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Tenapanor Improves Long-Term Control of Hyperphosphatemia in Patients Receiving Maintenance Dialysis: the NORMALIZE Study

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Key Points

- Tenapanor is a first-in-class, minimally systemic sodium–hydrogen exchanger 3 inhibitor with a mechanism of action distinct from phosphate binders.
- Tenapanor alone or with phosphate binders led to 35%–49% of patients achieving serum phosphate ≤4.5 mg/dl over an 18-month period versus 22% at baseline.
- Tenapanor alone or with phosphate binders may help adults with CKD on maintenance dialysis achieve normal serum phosphate concentrations.

Abstract

Background Most patients with ESKD and hyperphosphatemia have difficulty controlling serum phosphate (sP) concentrations despite maintenance dialysis, dietary restriction, and phosphate binder treatment. NORMALIZE evaluated the efficacy and safety of tenapanor 30 mg twice daily alone or in combination with phosphate binders to achieve sP within the adult population reference range (2.5–4.5 mg/dl).

Methods Patients who completed the Phase 3 PHREEDOM study could enroll in NORMALIZE. Patients enrolled in NORMALIZE who had received tenapanor during the PHREEDOM study (n=111) added sevelamer carbonate if sP was >4.5 mg/dl. Patients who had received sevelamer carbonate during the PHREEDOM study (n=61) added tenapanor and decreased sevelamer carbonate if sP was ≤4.5 mg/dl, per protocol titration schedule. Patients were followed in NORMALIZE for up to 18 months. We assessed efficacy in the full analysis set, defined as patients who received ≥1 dose of study drug and had ≥1 post-treatment sP measurement (n=171). We assessed safety in all patients who received ≥1 dose of study drug (n=172).

Results At the end point visit, 57 of 171 patients (33%) in the full analysis set achieved sP between 2.5 and 4.5 mg/dl. Eight of 23 patients (35%) who were on tenapanor alone at the end point visit achieved sP between 2.5 and 4.5 mg/dl. The mean reduction from PHREEDOM baseline to end of NORMALIZE in sP was 2.0 mg/dl. Serum intact fibroblast growth factor-23 was significantly reduced; serum intact parathyroid hormone was significantly reduced among patients with intact parathyroid hormone ≥300 pg/ml at PHREEDOM baseline. The most commonly reported treatment-emergent adverse event was diarrhea in 38 of 172 patients (22%), which led to tenapanor discontinuation in four patients (2%).

Conclusions Tenapanor alone or in combination with phosphate binders helped adult patients on maintenance dialysis achieve normal sP concentrations. Safety was consistent with previous studies of tenapanor.

Clinical trial registry name and registration number A Long-Term Study to Evaluate the Ability of Tenapanor Alone or in Combination With Sevelamer to Treat to Goal Serum Phosphorus in Patients With ESKD on Dialysis (NORMALIZE), NCT03988920.

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Introduction

As kidney function declines, mineral homeostasis becomes increasingly dysregulated.[1,2] Phosphate balance is initially maintained by compensatory elevations in parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23)[1]; however, with markedly impaired kidney function, patients develop hyperphosphatemia, secondary hyperparathyroidism, and other manifestations of CKD–mineral bone disorders, including renal osteodystrophy and vascular calcifications.[1–7] Hyperphosphatemia is common in patients receiving maintenance dialysis and is associated with an increased risk of cardiovascular morbidity and mortality, hospitalization (all-cause, cardiovascular-related, and fracture-related), and all-cause mortality.[1,6,8–10]

Clinical practice guidelines recommend maintaining serum phosphate (sP) concentrations within the population reference (normal) range of 2.5–4.5 mg/dl.[11,12] Hyperphosphatemia management strategies include dietary phosphate restriction, removal of phosphate with dialysis, and reduction in intestinal phosphate absorption through ingestion of phosphate binders.[13] Adherence to dietary phosphate restriction is difficult, due in part to challenges in identifying low phosphate foods and the presence of hidden phosphate in preservatives and other food additives.[14,15] Phosphate binders reduce intestinal phosphate absorption by binding dietary phosphate in the intestine, resulting in elimination of ingested phosphates in the stool.[13] Despite phosphate binder availability, hyperphosphatemia in patients on maintenance dialysis remains poorly controlled; ≈70% of patients fail to consistently achieve clinical practice guideline targets.[16,17]

Tenapanor is a first-in-class, minimally systemic phosphate absorption inhibitor with a mechanism of action distinct from phosphate binders. Tenapanor selectively inhibits the intestinal sodium–hydrogen exchanger 3, causing a transient increase in the intracellular proton concentration of intestinal epithelial cells, which induces a conformational change in tight junctions that increases transepithelial electrical resistance and reduces permeability specific to phosphate. Thus, tenapanor blocks the paracellular pathway of phosphate absorption in the gut.[18,19]

Several clinical trials have evaluated tenapanor, as monotherapy or in combination with phosphate binders, for the treatment of hyperphosphatemia in patients receiving maintenance dialysis.[20–23] In the Phase 3 PHREEDOM study (NCT03427125), tenapanor monotherapy reduced sP with an acceptable safety and tolerability profile.[22] Patients who responded to 26 weeks of tenapanor treatment in the randomized treatment period and continued on tenapanor during the 12-week randomized withdrawal period (RWP) had a significant decrease in sP compared with those switching to placebo (1.4 mg/dl; $P < 0.0001$) at the end of the RWP.[22] Patients who completed PHREEDOM were eligible to enroll in the 18-month Phase 3, open-label NORMALIZE study (NCT03988920). Here we present results from NORMALIZE, where we examine the investigational use of tenapanor alone or in combination with sevelamer carbonate to achieve sP in the range of 2.5–4.5 mg/dl.

