Addition of Tenapanor and Reduction of Phosphate Binders Improved Phosphate Control Similarly in Patients Undergoing Hemodialysis and Peritoneal Dialysis

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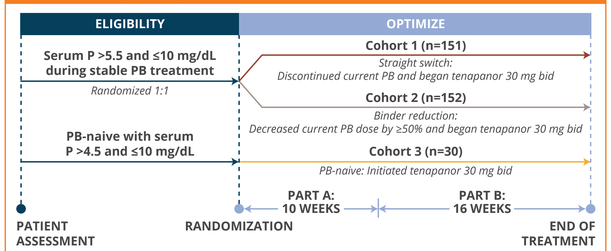
Background

- Adequate control of serum phosphate (P) remains challenging in patients with chronic kidney disease undergoing either hemodialysis (HD) or peritoneal dialysis (PD).[1]
- Tenapanor is a first-in-class, minimally absorbed, phosphate absorption inhibitor that targets the primary pathway of phosphate absorption in the gastrointestinal tract, the paracellular pathway, by selectively inhibiting sodium hydrogen exchanger isoform 3 (NHE3).[2-4]
- Real-world data show that nearly 70% of patients receiving dialysis are unable to consistently achieve and maintain adequate control of serum P during a 6-month period with the use of phosphate binders alone.[5]
- Tenapanor offers an alternative mechanism of action to phosphate binders for reduction of serum P in adult patients with chronic kidney disease receiving maintenance dialysis.[6]
- In the OPTIMIZE study, the effect of adding tenapanor and reducing phosphate binder dose during a 10-week treatment period was evaluated in patients who had chronic kidney disease treated with dialysis and had uncontrolled serum P with binders alone.[7]
- In this post hoc analysis, the aim was to investigate the effects of tenapanor initiation and binder reduction on serum P in patients receiving either HD or PD in the OPTIMIZE study.

Methods

- In OPTIMIZE, binder-treated patients with serum P >5.5 mg/dL were randomized to add tenapanor and discontinue binders (Cohort 1: Straight Switch) or add tenapanor and reduce binder dose by at least 50% (Cohort 2: Binder Reduction) on day 1 (**Figure 1**).[7]
- After week 2, investigators could adjust both tenapanor and phosphate binder doses to achieve serum P ≤5.5 mg/dL; an elective, 16-week, open-label safety extension followed the randomized treatment period (RTP).[7]
- Here, for Cohort 1 and Cohort 2 patients, the reduction in serum P and overall pill burden during the 10-week RTP, as well as the patients' assessment of binder regimen at the end of the RTP by dialysis modality and cohort, were analyzed.

Figure 1. Study Design.[a,b,7]



[a]A third cohort of patients was included in the OPTIMIZE study; however, patients from that cohort were excluded from this analysis because they were naive to treatment with phosphate binders. [b]If patients were taking an odd number of binder pills, they decreased the number of pills by more than 50%. For example, 3 pills were decreased to 1; five pills were decreased to 2.
bid, twice a day; P, phosphate; PB, phosphate binder.

Results

Patients

- Overall, 243 patients receiving HD and 60 receiving PD were randomized to Cohort 1 (Straight Switch: HD, n=119; PD, n=32) or Cohort 2 (Binder Reduction: HD, n=124; PD, n=28).
- Baseline demographics and characteristics were generally well balanced between the cohorts, with minor exceptions in the smaller PD cohorts (**Table 1**).
  - The patients receiving PD had a shorter duration since first dialysis than patients undergoing HD.

Table 1. Baseline Demographics and Disease Characteristics (Full Analysis Set).

