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

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Conclusion

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.

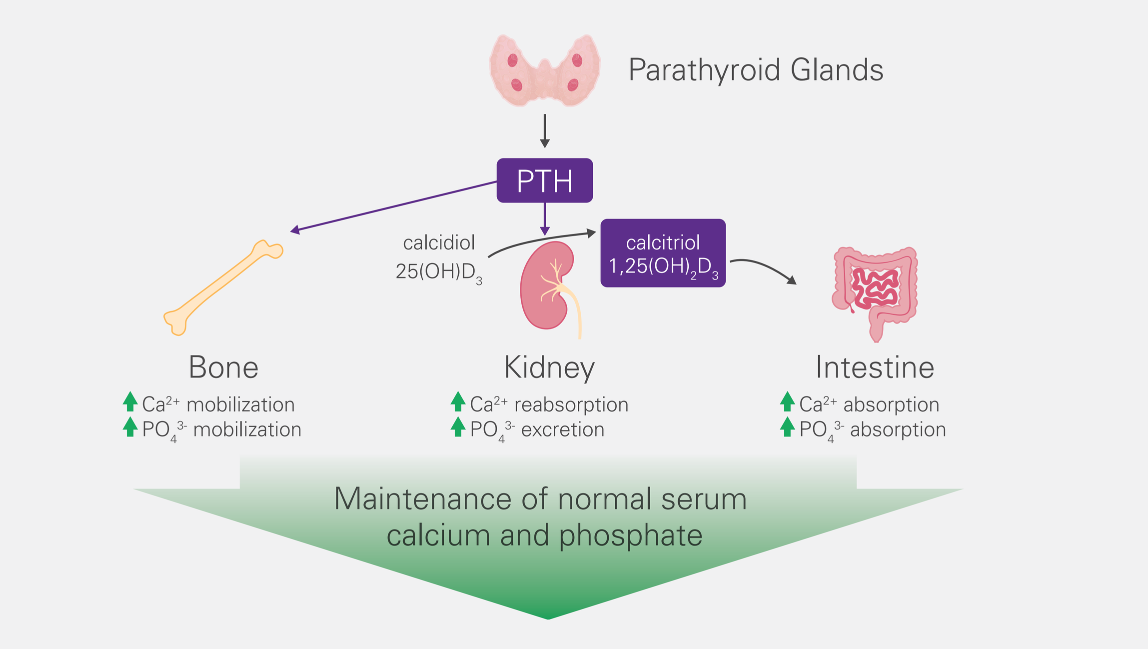
Reductions in 24-hour urinary calcium excretion were observed and maintained within the normal range through Year 3.

Palopegteriparatide for the treatment of hypoparathyroidism maintained safety and efficacy through Year 3.

Background

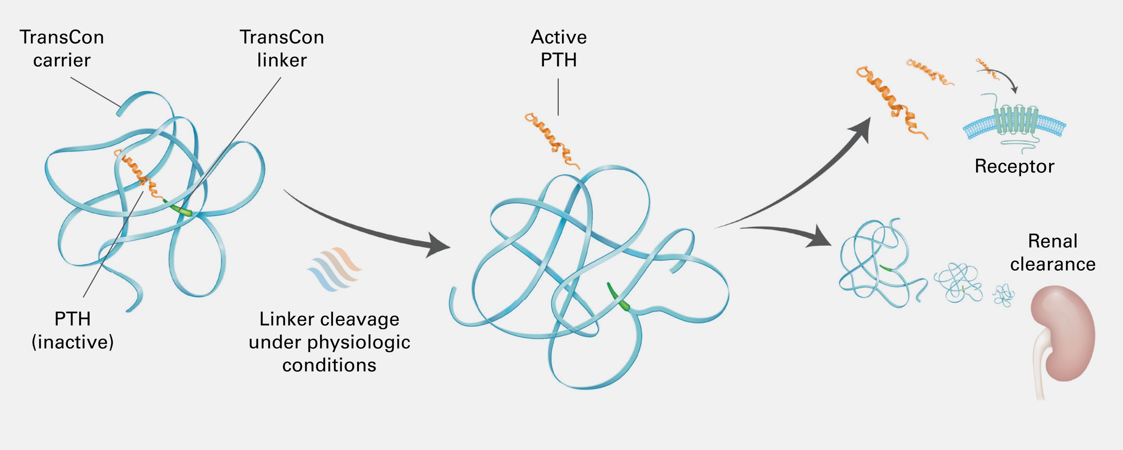
- An intact PTH axis maintains normal serum and urine calcium and phosphate homeostasis[1,2,3]
- PTH is the primary regulator of calcium/phosphate balance, acting directly on bone and kidney, and indirectly on the intestine[4,5]
- Conventional therapy for hypoparathyroidism (active vitamin D (calcitriol) 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 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

