SUPPLEMENTAL MATERIAL

Safety and Efficacy of Tenapanor for Long-term Serum Phosphorus Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM)

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Supplemental Information 1. Selection of trial population

Inclusion criteria

A patient was eligible for trial participation if he/she met the following criteria:

1. Signed and dated informed consent before any study-specific procedures.

2. Males or females ≥18 years of age.

3. Females must have been non-pregnant, non-lactating, and fulfilled one of the following:

    a. Post-menopausal, defined as amenorrhea for ≥12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone (FSH) levels in the laboratory-defined post-menopausal range.

    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

    c. Use of acceptable contraceptive method: intrauterine device (IUD) with spermicide; a female condom with spermicide; contraceptive sponge with spermicide; an intravaginal system (*e.g.*, NuvaRing®); a diaphragm with spermicide; a cervical cap with spermicide; or oral, implantable, transdermal, or injectable contraceptives; sexual abstinence; or a sterile sexual partner.

4. Males must have agreed to avoid fathering a child (or donating sperm), and therefore, be either sterile or agreed to use, from the time of enrollment until 45 days after end of study, one of the following approved methods of contraception: a male condom with spermicide; a sterile sexual partner; use by female sexual partner of an IUD with spermicide, a female condom with spermicide, contraceptive sponge with spermicide, an intravaginal system (*e.g.*, NuvaRing), a diaphragm with spermicide, a cervical cap with spermicide, or oral, implantable, transdermal, or injectable contraceptives.

5. Chronic maintenance hemodialysis (HD) 3 times per week for ≥3 months or chronic maintenance peritoneal dialysis (PD) for a minimum of 6 months. If modality of dialysis had changed, patient must have met 1 of the 2 dialysis criteria above and been on the new modality of dialysis for a minimum of 1 month.

6. Stable vascular access as assessed by Investigator if on HD.

7. Kt/V_{urea} (a measure of dialysis dose) ≥1.2 at most recent measurement within 30 days before screening.

8. Prescribed and was taking ≥3 doses of phosphate binder per day. The prescribed dose should have been unchanged during the last 3 weeks before screening.

9. Serum phosphorus levels should have been between 4.0 and 8.0 mg/dl (inclusive) at screening analyzed at the central laboratory used in the study.

10. For enrollment in the study, patients must have had serum phosphorus (s-P) concentration of ≥6.0 mg/dl but <10.0 mg/dl and must have had an increase of ≥1.5 mg/dl versus pre-washout value after 1, 2, or 3 weeks washout of phosphate binders.

11. Able to have understood and complied with the protocol.

Exclusion criteria

A patient was not eligible for study participation if he/she met any of the exclusion criteria, or was discontinued at the discretion of the Investigator if he/she developed any of the following exclusion criteria during the study:

1. Severe hyperphosphatemia defined as s-P greater than 10.0 mg/dl on phosphate binders at any time point during clinical monitoring for the 3 preceding months before the screening visit.

2. Serum/plasma parathyroid hormone (PTH) >1200 pg/ml. The most recent value from patients' medical records should have been used.

3. Clinical signs of hypovolemia at enrollment as judged by the Investigator.

4. History of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome.

5. Scheduled for living donor kidney transplant, had plans to change to a different method of dialysis, home HD or plans to relocate to another center during the study period.

6. Any evidence of or treatment of malignancy within 1 year, excluding non-melanomatous malignancies of the skin.

7. Positive serology (hepatitis C or B infection, or human immunodeficiency virus) with evidence of significant hepatic impairment or white blood cell elevation according to the Investigator.

8. History of alcohol abuse, illicit drug use, significant mental illness, or any history of drug abuse or addiction within 12 months of study enrollment.

9. Life expectancy <12 months.

10. Use of an investigational agent within 30 days before screening.

11. Previous enrollment into this study.

12. Previous exposure to tenapanor.

13. Involvement in the planning and/or conduct of the study (applied to both Ardelyx/Clinical Research Organization [CRO] staff and/or staff at the study site).

14. If, in the opinion of the Investigator, the patient was unable or unwilling to fulfill the requirements of the protocol or had a condition which would have rendered the results uninterpretable.

