Tenapanor as Therapy for Hyperphosphatemia in Maintenance Dialysis Patients: Results from the OPTIMIZE Study

Stuart M. Sprague[1,2] *Daniel E. Weiner*[3] *David P. Tietjen*[4] *Pablo E. Pergola*[5] *Steven Fishbane*[6] *Geoffrey A. Block*[7] *Arnold L. Silva*[8] *Stephen Z. Fadem*[9] *Robert I. Lynn*[10] *George Fadda*[11] *Lynae Pagliaro*[12] *Suling Zhao*[12] *Susan Edelstein*[12] *David M. Spiegel*[12] *and David P. Rosenbaum*[12]

Key Points

- Tenapanor, a first-in-class local inhibitor of sodium/hydrogen exchanger isoform 3, acts as a phosphate absorption inhibitor by decreasing paracellular phosphate absorption.
- Tenapanor alone or with phosphate binders achieved $P \leq 5.5$ mg/dl over 10 weeks in 34%–38% of patients taking phosphate binders at baseline.
- Tenapanor can help adults with CKD on maintenance dialysis achieve normal serum phosphate concentrations.

Abstract

Background OPTIMIZE was a randomized, open-label study evaluating different tenapanor initiation methods. OPTIMIZE evaluated tenapanor alone and in combination with phosphate binders (PBs) to achieve target serum phosphate (P) ≤5.5 mg/dl.

Methods Patients with inadequately controlled P receiving maintenance dialysis from 42 US locations who were taking PBs with baseline $P > 5.5$ mg/dl and ≤ 10.0 mg/dl, or were PB-naive with baseline $P > 4.5$ mg/dl and ≤ 10.0 mg/dl, were included in OPTIMIZE. Participants taking PBs at baseline were randomized to switch from PBs to tenapanor (*Straight Switch*; $n=151$) or reduce PB dosage by ≥50% and add tenapanor (*Binder Reduction*; $n=152$); PB-naive patients started tenapanor alone (*Binder-Naive*; $n=30$). Participants received tenapanor 30 mg twice a day for 10 weeks (part A), followed by an elective, 16-week open-label extension (part B). Outcomes included changes from baseline in P, intact fibroblast growth factor 23, parathyroid hormone, serum calcium, and medication burden; patient-reported outcomes; and safety.

Results By part A end point, 34.4% (*Straight Switch*), 38.2% (*Binder Reduction*), and 63.3% (*Binder-Naive*) of patients achieved $P \leq 5.5$ mg/dl. Mean P reduction and median pill burden reduction from baseline to part A end point were 0.91±1.7 mg/dl and 4 pills/d for the *Straight Switch* and 0.99±1.8 mg/dl and 1 pill/d for the *Binder Reduction* group. The mean P reduction for *Binder-Naive* patients was 0.87±1.5 mg/dl. Among *Straight Switch* and *Binder Reduction* patients who completed patient experience questionnaires, 205 of 243 (84.4%) reported an improved phosphate management routine. Diarrhea was the most common adverse event (133 of 333 [39.9%]).

Conclusions Tenapanor as monotherapy or in combination with PBs effectively lowered P toward the target range in patients who were PB-naive or who were not at goal despite PB use.

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Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Stuart M. Sprague, email: SSprague@northshore.org

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L. Pagliaro: affiliation at time work was conducted.

Introduction

In patients with CKD who require maintenance dialysis, hyperphosphatemia has been reported in approximately half the population.[1–3] Hyperphosphatemia is associated with an increased risk of mortality, cardiovascular morbidity, and all-cause hospitalization.[1,4–7] In patients with CKD receiving maintenance dialysis, management of hyperphosphatemia by reducing serum phosphate (P) toward the normal range (2.5–4.5 mg/dl) is recommended by the 2017 Kidney Disease Improving Global Outcomes guidelines.[8]

Clinical practice guidelines recommend restricting dietary phosphate and including phosphate-lowering therapies for the treatment of hyperphosphatemia in patients with CKD receiving maintenance dialysis.[9,10] However, these treatment strategies can be difficult for patients to implement.[11,12] Patients struggle to restrict dietary phosphate while maintaining adequate nutrition because of difficulties in finding nutritious, low-phosphate foods.[13,14] Use of phosphate binders (PBs) often requires patients to ingest a substantial number of large pills with every meal.[11] In the United States, ≈80% of patients receiving dialysis take PBs, for an average of 7.4 pills/d, and 57% reported skipping ≥1 dose in the past month.[15] In addition, PBs tend to be associated with gastrointestinal side effects, such as bloating, constipation, nausea, and diarrhea. According to the Dialysis Outcomes and Practice Patterns Study Practice Monitor, ≈40% of patients have $P > 5.5$ mg/dl in any given month, suggesting that current treatments are insufficient.[14,16]

Tenapanor is a novel phosphate absorption inhibitor that targets the primary pathway of phosphate absorption in the gastrointestinal tract. Tenapanor selectively inhibits sodium/hydrogen exchanger isoform 3, causing a conformational change in tight junction proteins that leads to a decrease in paracellular permeability specific to phosphate.[17–19] Tenapanor monotherapy has been investigated as a treatment for hyperphosphatemia in patients with CKD receiving maintenance dialysis in phase 2 and 3 clinical trials (NCT02081534; NCT02675998; PHREEDOM [NCT03427125]).[20–22] These trials met their primary and key secondary end points, demonstrating significant reduction of P with tenapanor 30 mg twice a day compared with placebo.[20–22] The phase 3 AMPLIFY study (NCT03824587) demonstrated that the addition of tenapanor to the standard-of-care PB treatment used at study entry resulted in significantly reduced P compared with placebo plus PBs.[23] This dual-mechanism approach was further validated in the long-term, phase 3, open-label NORMALIZE study (NCT03988920), where tenapanor as monotherapy or in combination with a PB resulted in lower P in patients with CKD receiving dialysis.[24] In all trials, mild-to-moderate diarrhea was the most frequently reported adverse event (AE).[20–23]

OPTIMIZE (NCT04549597) was a randomized, open-label study to evaluate phosphate management strategies to achieve $P \leq 5.5$ mg/dl using tenapanor as core therapy for the treatment of hyperphosphatemia. Patients had inadequately controlled P on maintenance dialysis and were prescribed PB therapy or were PB-naive. Here we report efficacy and patient-reported outcomes from OPTIMIZE after up to 10 weeks of treatment and safety for up to 26 weeks of treatment (inclusive of a 10-week treatment period and an elective 16-week extension).