Methods

Patients

The PHREEDOM and NORMALIZE studies investigated hyperphosphatemia management in adults receiving maintenance dialysis (Supplemental Figure 1). PHREEDOM enrolled adults receiving hemodialysis 3 times/week for ≥3 months or peritoneal dialysis for ≥6 months who were taking ≥3 doses of phosphate binder daily with sP between 4.0 and 8.0 mg/dl, Kt/V_{urea} ≥1.2 within 30 days before screening, serum intact PTH (iPTH) ≤1200 pg/ml at screening, and no history of prominent gastrointestinal disorders.[24] After a 1- to 3-week phosphate binder washout, patients had to have sP between 6.0 and 10.0 mg/dl with a ≥1.5 mg/dl increase compared with prewashout. Patients were randomized to receive tenapanor (starting at 30 mg twice a day for the first 26 weeks or the active control sevelamer carbonate (hereafter referred to as sevelamer) for the entire 52 weeks; dietary restriction of phosphate was not required nor was dietary intake in any way protocolized. Patients in the tenapanor arm who completed the 26-week randomized treatment period were rerandomized to receive tenapanor or placebo for up to 12 weeks during the RWP, followed by an additional 14 weeks of tenapanor treatment during an open-label safety extension.

Patients who completed PHREEDOM were eligible to enroll in NORMALIZE. We excluded patients who were scheduled for kidney transplant, planned to change dialysis modality, or whose investigator-determined life expectancy was <12 months.

All patients provided written informed consent before entering NORMALIZE (NCT03988920), which was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and all applicable local laws and regulations. Participating sites obtained independent ethics committee/institutional review board approval. The study was registered on June 18, 2019.

Study Design

NORMALIZE aimed to evaluate the efficacy of tenapanor alone or in combination with sevelamer to achieve sP between 2.5 and 4.5 mg/dl in adult patients receiving maintenance dialysis with hyperphosphatemia, in accordance with 2017 clinical practice guidelines from Kidney Disease: Improving Global Outcomes.[11] Patients who entered NORMALIZE continued on or were transitioned to tenapanor, depending on their PHREEDOM treatment assignment (Table 1). Patients from the PHREEDOM tenapanor arm continued tenapanor and, if necessary, added sevelamer to lower sP; these patients were categorized as NORMALIZE group 1 (tenapanor or tenapanor+sevelamer carbonate [T/T+S]). Group 1 (T/T+S) included all patients from the PHREEDOM tenapanor arm, irrespective of whether they received tenapanor or placebo during the 12-week RWP in PHREEDOM. NORMALIZE group 2 (sevelamer+tenapanor [S+T]) consisted of patients from the PHREEDOM sevelamer arm. These patients gradually switched from sevelamer to tenapanor, adding tenapanor (starting at 30 mg once a day) and decreasing sevelamer dosage per protocol aiming to maintain control of hyperphosphatemia. For each group, specific guidance was provided for sevelamer and tenapanor

Table 1. Overview of study drug dosing

Groups	PHREEDOM Treatment	NORMALIZE Treatment[a]
Group 1 (tenapanor or tenapanor +sevelamer carbonate)	Tenapanor[b]	• Continue tenapanor alone if sP was ≤4.5 mg/dl • If sP was >4.5 mg/dl, add sevelamer in a stepwise, protocol-specified manner • Protocol-specified guidance provided for dosing adjustment to ensure patient safety from sP concentrations dropping too low
Group 2 (sevelamer +tenapanor)	Sevelamer[c]	• Add tenapanor to sevelamer • Aim to decrease sevelamer dose using a stepwise, protocol-specified dose-titration schedule once sP was controlled at ≤4.5 mg/dl • Protocol-specified guidance provided for dosing adjustment to ensure patient safety from sP concentrations dropping too low

sP, serum phosphate.
[a]Specific details of protocol-specified dosing guidance are described in the Supplemental Methods.
[b]Patients from the PHREEDOM tenapanor arm received 26 weeks of tenapanor in the randomized treatment period, 12 weeks of tenapanor or 12 weeks of placebo in the randomized withdrawal period, and 14 weeks of tenapanor in the open-label extension.
[c]Patients from the PHREEDOM sevelamer arm received 52 weeks of sevelamer during the PHREEDOM study.

dosing to prevent sP falling below 2.5 mg/dl (Supplemental Methods).

We monitored patients with in-office and telephone visits for up to 18 months. Laboratory efficacy measures were assessed throughout the study. sP was measured by a central laboratory at baseline (BL); weeks 1–4, 6, and 8; and months 3, 6, 9, 12, 15, and 18. Plasma intact FGF23 (iFGF23) and iPTH were assessed at BL and months 3, 6, 9, 12, 15, and 18. Samples for clinical laboratory tests were collected predialysis.