Supplemental Information 2. Statistical methods for secondary endpoints and subgroup analysis

- We performed treatment comparison of the mean change in serum phosphorus concentration from period-specific baseline at each post-baseline visit during the randomized withdrawal period using a mixed-effects model for repeated measures, with geographic region, treatment, visit, and treatment-by-visit interaction as fixed effects; baseline serum phosphorus concentration of the randomized withdrawal period and baseline-by-visit as covariates; patient as random effect (efficacy and ITT analysis sets).

- Similar mixed-effects model for repeated measures analyses without covariates involving period-specific baseline (i.e. baseline of the randomized withdrawal period and baseline-by-visit) were performed for logarithmic-transformed relative changes from the end of the randomized treatment period in iFGF23 and cFGF23 concentrations at Week 4, Week 8 and Week 12. Back-transformed point estimates and 95% CIs were reported for both FGF23 endpoints.

- To assess the heterogeneity of treatment effects among subgroups, we analyzed the primary efficacy endpoint by age group (<45 years, ≥45 and <65 years, or ≥65 years), sex (male or female), race (self-defined white or Black/African American), geographic region (West, Central or East), baseline serum phosphorus concentration (<7.5 mg/dl or ≥7.5 mg/dl) and dialysis modality (hemodialysis or peritoneal dialysis).