Methods

Patients

OPTIMIZE (NCT04549597) was a two-part, randomized, open-label, interventional study that ran from September 2020 to March 2023. It evaluated different methods for initiating tenapanor to treat hyperphosphatemia in patients with CKD and inadequately controlled P receiving maintenance dialysis. Patients were eligible for inclusion if taking PBs ≥3 times a day or if PB-naive, aged 18–80 years, and receiving chronic maintenance dialysis with Kt/V ≥1.2 before screening. To be eligible at screening, patients taking PBs were required to have *P* values of >5.5 and ≤10 mg/dl (*i.e.*, uncontrolled P despite treatment) and >4.5 and ≤10 mg/dl if PB-naive.

All patients provided written and informed consent before study entry. Study site investigators ensured the study protocol was approved by the appropriate institutional review board and/or independent ethics committee before trial initiation. The trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and all applicable local laws and regulations.

Study Design

The primary objective of the study was to evaluate the effect of tenapanor as core therapy alone or in combination with PBs to achieve $P \leq 5.5$ mg/dl, a level suggested by the 2017 Kidney Disease Improving Global Outcomes clinical practice guidelines.[8] Patients receiving stable PB treatment at enrollment were randomized (1:1) to two treatment groups: *Straight Switch* patients discontinued PBs and started tenapanor 30 mg twice a day, while *Binder Reduction* patients decreased their dose by ≥50% (may have been >50% if taking an odd number of pills), with the ability to switch the binder regimen from thrice daily to twice a day or to once daily and adding tenapanor 30 mg twice a day to their regimen. These patients were stratified by type of PB and P level at screening. Patients not taking binders at baseline (*Binder-Naive*) received tenapanor 30 mg twice a day without PBs (Supplemental Figure 1). These individuals were not randomized. Part A was a 10-week treatment period designed to evaluate the efficacy and safety of tenapanor therapy alone or in combination with PBs; patients were evaluated at in-center visits at weeks 1, 2, 3, 4, 6, 8, and 10. Part B included patients who agreed to participate in an elective, 16-week treatment extension to monitor safety and included four additional in-center visits (weeks 14, 18, 22, and 26).

Patients were instructed at time of randomization to discontinue medications, such as stool softeners and laxatives (see Supplemental Methods). After week 2, investigators were permitted to adjust tenapanor and PB dose at any time during the treatment period on the basis of P measurements (see Supplemental Methods for details on dose adjustments). Per protocol, the dialysis prescription was to remain unchanged.

End Points

Efficacy end points were assessed by treatment group and included measures of P, intact fibroblast growth factor

23 (iFGF23), parathyroid hormone (PTH), and phosphate-lowering medication burden. Patients who achieved $P \leq 5.5$ mg/dl and $P \leq 4.5$ mg/dl were considered P responders and normal P responders, respectively. Change from baseline was evaluated for P, iFGF23, PTH, and total daily pill number of phosphate-lowering medication (tenapanor and PB combined). Patient-reported outcomes were collected using a patient experience questionnaire administered at week 10 or at the early termination visit in part A.

Safety was assessed by monitoring AEs, clinical laboratory tests (including serum electrolytes), body weight and vital signs, echocardiogram, and physical examination.

Statistical Analysis

The safety population included all patients who received ≥1 dose of tenapanor during the study. The full analysis set included all patients who received ≥1 dose of tenapanor and had ≥1 postbaseline *P* value available.

Efficacy variables were summarized using descriptive statistics for the full analysis set and presented by planned group at each postbaseline visit and the part A end point. Response end points were derived on the basis of observed cases. For all patients, the part A end point is the last observed value during part A, which could occur before week 10, if the patient withdrew early. This differs from week 10 data, which only include data for patients who completed the week 10 visit.

A mixed-effects model for repeated measures (MMRM) on observed cases was performed for change from baseline in P at each postbaseline visit during part A for *Straight Switch* and the *Binder Reduction* patients only. The MMRM included cohort, randomization stratum, postbaseline visit (weeks 1–10), and the cohort-by-visit interaction as fixed effect factors; baseline *P* values and the baseline-by-visit interaction as fixed effect covariates; and patient as a random effect.

Safety data were summarized descriptively for the safety population and presented by actual treatment group.