End Points

The primary efficacy end point was the percentage of patients achieving sP within the population reference range (2.5−4.5 mg/dl) at the end point visit. The percentage of patients with sP within the population reference range at each postBL visit was a secondary efficacy end point. Additional secondary end points included the percentage of patients with sP ≤4.5 mg/dl or <5.5 mg/dl at each visit and end point visit, change in sP from BL at each visit and end point visit, relative change in iFGF23 from BL at study-specified visits (months 3, 6, 9, 12, 15, and 18) and end point visits, and Kidney Disease Quality of Life composite score and Dialysis Symptom Index at months 6, 12, and 18 and at the end point visit.[24,25] Relative change in iPTH from BL was an exploratory end point at study-specified (same timing as iFGF23) and end point visits. We recorded changes in the daily dosage of sevelamer after starting tenapanor in patients from group 2 (S+T). We assessed safety by monitoring adverse events, vital signs, body weight, physical examination, clinical laboratory tests, and 12-lead electrocardiograms.

Statistical Analysis

The safety analysis set included all patients who received ≥1 dose of study drug during the NORMALIZE study. The full analysis set (FAS) included all patients who met study eligibility criteria, received ≥1 dose of study drug, and had ≥1 post-treatment sP measurement during the NORMALIZE study. All laboratory and other measures were summarized for the overall population and within each group. The last observed assessment in PHREEDOM was the study BL for NORMALIZE. The end point visit was the visit with the last observed assessment during the NORMALIZE study.

Results

Patients

NORMALIZE enrolled 172 patients: 111 in group 1 (T/T+S) and 61 in group 2 (S+T). All were included in the safety analysis set. Of the 172 patients, 124 (72%) completed the 18-month study, comprising 89 (80%) patients from group 1 and 35 (57%) patients from group 2. Reasons for study discontinuation are provided in Supplemental Table 1. One patient from group 2 did not have a post-treatment sP concentration recorded, so the FAS consisted of 171 patients. In the FAS, mean age was 56.8 years at informed consent, 37% were female, 56% were non-White, and mean sP at NORMALIZE BL was 5.8 mg/dl (Table 2).

Achievement of Target sP

Tenapanor treatment alone and in combination with sevelamer led to a reduction from BL in sP over 18 months in NORMALIZE, with a more rapid decline seen in group 2 than in group 1 through weeks 2–3 (Figures 1 and 2). For the primary end point, 57 of the 171 patients (33%) in the FAS achieved sP between 2.5 and 4.5 mg/dl (Figure 1A), and the mean (SEM) reduction in sP was 2.0 (0.2) mg/dl from PHREEDOM BL to the NORMALIZE end point visit (Figures 1B and 2). Similar results were observed in groups 1 (T/T+S) and 2 (S+T) (Figure 1, A and C).

The percentage of patients achieving sP ≤4.5 mg/dl was higher at all postbaseline visits through 18 months, ranging from 35% to 49% compared with 22% at NORMALIZE BL (Figure 3). The percentage of patients achieving sP <5.5 mg/dl ranged from 56% to 69% across postbaseline visits through month 18, compared with 44% at NORMALIZE BL. Consistent results were observed in groups 1 and 2. Between NORMALIZE BL and the end

Table 2. Demographic and baseline characteristics

Variable	FAS (*N*=171)	Group 1 (T/T+S) (*N*=111)	Group 2 (S+T) (*N*=60)
Age at informed consent, yr, *n* (%)	56.8 (12.9)	56.0 (12.1)	58.3 (14.1)
Sex, *n* (%)			
Male	108 (63)	65 (59)	43 (72)
Female	63 (37)	46 (41)	17 (28)
Race, *n* (%)			
Black/African American	85 (50)	59 (53)	26 (43)
White	75 (44)	44 (40)	31 (52)
American Indian or Alaska Native	7 (4)	7 (6)	0
Asian	4 (2)	1 (1)	3 (5)
Ethnicity, *n* (%)			
Non-Hispanic/Latino	120 (70)	80 (72)	40 (67)
Hispanic/Latino	51 (30)	31 (28)	20 (33)
Body mass index, kg/m^2	31.0 (7.5)	31.9 (7.4)	29.4 (7.5)
Type of dialysis, *n* (%)			
Hemodialysis	157 (92)	105 (95)	52 (87)
Peritoneal dialysis	14 (8)	6 (5)	8 (13)
Duration since first dialysis, mo, *n* (%)[a]	64.5 (46.8)	59.2 (40.0)	74.3 (56.3)
NORMALIZE BL, *n* (%)			
sP, mg/dl	5.8 (1.5)	5.8 (1.5)	5.8 (1.6)
iFGF23, pg/ml	9512.9 (12,147.1)	8800.6 (10,133.2)	10,830.5 (15,198.4)
iPTH, pg/ml	397.1 (289.6)	424.2 (321.7)	347.1 (211.9)
Kt/V level	1.8 (0.8)	1.7 (0.6)	1.9 (1.1)
PHREEDOM BL, *n* (%)			
sP, mg/dl	7.3 (1.4)	7.4 (1.5)	7.1 (1.4)
iFGF23, pg/ml	12,838.9 (16,299.6)	12,643.4 (15,647.3)	13,200.6 (17,573.6)
iPTH, pg/ml	449.6 (275.3)	459.9 (266.8)	430.5 (291.5)
Kt/V level	1.6 (0.3)	1.6 (0.3)	1.7 (0.4)

