Kidney360

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

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Key Points

- Tenapanor is a first-in class inhibitor of NHE3 and acts *via* a nonphosphate-binding mechanism to reduce intestinal phosphate absorption.
- In the efficacy analysis set, patients randomized to tenapanor experienced a decrease in serum phosphate from 7.7 mg/dl to 5.1 mg/dl.
- Diarrhea was the only drug-related adverse event reported for more than 5% of patients and resulted in drug discontinuation in 16% of patients.

Abstract

Background Treating hyperphosphatemia is a tenet of dialysis care. This trial assessed the safety and efficacy of tenapanor for the management of hyperphosphatemia.

Methods In this 52-week phase 3 study (NCT03427125), participants receiving maintenance dialysis with both hyperphosphatemia (serum phosphate 6.0–10.0 mg/dl) and a 1.5 mg/dl increase after phosphate binder washout were randomized (3:1) to tenapanor 30 mg twice daily for 26 weeks (randomized treatment period) or sevelamer carbonate (52-week safety control). Participants completing 26 weeks of treatment with tenapanor were rerandomized (1:1) to tenapanor or placebo for 12 weeks (randomized withdrawal period), and were eligible to enter the 14-week safety extension period. With input from the US Food and Drug Administration, the primary efficacy end point was the difference in the change in serum phosphate from the end of the randomized treatment period to the end of the randomized withdrawal period, among participants who achieved ≥1.2 mg/dl decrease in serum phosphate during the randomized treatment period (efficacy analysis set). Efficacy was also evaluated in the intention-to-treat (ITT) analysis set.

Results Of 564 eligible participants randomized to receive tenapanor (n=423) or sevelamer carbonate (n=141) during the randomized treatment period, 255 (60%) in the tenapanor group subsequently were rerandomized to tenapanor (n=128) or placebo (n=127) during the randomized withdrawal period. In the efficacy analysis set (n=131), the difference in estimated mean change in serum phosphate level between tenapanor and placebo from the beginning to the end of the randomized withdrawal period was −1.4 mg/dl (P<0.0001); in the ITT analysis set (n=243), the estimated mean difference was −0.7 mg/dl (P=0.002). Loosened stools were the most frequently reported adverse event (53% during the randomized treatment period). Serious adverse events were reported more frequently for participants treated with sevelamer carbonate (16%–23% across the three study periods) compared with tenapanor (11%–17%).

Conclusions Tenapanor reduced serum phosphate concentrations and maintained control of serum phosphate in participants receiving maintenance dialysis, with an acceptable safety and tolerability profile.

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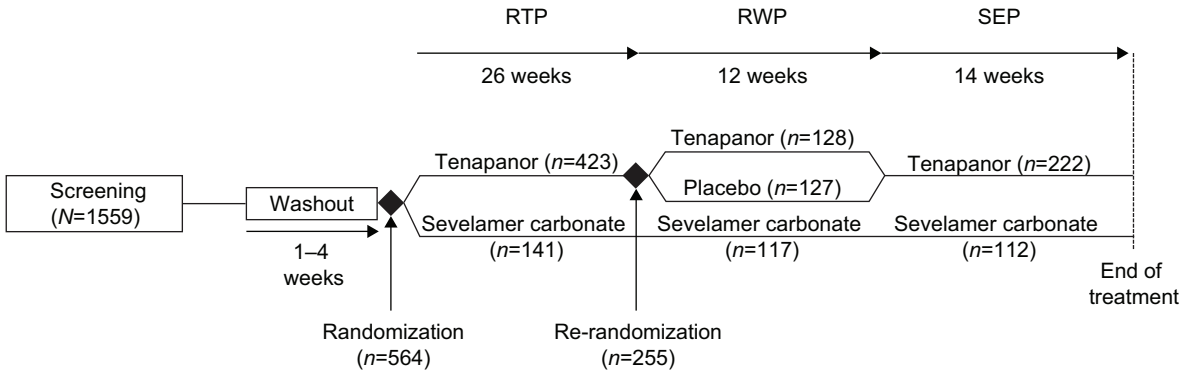

Figure 1. | **Overview of study design.** The safety analysis set included all participants who received at least one dose of the study drugs for the study period. RTP, randomized treatment period; RWP, randomized withdrawal period; SEP, safety extension period.

Introduction

Hyperphosphatemia is a common complication among patients receiving maintenance dialysis and is associated with dystrophic calcification (affecting vasculature and heart valves), fractures, cardiovascular mortality, and all-cause mortality (1–3). Current approaches to hyperphosphatemia management—increasing hemodialysis session length or frequency, dietary phosphate restriction, and phosphate binder therapy—are difficult to implement (4–7). Phosphate binder therapy is associated with poor gastrointestinal (GI) tolerability, frequent dosing, and a high pill burden (2,8). Adherence to a nutritionally appropriate diet with reduced phosphate content is challenging, owing in part to the absence of total phosphate content on food labels (5,6). Despite best efforts, most patients receiving dialysis are unable to consistently achieve target serum phosphate concentrations (4).

Tenapanor is a first-in-class phosphate absorption inhibitor. Whereas phosphate binders act by binding dietary phosphate to form insoluble complexes that pass through the GI tract, tenapanor blocks paracellular absorption of phosphate in the GI tract through local inhibition of the intestinal sodium–hydrogen exchanger 3 (NHE3) (9,10).

Inhibition of NHE3 transiently increases the intracellular proton concentration of cells lining the GI lumen and is proposed to induce a conformational change in tight junction proteins that reduces permeability specific to paracellular phosphate transport (9). The reduction in serum phosphate concentration that can result from targeted inhibition of paracellular phosphate transport is not available with current treatment options (9,11,12). Recent work has highlighted the potential of targeting this pathway to improve control of hyperphosphatemia (13–15).

In previous 4-week phase 2 and 8-week phase 3 studies, tenapanor significantly lowered serum phosphate concentration in participants receiving maintenance dialysis (16–18). In this study we report on the safety and efficacy of tenapanor when used for as long as 52 weeks for the management of hyperphosphatemia in participants receiving maintenance dialysis.