Supplemental Information 3. Breach of Good Clinical Practice

- There was a serious breach of Good Clinical Practice identified at one site involved with the study.
- The Sponsor found several instances of significant non-compliance in the areas of drug accountability, failure to meet inclusion/exclusion criteria and missing/incomplete source data as required per the protocol. Participants associated with this site were excluded from all analysis sets:
  - two (1%) participants receiving sevelamer and two (0.5%) participants receiving tenapanor during the randomized treatment period
  - one (1%) participant receiving sevelamer, one (1%) participant receiving placebo and one (1%) participant receiving tenapanor during the randomized withdrawal period
  - one (1%) participant receiving sevelamer and two (1%) participants receiving tenapanor during the safety extension period.
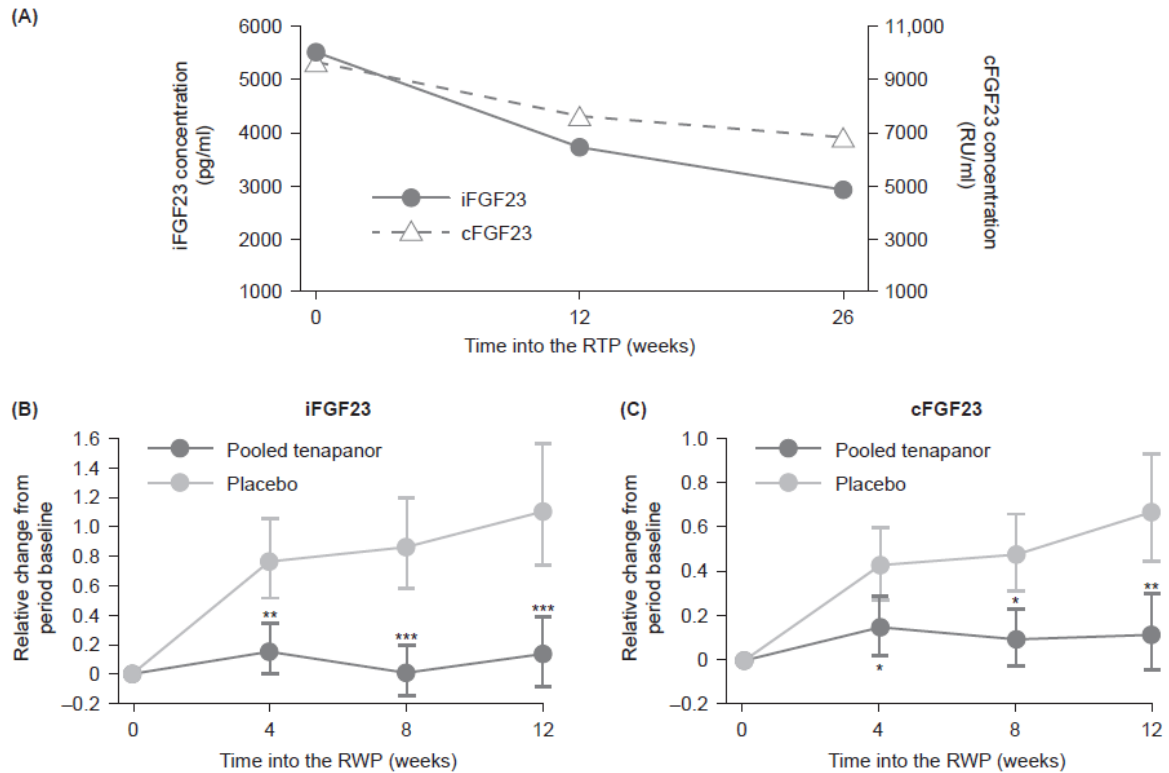
Supplemental Figure 1. Change in FGF23 concentrations over (A) the 26-week RTP and (B, C) the RWP. ***$P<0.0001$, **$P\leq0.0002$ and *$P\leq0.0102$ vs placebo. (A) Geometric mean concentrations of iFGF23 and cFGF23 over the RTP (ITT analysis set). The estimated mean relative change (95% CI) from period-specific baseline in (B) iFGF23 and (C) cFGF23 concentrations is shown at post-baseline visits during the RWP (efficacy analysis set). cFGF23, C-terminal FGF23; CI, confidence interval; FGF23, fibroblast growth factor 23; iFGF23, intact FGF23; ITT, intention-to-treat; RTP, randomized treatment period; RWP, randomized withdrawal period.
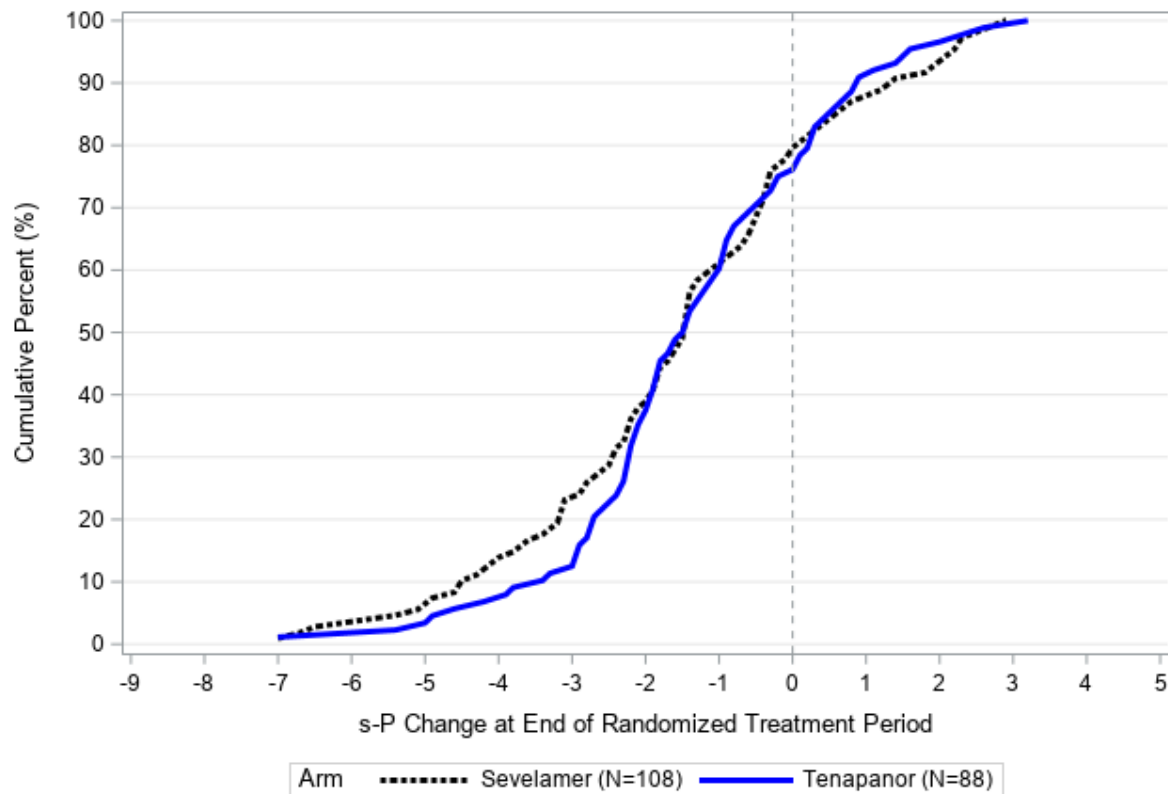
Supplemental Figure 2. Cumulative distribution function of change in serum phosphorus (mg/dl) at end of the randomized treatment period for participants in the ITT analysis set that received tenapanor continuously (blue) or sevelamer (black) throughout the 52-week study. The end of the RTP is defined as the last assessment during the RTP. ITT, intention-to-treat; RTP, randomized treatment period; s-P, serum phosphorus.

