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The Predictive Value of Early Response to Tenapanor for the Treatment of Hyperphosphatemia in Patients Receiving Maintenance Dialysis

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Background

- Serum phosphate (sP) control is challenging for many patients receiving maintenance dialysis.[1-4]
- Tenapanor is a first-in-class, investigational phosphate absorption inhibitor (PAI) dosed twice a day (bid).
- Tenapanor blocks the paracellular absorption of dietary phosphate in the gastrointestinal tract by local inhibition of intestinal sodium/hydrogen exchanger isoform 3 (NHE3), which:
  - Increases transepithelial electrical resistance and decreases intestinal permeability to phosphate,[5] and
  - Increases stool sodium and water content.[5,6]
- Tenapanor met the primary sP-lowering endpoint in 2 phase 3 monotherapy trials (NCT02675998, PHREEDOM [NCT03427125]) and was generally well tolerated.[7,8]
- Tenapanor also improved control of hyperphosphatemia in patients receiving maintenance dialysis when used in combination with phosphate binders compared with phosphate binders alone in the phase 3 AMPLIFY trial (NCT03824587).[9]
- This post hoc analysis of the phase 3 PHREEDOM study evaluated whether an early reduction in sP, occurring within the first month of tenapanor treatment, predicts continued control of sP during subsequent treatment.

Methods

- The PHREEDOM trial design and patient population have been reported previously.[8]
  - Eligibility criteria included maintenance dialysis with sP ≥6.0 and ≤10.0 mg/dL and a ≥1.5 mg/dL increase in sP after phosphate binder washout.
  - Patients were randomized (3:1) to tenapanor for 26 weeks starting at a dose of 30 mg bid (randomized treatment period) or sevelamer carbonate for 52 weeks.
  - Patients who completed 26 weeks of tenapanor treatment were re-randomized (1:1) to tenapanor or placebo for a 12-week randomized withdrawal period, followed by a 14-week open-label safety extension.
  - sP was assessed at weeks 1, 2, 4, 8, 12, 17, 22, and 26 during the randomized treatment period.
- This post hoc analysis included patients treated with tenapanor during the randomized treatment phase of PHREEDOM from the intent-to-treat analysis set.
  - The intent-to-treat analysis set included all patients who met enrollment criteria, received ≥1 dose of study treatment, and had at least one post-treatment sP measurement.
- Early responders were defined as those with ≥2 of 3 sP measurements with a reduction of ≥1.2 mg/dL from baseline at weeks 1, 2, and 4 (ie, within the first month of tenapanor treatment).
  - All other patients were categorized as early non-responders.
- Early responders were assessed for continued response at week 12 and during weeks 17 to 26 of the randomized treatment period of the study.
  - At week 12, a continued response was defined as having sP ≥1.2 mg/dL lower than baseline.
  - For weeks 17, 22, and 26, a continued response was defined as having sP ≥1.2 mg/dL lower than baseline for ≥2 of 3 sP measurements.
- Continued response rates were estimated using 2 approaches:
  - Conservative – early responders who missed sP measurement at week 12 or did not have ≥2 of 3 sP measurements at weeks 17, 22, and 26 were considered late non-responders.
  - Observed Case – only early responders who remained on treatment and had sP measurement at week 12 or had ≥2 of 3 sP measurements at weeks 17, 22, and 26 were included in analysis.

Results

Patients

- In PHREEDOM, 189/407 (46.4%) of tenapanor-treated patients achieved an early response; 218/407 (53.6%) were categorized as early non-responders.
- Baseline demographics and disease characteristics were generally similar between early responders and early non-responders (**Table 1**).
  - Early responders on average had numerically higher baseline sP concentrations.

Table 1. Baseline Demographics and Disease Characteristics by Early Response Status

	Early responders (n=189)	Early non-responders (n=218)
Age, mean years (SD)	56.8 (12.3)	58.6 (12.9)
Sex, n (%)		
Male	119 (63.0)	139 (63.8)
Female	70 (37.0)	79 (36.2)
Race, n (%)		
Black or African American	77 (40.7)	110 (50.5)
White	95 (50.3)	90 (41.3)
Asian	10 (5.3)	11 (5.0)
American Indian or Alaska Native	5 (2.7)	6 (2.8)
Other[a]	2 (1.0)	1 (0.5)
Ethnicity, n (%)		
Not Hispanic or Latino	133 (70.4)	159 (72.9)
Hispanic or Latino	56 (29.6)	57 (26.2)
Not reported/unknown	0	2 (0.9)
BMI, mean kg/m² (SD)	31.6 (7.2)	30.9 (7.5)
Duration since ESRD diagnosis, mean years (SD)	4.8 (4.6)	4.6 (4.3)
Type of dialysis, n (%)		
Hemodialysis	170 (90.0)	195 (89.4)
Peritoneal dialysis	19 (10.0)	23 (10.6)
Duration since first dialysis, mean months (SD)	53.1 (49.6)	53.6 (51.7)
Baseline sP, mean mg/dL (SD)	8.0 (1.4)	7.0 (1.3)
Baseline sP category, n (%)		
<7.5 mg/dL	63 (33.3)	140 (64.2)
≥7.5 mg/dL	126 (66.7)	78 (35.8)
Baseline iFGF23, mean pg/mL (range)	6674 (88-66,000)	6168 (21-66,000)
Baseline PTH, mean pg/mL (range)	397.0 (31.0-1558.0)	335.5 (40.0-1113.0)
Most recent Kt/V, mean (SD)	1.6 (0.3)	1.6 (0.4)