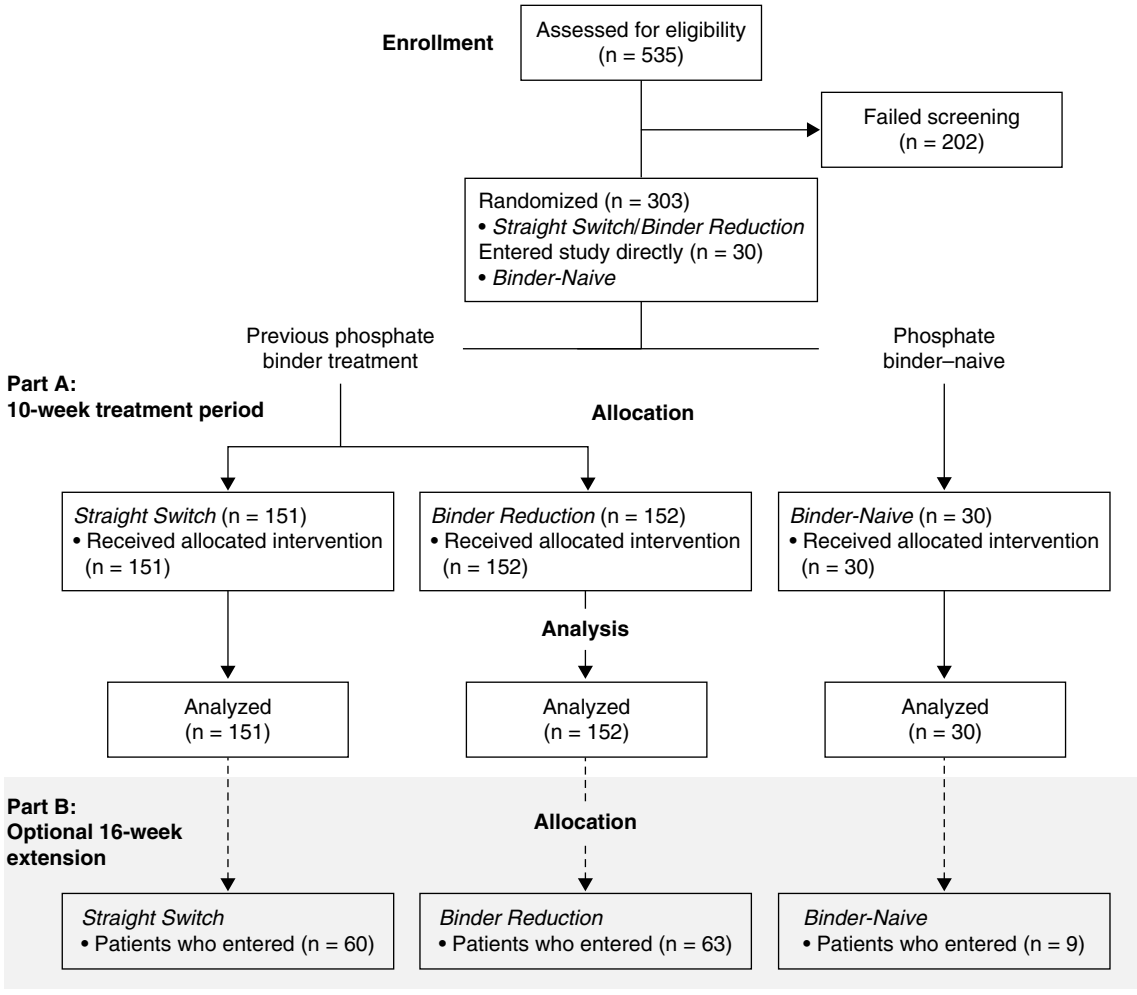

Figure 1. Patient disposition. In part A, 333 patients were enrolled, with 151 randomized to *Straight Switch* and 152 to *Binder Reduction*; 30 *Binder-Naive* participants entered the study directly. Patients who received at least one dose of tenapanor during the study were included in the safety analysis set. The full analysis set included patients who received at least one dose of tenapanor and had at least one postbaseline *P* value during the study.

Table 1. Baseline demographics and characteristics (full analysis set[a])

Characteristic	Straight Switch, n=151	Binder Reduction, n=152	Binder-Naive, n=30
Age at screening, yr	52.4 (11.1)	53.2 (12.1)	55.4 (16.5)
Sex, *n* (%)			
Female	44 (29.1)	50 (32.9)	12 (40.0)
Male	107 (70.9)	102 (67.1)	18 (60.0)
Race, *n* (%)			
American Indian or Alaska Native	3 (2.0)	6 (3.9)	1 (3.3)
Asian	13 (8.6)	3 (2.0)	0
Black or African American	66 (43.7)	71 (46.7)	9 (30.0)
Native Hawaiian or other Pacific Islander	2 (1.3)	4 (2.6)	0
White	64 (42.4)	62 (40.8)	20 (66.7)
Other/unknown	3 (2.0)	6 (3.9)	0
Ethnicity, *n* (%)			
Not Hispanic or Latino	109 (72.2)	114 (75.0)	17 (56.7)
Hispanic or Latino	42 (27.8)	38 (25.0)	13 (43.3)
Baseline weight (predialysis), kg, mean (SD)	95.2 (24.1)	94.3 (25.9)	83.9 (23.5)
Baseline height, cm, mean (SD)	170.9 (10.1)	171.7 (11.1)	166.1 (14.2)
Baseline BMI, kg/m^2, mean (SD)	32.7 (8.4)	31.9 (8.3)	30.5 (7.9)
Type of dialysis at screening, *n* (%)			
Hemodialysis	119 (78.8)	124 (81.6)	25 (83.3)
Peritoneal dialysis	32 (21.2)	28 (18.4)	5 (16.7)
Duration since first dialysis at baseline, mo, mean (SD)	57.4 (52.4)	57.7 (49.5)	19.3 (20.7)
Type of PB taken at screening, *n* (%)			
Calcium-based binder	23 (15.2)	20 (13.2)	0
Combination	26 (17.2)	26 (17.1)	0
Iron-based binder	39 (25.8)	41 (27.0)	0
Other nonsevelamer binder	6 (4.0)	4 (2.6)	0
Sevelamer binder	57 (37.7)	61 (40.1)	0
Baseline *P* value, mg/dl, mean (SD)	7.1 (1.0)	7.2 (1.1)	6.1 (0.8)
Baseline *P* value, mg/dl, *n* (%)			
$P \leq 5.5$	0	0	7 (23.3)
$P > 5.5$ and < 7.5	99 (65.6)	99 (65.1)	21 (70.0)
$P \geq 7.5$	52 (34.4)	53 (34.9)	2 (6.7)
Baseline iFGF23 value, pg/ml, median (min–max)	6886.5 (197.3–66,000.0)	11,434.5 (157.3–66,000.0)	1631.6 (64.6–27,342.0)
Baseline PTH value, pg/ml, mean (SD)	428.3 (242.9)	391.6 (243.3)	320.8 (132.1)
Baseline serum calcium, mg/dl, mean (SD)	8.5 (0.7)	8.7 (0.8)	8.4 (0.7)
Baseline total daily phosphate-lowering medication pill number, mean (SD)	8.8 (3.8)	9.3 (4.0)	0

Baseline is the last observed measurement collected before the first dose of tenapanor. BMI, body mass index; iFGF23, intact fibroblast growth factor 23; PB, phosphate binder; PTH, parathyroid hormone; P, serum phosphate.
[a]The patients from full analysis set are grouped by the planned treatment group.

Results

Patients

In part A, 333 patients were enrolled, with 151 randomized to *Straight Switch* and 152 to *Binder Reduction*; there were 30 *Binder-Naive* participants (Figure 1). Patients in *Straight Switch* and the *Binder Reduction* groups had similar mean ages (52.4 and 53.2 years, respectively), were predominantly male and White or African American, and had similar baseline mean *P* values and similar duration since first dialysis (Table 1). The 30 *Binder-Naive* patients had a mean age of 55.4 years and were predominantly male and White, with lower baseline mean *P* value and shorter mean duration since first dialysis compared with randomized patients (Table 1).

Efficacy End Points

For patients in the *Straight Switch* and *Binder Reduction* groups, mean P reductions were similar from baseline to the part A end point and from baseline to week 10 (Figure 2 and Supplemental Figure 2A). Baseline *P* values were 7.1 and 7.2 mg/dl for the *Straight Switch* and *Binder Reduction* groups, respectively. During the first 6 weeks of treatment, the *Binder Reduction* group had a significantly greater least squares mean P reduction compared with the *Straight Switch* group at each visit in MMRM analysis (range, $P = 0.0001$ to $P = 0.025$). The least squares mean difference in P reduction between the *Straight Switch* and *Binder Reduction* groups was not significant at weeks 8 or 10. Mean reductions in P were similar for the *Straight Switch*