(A)

Subgroup	Number of subjects	LS mean change difference and 95% CI	LS mean change Placebo	LS mean change Tenapanor
All subjects	131		1.80	0.43
Age				
<45 years	24		1.52	0.12
≥45 years and <65 years	67		1.81	0.15
≥65 years	40		2.21	1.03
Sex				
Male	81		1.62	0.62
Female	50		2.02	0.06
Race				
White	59		1.88	0.43
Black or African American	66		2.03	0.67
Geographic region				
West	36		1.89	0.42
Central	40		2.41	0.62
East	55		1.21	0.21
Baseline s-P level of the RWP				
<7.5 mg/dl	125		1.87	0.53
≥7.5 mg/dl	6		0.20	−1.55
Type of dialysis				
Hemodialysis	119		1.90	0.56
Peritoneal dialysis	12		1.09	−0.94

Axis: −10 −8 −6 −4 −2 0 2 4 — Tenapanor better ← | → Placebo better

(B)

Subgroup	Number of subjects	LS mean change difference and 95% CI	LS mean change Placebo	LS mean change Tenapanor
All subjects	243		0.88	0.22
Age				
<45 years	38		0.86	0.63
≥45 years and <65 years	137		0.73	−0.12
≥65 years	68		1.64	0.75
Sex				
Male	150		0.95	0.30
Female	93		0.76	0.04
Race				
White	102		0.99	−0.02
Black or African American	124		0.70	0.30
Geographic region				
West	62		0.88	0.18
Central	84		1.21	0.16
East	97		0.60	0.25
Baseline s-P level of the RWP				
<7.5 mg/dl	208		1.26	0.46
≥7.5 mg/dl	35		−1.40	−1.17
Type of dialysis				
Hemodialysis	226		0.88	0.26
Peritoneal dialysis	17		1.00	−0.69

Axis: −4 −3 −2 −1 0 1 2 — Tenapanor better ← | → Placebo better

Supplemental Figure 3. LS mean difference in change in serum phosphorus (mg/dl) from baseline at end of the randomized withdrawal period for (A) the EAS and subgroups and (B) the ITT analysis set and subgroups. The LS means and 95% CIs are from an ANCOVA model with change from period-specific baseline in serum phosphorus concentration at the end of the RWP as a response variable; treatment and geographic region as factors; and period-specific baseline value as covariate. Baseline is defined as the measurement collected before the first dose of study drug during the RWP. The end of the RWP is defined as the last assessment during the RWP. ANCOVA, analysis of covariance; CI, confidence interval; EAS, efficacy analysis set; ITT, intention-to-treat; LS, least squares; RWP, randomized withdrawal period; s-P, serum phosphorus.

Supplemental Table 1. Schedule of visits in study

	Study day
Screening	
Visit 1	−21
Washout period	
Visit 2	−14
Visit 3	−7
Visit 4	−1
RTP	
Visit 5/randomization	1
Visit 6	8
Visit 7	15 ± 5
Visit 8	29 ± 5
Visit 9	57 ± 7
Visit 10	85 ± 7
Visit 11	120 ± 7
Visit 12	155 ± 7
Visit 13[a]	183 ± 7
RWP	
Visit 14[b]	197 ± 7
Visit 15	211 ± 7
Visit 16[b]	225 ± 7
Visit 17	239 ± 7
Visit 18[b]	253 ± 7
Visit 19[c]	267 ± 7
Safety extension period	
Visit 20	281 ± 7
Visit 21	309 ± 7
Visit 22	337 ± 7
Visit 23/End of Treatment	365 ± 7

RTP, randomized treatment period; RWP, randomized withdrawal period.
[a]Serves as baseline for RWP. [b]For participants on tenapanor or placebo only. [c]Serves as baseline for safety extension period.