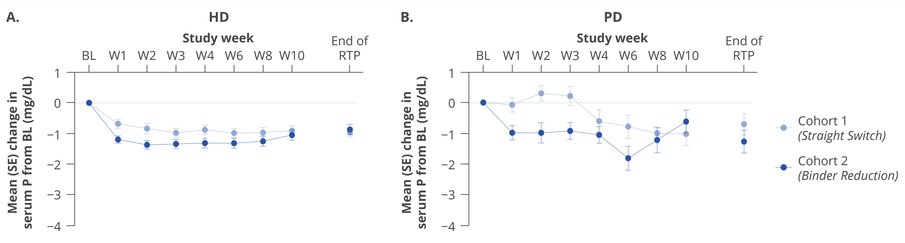
Characteristic	HD (N=243)		PD (N=60)[a]	
	Cohort 1 (Straight Switch) n=119	Cohort 2 (Binder Reduction) n=124	Cohort 1 (Straight Switch) n=32	Cohort 2 (Binder Reduction) n=28
Age, mean (SD), y	52.4 (11.0)	53.9 (11.6)	52.2 (11.8)	50.2 (13.8)
Female, n (%)	37 (31.1)	37 (29.8)	7 (21.9)	13 (46.4)
Race, n (%)				
Black or African American	58 (48.7)	62 (50.0)	8 (25.0)	9 (32.1)
White	48 (40.3)	48 (38.7)	16 (50.0)	14 (50.0)
Asian	5 (4.2)	0 (0)	8 (25.0)	3 (10.7)
Native American or Alaskan	3 (2.5)	5 (4.0)	0 (0)	1 (3.6)
Native Hawaiian or Pacific Islander	2 (1.7)	3 (2.4)	0 (0)	1 (3.6)
Other/Unknown	3 (2.5)	6 (4.8)	0 (0)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	38 (31.9)	32 (25.8)	4 (12.5)	6 (21.4)
BMI, mean (SD), kg/m²	33.3 (8.8)	32.6 (8.7)	30.4 (6.4)	29.1 (5.4)
Duration since first dialysis at baseline, mean (SD), mo	65.9 (55.0)	64.5 (51.2)	26.1 (22.0)	27.4 (24.3)
Binder type at screening, n (%)				
Sevelamer binder	52 (43.7)	48 (38.7)	5 (15.6)	13 (46.4)
Calcium-based binder	16 (13.5)	17 (13.7)	7 (21.9)	3 (10.7)
Iron-based binder	30 (25.2)	34 (27.4)	9 (28.1)	7 (25.0)
Other non-sevelamer binder	5 (4.2)	3 (2.4)	1 (3.1)	1 (3.6)
Combination	16 (13.5)	22 (17.7)	10 (31.3)	4 (14.3)
Binder pills per day at baseline, median (range), pills	9 (3-22)	9 (3-21)	9 (3-21)	9 (4-23)
Serum P at baseline, mean (SD), mg/dL	7.1 (1.0)	7.1 (1.1)	7.1 (1.2)	7.3 (1.2)

[a]Imbalance of baseline demographics and characteristics between cohorts in patients receiving PD may be attributable to small sample sizes.
BMI, body mass index; HD, hemodialysis; P, phosphate, PB, phosphate binder; PD, peritoneal dialysis.

Serum Phosphate Response

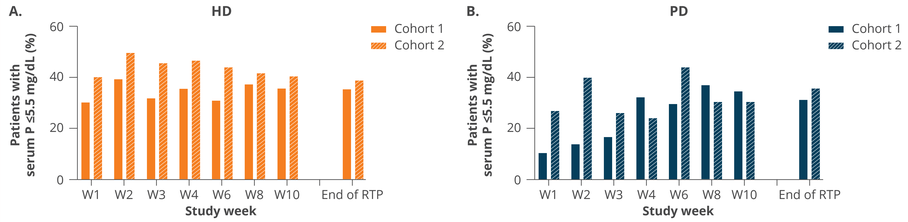
- Both HD and PD patients achieved a decrease in serum P from baseline, with similar mean reductions seen at the end of the RTP (HD, 1.0 mg/dL; PD, 0.9 mg/dL).
- Additionally, mean serum P reductions at the end of the RTP were similar among the 4 subgroups by modality and cohort (range, 0.8-1.0 mg/dL).
- A reduction of ≈1 mg/dL in serum P from baseline was observed at the end of the RTP in both HD and PD patients following the addition of tenapanor and adjustment of phosphate binders (**Figure 2**).
- Consistent control of serum P throughout the 10-week RTP (serum P, ≤5.5 mg/dL) was achieved by adding tenapanor as monotherapy or in combination with a reduced dose of binders in patients receiving HD and patients receiving PD (**Figure 3**).

Figure 2. Change in Serum P From Baseline During the Randomized Treatment Period[a] in (A) Patients Receiving HD and (B) Patients Receiving PD.



[a]For all patients, the RTP end point is the last observed value during the RTP, which could occur before week 10, if the patient withdrew early.
BL, baseline; HD, hemodialysis; P, phosphate; PD, peritoneal dialysis; RTP, randomized treatment period.