Materials and Methods

Study Design

PHREEDOM (ClinicalTrials.gov identifier: NCT03427125) was a multicenter, phase 3 trial comprising three periods: a 26-week open-label randomized treatment period, a 12-week double-blind placebo-controlled randomized withdrawal period, and a 14-week open-label safety extension period (Figure 1). We enrolled participants from 104 centers in the United States, starting in January 2018; the trial was completed in February 2020. Patients with a serum phosphate 4.0–8.0 mg/dl (inclusive) at the screening visit were eligible to enter the phosphate binder washout period of 1 to 4 weeks in duration. Patients whose serum phosphate had increased by ≥1.5 mg/dl during this period, and who had a measured serum phosphate ≥6.0 mg/dl and <10.0 mg/dl at the end of the washout period, were randomly assigned (3:1) to receive either tenapanor at a starting dose of 30 mg orally, twice daily for 26 weeks (randomized treatment period), or sevelamer carbonate (on the basis of standard of care) for 52 weeks. At the end of the randomized treatment period, we rerandomized (1:1) participants who completed the 26-week treatment with tenapanor to either continue to receive tenapanor treatment at the same dose, or switch to placebo for 12 weeks (randomized withdrawal period). On completion of, or discontinuation from, the randomized withdrawal period, all rerandomized participants were eligible to enter a 14-week safety extension period, wherein tenapanor treatment was provided.

To compare the rates of serious adverse events (SAEs) among the high-risk population enrolled in the study, we followed participants taking open-label sevelamer for the 52-week study as a control group for safety comparison only. Efficacy data are not presented for this group, because these participants received sevelamer as "standard of care." The US Food and Drug Administration (FDA) package insert was used for guidance on starting dose and dose adjustment. Sevelamer could be titrated up or down as needed; there was no upper dose limit specified in the protocol. In accordance with community standard of care, the protocol guidance recommended targeting a serum phosphate concentration <5.5 mg/dl in both treatment arms. The use of phosphate binders to treat hyperphosphatemia (other than sevelamer used in the safety control group) was prohibited.

For participants assigned to receive tenapanor, titration was permitted during the randomized treatment period and safety extension period. Investigators were permitted to titrate the tenapanor dose in 10 mg increments, down to

a minimum of 10 mg twice daily, or to increase tenapanor to a maximum dose of 30 mg twice daily, on the basis of serum phosphate concentration and GI tolerability. Participants receiving tenapanor or placebo were withdrawn from the study on the basis of predefined serum phosphate: ≤2.5 mg/dl at any time; ≥10.0 mg/dl at any time after week 2 of the randomized treatment period; ≥9.0 mg/dl for two consecutive visits during the randomized treatment period or safety extension period; or ≥9.0 mg/dl during the randomized withdrawal period. Because sevelamer is the standard of care, no specific discontinuation criteria were included in the protocol for this arm; however, reasons for discontinuation were recorded for all participants.

The trial was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before trial entry. All participating sites obtained independent Ethics Committee/Institutional Review Board approval.

Participants

Full inclusion and exclusion criteria used in this trial are listed in Supplemental Information 1. Men and women aged ≥18 years or older were eligible for randomization if they had received maintenance hemodialysis three times weekly for ≥90 days with a per-session Kt/V_{urea} of ≥1.2 within 30 days before screening or had received maintenance peritoneal dialysis for ≥6 months; were taking phosphate binders at least three times daily with stable dosing during the 3 weeks before screening; and had a serum phosphate 4.0–8.0 mg/dl inclusive, at either screening or rescreening. Participants may have been rescreened after ≥1 week if serum phosphate concentrations at screening were outside of the inclusion range and the participant had historical serum phosphate >4.5 mg/dl and <7.5 mg/dl during the 2 months immediately before the screening date.

Key exclusion criteria were serum phosphate >10.0 mg/dl while receiving phosphate binders at any time point during the 3 months preceding the screening visit; intact parathyroid hormone (PTH) concentration >1200 pg/ml; clinical signs of hypovolemia at enrollment; or a history of inflammatory bowel disease/irritable bowel syndrome with diarrhea.

Analysis Sets

Two sets of analyses were defined for each of the three study periods: the safety analysis set, which included all participants who received at least one dose of the study drug for that study period, and the intention-to-treat (ITT) analysis set, which included all participants who met the enrollment criteria, received at least one dose of tenapanor and/or placebo, and had at least one post-treatment serum phosphate measurement for that study period. Participants assigned to the sevelamer (safety control) group were not included in the ITT analysis set for any study period; no prospective efficacy analyses were performed comparing tenapanor and sevelamer. The 52-week treatment period for participants receiving sevelamer was split into three study periods (treatment, withdrawal, and safety extension) to facilitate a safety comparison with participants treated with tenapanor and/or placebo during the corresponding study periods.

Additionally, a predefined efficacy analysis set was evaluated exclusively during the randomized withdrawal period. The efficacy analysis set was a subset of participants from the ITT analysis set of the randomized withdrawal period who had also received at least one dose of tenapanor during the randomized treatment period, completed the randomized treatment period, and achieved a reduction of ≥1.2 mg/dl in serum phosphate from baseline to the end of the randomized treatment period.

Efficacy End Points and Assessments

With input from the regulatory authority (US FDA), the primary efficacy end point, which was evaluated for the efficacy analysis set in the primary analysis, was the difference in the change in serum phosphate from period-specific baseline to the end of the randomized withdrawal period between the pooled tenapanor group (all doses combined; hereafter "tenapanor group") and placebo group. In each study period, the period-specific baseline was defined as the last measurement collected before the first dose of study drug during that study period. Serum phosphate concentration was measured at each scheduled visit (Supplemental Table 1).

Secondary end points assessed included change in serum phosphate concentration from period-specific baseline at each postbaseline visit and relative change from period-specific baseline in intact fibroblast growth factor 23 (iFGF23) and C-terminal FGF23 (cFGF23) at each postbaseline visit (where relative change was defined as the ratio of postbaseline value to period-specific baseline value − 1).