Background

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

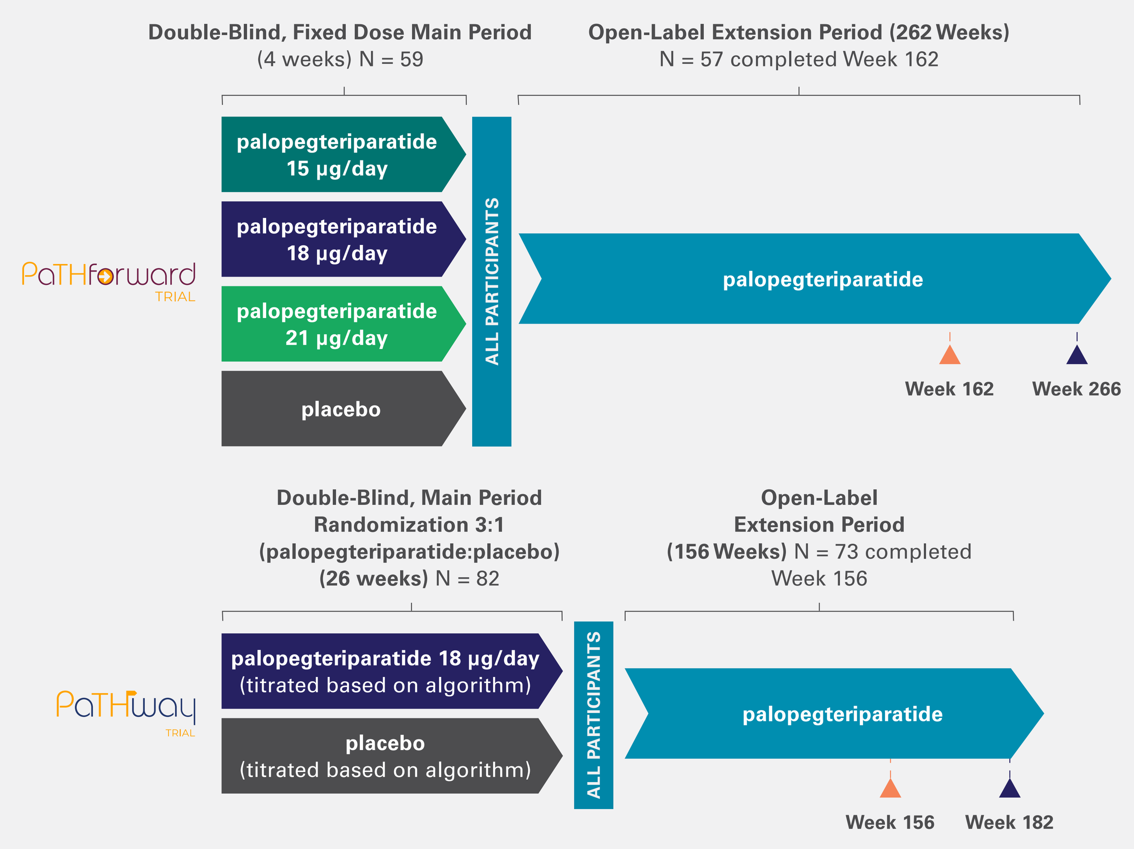

TransCon carrier
TransCon linker
Active PTH
Receptor
Renal clearance
PTH (inactive)
Linker cleavage under physiologic conditions

