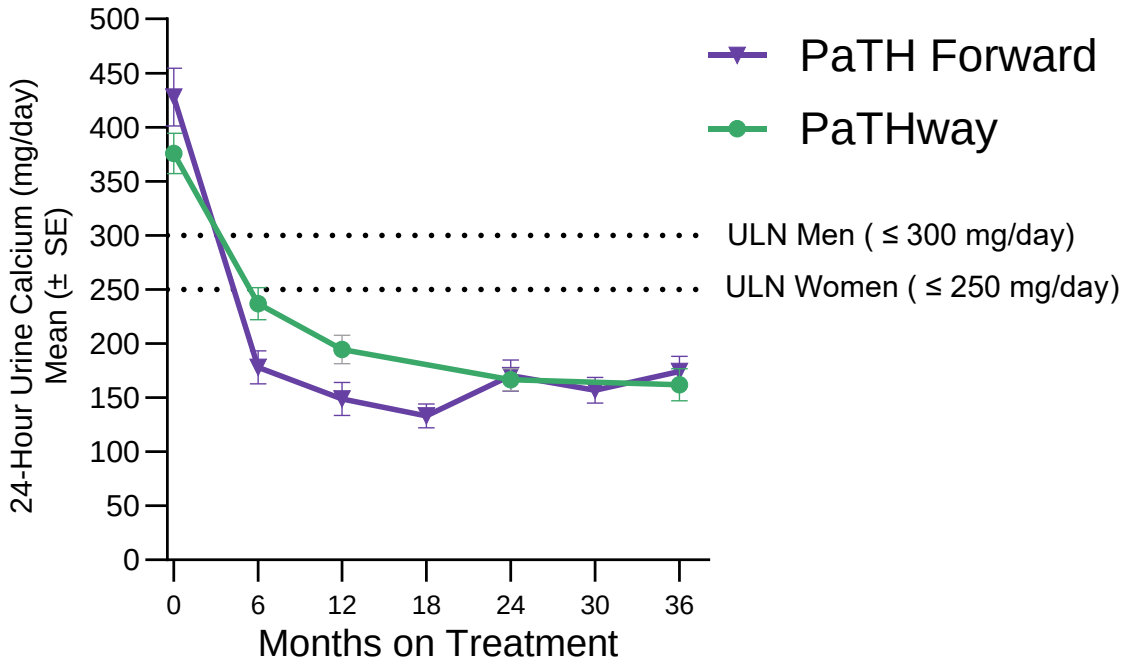
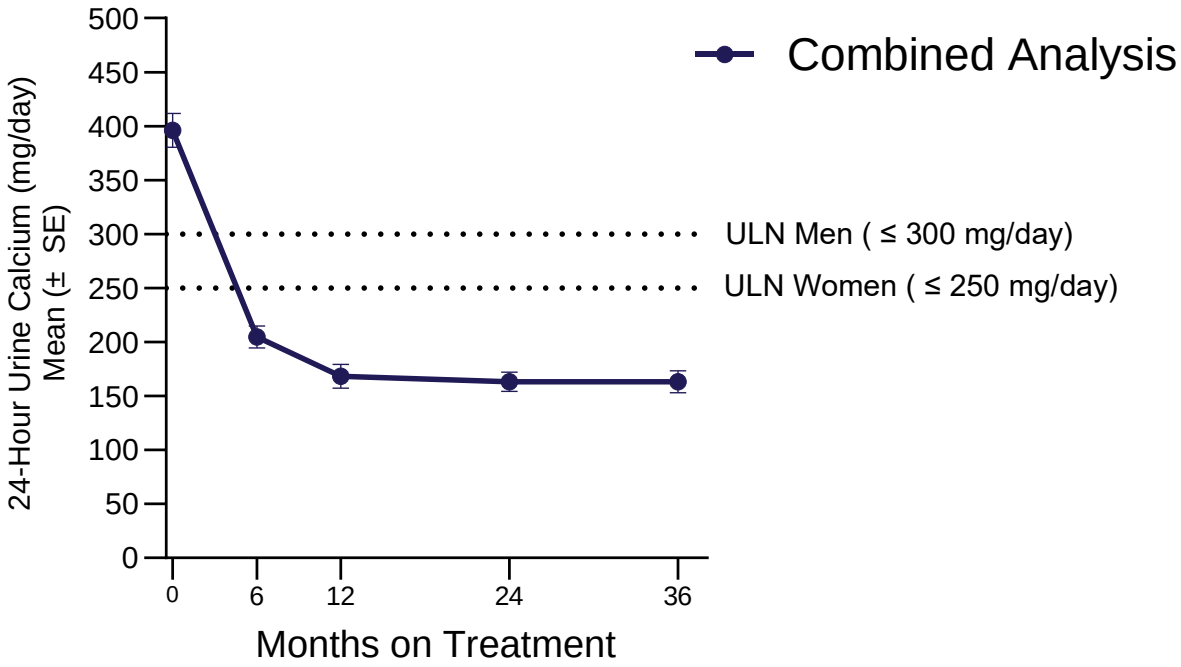
Normalization of 24-Hour Urinary Calcium Through Year 3 of PaTH Forward and PaTHway





ULN, upper limit of normal; SE, standard error
Values reflect total study population with data available from baseline and corresponding subsequent visits.
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Summary of Adverse Events Through Year 3

Treatment Emergent Adverse Events (TEAEs), n (%)	All Participants N=139
Any TEAE	133 (95.7%)
Serious TEAE	26 (18.7%)
Related TEAE	72 (51.8%)
Serious related TEAE	2 (1.4%)
TEAE related to hyper- or hypocalcemia leading to ER/urgent care visit and/or hospitalization	6 (4.3%)
TEAE leading to discontinuation of study drug[a]	3 (2.2%)
TEAE leading to discontinuation of trial[b]	1 (0.7%)
TEAE leading to death[b]	1 (0.7%)

Treatment-related TEAEs occurring at a rate of ≥ 5% among all participants (N=139) included:

- Injection site reaction (15.1%)
- Hypercalcemia (10.8%)
- Headache (9.4%)
- Hypocalcemia (7.9%)
- Nausea (7.9%)

Most TEAEs were classified as mild or moderate[c]

TEAE, treatment-emergent adverse event
[a]Includes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (participants who received ≥1 dose of palopegteriparatide): [a]TEAEs leading to treatment discontinuation were deemed unrelated to study drug. [b]One participant had a TEAE (fatal cardiac arrest unrelated to study drug) leading to discontinuation of the trial and death during blinded treatment. [c]Classified using the World Health Organization toxicity grading scale (1=mild, 2=moderate, 3=severe, 4=life-threatening)
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Author’s Conclusions

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- Clinically meaningful early improvements in eGFR with palopegteriparatide observed in PaTH Forward and PaTHway were sustained through Year 3

- The greatest increases in eGFR were observed in the first 6 months, with a continued upward trend thereafter
- Reductions in 24-hour urinary calcium excretion were observed and maintained within the normal range through Year 3
- Palopegteriparatide for the treatment of hypoparathyroidism maintained safety and efficacy through Year 3

eGFR, estimated glomerular filtration rate
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