Safety Outcomes and Assessments

Safety assessments were on the basis of reported AEs, clinical laboratory tests, vital signs, electrocardiograms, and physical examinations. For analysis purposes, AE reports with the recorded start date before baseline were treated as medical history events. Only treatment-emergent AEs were included for AE summaries in this study; all AEs described in this study are treatment-emergent AEs. Drug-related AEs were those that had been judged by the investigator as related or possibly related to the study drug.

AEs were coded to system organ class and preferred term, using the Medical Dictionary for Regulatory Activities (MedDRA; v21.0).

Statistical Methods

For the primary analysis of the primary efficacy end point, we performed a treatment comparison of the mean change in serum phosphate concentration from period-specific baseline to the end of the randomized withdrawal period using an analysis of covariance, with treatment and geographic region as factors and period-specific baseline value as a covariate on the efficacy analysis set. Assuming a common SD of 1.6 mg/dl, a sample size of 146 participants (73 participants/group) was expected to provide 96% power to detect a treatment difference of 1.0 mg/dl in the primary efficacy end point between the pooled tenapanor and placebo groups using a two-sided t test at the 0.05 significance level.

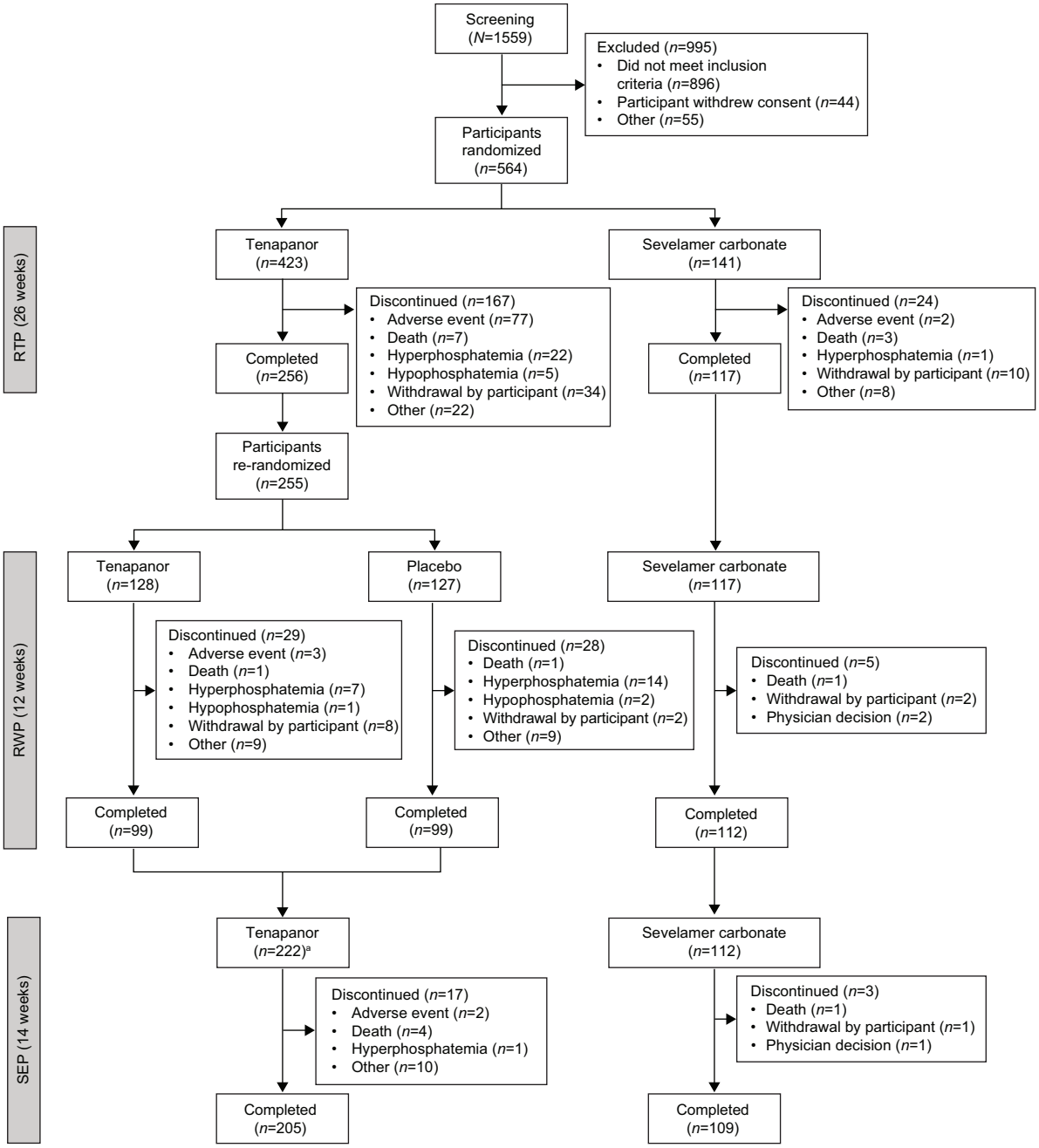

Figure 2. | **Overview of participant flow through the trial**. The safety analysis set included all participants who received at least one dose of the study drug for the study period. The ITT analysis set included all participants who met the study inclusion criteria, received at least one dose of tenapanor and/or placebo, and had at least one post-treatment serum phosphate measurement for the study period. The efficacy analysis set included all ITT participants who met the entry criteria, received at least one dose of tenapanor during the 26-week RTP, completed the RTP, and achieved a reduction of ≥1.2 mg/dl in serum phosphate concentration from baseline to the end of the RTP. Participants from the site with a serious GCP breach were excluded from all analysis sets. Participants receiving tenapanor or placebo were to be withdrawn if they had serum phosphate ≤2.5 mg/dl at any time, serum phosphate ≥10.0 mg/dl at any time after week 2 of the RTP, serum phosphate ≥9.0 mg/dl for two consecutive visits during the RTP or SEP, or serum phosphate ≥9.0 mg/dl during the RWP. The primary reason for discontinuation from the study is listed. GCP, Good Clinical Practice.