Supplemental Table 2. Analysis of change from period-specific baseline in serum phosphorus concentration (mg/dl) by dose group at end of the randomized withdrawal period for the (A) EAS and (B) ITT analysis set

(A)

	PBO	TEN 10 mg bid	TEN 20 mg bid	TEN 30 mg bid
Period-specific baseline[a]				
n	68	6	22	35
Mean (SD)	5.08 (1.25)	5.57 (1.25)	5.04 (0.85)	5.26 (1.27)
Change from period-specific baseline to the end of the 12-week RWP[b]				
LS mean (SE)	1.81 (0.20)	0.79 (0.64)	0.85 (0.34)	0.11 (0.27)
95% CI LS mean	1.42, 2.19	−0.49, 2.06	0.18, 1.51	−0.41, 0.64
LS mean difference (SE) (vs placebo)		−1.02 (0.67)	−0.96 (0.39)	−1.69 (0.33)
95% CI LS mean difference (vs placebo)		−2.35, 0.31	−1.72, −0.20	−2.35, −1.04
P value (vs placebo)			0.0138	<0.0001

(B)

	PBO	TEN 10 mg bid	TEN 20 mg bid	TEN 30 mg bid
Period-specific baseline[a]				
n	123	14	32	74
Mean (SD)	5.80 (1.44)	6.44 (1.21)	5.56 (1.16)	5.99 (1.63)
Change from period-specific baseline to the end of the 12-week RWP[b]				
LS mean (SE)	0.88 (0.15)	0.56 (0.44)	0.35 (0.29)	0.10 (0.19)
95% CI LS mean	0.59, 1.18	−0.31, 1.42	−0.22, 0.92	−0.28, 0.47
LS mean difference (SE) (vs placebo)		−0.32 (0.46)	−0.53 (0.32)	−0.78 (0.24)

		−1.24, 0.59	−1.16, 0.11	−1.26, −0.30
95% CI LS mean difference (vs placebo)				
P value (vs placebo)			0.1047	0.0015

ANCOVA, analysis of covariance; bid, twice daily; CI, confidence interval; EAS, efficacy analysis set; ITT, intention-to-treat; LS, least squares; RWP, randomized withdrawal period; SD, standard deviation; SE, standard error.

[a]For the 12-week RWP, period-specific baseline was defined as the last measurement collected before the first dose of study drug during the 12-week RWP.

[b]The end of the 12-week RWP was defined as the last assessment during the 12-week RWP. Only dose groups with ≥15 participants in the EAS or ITT analysis set were included in statistical comparisons with placebo. The LS means, SEs, 95% CIs, and P values were from an ANCOVA model with treatment and geographic region as factors and period-specific baseline value as a covariate.

Supplemental Table 3. Summary of AEs during the 26-week randomized treatment period split by 13-week periods (safety analysis set)

	26-week randomized treatment period (weeks 1–13)		26-week randomized treatment period (weeks 14–26)	
	SC, *n*=137 *n* (%)	TEN, (*n*=419) *n* (%)	SC, *n*=137 *n* (%)	TEN *n*=419 *n* (%)
Participants with any AE	72 (53)	302 (72)	49 (36)	139 (33)
Participants with any drug-related AE	5 (4)	227 (54)	0 (0)	35 (8)
Participants with any SAE	20 (15)	48 (11)	18 (13)	39 (9)
Participants with any serious drug-related AE	0 (0)	3 (1)	0 (0)	0 (0)
Participants with any AE leading to death	0 (0)	1 (0.2)	0 (0)	0 (0)
Participants with any AE leading to study drug discontinuation	1 (1)	87 (21)	1 (1)	15 (4)
Participants with any drug-related AE leading to study drug discontinuation	0 (0)	77 (18)	0 (0)	11 (3)
AEs with incidence ≥2% by preferred term[a]				
Diarrhea	7 (5)	211 (50)	4 (3)	22 (5)
Nausea	4 (3)	9 (2)	0 (0)	6 (1)
Vomiting	3 (2)	10 (2)	2 (1)	4 (1)
Abdominal pain	4 (3)	2 (0.5)	1 (1)	0 (0)
Constipation	4 (3)	0 (0)	2 (1)	2 (0.5)
Gastro-esophageal reflux disease	3 (2)	1 (0.2)	0 (0)	4 (1)
Hyperphosphatemia	3 (2)	16 (4)	0 (0)	11 (3)
Hyperkalemia	5 (4)	8 (2)	1 (0.7)	12 (3)
Fluid overload	4 (3)	6 (1)	3 (2)	2 (0.5)
Pneumonia	2 (1)	3 (0.7)	5 (4)	1 (0.2)
Nasopharyngitis	4 (3)	5 (1)	0 (0)	3 (0.7)