Data are mean (SD) or *n* (%) for the efficacy analysis set. PHREEDOM baseline was defined as the last measurement collected before the first dose of study drug in PHREEDOM, and data presented are limited to patients from PHREEDOM who enrolled in NORMALIZE. NORMALIZE BL was defined as the last measurement collected before first dose of study drug in NORMALIZE; in general, the PHREEDOM end-of-treatment visit was the BL visit for NORMALIZE. The efficacy analysis set included all patients who met study eligibility criteria, received ≥1 dose of study drug, and had ≥1 post-treatment serum phosphate measurement during the study. One enrolled patient was treated with tenapanor but did not have a post-treatment serum phosphate measurement and was excluded from the efficacy analysis set. FAS, full analysis set; T/T+S, tenapanor or tenapanor+sevelamer; S+T, sevelamer+tenapanor; BL, baseline; sP, serum phosphate; iFGF23, intact fibroblast growth factor 23; iPTH, intact parathyroid hormone; Kt/V, a measure of dialysis dose.
[a]At informed consent for NORMALIZE, value was calculated by adding the duration since ESKD diagnosis or first dialysis at PHREEDOM baseline to the duration from PHREEDOM baseline to informed consent for NORMALIZE.

point visit, the percentage of patients with sP ≤4.5 mg/dl increased from 17% to 34% in group 1 and from 30% to 35% in group 2. The percentage of patients with sP <5.5 mg/dl increased from 44% to 50% in group 1 and from 43% to 55% in group 2.

Additional Efficacy Outcomes

In the FAS, 23 patients were on tenapanor alone at the end of the study (19 and 4 from groups 1 [T/T+S] and 2 [S+T], respectively); 12 (52%) of these patients achieved sP <5.5 mg/dl at the end point visit, 8 (35%) of whom achieved sP between 2.5 and 4.5 mg/dl. Ten patients were on tenapanor alone throughout the entire study (all from group 1); four of these patients achieved sP <5.5 mg/dl at the end point visit, three of whom also had sP between 2.5 and 4.5 mg/dl.

The 57 patients (33%) in the FAS who achieved sP between 2.5 and 4.5 mg/dl at the end point visit received tenapanor and a median of four sevelamer tablets daily (25%, 75% range, 2–8).

The 60 patients in the FAS from group 2 (S+T) had a mean percent reduction of 23% in daily sevelamer dosage; the median daily sevelamer dosage was 8.5 tablets at NORMALIZE BL, which decreased to 6.0 tablets at the end point visit (Supplemental Figure 2). The median daily sevelamer dosage among patients in group 1 (T/T+S) is summarized in Supplemental Figure 3.

Over 18 months, treatment with tenapanor alone or combined with sevelamer significantly reduced iFGF23 in the FAS and in groups 1 (T/T+S) and 2 (S+T) (Figure 4A); iPTH was significantly reduced in patients with NORMALIZE BL iPTH ≥300 pg/ml (Figure 4B). We observed no clinically meaningful changes from PHREEDOM BL to end point in the Kidney Disease Quality of Life composite score or subscales or the Dialysis Symptom Index (Supplemental Table 2).

Safety

Treatment-emergent adverse events (TEAEs) were reported in 143 of 172 patients (83%) from the safety