To control the overall Type I error rate at the 0.05 level, key secondary analyses of efficacy were performed in a hierarchical manner after the primary analysis on the efficacy analysis set met statistical significance as follows: a treatment comparison between tenapanor and placebo groups using analysis of covariance on the ITT analysis set, then comparisons between individual doses of tenapanor (for dose groups with ≥15 participants) and placebo

Table 1. Participant demographics and baseline characteristics (safety analysis set)

	26-week Randomized Treatment Period			12-week Randomized Withdrawal Period				14-week Safety Extension Period		
Demographic/ Characteristic	Sevelamer Carbonate, *n*=137	Tenapanor, *n*=419	Total, *n*=556	Sevelamer Carbonate, *n*=116	Placebo, *n*=126	Tenapanor, *n*=125	Total, *n*=367	Sevelamer Carbonate,*n*=110	Tenapanor, *n*=220	Total, *n*=330
Age, years	59 (13)	58 (13)	58 (13)	58 (13)	58 (13)	57 (11)	57 (12)	58 (13)	57 (12)	58 (12)
Male, *n* (%)	91 (66)	265 (63)	356 (64)	75 (65)	72 (57)	82 (66)	229 (62)	73 (66)	134 (61)	207 (63)
Race, *n* (%)										
White	70 (51)	189 (45)	259 (47)	60 (52)	49 (39)	57 (46)	166 (45)	56 (51)	91 (41)	147 (45)
Black	60 (44)	195 (47)	255 (46)	50 (43)	68 (54)	60 (48)	178 (49)	48 (44)	114 (52)	162 (49)
Other[a]	7 (5)	35 (8)	42 (8)	6 (5)	9 (7)	8 (6)	23 (6)	6 (5)	15 (7)	21 (6)
Ethnicity, *n* (%)										
Hispanic or Latino	41 (30)	115 (27)	156 (28)	32 (28)	30 (24)	39 (31)	101 (28)	30 (27)	59 (27)	89 (27)
Other[b]	96 (70)	304 (73)	400 (72)	84 (72)	96 (76)	86 (69)	266 (72)	80 (73)	161 (73)	241 (73)
BMI, kg/m^2	31.4 (9.9)	31.3 (7.5)	31.3 (8.2)	31.3 (10.5)	32.1 (7.7)	32.2 (7.4)	31.9 (8.6)	31.2 (10.7)	32.2 (7.5)	31.8 (8.7)
Duration of ESKD, years	5.1 (5.1)	4.8 (4.4)	4.9 (4.6)	5.3 (5.3)	4.6 (4.5)	4.5 (4.1)	4.8 (4.6)	5.5 (5.4)	4.7 (4.4)	5.0 (4.8)
Hemodialysis, *n* (%)	122 (89)	376 (90)	498 (90)	102 (88)	116 (92)	117 (94)	335 (91)	98 (89)	206 (94)	304 (92)
Duration of dialysis treatment, months	59.2 (57.5)	54.2 (51.0)	55.5 (52.7)	61.2 (59.1)	49.4 (47.0)	53.6 (50.1)	54.6 (52.2)	63.1 (60.0)	53.2 (49.6)	56.5 (53.4)
Baseline s-P (mg/dl)	7.2 (1.5)	7.4 (1.4)	7.4 (1.4)	7.3 (1.5)	7.2 (1.5)	7.3 (1.3)	7.2 (1.4)	7.3 (1.5)	7.2 (1.4)	7.2 (1.4)
Baseline iFGF23 (pg/ml)	11,467.0 (14,054.7)	12,316.4 (14,772.9)	12,107.1 (14,591.3)	11,891.8 (14,516.5)	11,460.0 (15,026.4)	9556.0 (13,391.0)	10,948.0 (14,321.8)	12,133.2 (14,807.7)	10,409.9 (14,233.3)	10,984.3 (14,427.7)
Baseline cFGF23 (RU/ml)	17,057.8 (20,616.4)	17,048.5 (20,567.5)	17,050.8 (20,561.0)	17,702.3 (21,422.6)	16,882.8 (22,235.6)	15,178.0 (18,768.3)	16,561.2 (20,820.7)	18,126.9 (21,857.0)	15,933.2 (20,443.2)	16,664.4 (20,917.5)
Baseline PTH (pg/ml)	402.0 (255.0)	421.4 (252.2)	416.6 (252.8)	398.8 (251.2)	445.3 (242.3)	369.4 (233.6)	404.8 (243.7)	398.6 (256.6)	410.7 (250.3)	406.7 (252.1)
Baseline Ca (mg/dl)	8.4 (0.8)	8.4 (0.8)	8.4 (0.8)	8.3 (0.8)	8.5 (0.7)	8.2 (0.8)	8.4 (0.8)	8.3 (0.8)	8.4 (0.8)	8.4 (0.8)
Concomitant calcimimetic, *n* (%)	18 (13)	41 (10)	59 (11)	10 (9)	17 (13)	4 (3)	31 (8)	8 (7)	10 (5)	18 (5)
Concomitant vitamin D and analogs, *n* (%)	27 (20)	53 (13)	80 (14)	17 (15)	18 (14)	13 (10)	48 (13)	14 (13)	20 (9)	34 (10)
Concomitant calcium supplements, *n* (%)	5 (4)	2 (0.5)	7 (1)	3 (3)	0 (0)	0 (0)	3 (0.8)	1 (0.9)	0 (0.0)	1 (0.3)

Unless otherwise indicated, data are mean (SD). Baseline was defined as the last measurement collected before the first dose of study drug in the study. BMI, body mass index; s-P, serum phosphate; iFGF23, intact fibroblast growth factor 23; cFGF23, C-terminal fibroblast growth factor 23; PTH, parathyroid hormone.

[a]Includes Asian, Native American or Alaskan, Native Hawaiian or Pacific Islander, and other.

[b]Includes "Not Hispanic or Latino," not reported, and unknown.