- 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, EU, and several other countries[a,b]

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

Methods

Figure 3: **Schematics of Trial Designs Used in Combined Analysis**


Double-Blind, Fixed Dose Main Period
(4 weeks) N = 59
Open-Label Extension Period (262 Weeks)
N = 57 completed Week 162
PaTHforward
TRIAL
palopegteriparatide 15 µg/day
palopegteriparatide 18 µg/day
palopegteriparatide 21 µg/day
placebo
ALL PARTICIPANTS
palopegteriparatide
Week 162
Week 266
Double-Blind, Main Period
Randomization 3:1
(palopegteriparatide:placebo)
(26 weeks) N = 82
Open-Label
Extension Period
(156 Weeks) N = 73 completed
Week 156
PaTHway
TRIAL
palopegteriparatide 18 µg/day
(titrated based on algorithm)
placebo
(titrated based on algorithm)
ALL PARTICIPANTS
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

Combined Renal Analysis Study
- Changes in eGFR from baseline
- Proportion of participants with increase in eGFR ≥ 5 mL/min/1.73 m²
- Levels of 24-hour urinary calcium

Note: Analyses include only participants who received at least one dose of palopegteriparatide. Analyses were performed by time since the first dose of active drug.

Methods

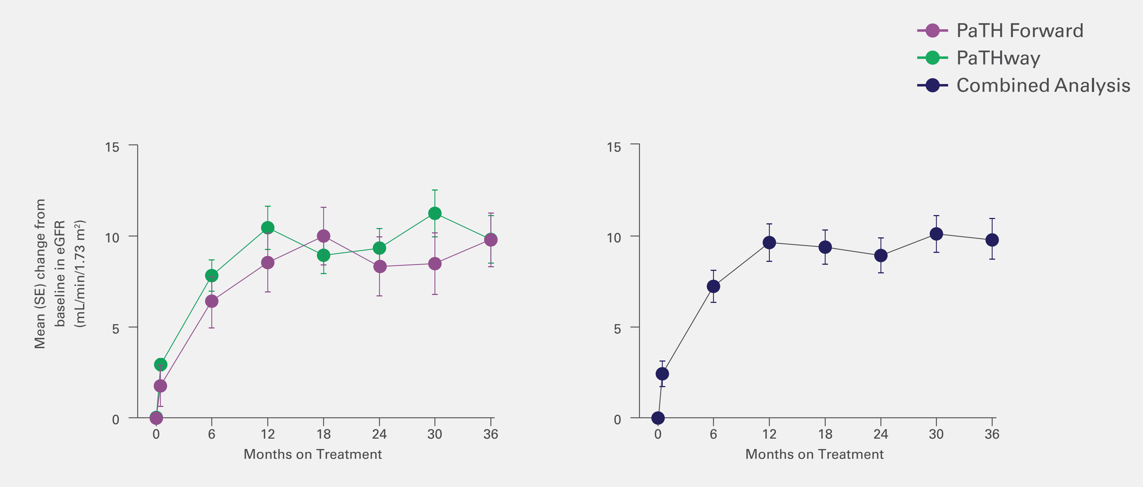
Table 1: **Baseline Demographics and Disease Characteristics**

Variable	Statistic or Category	Baseline GFR < 60 mL/min/1.73 m²	Baseline GFR ≥ 60 mL/min/1.73 m²	All Participants
		(N = 41)	(N = 98)	(N = 139)
Mean age, years (SD)		52 (12)	48 (12)	49 (12)
Sex, n (%)	Female	33 (80)	78 (80)	111 (80)
	Postmenopausal	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)	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)

Note: Numbers may not add to 100% due to rounding.
*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].