Figure 3. Percentage of Patients With Serum P ≤5.5 mg/dL in (A) Patients Receiving HD and (B) Patients Receiving PD.



HD, hemodialysis; P, phosphate; PD, peritoneal dialysis; RTP, randomized treatment period.

Pill Burden

- At end of the RTP, the median daily pill reduction (including binders and tenapanor) was 4 pills for patients receiving HD or PD in Cohort 1 (Straight Switch) and 2 pills and 1 pill for patients receiving HD and patients receiving PD in Cohort 2 (Binder Reduction), respectively.

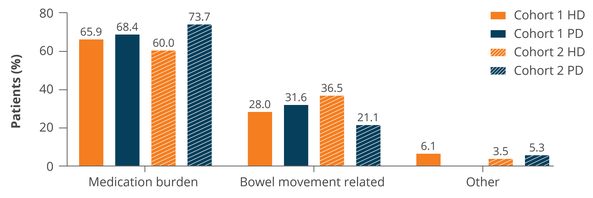
Phosphate Management Routine

- In both cohorts, 85% of patients receiving HD and 83% of patients receiving PD felt that their phosphate management routine was improved, with 64% attributing this improvement to the change in medication burden (less frequent and/or smaller pills) and 31% to bowel movements (**Figure 4**).

Safety

- 77% of patients receiving PD and 67% of patients receiving HD reported treatment-emergent adverse events (**Table 2**).
- Diarrhea was the most commonly reported adverse event in 39% of patients receiving HD and 47% of patients receiving PD; it was generally mild to moderate in severity.
- Overall, 7.3% of patients in Cohort 1 and 6.6% of patients in Cohort 2 discontinued tenapanor due to diarrhea, with similar rates across modalities.

Figure 4: Primary Reasons for Improved Perception of Phosphate Management Routine.



HD, hemodialysis; PD, peritoneal dialysis.

Table 2. Adverse Events.

n (%)	HD (Cohorts 1 and 2) N=243	PD (Cohorts 1 and 2) N=60[a]
TEAEs	163 (67.1)	46 (76.7)
TEAEs leading to tenapanor discontinuation	28 (11.5)	7 (11.7)
TEAEs leading to PB discontinuation	17 (7.0)	3 (5.0)
TEAEs experienced by ≥5% patients by PT		
Diarrhea	95 (39.1)	28 (46.7)
Nausea	10 (4.1)	4 (6.7)
Vomiting	4 (1.6)	6 (10.0)
COVID-19 infection	9 (3.7)	4 (6.7)
Peritonitis	-	4 (6.7)
Abdominal pain	6 (2.5)	3 (5.0)
Constipation	6 (2.5)	3 (5.0)
Hyperkalemia	3 (1.2)	3 (5.0)
Hypertensive urgency	-	3 (5.0)

[a]Numeric differences between the cohorts and groups could be due to the relatively small sample size of the peritoneal dialysis cohorts.
COVID-19, coronavirus disease 2019; PB, phosphate binder; PD, peritoneal dialysis; PT, preferred term; TEAE, treatment-emergent adverse event.

Conclusions

Phosphate control and patients' perception of their phosphate management regimen is improved in patients receiving HD or PD when tenapanor is added and binders are discontinued or reduced and then titrated as needed to achieve control of phosphate levels.

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Disclosures

John Manley is a nephrologist at Mountain Kidney and Hypertension Associates in Asheville, North Carolina, and is affiliated with Mission Hospital – St Joseph Campus, Harris Regional Hospital, and Haywood Regional Medical Center. Daniel Weiner is the Medical Director of Clinical Research for Dialysis Clinic, Inc (DCI) with institutional support from DCI paid to Tufts Medical Center. He was a site principal investigator for several tenapanor clinical trials from Ardelyx, Inc. (not compensated). Susan Edelstein, Suling Zhao, Yang Yang, David P. Rosenbaum, and David M. Spiegel are employees of Ardelyx, Inc.

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INDICATION

XPHOZAH (tenapanor) is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43% to 53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild to moderate in severity and resolved over time or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

For additional safety information, please see full Prescribing Information, available here.

CKD, chronic kidney disease.

XPHOZAH (tenapanor hydrochloride). Prescribing information. Ardelyx, Inc; 2025.