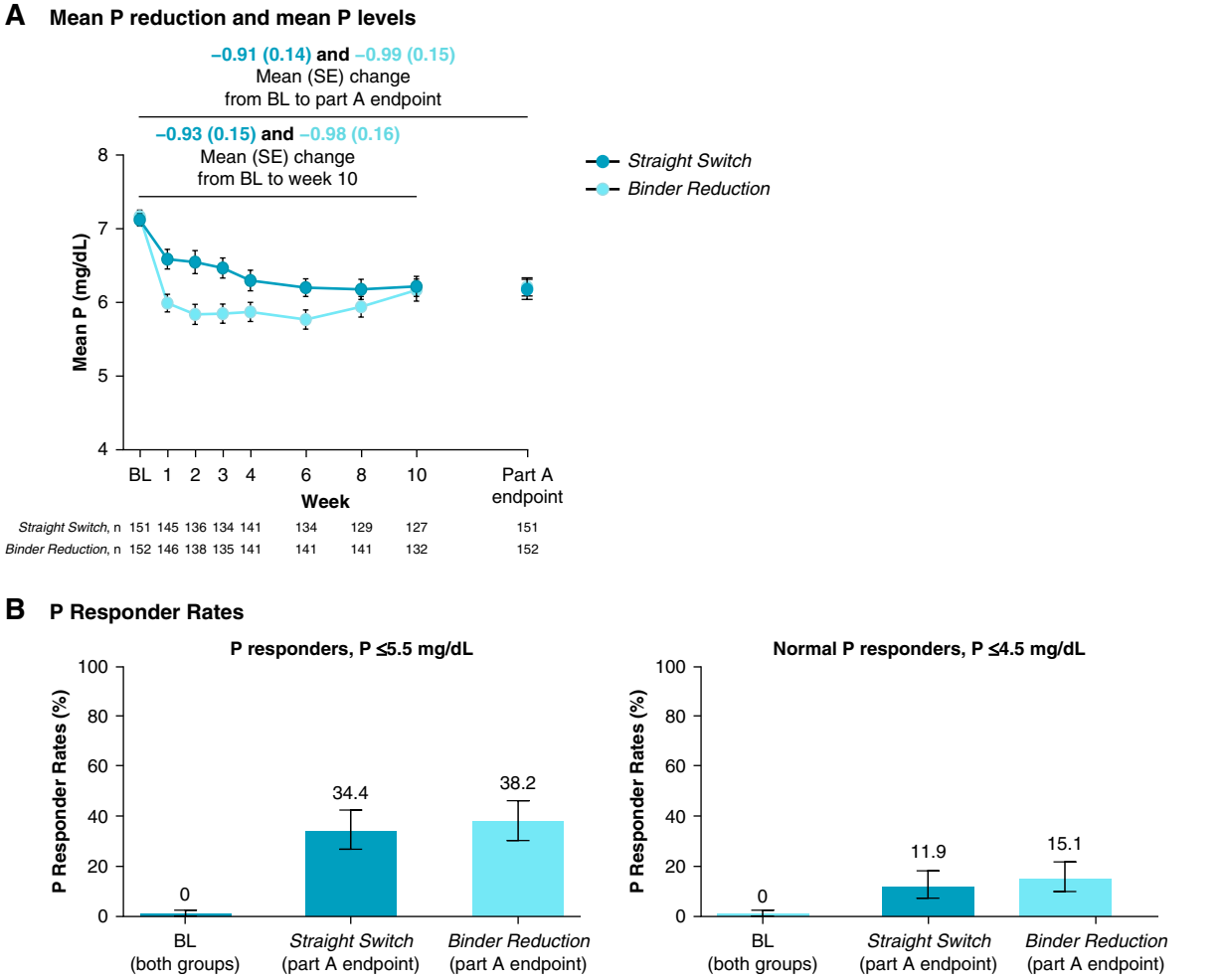

Figure 2. Serum phosphate reduction and responder rates in the Straight Switch and Binder Reduction cohorts. Change in P levels from baseline to part A end point[a] and mean P levels by visit during part A period (A) and P responder rates at baseline and part A end point[a] (B) for *Straight Switch* and *Binder Reduction* cohorts. (A) Error bars for mean *P* value represent SEM. (B) Error bars for P responder rates at the part A end point represent Clopper–Pearson 95% confidence intervals. Responder rates were derived on the basis of observed cases. [a]For all patients, the part A end point is the last observed value during part A, which could occur before week 10, if the patient withdrew early. BL, baseline; P, serum phosphate.

and *Binder Reduction* groups at the part A end point, with mean (SEM) P reductions of 0.91 (0.14) and 0.99 (0.15) mg/dl, respectively. The proportion of patients achieving P targets was also similar for *Straight Switch* and *Binder Reduction* patients at the part A end point, with 34.4% and 38.2%, respectively, achieving $P \leq 5.5$ mg/dl (primary objective) and 11.9% and 15.1%, respectively, achieving $P \leq 4.5$ mg/dl (secondary objective; Figure 2). These values were similar at week 10, with responder rates for $P \leq 5.5$ mg/dl of 35.4% for *Straight Switch* and 38.6% for *Binder Reduction* patients and responder rates for $P \leq 4.5$ mg/dl of 11.0% and 15.2%, respectively.

On average, the phosphate-lowering medication burden was reduced among patients in the *Straight Switch* and the *Binder Reduction* groups (Figure 3). The median total daily pill number was nine in both groups at baseline (Supplemental Table 1). After a protocol-driven initial decrease in total daily number of pills, the total daily pill number increased from its early nadir over the course of the study (Supplemental Table 1) as the dosage of tenapanor and PBs was adjusted to achieve goal *P* values and gastrointestinal tolerability (see Supplemental Methods, Dose Adjustments). At the part A end point, pill burden was reduced to a median of 4 pills/d for *Straight Switch* patients, with a median percent reduction of 44.4% from baseline; for *Binder Reduction* patients, pill burden was reduced to a median of 6 pills/d, with a median percent reduction of 16.7% (Figure 3 and Supplemental Table 1).

Binder-Naive patients had a mean (SEM) P reduction of 0.87 (0.27) mg/dl at the part A end point and 0.93 (0.32) mg/dl at week 10. The baseline *P* value was 6.1 mg/dl. The responder rates at the part A end point for this group were 63.3% for $P \leq 5.5$ mg/dl and 43.3% for $P \leq 4.5$ mg/dl (Figure 4 and Supplemental Figure 2B). Of 30 patients, 73.9% of patients were taking tenapanor alone at week 10, and 76.7% of patients were taking tenapanor alone at the part A end point (Supplemental Table 2).