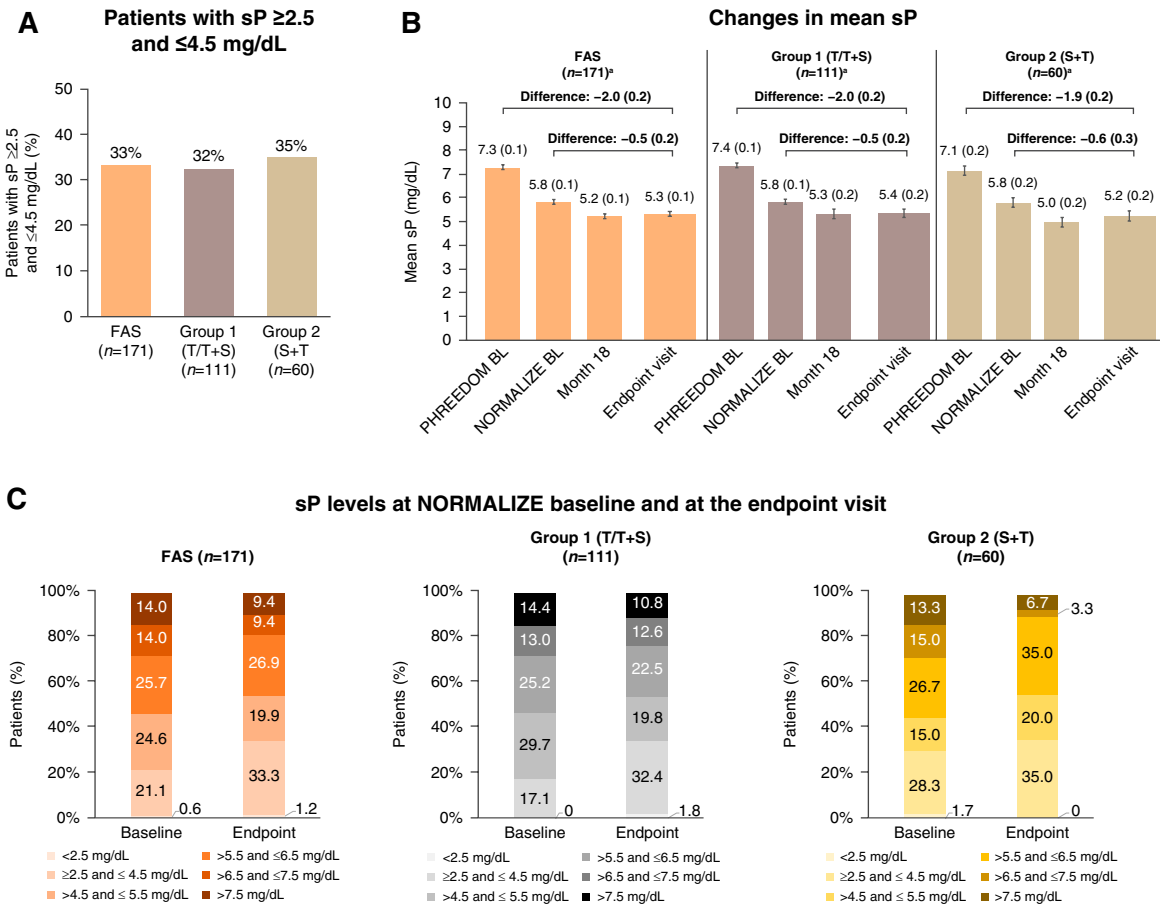

Figure 1. Primary and secondary analyses of sP. Error bars show standard error. [a]Values at PHREEDOM BL, NORMALIZE BL, and the end point visit are based on the total number of patients shown. Month 18 data are based on 124 patients in the FAS, 89 patients in group 1 (T/T+S), and 35 patients in group 2 (S+T). BL, baseline; FAS, full analysis set; sP, serum phosphate; S+T, sevelamer+tenapanor; T/T+S, tenapanor or tenapanor+sevelamer.

analysis set (Table 3), and TEAEs led to tenapanor discontinuation in 18 patients (10%). Diarrhea was the most commonly reported TEAE (38 of 172 patients [22%]) and the most commonly reported TEAE leading to tenapanor discontinuation (four of 172 patients [2%]). Other TEAEs leading to tenapanor discontinuation included coronavirus disease 2019 (COVID-19) pneumonia, sepsis, cardiac arrest, and intracranial hemorrhage (two of 172 patients [1%] for each preferred term). TEAEs led to sevelamer discontinuation in 13 patients (8%); reasons included

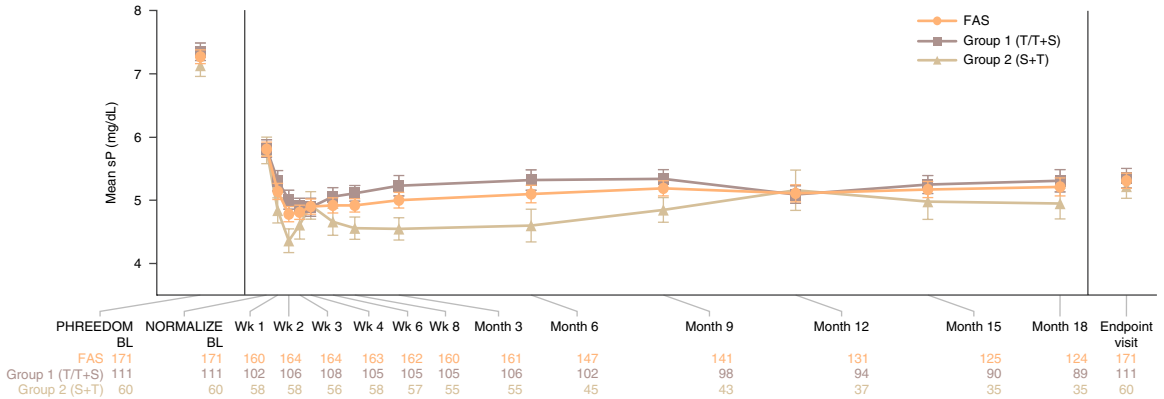

Figure 2. Mean sP at NORMALIZE BL and each postbaseline visit. Error bars show standard error.