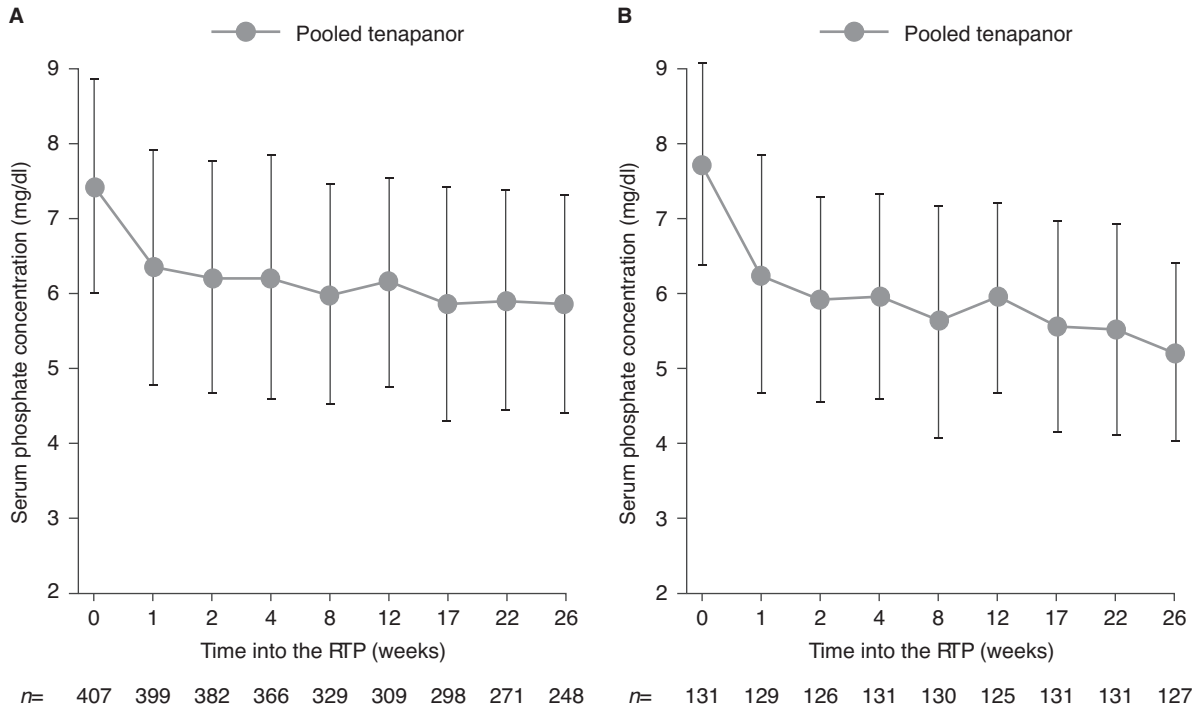

Figure 3. | Change in serum phosphate concentration in participants receiving tenapanor during the 26-week RTP. Serum phosphate concentration in participants receiving tenapanor over the 26-week RTP for the (A) ITT analysis set and (B) the subset of participants who achieved a reduction of ≥1.2 mg/dl in serum phosphate from baseline at week 26 and continued into the randomized withdrawal period. Data are mean serum phosphate concentrations ±SD.

groups on the efficacy analysis set, followed by comparisons for individual doses of tenapanor on the ITT analysis set.

Statistical methods for the subgroup analysis and analysis of secondary end points are described in Supplemental Information 2.

We performed all data summaries and inferential analyses using SAS version 9.4. We described all safety measures by treatment received and for the entire safety analysis set; we did not perform inference testing on safety measures.

Results

Participants

Of 1559 patients screened, 564 individuals met the enrollment criteria and were randomly assigned into the 26-week randomized treatment period (Figure 2). There were 423 participants assigned to receive tenapanor, of whom 256 (61%) completed the randomized treatment period. Of 141 participants assigned to receive sevelamer, 117 (83%) completed 26 weeks of treatment. A total of 310 participants completed the 12-week randomized withdrawal period (83% of the 372 participants who entered the period): 112 (96%) participants in the sevelamer group, 99 (78%) participants in the placebo group, and 99 (77%) participants in the tenapanor group. Overall, 334 participants entered the safety extension period, which was completed by 205 (92%) participants in the tenapanor group and 109 (97%) participants in the sevelamer group. Participant baseline characteristics were well balanced between treatment groups in the safety analysis set for each of the three study periods (Table 1). There was a serious breach of Good Clinical Practice identified at one site involved with the study (Supplemental Information 3); participants associated with this site were excluded from all analysis sets.

Mean treatment adherence was >78% for all treatment groups within each study period. For the efficacy analysis set, the fixed tenapanor dose administered during the randomized withdrawal period (and the final tenapanor dose of the randomized treatment period) was 30 mg twice daily for 75 (57%) participants, 20 mg twice daily for 39 (30%) participants, and 10 mg twice daily for 17 (13%) participants, with a mean value of 24.4 mg twice daily. For the safety control group, the median starting dose of sevelamer was 4800 g (6 tablets) daily and median final dose at 52 weeks was 7200 g (9 tablets) daily.

Study Assessments

Randomized treatment period

For the ITT analysis set, which comprised 407 participants randomized to tenapanor, the mean serum phosphate decreased from 7.4 mg/dl at period-specific baseline to 5.9 mg/dl at week 26 (n=248), with a mean (standard deviation) decrease of 1.4 (1.8) mg/dl (Figure 3A). Among the ITT analysis set, 131 participants achieved a reduction of ≥1.2 mg/dl in serum phosphate from baseline at week 26 and continued into the randomized withdrawal period; in this subset of participants, mean serum phosphate decreased from 7.7 mg/dl at period-specific baseline to 5.2 mg/dl at week 26 (n=127), with a mean (SD) decrease of