[a]Native Hawaiian or other Pacific Islander or other.
BMI, body mass index; ESRD, end stage renal disease; iFGF23, intact fibroblast growth factor 23; PTH, parathyroid hormone; sP, serum phosphate.

Predictive response in early responders

- More than half of early responders had a continued response at week 12 (**Figure 1**) and more than half also had a continued response during weeks 17-26 (**Figure 1, Figure 2**).
- Most early non-responders remained non-responders throughout the study (**Figure 3**).

Figure 1. Summary of Continued Response to Tenapanor Among Early Responders

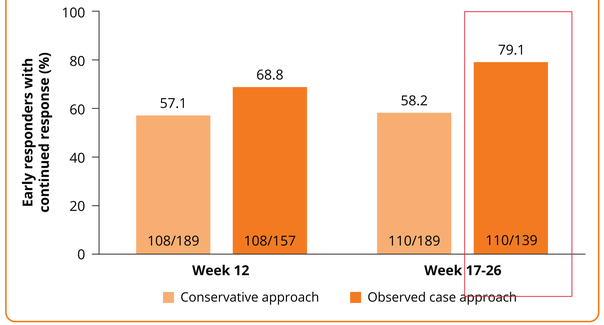
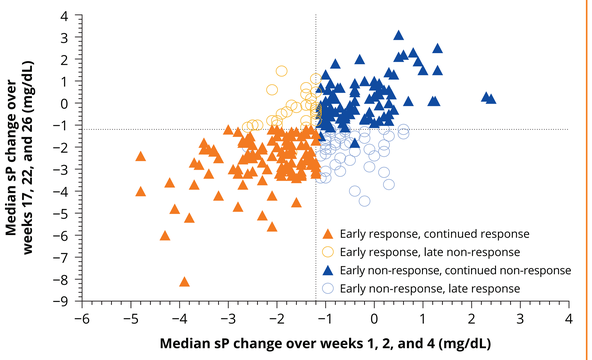
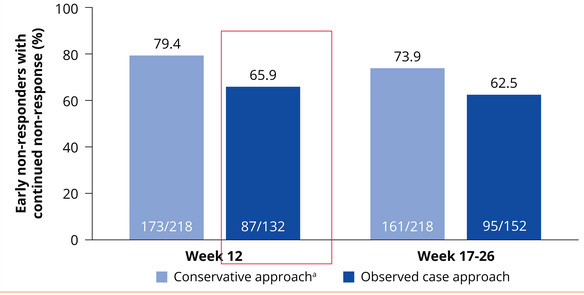


Figure 2. Median sP Change in the First Month of Tenapanor Treatment (Weeks 1, 2, and 4) Versus Median sP Change During Subsequent Treatment (Weeks 17, 22, and 26) – Observed Case Approach



Data are shown for all patients with ≥2 of 3 sP measurements at weeks 17, 22, and 26. Dotted lines indicate cutoffs for a reduction of ≥1.2 mg/dL from baseline.
sP, serum phosphate.

Figure 3. Summary of Continued Non-Response to Tenapanor Among Early Non-Responders



[a]As patients with missing response status at week 12 or during the second half of the 26-week treatment period are considered non-responders, this approach may overestimate the percentage of patients with a late non-response.

Conclusions

- Among patients receiving maintenance dialysis who had an early response to tenapanor within the first month of treatment and remained on treatment, ≈70% had a response at week 12 and ≈80% had a response during weeks 17-26 of the treatment period.
- This suggests that patients receiving maintenance dialysis who demonstrate a lowering of sP early during treatment with tenapanor generally maintain that response with continued treatment.
- Therefore, assessment of early response to tenapanor could provide useful information to help guide real-world clinical practice if tenapanor receives approval for the treatment of hyperphosphatemia in patients receiving maintenance dialysis.

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Disclosures

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