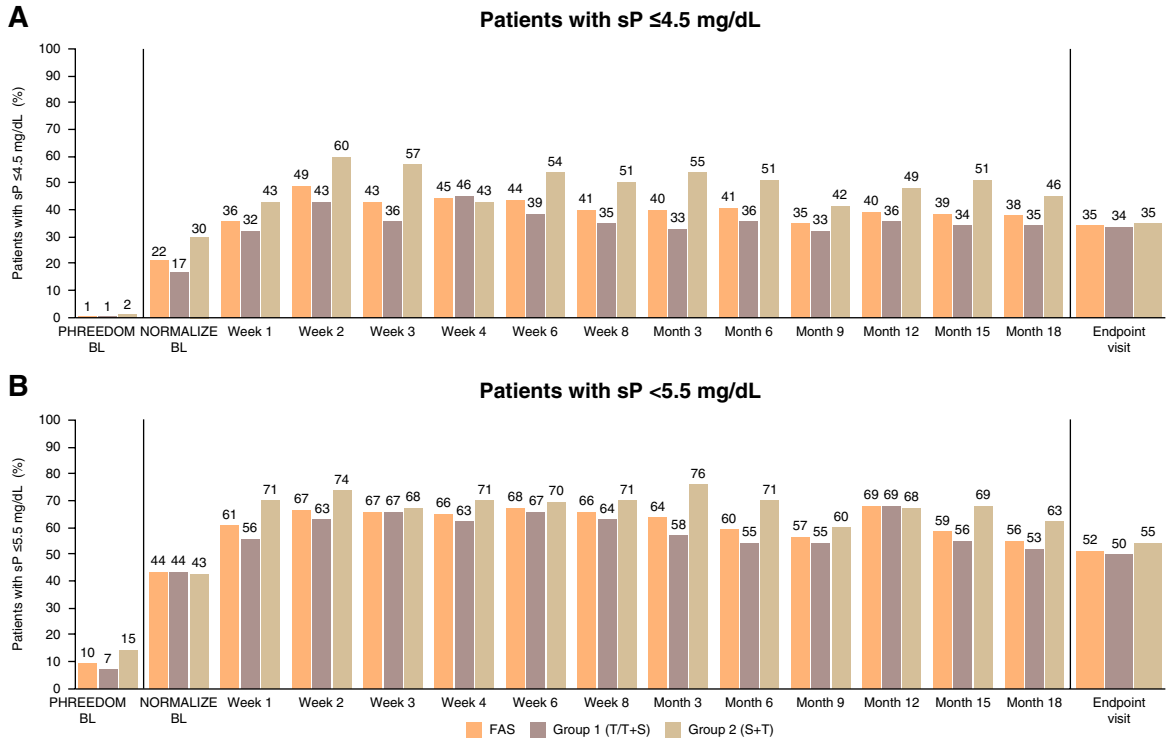

Figure 3. Proportion of patients achieving sP concentrations ≤4.5 and <5.5 mg/dl. Percentages calculated on basis of the proportion of patients meeting the sP response criterion divided by the number of observations for the time point shown.

diarrhea, sepsis, and intracranial hemorrhage (two of 172 patients [1%] for each).

Serious adverse events were reported in 78 of 172 patients (45%) from the safety analysis set. The most common serious adverse event was COVID-19 (seven of 172 [4%]), followed by COVID-19 pneumonia, cellulitis, sepsis, acute myocardial infarction, and hyperkalemia (five of 172 patients [3%] for each preferred term). Overall, these serious adverse events were not considered by the investigator to be related to tenapanor and were consistent with comorbidities experienced by patients receiving maintenance dialysis. Fourteen patients of 172 died during the 18 months on study because of an adverse event (equal to 5.4% per year), nine of which were TEAEs, and none of the deaths were considered tenapanor-related (Supplemental Table 3). We observed no clinically meaningful changes in vital signs, physical examination findings, other laboratory tests, or electrocardiograms (data not shown).

Discussion

In the 18-month NORMALIZE study, which was an extension of the 1-year PHREEDOM study, treatment with tenapanor alone or in combination with sevelamer led to a persistent reduction in sP in adult patients with hyperphosphatemia receiving maintenance dialysis. The mean sP reduction achieved was 2.0 mg/dl, and 35% of patients in the FAS achieved sP ≤4.5 mg/dl at the NORMALIZE end point visit. No new safety signals were observed when tenapanor was combined with sevelamer. The addition of tenapanor to sevelamer (group 2) allowed for a clinically meaningful reduction in daily phosphate binder dosage.

The sP-lowering effects of tenapanor alone or combined with sevelamer in NORMALIZE were consistent with findings from other Phase 3 studies.[21–23] In NCT02675998 and PHREEDOM, mean reduction in sP was 1.0–1.4 mg/dl with tenapanor alone, and up to 41% of patients achieved sP <5.5 mg/dl by the end of the RWP.[21,22] In the 4-week AMPLIFY trial (NCT03824597) of tenapanor in combination with phosphate binders, mean reduction in sP was 0.84 mg/dl, and 49% of patients had sP <5.5 mg/dl.[23] We observed a similar response in NORMALIZE, where 56%–68% of patients achieved sP <5.5 mg/dl at each individual study visit. In addition, 51% of patients with sP <5.5 mg/dl at NORMALIZE BL maintained this sP <5.5 mg/dl concentration through the end point visit, and 53% of patients with sP ≥5.5 mg/dl at NORMALIZE BL achieved sP <5.5 mg/dl.

Within the first 2–3 weeks of the NORMALIZE study, mean sP declined sharply in group 2, whereas a more modest decline was observed in group 1 (Figure 2). This was anticipated because patients in group 2 transitioned to tenapanor after 52 weeks of sevelamer monotherapy in PHREEDOM. Patients in group 1, however, were already on and continued tenapanor in NORMALIZE. A slight increase in mean sP was observed at month 6 in group 2, which was likely due, at least in part, to the smaller sample size (60 versus 111) and higher rate of study discontinuation (43% versus 20%) in group 2 than in group 1. The withdrawal rate in group 2 was likely due to the higher incidence of diarrhea relative to group 1 (44% versus 10%),