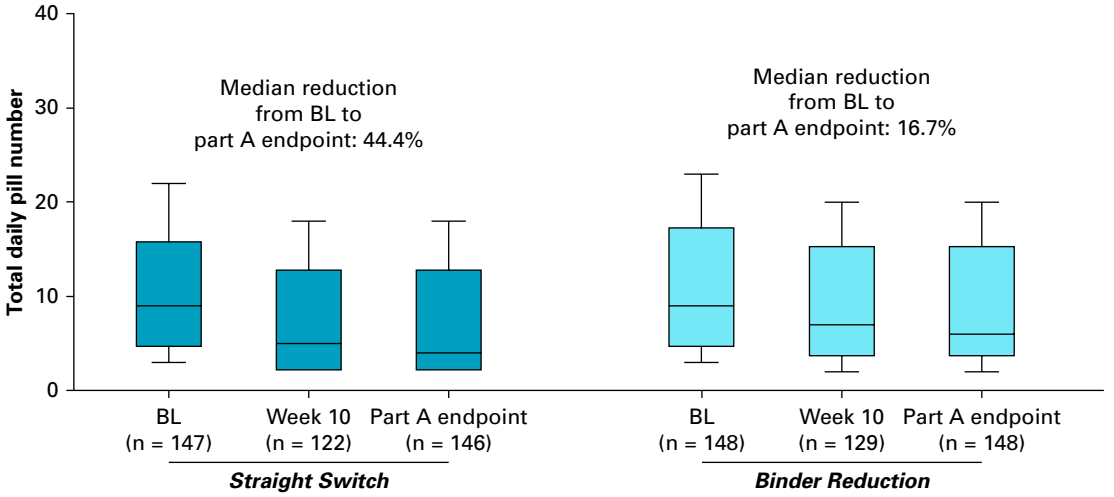

Figure 3. Median total daily pill number of phosphate-lowering medication at baseline, week 10, and part A end point in the Straight Switch and Binder Reduction cohorts[a]. The boxplot represents median total daily pill number (the combined number of tenapanor and PB tablets). The lines inside the boxes indicate the median values. The top and bottom edges of the boxes indicate the interquartile range (IQR) from the 25th to 75th percentile. The whiskers extend 1.5 times the IQR. [a]For all patients, the part A end point is the last observed value during part A, which could occur before week 10, if the patient withdrew early. PB, phosphate binder.

Median relative reductions in iFGF23 from baseline to the part A end point of 12.2% and 22.0% were observed for *Straight Switch* and *Binder Reduction* patients, respectively (Supplemental Figure 3A). Similar median relative reductions were observed at week 10. The estimated mean relative reduction from baseline in iFGF23 was 15% and 30% for the *Straight Switch* and *Binder Reduction* groups, respectively. The comparison of the part A end point iFGF23 to baseline iFGF23 was statistically significant between these two groups ($P = 0.017$). *Binder-Naive* patients had a median relative reduction from baseline to the part A end point of 38.7% and a reduction of 38.8% from baseline to week 10.

In each treatment group, no clinically meaningful changes in PTH or serum calcium values were observed (Supplemental Table 3). The subgroup of patients with normal baseline PTH concentrations (PTH <600 pg/ml) experienced negligible increases in PTH from baseline to week 10 and the part A end point (Supplemental Figure 3B). However, in a subgroup of patients ($n=55$) with PTH ≥600 pg/ml at baseline, the median relative reduction from baseline in PTH for *Straight Switch* and

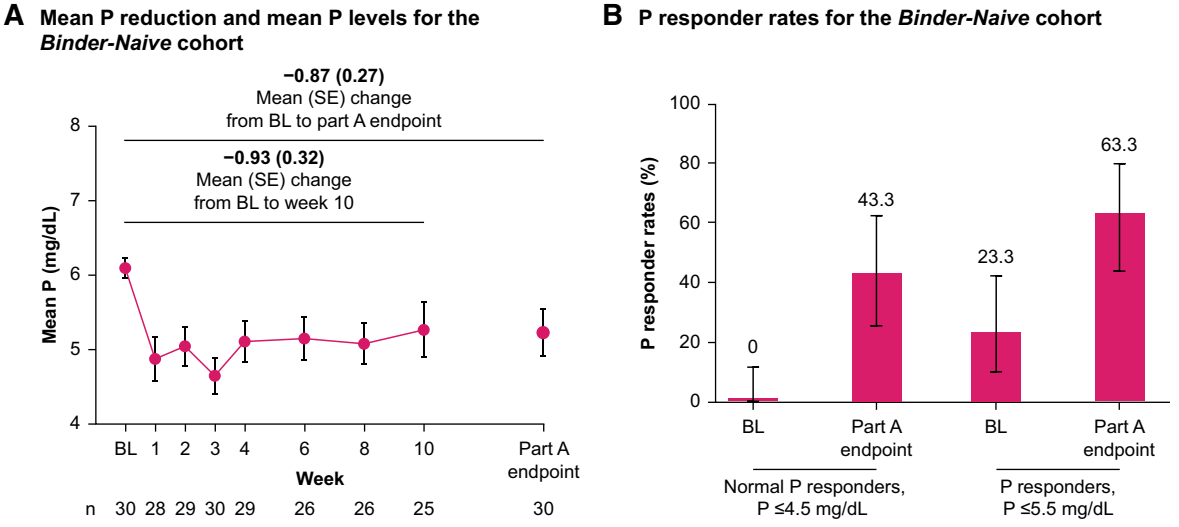

Figure 4. Serum phosphate reduction and responder rates in the Binder-Naive cohort.[a] Change in P levels from baseline to part A end point[a] and mean P levels by visit during part A period (A) and P responder rates at baseline and part A end point[a] (B) for the *Binder-Naive* cohort. (A) Error bars for mean *P* value represent SEM. (B) Error bars for P responder rates at the part A end point represent Clopper–Pearson 95% confidence intervals. Responder rates were derived on the basis of observed cases. [a]For all patients, the part A end point is the last observed value during part A, which could occur before week 10, if the patient withdrew early.