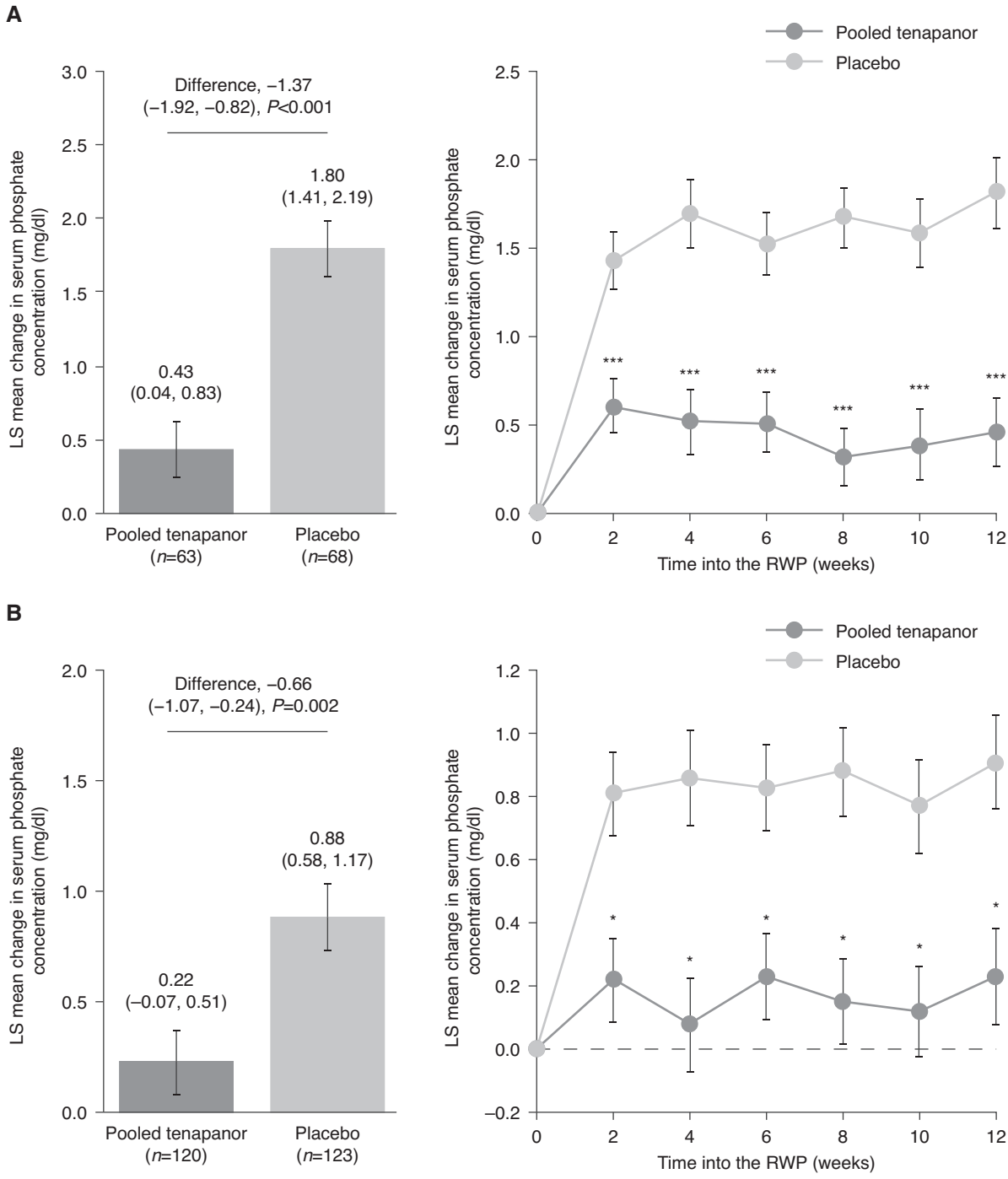

Figure 4. | **Change in serum phosphate concentration over the RWP.** Data are provided for the (A) efficacy analysis set and (B) ITT analysis set. ***$P<0.001$, *$P\leq0.002$ versus placebo. Bar chart data show LS mean change (95% confidence interval±SEM) in serum phosphate concentration from period-specific baseline to the end of the RWP. Line graph data show LS mean change (±SEM and *P* value) from period-specific baseline in serum phosphate concentration at postbaseline visits during the RWP. LS, least squares.

2.5 (1.2) mg/dl (Figure 3B). From period-specific baseline, there were median relative reductions of 23% for iFGF23 and 14% for cFGF23 at the end of the randomized treatment period for participants randomized to tenapanor (ITT analysis set; Supplemental Figure 1A).

Although the trial design did not allow for direct comparison of the efficacy of phosphate lowering between the tenapanor and sevelamer safety control groups, a *post-hoc* analysis demonstrated that the distribution of change in serum phosphate at the end of the randomized treatment period was nearly identical between participants in the ITT analysis set who received tenapanor for the entire 52-week study ($n=88$) and those who received sevelamer ($n=108$) (Supplemental Figure 2).

Randomized Withdrawal Period

In the efficacy analysis set (n=131), the least squares (LS) mean change in serum phosphate from period-specific baseline to the end of the randomized withdrawal period was 0.4 mg/dl for the tenapanor group and 1.8 mg/dl for the placebo group (primary efficacy end point; LS mean difference −1.4 mg/dl; P<0.001; Figure 4A). In the ITT analysis set (n=243), the LS mean change in serum phosphate from period-specific baseline at the end of the randomized withdrawal period was 0.2 mg/dl for the tenapanor group and 0.9 mg/dl for the placebo group (primary efficacy end point; LS mean difference −0.7 mg/dl; P=0.002). At all postbaseline visits during the randomized withdrawal period, there was a statistically significant difference between tenapanor and placebo, both for the efficacy analysis set (P<0.001; Figure 4A) and ITT analysis set (P≤0.002; Figure 4B). There were also more pronounced mean reductions in serum phosphate concentration compared with placebo at all doses of tenapanor and in all subgroups (Supplemental Figure 3, Supplemental Table 2). The treatment comparison of the log-transformed relative change in iFGF23 and cFGF23 was statistically significant at each postbaseline visit measured in the randomized withdrawal period (efficacy analysis set; Supplemental Figure 1, B and C). From period-specific baseline to the end of the randomized withdrawal period, there were median relative reductions of 19% for iFGF23 and 15% for cFGF23 for participants randomized to tenapanor (ITT analysis set).