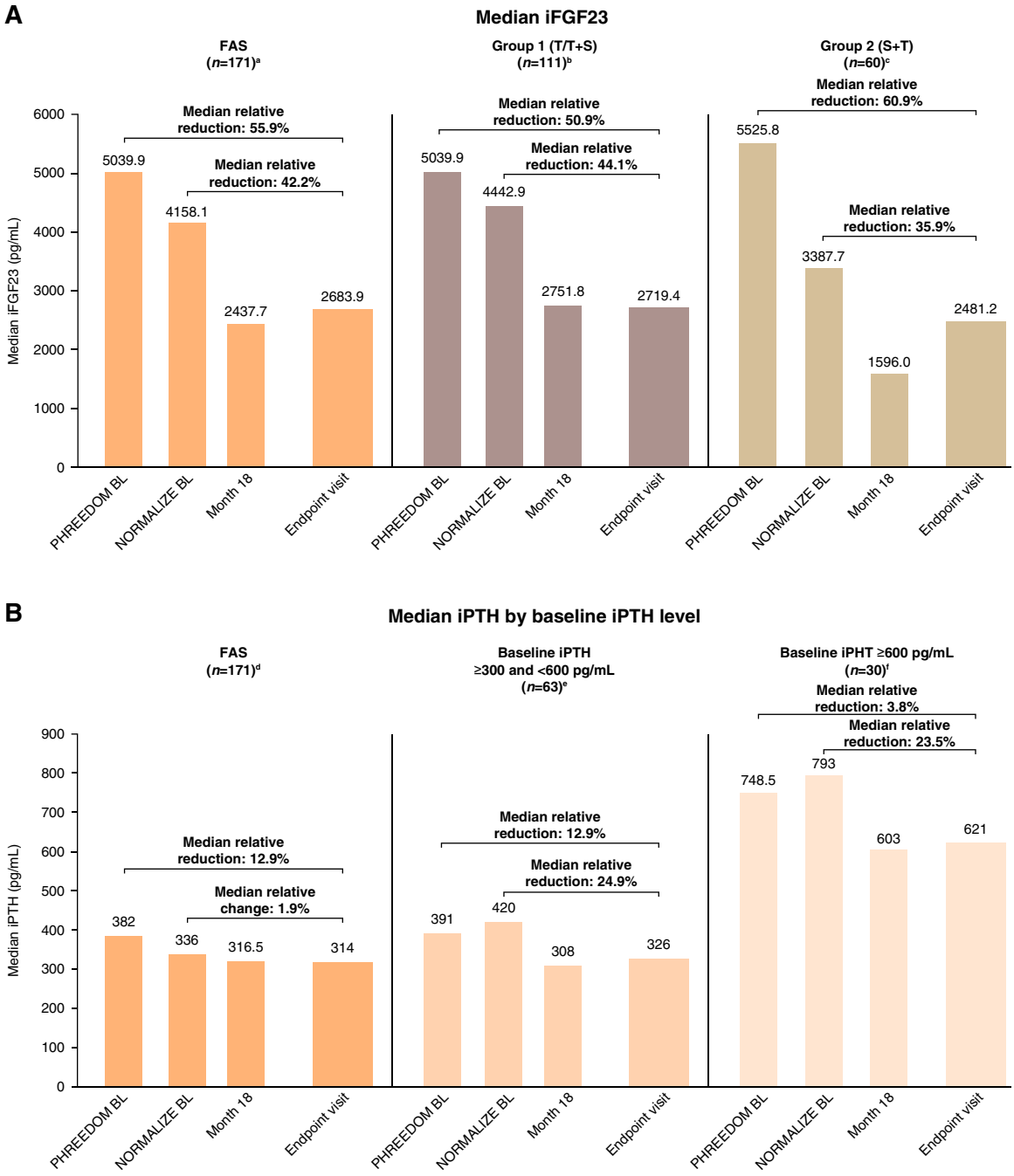

Figure 4. Relative changes in iFGF23 and iPTH. Values at PHREEDOM BL and NORMALIZE BL are based on the total number of patients shown. Patient numbers for month 18 and the end point visit are specified in the footnotes. [a]Medians are based on 122 patients at month 18 and 163 patients at the end point visit. [b]Medians are based on 87 patients at month 18 and 108 patients at the end point visit. [c]Medians are based on 35 patients at month 18 and 55 patients at the end point visit. [d]Medians are based on 122 patients at month 18 and 122 patients at the end point visit. [e]Medians are based on 47 patients at month 18 and 61 patients at the end point visit. iFGF23, intact fibroblast growth factor 23; iPTH, intact parathyroid hormone.

which was expected because patients in group 2 received their first dose of tenapanor in NORMALIZE. The increase in sP at month 6 may have also been influenced by the protocol amendment issued in May 2020. This amendment, which provided updated guidance on dose adjustments to prevent sP from becoming too low, affected patients differently depending on when they entered the study.

Generally, FGF23 elevation precedes PTH and sP elevation, is independently associated with mortality,[26–28] and is associated with an increased risk of myocardial infarction, heart failure, stroke, and cardiovascular death in patients with kidney failure.[26] Consistent with previous studies of tenapanor,[21–23,29] in NORMALIZE, tenapanor alone and in combination with sevelamer led to reduced iFGF23. In