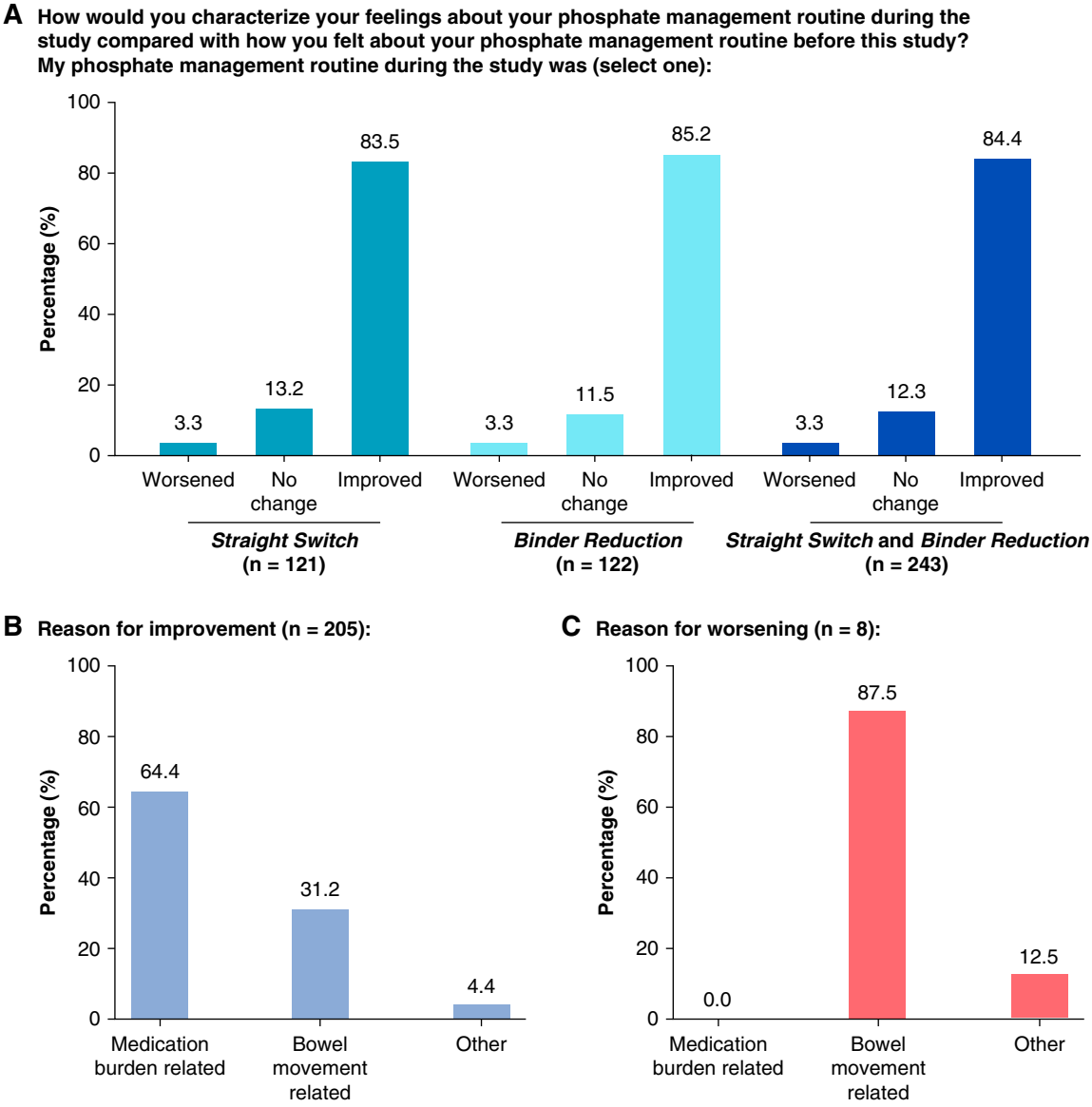

Figure 5. Patient-reported outcomes. Data reported are for the combined patients from the *Straight Switch* and *Binder Reduction* groups who completed the patient experience questionnaire; the *Binder-Naive* group was not included in this analysis because the selected questions were not applicable to this population. Columns show the percentage of patients who responded to each question. Breakdown of responses can be found in Supplemental Table 4.

Binder Reduction patients, respectively, was 10.0% and 24.0% at week 10 and 5.5% and 26.0% at the part A end point (Supplemental Figure 3C). Only two *Binder-Naive* patients had a baseline PTH value ≥600 pg/ml.

Patient-Reported Outcomes

Among the combined 243 patients from the *Straight Switch* and *Binder Reduction* groups who completed the patient experience questionnaire, 205 (84.4%) reported an improved phosphate management routine compared with previous therapy (Figure 5A and Supplemental Table 4). Among these, the primary reasons were reduced medication burden (*e.g.*, pill size, number, and dosing frequency) and bowel movement changes (*e.g.*, bowel movement form and frequency) (Figure 5B and Supplemental Table 4). When asked whether controlling their phosphate was difficult, 168 of 243 patients (69.1%) believed that controlling their phosphate was much less or somewhat less difficult (Supplemental Table 4).

Safety

Among 333 patients who received ≥1 dose of tenapanor for up to 26 weeks of treatment, 67.0% reported a treatment-emergent AE (TEAE) (Table 2). Similar percentages of *Straight Switch* and *Binder Reduction* patients had a TEAE (70.2% and 67.8%, respectively), with a lower proportion observed in the *Binder-Naive* group (46.7%). Besides coronavirus disease 2019 (COVID-19), gastrointestinal-related TEAEs were the most frequently

Table 2. Summary of safety

Event	Straight Switch, n=151	Binder Reduction, n=152	Binder-Naive, n=30
Any TEAE	106 (70.2)	103 (67.8)	14 (46.7)
Any severe AE[a]	19 (12.6)	21 (13.8)	4 (13.3)
Any SAE	20 (13.2)	26 (17.1)	4 (13.3)
Acute myocardial infarction[b]	3 (2.0)	0	1 (3.3)
Hyperkalemia[b]	3 (2.0)	2 (1.3)	1 (3.3)
COVID-19[b]	2 (1.3)	5 (3.3)	0
Pneumonia[b]	2 (1.3)	4 (2.6)	0
Peritonitis[b]	0	3 (2.0)	0
Any TEAE leading to tenapanor discontinuation	15 (9.9)	20 (13.2)	1 (3.3)
Diarrhea	11 (7.3)	10 (6.6)	1 (3.3)
Any TEAE leading to PB discontinuation	5 (3.3)	15 (9.9)	2 (6.7)
Diarrhea	4 (2.6)	8 (5.3)	1 (3.3)
Any TEAE leading to death	1 (0.7)	1 (0.7)	0

Values are n (%). Preferred terms are for any TEAE experienced by ≥3 patients. AE, adverse event; COVID-19, coronavirus disease 2019; PB, phosphate binder; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Severe AEs were defined as events where the patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.
[b]These SAEs included treatment-emergent and non–treatment-emergent SAEs.

reported (Table 3). Diarrhea was both the most common TEAE (n=133; 39.9%) and the most common cause of tenapanor discontinuation (n=22; 6.6%) (Tables 2 and 3). The incidence of diarrhea was similar between the *Straight Switch* and *Binder Reduction* groups and lower for the *Binder-Naive* group.

COVID-19 was reported by 13 patients (3.9%; Table 3). Six patients prematurely discontinued for reasons related to COVID-19 infection. COVID-19 was also the most frequently reported serious AE (*Straight Switch*, n=2 [1.3%]; *Binder Reduction*, n=5 [3.3%]; Table 2). Seven patients died during the study period, 2 (0.6%) because of a TEAE, and 5 (1.5%) because of non–treatment-emergent AEs. The TEAEs included *Staphylococcal* bacteremia (n=1) and COVID-19 (n=1). The non–treatment-emergent AEs included COVID-19–related serious AEs (n=2) reported after patients received their last dose of study drug, acute myocardial infarction (n=1), sepsis (n=1), or pulseless electrical activity (n=1). No death was assessed as related to tenapanor or PB.