Safety Assessments

Table 2 provides a summary of the AEs for the safety analysis sets during the three study periods. For participants treated with tenapanor, the incidence of AEs during the randomized treatment period (80%) occurred at a higher rate than during the randomized withdrawal period (46%) and the safety extension period (46%). AEs that resulted in discontinuation of tenapanor treatment were reported for 102 participants (24%) during the randomized treatment period, 11 participants (9%) during the randomized withdrawal period, and three participants (1%) during the safety extension period. In total, 17 participants (13%) receiving placebo discontinued study treatment owing to an AE during the randomized withdrawal period.

Diarrhea (per MedDRA preferred term, vide supra) was the only drug-related AE reported for >5% of participants. Drug-related diarrhea in participants receiving tenapanor resulted in study drug discontinuation for 67 (16%) participants during the randomized treatment period and for one (1%) participant during the randomized withdrawal period. Diarrhea related to tenapanor was generally reported as mild to moderate in severity; of the participants in the safety analysis set, 26 (6%) experienced severe drug-related diarrhea. Participants typically experienced their first diarrhea event within the first 2 weeks of tenapanor treatment, and the event resolved within approximately 2 weeks. The incidence of diarrhea in the tenapanor group in the second half of the randomized treatment period was similar to that reported for the sevelamer group (Supplemental Table 3).

Table 2. Overview of adverse events (safety analysis set)

Adverse Events	26-week Randomized Treatment Period	12-week Randomized Withdrawal Period		14-week Safety Extension Period
	Tenapanor, n=419	Placebo, n=126	Tenapanor, n=125	Tenapanor, n=220
Participants with any AE	337 (80)	70 (56)	58 (46)	102 (46)
Participants with any AE related to study drug	244 (58)	17 (13)	12 (10)	19 (9)
Participants with any drug-related serious AE	3 (1)	0 (0)	0 (0)	0 (0)
Participants with any AE leading to study drug discontinuation	102 (24)	17 (13)	11 (9)	3 (1)
Participants with any drug-related AE leading to study drug discontinuation	88 (21)	10 (8)	5 (4)	1 (0.5)
AEs by preferred term[a]				
Diarrhea	222 (53)	2 (2)	5 (4)	15 (7)
Hyperphosphatemia	27 (6)	15 (12)[b]	7 (6)	3 (1)
Hypertension	15 (4)	0 (0)	2 (2)	3 (1)
Drug-related AEs by preferred term[a]				
Diarrhea	219 (52)	2 (2)	4 (3)	14 (6)

Data are n (%). Hyperphosphatemia was reported as an AE but may represent a worsening of the participant's underlying condition or indicative of a lack of treatment effect for that participant. AE, adverse event.

[a]AEs listed here occurred in ≥3% of participants overall in any treatment group and study period.

[b]One participant did not complete the randomized withdrawal period due to hyperphosphatemia and entered the safety extension period per protocol; this participant subsequently died during the safety extension period and was therefore counted under the primary discontinuation reason of "Death" instead of "Hyperphosphatemia.".

Of the participants who received tenapanor during the randomized treatment period, 43 (10%) were taking loperamide, six (1%) were taking probiotics, and three (1%) were taking bismuth preparations. Antidiarrheal agents were not prescribed in a systematic manner. There were no reports of constipation from participants receiving tenapanor in the first half of the randomized treatment period; two (0.5%) participants reported constipation in the second half.

SAEs were reported more frequently for participants treated with sevelamer (16%–23% across all study periods) compared with tenapanor (11%–17%) (Table 3). Drug-related SAEs were reported for three (1%) participants receiving tenapanor during the randomized treatment period. During the study, five participants randomized to receive sevelamer and 13 randomized to receive tenapanor died (including one participant who died during the randomized withdrawal period after receiving placebo); consistent with the 3:1 randomization of participants. Of the 18 deaths reported during the study, only two deaths were caused by treatment-emergent medical conditions: one participant in the tenapanor group died of respiratory failure during the randomized treatment period and one participant in the sevelamer group who died of cardiorespiratory arrest during the randomized withdrawal period. None of the deaths were deemed to be drug related.

There were no significant differences in electrocardiographic parameters, vital signs, and physical examination between treatment groups during the trial. Similarly, no clinically significant differences between groups were found in the evaluation of key laboratory parameters, including serum bicarbonate, potassium, magnesium, and sodium concentrations (Supplemental Table 4). Changes in median levels of PTH were generally similar between groups; notably, meaningful changes in median PTH were observed in the subset of participants with high PTH (≥600 ng/l) at the start of PHREEDOM (Supplemental Table 5).

Discussion

In this phase 3 study enrolling patients receiving maintenance dialysis with hyperphosphatemia, the primary end point was achieved; treatment with tenapanor resulted in a statistically significant decrease in serum phosphate during the randomized withdrawal period (difference of −1.4 mg/dl versus placebo; $P<0.0001$). Additionally, during the initial 6-month randomized treatment period, mean serum phosphate was reduced by 1.4 mg/dl in the tenapanor group. Overall, these results were consistent with a previous study comprised of an 8-week randomized treatment period and 4-week randomized withdrawal period (17). Relative reductions in FGF23 concentrations with tenapanor were consistent with a previous 4-week phase 2 study (18), and two other phase 3 studies (17,19).

Although complex, the study design enabled the investigation of several key aspects. The 26-week treatment period that preceded the placebo-controlled period could assess for diminishing response to tenapanor over time, a placebo control was not deemed ethical for the entire study period, the use of a safety control could help to assess safety issues given the high frequency of hospitalization among this patient population, and 52 weeks of total exposure to tenapanor could establish its long-term safety profile.