Table 3. Adverse events

Variable	Safety Analysis Set (*N*=172)	Group 1 (T/T+S) (*N*=111)	Group 2 (S+T) (*N*=60)
Any TEAE, *n* (%)	143 (83)	91 (82)	52 (85)
Any serious adverse event, *n* (%)	78 (45)	56 (50)	22 (36)
TEAE leading to tenapanor discontinuation, *n* (%)	18 (10)	9 (8)	9 (15)
TEAE leading to sevelamer discontinuation, *n* (%)	13 (8)	6 (5)	7 (12)
TEAE in >5% of patients in either group, *n* (%)			
Diarrhea	38 (22)	11 (10)	27 (44)
Fall	15 (9)	9 (8)	6 (10)
Hyperkalemia	14 (8)	8 (7)	6 (10)
COVID-19 infection	12 (7)	8 (7)	4 (7)
Hypotension	11 (6)	8 (7)	3 (5)
Nausea	10 (6)	8 (7)	2 (3)
Vomiting	10 (6)	5 (4)	5 (8)
Cellulitis	10 (6)	7 (6)	3 (5)
Nasopharyngitis	10 (6)	9 (8)	1 (2)
Hypertension	10 (6)	7 (6)	3 (5)
Pain in extremity	10 (6)	7 (6)	3 (5)
Pneumonia	9 (5)	5 (4)	4 (7)
Anemia	9 (5)	5 (4)	4 (7)
Sepsis	8 (5)	6 (5)	2 (3)
Arteriovenous fistula site complication	8 (5)	7 (6)	1 (2)
Constipation	7 (4)	3 (3)	4 (7)
Dyspnea	7 (4)	6 (5)	1 (2)
Troponin increased	5 (3)	1 (1)	4 (7)

Data are *n* (%). T/T+S, tenapanor or tenapanor+sevelamer; S+T, sevelamer+tenapanor; TEAE, treatment-emergent adverse event; COVID-19, coronavirus disease 2019.

patients with BL iPTH ≥300 pg/ml, tenapanor treatment also led to reduced iPTH.

While the PHREEDOM study demonstrated that tenapanor is effective as monotherapy for the treatment of hyperphosphatemia in adult patients on maintenance dialysis, the NORMALIZE study demonstrates that tenapanor and phosphate binders can work together to reduce sP concentrations in a dual mechanism approach, which is consistent with the results of previous animal and short-term clinical studies.[23,30]

The results from NORMALIZE support the long-term safety of tenapanor alone and combined with sevelamer; adverse events were similar to those of previous clinical trials, and no new safety signals were identified.[21–23] As in other studies,[21–23] diarrhea (defined as any bothersome loose or mushy stools) was the most common TEAE, reported in 10% of group 1 (T/T+S) and 44% of group 2 (S+T). Diarrhea rarely resulted in study treatment discontinuation. In a 12-week monotherapy trial (NCT02675998), tenapanor treatment resulted in softer and/or more frequent bowel movements; however, on average, these remained within the normal range of stool consistency as gauged by the Bristol Stool scale.[21] Diarrhea tends to be mild to moderate in severity and transient, with a median resolution within ≈2 weeks across multiple studies of tenapanor.[31] The higher rate of diarrhea in patients from group 2, who started tenapanor during NORMALIZE, compared with the rate of diarrhea in patients from group 1, who started tenapanor approximately 12 months earlier in the PHREEDOM study, is consistent with the observation that the change in stool consistency is seen early in the course of treatment and is either attenuated or accommodated.

The NORMALIZE study had several strengths. The population was diverse by age, sex, self-reported race/ethnicity, primary cause of kidney failure, and dialysis vintage, and a relatively high percentage of patients completed the study despite the chronic nature of their underlying illness and burden of comorbidities. NORMALIZE provides additional long-term safety and efficacy data for tenapanor alone or in combination with sevelamer. The study included patients receiving peritoneal dialysis and hemodialysis, enhancing the generalizability of the results. However, the study also had some limitations. NORMALIZE was an open-label clinical trial without a control arm which can create bias in the interpretation of results. While results of the NORMALIZE study contribute to the evidence base of the phosphate absorption inhibitor tenapanor as both monotherapy and in combination with the phosphate binder sevelamer, the open-label OPTIMIZE trial (NCT04549597) will provide additional information on the optimal approach to introduce tenapanor, whether alone or in combination with the patient's current phosphate binders, for the treatment of hyperphosphatemia in patients receiving maintenance dialysis.

In summary, tenapanor, a phosphate absorption inhibitor, facilitates management of hyperphosphatemia by reducing paracellular phosphate transport and has an acceptable safety profile.[19] The NORMALIZE study supports both the use of tenapanor as monotherapy or in addition to phosphate binders as a dual mechanism approach for the control of hyperphosphatemia in adult patients receiving maintenance dialysis.

Disclosures

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Data Sharing Statement

Partial restrictions to the data and/or materials apply. Ardelyx will consider reasonable requests for data sharing such as the study protocol, SAP, and ICF on a case-by-case basis based on data availability, burden, and data privacy issues. This will go into effect immediately after publication for a period of up to 1 year. Data will be shared to achieve aims in an investigator-submitted proposal, which has been approved by Ardelyx. Proposals should be directed to medinfo@ardelyx.com. To gain access to data, requestors will need to sign a data access agreement.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A396.

Supplemental Methods. Study drug dosing.

Supplemental Figure 1. Study design.

Supplemental Figure 2. Pill burden reduction in group 2 (sevelamer+tenapanor) of FAS.

Supplemental Figure 3. Median sevelamer pill burden in group 1 (tenapanor or tenapanor+sevelamer) of FAS.

Supplemental Table 1. Patient disposition.

Supplemental Table 2. Summary of KDQoL and DSI scores.

Supplemental Table 3. Individual listing of deaths due to adverse events.

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