Tenapanor Treatment Added to Phosphate Binders Improved Long-Term Serum Phosphate Control as Measured by Reduction in Average Daily Phosphate Area Under the Curve

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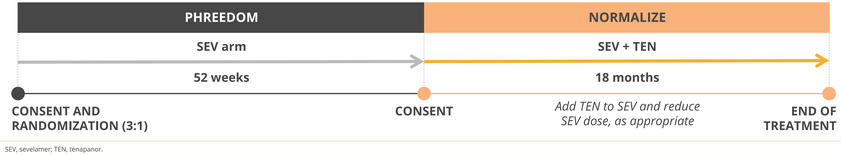
Introduction

- 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).[1-3]
- Tenapanor is approved as add-on therapy to reduce serum phosphorus in patients with chronic kidney disease on dialysis who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.[4]
- The randomized, phase 3 PHREEDOM trial (NCT03427125) demonstrated that tenapanor as monotherapy safely reduced serum phosphate (P) in patients on maintenance dialysis.[5] Sevelamer monotherapy was employed as a safety control arm.
- NORMALIZE (NCT03988920), a post-registrational, open-label extension study of the PHREEDOM study, evaluated tenapanor alone or in combination with sevelamer to reduce serum P.[6]
- Assessments accounting for serum P increase over the reference range (≥2.5-4.5 mg/dL), and time out of range, such as area under the curve (AUC), appear superior to single serum P measurements for evaluating the efficacy of phosphate management.[7,8]
- We evaluated the average daily AUC for serum P above the reference range for patients on sevelamer during the phase 3 PHREEDOM study who had tenapanor added to sevelamer during the NORMALIZE open-label extension study.

Methods

- Methods for PHREEDOM have been previously described[5]; briefly:
  - PHREEDOM enrolled patients on maintenance dialysis with serum P ≥6.0 and <10.0 mg/dL and a ≥1.5 mg/dL increase in serum P after phosphate binder washout.
  - Patients were randomized 3:1 to initiate treatment with tenapanor 30 mg twice a day (bid) or sevelamer per standard of care. In the sevelamer arm, treatment was adjusted per standard of care and maintained for 52 weeks.
- At study entry into NORMALIZE, patients from the sevelamer arm of PHREEDOM had tenapanor 30 mg once or twice daily (bid) added (defined by protocol) to their sevelamer dose **(Figure 1)**.[6]
- After starting tenapanor, the sevelamer dose was reduced as appropriate, with a goal to achieve serum P ≤4.5 mg/dL (relaxed by study protocol to serum P ≤5.5 mg/dL) with as low a dose of phosphate binder as possible.[6]
  - Similarly, the tenapanor dose was reduced to a minimum of 10 mg once daily or increased to a maximum of 30 mg bid based on serum P levels and gastrointestinal tolerability.
- We calculated average daily serum P AUC above 4.5 mg/dL by study for each sevelamer-treated patient in PHREEDOM who continued into NORMALIZE.
  - The total serum P AUC was calculated by plotting serum P (y-axis) against time (x-axis) and solving for the total surface area of all trapezoids and/or triangles created by the amount of time spent above serum P >4.5 mg/dL.[7,8]
  - The average daily serum P AUC for each study was then derived as the total serum P AUC of the study divided by the number of study days between the baseline serum P assessment and the last serum P assessment of the study.

Figure 1: Study Design of the Sevelamer Arm of PHREEDOM-NORMALIZE[6]



SEV, sevelamer; TEN, tenapanor.

Results

Patients

- Patients from the sevelamer arm of the PHREEDOM study (N=60 with ≥1 post-enrollment serum P measurement) were enrolled in the NORMALIZE study and had tenapanor 30 mg added to their sevelamer dose.
- Patients were predominately male with a mean age of 58.3 years and a mean (SD) baseline serum P of 7.1 (1.4) mg/dL for PHREEDOM and 5.8 (1.6) mg/dL for NORMALIZE (**Table 1**).

Table 1: Baseline Demographics and Disease Characteristics (Sevelamer Arm of PHREEDOM)

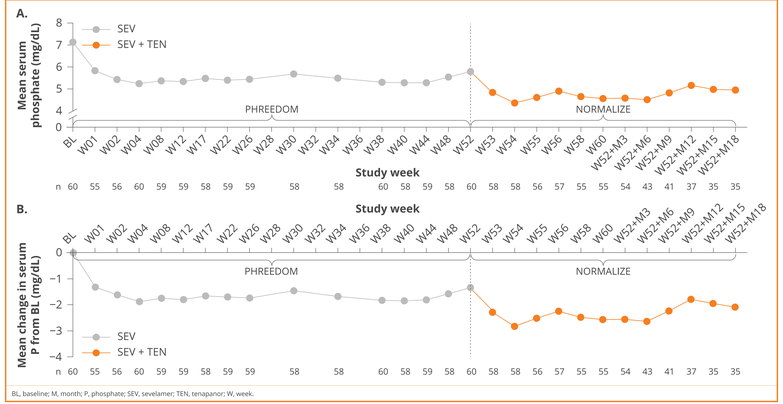
	N=60
Mean age, years (SD)[a]	58.3 (14.1)
Male, n (%)	43 (72)
Race, n (%)	
White	31 (52)
Black or African American	26 (43)
Asian	3 (5)
Ethnicity, n (%)	
Non-Hispanic/Latino	40 (67)
Hispanic/Latino	20 (33)
Mean BMI, kg/m² (SD)	29.4 (7.5)
Type of dialysis, n (%)	
Hemodialysis	52 (87)
Peritoneal dialysis	8 (13)
Mean duration of dialysis treatment, months (SD)[a]	74.3 (56.3)
PHREEDOM BL mean serum P, mg/dL (SD)	7.1 (1.4)
NORMALIZE BL mean serum P, mg/dL (SD)	5.8 (1.6)

[a]At informed consent for NORMALIZE
BL, baseline; BMI, body mass index; P, phosphate.