Results

Figure 4: **Improvements in eGFR: Combined Analysis**


PaTH Forward
PaTHway
Combined Analysis
Mean (SE) change from baseline in eGFR (mL/min/1.73 m²)
Months on Treatment

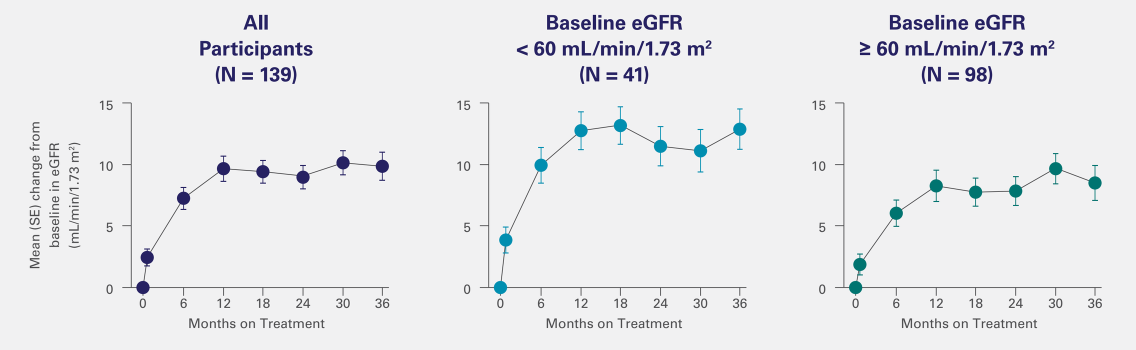
PaTH Forward
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **12.47**
- 6-36 Months: **0.99**

PaTHway
eGFR Slope Change (mL/min/1.73 m²/year)
- 0-6 Months: **15.64**
- 6-36 Months: **0.86**

Combined Analysis
eGFR Slope Change (mL/min/1.73 m²/year):
- 0-6 Months: **14.33**
- 6-36 Months: **0.89**

Results

Figure 5: **Sustained Improvements in eGFR From Baseline**


All Participants (N = 139)
Baseline eGFR < 60 mL/min/1.73 m² (N = 41)
Baseline eGFR ≥ 60 mL/min/1.73 m² (N = 98)
Mean (SE) change from baseline in eGFR (mL/min/1.73 m²)
Months on Treatment

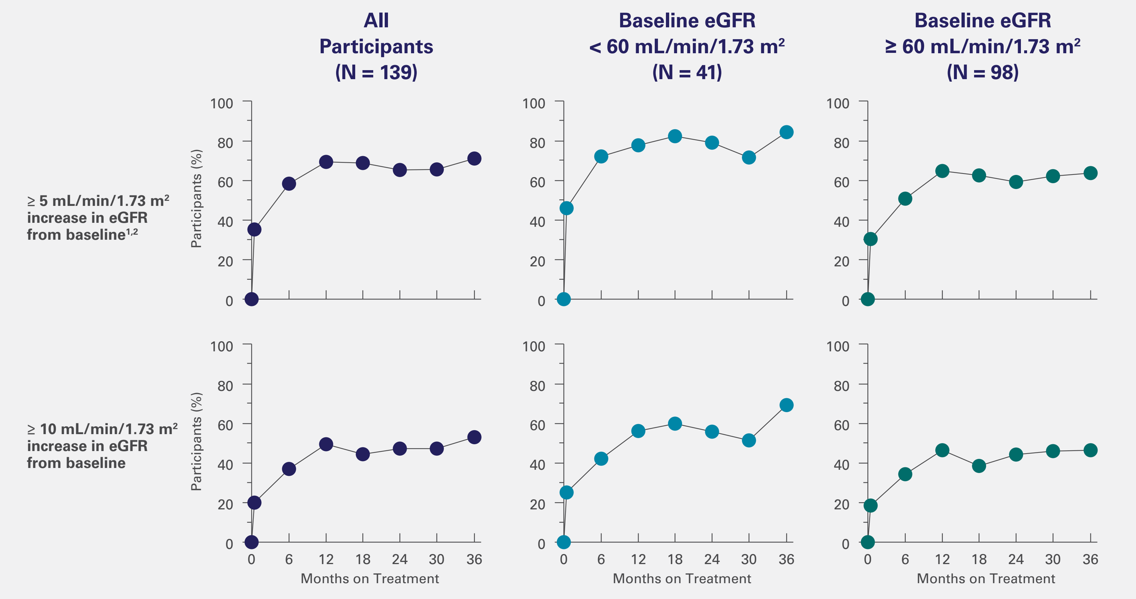
A numerically greater improvement was observed in participants with lower baseline eGFR at month 36.