Results from this study support an acceptable tolerability profile for tenapanor. MedDRA classifies any report of "bothersome" loose stool(s), loose bowels and/or mushy stool(s) as "diarrhea" events, whether or not there was a reported increase in stool frequency, and incidence of MedDRA-classified diarrhea was generally consistent with previous studies of tenapanor (16–18,20,21). This side effect is anticipated, as tenapanor inhibits NHE3, which in addition to reducing paracellular phosphate absorption in the GI tract, reduces dietary sodium absorption and increases the sodium and water content of stools, softening stools and increasing bowel movement frequency (9,10). Rates of drug

Table 3. Overview of serious adverse events (safety analysis set)

	26-week Randomized Treatment Period			12-week Randomized Withdrawal Period				14-week Safety Extension Period		
	Sevelamer Carbonate, *n*=137	Tenapanor, *n*=419	Total, *N*=556	Sevelamer Carbonate, *n*=116	Placebo, *n*=126	Tenapanor, *n*=125	Total, *N*=367	Sevelamer Carbonate, *n*=110	Tenapanor, *n*=220	Total, *N*=330
Participants with any SAE	32 (23)	73 (17)	105 (19)	19 (16)	13 (10)	14 (11)	46 (13)	22 (20)	35 (16)	57 (17)
Participants with any drug-related SAE	0 (0)	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Participants with any AEs leading to death[a]	3 (2)	7 (2)	10 (2)	1 (1)	1 (1)	1 (1)	3 (1)	1 (1)	4 (2)	5 (2)
SAEs with incidence ≥3% by preferred term[b]										
Pneumonia	5 (4)	3 (1)	8 (1)	1 (1)	0 (0)	1 (1)	2 (1)	2 (2)	2 (1)	4 (1)

Data are *n* (%). SAE, serious adverse event.
[a]Participants with any AEs leading to death are tabulated by study period, regardless whether the fatal AEs were treatment emergent or not. Of the 18 deaths reported during the study, only two deaths were caused by treatment-emergent medical conditions.
[b]SAEs listed here occurred in ≥3% of participants overall in any treatment group and study period.

discontinuation because of loosened stools declined over time, suggesting participants either became accustomed to the change in stool form or frequency (previously estimated as three additional stools per week) (17) or that tolerability manifested early in the treatment course. Although reported as an AE in accordance with trial conduct, softer stools induced by tenapanor *via* its known mechanism of action and primary pharmacology of inhibition of sodium absorption could be beneficial in this population. Indeed, tenapanor is approved for use by the FDA in irritable bowel syndrome with constipation (22). A sizeable proportion of patients treated with dialysis experience constipation (23); among patients receiving peritoneal dialysis, constipation can be particularly troublesome, because colonic distension with stool can impair dialysate inflow and drainage and can contribute to modality failure (23,24).

Limitations of the trial should be acknowledged. Data suggest that tenapanor and phosphate binder therapy could assume complementary roles in hyperphosphatemia management (19,25); however, we did not include a treatment arm in which participants received dual treatment with tenapanor and sevelamer. Furthermore, the trial was largely nonblinded. Participants who discontinued tenapanor during the randomized treatment period were not included in subsequent study periods; thus, the randomized withdrawal and safety extension periods may have been enriched for individuals who were better able to tolerate tenapanor. Another limitation was that insufficient data were collected on the change in dose of concomitant medications that are known to affect serum phosphate (*e.g.*, active vitamin D analogs, calcimimetics). There were several strengths. PHREEDOM is the longest study to date of tenapanor to treat hyperphosphatemia in patients on dialysis, and all recruitment targets were met. The population was diverse in age, sex, self-reported race, ethnicity, and underlying cause of kidney failure; moreover, patients receiving peritoneal dialysis and hemodialysis were included, adding to the robustness and generalizability of the results.

In conclusion, the PHREEDOM trial confirms and extends evidence derived from other shorter-term randomized controlled trials, demonstrating the tolerability and efficacy of tenapanor for hyperphosphatemia in patients receiving maintenance dialysis.

Disclosures

A.J. Bleyer reports no affiliation with Ardelyx, Inc. aside from his role as Principal Investigator in the PHREEDOM study. A.L. Silva reports receiving research funding from Ardelyx, Inc. D.E. Weiner reports being the Medical Director of Clinical Research for Dialysis Clinic, Inc., with support paid to his institution by Dialysis Clinic, Inc.; he reports consulting for Akebia, Cara Therapeutics, Janssen Biopharmaceuticals, and Tricida, and has no affiliation with or received funding from Ardelyx, Inc., aside from his role as site Principal Investigator in several tenapanor trials. D.P. Rosenbaum reports being an employee of, and having an ownership interest in, Ardelyx, Inc. G.A. Block reports being a Director for Ardelyx, Inc. and is the Associate Chief Medical Officer for US Renal Care, Inc. G.M. Chertow reports being a consultant to, and has equity ownership interest in, Ardelyx, Inc. R.I. Lynn has no affiliation with Ardelyx, Inc. aside from his role as Principal Investigator in the PHREEDOM and NORMALIZE studies. Y. Yang reports being an employee of Ardelyx, Inc.

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Author Contributions

A. Bleyer, G. Block, G. Chertow, R. Lynn, D. Rosenbaum, A. Silva, and D. Weiner conceptualized the study; Y. Yang was responsible for data curation; G. Block and Y. Yang were responsible for the formal analysis; A. Bleyer, G. Block, G. Chertow, R. Lynn, A. Silva, and D. Weiner were responsible for the investigation; G. Block and D. Rosenbaum were responsible for the methodology; D. Rosenbaum was responsible for the resources; and A. Bleyer, G. Block, G. Chertow, R. Lynn, D. Rosenbaum, A. Silva, D. Weiner, and Y. Yang reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0002002021/-/DCSupplemental.

Supplemental Information 1. Selection of trial population.

Supplemental Information 2. Statistical methods for secondary end points and subgroup analysis.

Supplemental Information 3. Breach of Good Clinical Practice.

Supplemental Figure 1. Change in FGF23 concentrations over (A) the 26-week RTP and (B, C) the RWP.

Supplemental Figure 2. Cumulative distribution function of change in serum phosphate (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.

Supplemental Figure 3. LS mean difference in change in serum phosphate (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.

Supplemental Table 1. Schedule of visits in study.

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

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

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

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

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