Bronchitis	3 (2)	4 (1)	1 (0.7)	2 (0.5)
Upper respiratory tract infection	4 (3)	2 (0.5)	2 (1)	4 (1)
Fall	4 (3)	6 (1)	6 (4)	5 (1)
Arteriovenous fistula thrombosis	4 (3)	2 (0.5)	4 (3)	5 (1)
Arteriovenous fistula site complication	2 (1)	4 (1)	3 (2)	3 (0.7)
Cough	6 (4)	8 (2)	4 (3)	1 (0.2)
Pulmonary mass	3 (2)	0 (0)	2 (1)	0 (0)
Pain in extremity	3 (2)	3 (0.7)	2 (1)	0 (0)
Hypertension	3 (2)	9 (2)	6 (4)	7 (2)
Hypotension	4 (3)	5 (1)	2 (1)	0 (0)
Headache	3 (2)	6 (1)	1 (0.7)	2 (0.5)
Pyrexia	4 (3)	1 (0.2)	1 (0.7)	1 (0.2)
Drug-related AEs by preferred term[a]				
Diarrhea	2 (1)	208 (50)	0 (0)	20 (5)

AE, adverse event; SAE, serious adverse event; SC, sevelamer carbonate; TEN, tenapanor.
[a]AEs by preferred term listed here occurred in ≥2% participants overall in any treatment group and over the entire 26 weeks of the randomized treatment period.

It is important to note that direct comparisons of AE rates between tenapanor and sevelamer carbonate are not fully representative of treatment differences; SC was standard of care and the protocol specified that side effects in a participant's medical history were not considered AEs unless there was a change in duration or severity.

Supplemental Table 4. Summary of changes in clinically important laboratory parameters across study periods (safety analysis set)[a]

	Week 26 (randomized treatment period)	Week 38 (randomized withdrawal period)		Week 52/ end of study (safety extension period)
	TEN	PBO	TEN	TEN
Bicarbonate (mmol/l)	*n*=250	*n*=114	*n*=104	*n*=209
Mean change from baseline	0.40	0.90	0.70	0.60
SD	3.44	3.23	3.64	3.37
Magnesium (mg/dl)	*n*=250	*n*=114	*n*=104	*n*=209
Mean change from baseline	0.01	0.01	0.03	0.00
SD	0.34	0.28	0.29	0.31
Potassium (mmol/l)	*n*=240	*n*=111	*n*=101	*n*=200
Mean change from baseline	0.08	−0.12	0.15	0.00
SD	0.75	0.63	0.89	0.78
Sodium (mmol/l)	*n*=249	*n*=114	*n*=104	*n*=207
Mean change from baseline	−0.20	0.80	−0.60	−0.20
SD	3.25	2.65	4.36	3.54

PBO, placebo; SD, standard deviation; TEN, tenapanor.
[a]Data are shown for participants exposed to tenapanor, by actual treatment received during each study period.
Baseline is defined as the last measurement collected before the first dose of study medication in the study. *n* is the number of participants with values during the specified period.

Supplemental Table 5. Summary of changes in PTH (safety analysis set)[a]

	Week 26 (randomized treatment period)	Week 38 (randomized withdrawal period)		Week 52/ end of study (safety extension period)
	TEN	PBO	TEN	TEN
Entire safety analysis set				
PTH, intact (ng/l)	*n*=250	*n*=111	*n*=97	*n*=199
Median change from baseline	−11.5	6.0	−14.0	−17.0
Range	−990, 1232	−1149, 652	−796, 567	−1165, 792
Participants in the safety analysis set with PTH ≥600 ng/l at the start of PHREEDOM				
PTH, intact (ng/l)	*n*=49	*n*=27	*n*=17	*n*=40
Median change from baseline	−275.0	−194.0	−355.0	−239.0
Range	−990, 819	−1149, 652	−796, 223	−1165, 792

PBO, placebo; PTH, parathyroid hormone; TEN, tenapanor.
[a]Data are shown for participants exposed to tenapanor, by actual treatment received during each study period.
Baseline is defined as the last measurement collected before the first dose of study medication in the study. *n* is the number of participants with values during the specified period.