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**

Figure 6: **Proportion of Participants With Clinically Meaningful Increases in eGFR**


All Participants (N = 139)
Baseline eGFR < 60 mL/min/1.73 m² (N = 41)
Baseline eGFR ≥ 60 mL/min/1.73 m² (N = 98)
≥ 5 mL/min/1.73 m² increase in eGFR from baseline[1,2]
≥ 10 mL/min/1.73 m² increase in eGFR from baseline
Participants (%)
Months on Treatment

In 70.3% of all participants, sustained, clinically meaningful improvement in eGFR was observed at month 36.[10,11]

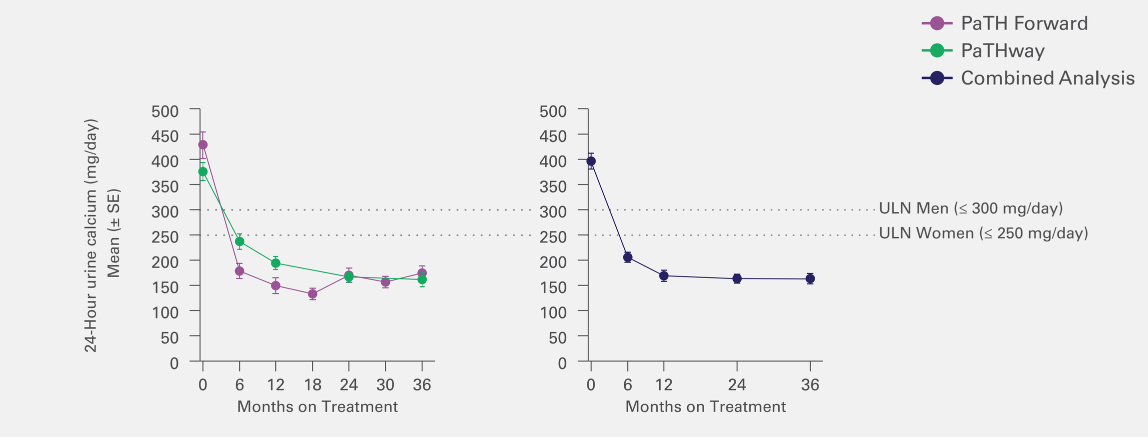
Note: Only 1 participant exceeded the decline in eGFR outcome with a reduction ≥ 30% from baseline of ≥ 2 consequent visits for at least 3 months (90 days) apart. This was secondary to nephrectomy due to malignancy.
[a]Clinically meaningful increases in eGFR were those ≥ 5 mL/ min / 1.73 m².

Table 2: **High Proportion of Participants Independent From Conventional Therapy at 3 Years**

Variable	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[a]	118 (91%)
Independence from active vitamin D[b]	128 (99%)
Independence from therapeutic doses of calcium[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.

Figure 7: **Normalization of 24-Hour Urinary Calcium Through Year 3 of PaTH Forward and PaTHway**


PaTH Forward
PaTHway
Combined Analysis
24-Hour urine calcium (mg/day) Mean (± SE)
ULN Men (≤ 300 mg/day)
ULN Women (≤ 250 mg/day)
Months on Treatment

Note: Values reflect total study population with data available from baseline and corresponding subsequent visits.

Table 3: **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]

[a]Includes TEAEs occurring on or after the first dose of palopegteriparatide in the Safety Analysis Population (participants who received ≥1 dose of palopegteriparatide): 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)

Abbreviations

AE = adverse event; **eGFR** = estimated glomerular filtration rate; **EU** = European Union; **MDRD** = Modified Diet in Renal Disease equation; **N** = number; **PTH** = parathyroid hormone; **SAE** = serious adverse event; **SD** = standard deviation; **SE** = standard error; **TDD** = total daily dose; **TEAE** = treatment emergent adverse event; **TransCon** = transient conjugation; **US** = United States

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