Albumin concentrations were stable throughout the study. No new safety signals were identified in clinical

Table 3. Treatment-emergent adverse events experienced by ≥4 patients, by preferred term

Adverse Event	Straight Switch, n=151	Binder Reduction, n=152	Binder-Naive, n=30
Diarrhea	59 (39.1)	64 (42.1)	10 (33.3)
Mild	25 (16.6)	24 (15.8)	4 (13.3)
Moderate	30 (19.9)	33 (21.7)	5 (16.7)
Severe	4 (2.6)	7 (4.6)	1 (3.3)
Nausea	7 (4.6)	7 (4.6)	0
COVID-19	6 (4.0)	7 (4.6)	0
Vomiting	5 (3.3)	5 (3.3)	0
Arthralgia	4 (2.6)	2 (1.3)	0
Headache	4 (2.6)	1 (0.7)	0
Hyperkalemia	4 (2.6)	2 (1.3)	1 (3.3)
Pain in extremity	4 (2.6)	1 (0.7)	0
Arteriovenous fistula site complication	3 (2.0)	4 (2.6)	0
Constipation	3 (2.0)	6 (3.9)	0
Hypotension	3 (2.0)	4 (2.6)	0
Pneumonia	2 (1.3)	4 (2.6)	0
Abdominal pain	1 (0.7)	8 (5.3)	1 (3.3)
Peritonitis	0	4 (2.6)	0

Values are n (%). Mild TEAEs were defined as events where the patient experiences awareness of symptoms, but they are easily tolerated or managed without specific treatment. Moderate TEAEs were defined as events where the patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment. Severe TEAEs were defined as events where the patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures. COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

laboratory evaluations, vital signs, echocardiograms, and physical examinations.

Discussion

In the randomized, open-label OPTIMIZE study of patients with CKD with hyperphosphatemia receiving maintenance dialysis, 35%–40% of patients with $P > 5.5$ mg/dl with *Straight Switch* and *Binder Reduction* strategies, respectively, were able to reach target P. Overall reduced pill burden and improvement in patient-reported outcomes occurred over 10 weeks. These results demonstrate that treatment with tenapanor alone or in combination with PBs enabled patients to achieve guideline-established P targets and reduced P. The phosphate-lowering medication burden was also reduced for patients on PBs at study entry, and most of these patients reported improved patient experience with their phosphate management routine, most often because of decreased medication burden or improvement in bowel movement frequency and form.

Overall, tenapanor demonstrated an acceptable safety and tolerability profile, and no new safety signals were identified versus previous studies of tenapanor as monotherapy or in combination with PBs.[21–23] Notably, diarrhea incidence for the safety population in this study (39.9%) was lower than the incidence from prior phase 2 and 3 trials of tenapanor (47.9%–68.0%),[20–22] and the proportion of patients who discontinued because of diarrhea was also lower (6.6%) than prior phase 2 and 3 trials (8.3%–32.0%).[20–22] At the beginning of OPTIMIZE, patients were educated about the side effects of tenapanor, and the use of medications such as stool softeners or laxatives were prohibited per study protocol, which likely resulted in the reduced diarrhea incidence and the low rate of tenapanor discontinuation due to diarrhea.

This was the first study to evaluate various methods for initiating tenapanor therapy that may be used in clinical practice and the first to incorporate patients who were PB-naive. These results add to prior tenapanor clinical trials where patients have either initiated tenapanor treatment after a washout period where existing binder therapies were stopped[20–22] or after a run-in period where existing binder dose was stabilized.[23]

Tenapanor is a novel, first-in-class treatment for hyperphosphatemia that reduces the absorption of phosphate and effectively lowers P with one pill twice a day. The medication burden associated with PBs is often significant to patients and leads to challenges in effectively controlling P.[13–15] Thus, identifying a treatment for hyperphosphatemia in patients with CKD receiving maintenance dialysis is important. In this study, total daily pill burden was reduced for both the *Straight Switch* and *Binder Reduction* patients. The greater reduction among *Straight Switch* patients was evident in all study visits, but more evident in the early study period, and likely because of study design (*Straight Switch* stopped other PBs to switch to tenapanor, while *Binder Reduction* did not).

There were several strengths to the OPTIMIZE study. This study evaluated common, real-world clinical approaches to treatment and examined a variety of outcomes to provide overall robust efficacy and safety results. The results of this study should also be considered within the context of some limitations: This was an open-label study with no placebo control, and while *Straight Switch* and *Binder Reduction* sample sizes were relatively large, the *Binder-Naive* group only enrolled 30 patients, and therefore, statistical comparisons were not made, so the results for this group should be interpreted with caution.

In this study, treatment with tenapanor alone or in combination with PBs consistently reduced P levels throughout the entire treatment period in patients with CKD receiving dialysis with hyperphosphatemia. This study demonstrated that physicians can initiate tenapanor using different treatment approaches, including a straight switch from previous PB therapy, combined with a reduced PB therapy, or as the initial phosphate-lowering therapy for PB-naive patients. All three approaches led to an early onset of phosphate-lowering effect within the first week and a sustained reduction of P over the study period. Tenapanor provides a novel mechanism of action that, alone or in combination with PBs, effectively lowers P, helping patients achieve target phosphate goals, reducing medication burden, and improving patient experience. Furthermore, it offers nephrologists an additional tool to improve P control, while addressing the currently unmet need of reducing the phosphate-lowering medication burden.

Disclosures

G.A. Block reports the following: Employer: US Renal Care; Ownership Interest: Ardelyx, Inc. and US Renal Care, Inc.; Research Funding: Akebia; and Advisory or Leadership Role: Ardelyx, Inc.. S. Edelstein reports the following: Employer: Ardelyx, Inc.; Ownership Interest: Ardelyx, Inc.; Research Funding: Ardelyx, Inc.; Patents or Royalties: Ardelyx, Inc.; and Advisory or Leadership Role: Ardelyx, Inc.. G. Fadda reports the following: Employer: Balboa Nephrology Medical Group; Research Funding: AstraZeneca, Calliditas, and GSK; Honoraria: AstraZeneca, Calliditas, and GSK; and Speakers Bureau: AstraZeneca, Bayer, Calliditas, and GSK. S.Z. Fadem reports the following: Employer: Kidney Associates, PLLC; Ownership Interest: Apple—few shares; DaVita—few shares; and The rest—money managers; Research Funding: I am a PI and do research for Reata, Ardelyx, Inc. through DaVita Clinical Research; Patents or Royalties: Have patent on encrypted software—no royalties yet; Advisory or Leadership Role: AAKP Chair Medical Advisory Board and Co-editor of aakpRenalife; NKF Serving Texas—Chair Medical Advisory Board; and Other Interests or Relationships: Own Touchcalc, Founded Nephron Information Center. S. Fishbane reports the following: Employer: Northwell Health; Consultancy: Aredelyx, Inc., AstraZeneca, Cara Therapeutics, Galderma, GSK, and Vifor; Research Funding: AstraZeneca, Galderma, Otsuka, and Vertex; and Honoraria: Ardelyx, Inc., AstraZeneca, GSK, and Vifor. R.I. Lynn reports the following: Employer: Kidney Medical Associates. L. Pagliaro reports the following: Employer: Ardelyx, Inc.. P.E. Pergola reports the following: Employer: Renal Associates, P.A.; Consultancy: Ardelyx, Inc., AstraZeneca, Bayer, Calico, Furoscix, GSK, Lilac, Novo Nordisk, Renibus, and Unicycive; Ownership Interest: Unicycive Therapeutics; Research Funding: Prinicipal or subinvestigator on multiple clinical trials. The contracts are with my practice, not individual; and Advisory or Leadership Role: Ardelyx, Inc. and Unicycive. D.P. Rosenbaum reports the