Serum P Decrease

- During NORMALIZE, mean serum P decreased with the addition of tenapanor to sevelamer treatment (**Figure 2**).

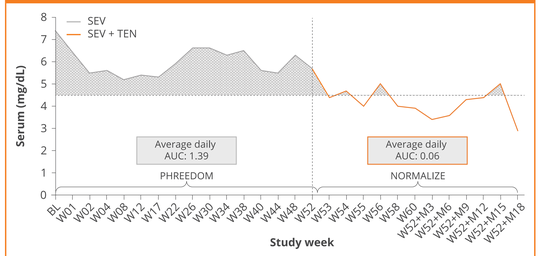
Figure 2: (A) Mean Serum P and (B) Mean Change in Serum P From PHREEDOM Baseline by Visit in PHREEDOM and NORMALIZE.



BL, baseline; M, month; P, phosphate; SEV, sevelamer; TEN, tenapanor; W, week.

- For the 60 sevelamer-treated patients entering NORMALIZE, the mean (SD) of average daily serum P AUC above 4.5 mg/dL decreased from 1.09 (0.73) (PHREEDOM) to 0.77 (0.75) (NORMALIZE).
- **Figure 3** shows the serum P AUC above 4.5 mg/dL (shaded area) for 1 sevelamer-treated patient entering NORMALIZE whose average daily serum P AUC decreased from 1.39 in PHREEDOM to 0.06 following the addition of tenapanor to sevelamer treatment during NORMALIZE.

Figure 3: An Example of Serum P AUC Above 4.5 mg/dL for 1 Sevelamer-Treated Patient From PHREEDOM Who Completed NORMALIZE.

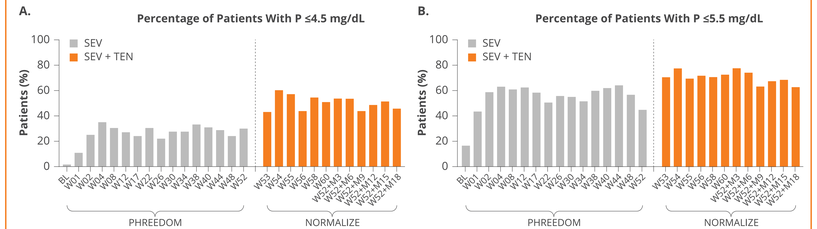


AUC, area under the curve; BL, baseline; M, month; P, phosphate; SEV, sevelamer; SEV+TEN, sevelamer arm from PHREEDOM beginning tenapanor treatment upon entering NORMALIZE; W, week.

Proportion of Patients Achieving Target Serum P

- In addition, the proportion of patients achieving a serum P ≤4.5 mg/dL and serum P ≤5.5 mg/dL increased during NORMALIZE (**Figure 4**).
- From week 2 to week 52 of PHREEDOM, the percentage of patients achieving a serum P ≤4.5 mg/dL ranged from ≈20% to 35% on sevelamer monotherapy, with the highest percentage at week 4 (35%).
  - During NORMALIZE, this percentage increased to ≈40% to 60%.
- The percentage of patients achieving serum P ≤5.5 mg/dL ranged from ≈40% to 60% on sevelamer monotherapy from week 2 to week 52 of PHREEDOM, with the highest percentages at week 4 (63%).
  - During NORMALIZE, this percentage increased to ≈60% to 78%.

Figure 4: Percentage of Patients With (A) Serum P ≤4.5 mg/dL and (B) Serum P ≤5.5 mg/dL



BL, baseline; P, phosphate; M, month; SEV, sevelamer; SEV + TEN, sevelamer arm from PHREEDOM beginning tenapanor treatment upon entering NORMALIZE; W, week.

Safety

- Diarrhea was reported in 44% to 53% of tenapanor-treated patients and was generally mild to moderate in intensity.
- Diarrhea resulted in study drug discontinuation in 16% of patients during the randomized treatment period of PHREEDOM and in 2% of patients during NORMALIZE.

Conclusions

Tenapanor added to sevelamer improved phosphate control by allowing more patients to achieve serum P ≤4.5 mg/dL or ≤5.5 mg/dL.

Tenapanor added to sevelamer also provided for better sustained serum P control as measured by average daily serum P AUC above 4.5 mg/dL.

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Disclosures

Kevin J. Martin is a paid consultant for Ardelyx, Inc., and participates in the data safety monitoring board or advisory board for Applied Therapeutics. David M. Spiegel, Susan Edelstein, Yang Yang, David P. Rosenbaum, and Laura Williams 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.