following: Employer: Ardelyx, Inc.; Ownership Interest: Ardelyx, Inc.; and Advisory or Leadership Role: Ardelyx, Inc.. A.L. Silva reports the following: Employer: Boise Kidney & Hypertension Institute; Consultancy: Aurinia, Boehringer-Ingelheim, GSK, Novartis, ProKidney, Reata Pharmaceuticals, and Travere; Research Funding: Akebia, Ardelyx, Inc., AstraZeneca, Cara, Cincor, Diamedica, Gilead, Goldfinch Bio, GSK, Mineralys, Novartis, OPKO Renal, ProKidney, Reata Pharmaceuticals, Regulus, Takeda, and Travere; Advisory or Leadership Role: Ardelyx, Inc., Aurinia, Boehringer Ingelheim, GSK, Novartis, ProKidney, Reata, and Travere; and Speakers Bureau: Amgen, AstraZeneca, Aurinia, Bayer, Boehringer-Ingelheim, Janssen, OPKO Renal, and Vifor. D.M. Spiegel reports the following: Employer: Ardelyx, Inc.; Ownership Interest: Stock grants and options from Ardelyx, Inc.; and Other Interests or Relationships: Member: ASN, ISN, and NKF. S.M. Sprague reports the following: Employer: NorthShore University Health System and University of Chicago Pritzker School of Medicine; Consultancy: Amgen, Ardelyx, Inc., Bayer, Fresenius, Horizon, Litholink Corp, OPKO, Shire, and Vifor; Ownership Interest: Individually owned stocks; Apple, Baxter, Bristol Myers, Coca Cola, First Australia Fund, IBM, and Walgreens; Research Funding: Amgen, Amylot, Ardelyx, Inc., OPKO, Reata, and Takeda; Honoraria: Amgen, Ardelyx, Inc., Bayer, Fresenius, OPKO, and Vifor; Advisory or Leadership Role: American Association of Endocrine Surgeons, *American Journal of Nephrology*, International Federation of Clinical Chemistry and Laboratory Medicine Work Group for Parathyroid Hormone, and National Kidney Foundation of Illinois; and Speakers Bureau: Amgen, Bayer, Fresenius, and OPKO. D.P. Tietjen reports the following: Employer: Nephrology Consultants, L.L.C. D.E. Weiner reports the following: Employer: Tufts Medical Center Physicians Organization; Research Funding: All compensation paid to Tufts MC: Bayer (site PI), Cara (site PI), and Vertex (site PI); Advisory or Leadership Role: Co Editor-in-Chief, NKF Primer on Kidney Diseases, 8th Edition; Editor-in-Chief, *Kidney Medicine*; Medical Director of Clinical Research, Dialysis Clinic Inc.; Member, ASN Quality and Policy Committees and ASN representative to KCP; Member, Scientific Advisory Board, National Kidney Foundation; and Other Interests or Relationships: Member, Adjudications Committee, ProKidney REACT Trial (WCG Clinical CRO) and Member, Safety and Clinical Events Committee for "A Prospective, Multi-Center, Open-Label Assessment of Efficacy and Safety of Quanta SC+ for Home Hemodialysis" Trial (Avania CRO). S. Zhao reports the following: Employer: Ardelyx and Google; and Ownership Interest: Ardelyx, Inc. and Google.

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Author Contributions

Conceptualization: Susan Edelstein, Lynae Pagliaro, David P. Rosenbaum, David M. Spiegel.
Data curation: Suling Zhao.
Formal analysis: Suling Zhao.
Investigation: Geoffrey A. Block, George Fadda, Stephen Z. Fadem, Steven Fishbane, Robert I. Lynn, Pablo E. Pergola, Arnold L. Silva, Stuart M. Sprague, David P. Tietjen, Daniel E. Weiner.
Writing – review & editing: Geoffrey A. Block, Susan Edelstein, George Fadda, Stephen Z. Fadem, Steven Fishbane, Robert I. Lynn, Lynae Pagliaro, Pablo E. Pergola, David P. Rosenbaum, Arnold L. Silva, David M. Spiegel, Stuart M. Sprague, David P. Tietjen, Daniel E. Weiner, Suling Zhao.

Data Sharing Statement

Partial restrictions to the data and/or materials apply. Partial restrictions to the data/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 on the basis of 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/A441.

Supplemental Methods

Supplemental References

Supplemental Table 1. Median total daily phosphate-lowering pill number.

Supplemental Table 2. Phosphate binder–naive group treatment regimen.

Supplemental Table 3. PTH and serum calcium values.

Supplemental Table 4. Patient experience questionnaire.

Supplemental Figure 1. Study design for OPTIMIZE.

Supplemental Figure 2. Boxplots of mean P levels by visit for the Straight Switch and Binder Reduction cohorts (A) and Binder-Naive cohort (B).

Supplemental Table 3. Median relative change from baseline to week 10 and part A end point[a] in intact FGF23 (A), PTH in patients with PTH <600 pg/ml at baseline (B), and in patients with PTH ≥600 pg/ml at baseline (C).

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AFFILIATIONS

[1]NorthShore University Health System, Evanston, Illinois
[2]University of Chicago Pritzker School of Medicine, Chicago, Illinois
[3]Tufts Medical Center, Boston, Massachusetts
[4]Nephrology Consultants LLC, Huntsville, Alabama
[5]Renal Associates PA, San Antonio, Texas
[6]Zucker School of Medicine at Hofstra & Northwell Health, Great Neck, New York
[7]US Renal Care, Denver, Colorado
[8]Boise Kidney and Hypertension Institute, Meridian, Idaho
[9]Kidney Associates, PLLC and Baylor College of Medicine, Houston, Texas
[10]Kidney Medical Associates, Bronx, New York
[11]Balboa Nephrology Medical Group, La Mesa, California
[12]Ardelyx, Inc., Waltham, Massachusetts