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Safety Analysis of Tenapanor Monotherapy vs Sevelamer Carbonate in Patients on Maintenance Dialysis With Hyperphosphatemia

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Background

- Per the Dialysis Outcomes and Practice Patterns Study practice monitor, approximately 70% of patients with chronic kidney disease (CKD) on dialysis have serum phosphate (sP) levels >4.5 mg/dL despite treatment for hyperphosphatemia, suggesting that current treatment strategies are insufficient.[1,2]
- Tenapanor is a first-in-class, minimally absorbed, small-molecule phosphate absorption inhibitor that targets the paracellular pathway, the primary pathway of phosphate absorption in the gastrointestinal tract, through selective inhibition of sodium/hydrogen exchanger isoform 3 (NHE3).[3-5]
- NHE3 inhibition may induce a conformational change in tight junction proteins that specifically decreases phosphate permeability through the paracellular pathway.[3,5]
- We previously reported results from PHREEDOM (NCT03427125), a phase 3 study that demonstrated the efficacy of tenapanor for the treatment of hyperphosphatemia in patients with CKD on maintenance dialysis.[6]
  - In PHREEDOM, the phosphate binder sevelamer carbonate (sevelamer) served as an active safety control.[6]
- Here, we present incidence and exposure-adjusted incidence of treatment-emergent adverse events (TEAEs) during the randomized treatment period (RTP) of the PHREEDOM study.

Methods

- As described previously,[6] PHREEDOM enrolled patients on maintenance dialysis with sP levels ranging from ≥6.0 to <10.0 mg/dL and a sP increase of ≥1.5 mg/dL following washout from a phosphate binder.
- Patients were randomized (3:1) to receive tenapanor 30 mg twice a day or sevelamer per standard of care during a 26-week RTP.
- The safety population comprised patients who received ≥1 dose of study drug during the RTP.
- Exposure-adjusted incidence rates for safety events were calculated per 100 patient-years of exposure.

Results

Patients

- In PHREEDOM, 419 patients received tenapanor and 137 received sevelamer (safety population).
- Baseline demographic and disease characteristics, which have been previously published,[6] are summarized in **Table 1**.
  - A total of 63.5% (n=87) of patients who received sevelamer during the RTP had previously received sevelamer prior to study entry.

Table 1. Baseline Demographics and Disease Characteristics (Safety Population)

	Tenapanor (N=419)	Sevelamer (N=137)
Age at screening, mean (SD), years	57.7 (12.6)	59.0 (12.6)
Male, n (%)	265 (63.2)	91 (66.4)
Race, n (%)		
White	189 (45.1)	70 (51.1)
Black	195 (46.5)	60 (43.8)
Other[a]	35 (8.4)	7 (5.1)
BMI, mean (SD), kg/m²	31.3 (7.5)	31.4 (9.9)
Duration of ESKD, mean (SD), years	4.8 (4.4)	5.1 (5.1)
Hemodialysis, n (%)	376 (89.7)	122 (89.1)
Duration of dialysis treatment, mean (SD), months	54.2 (51.0)	59.2 (57.5)
sP, mean (SD), mg/dL	7.4 (1.4)	7.2 (1.5)
iFGF23, median (range), pg/mL	6358.3 (21.0-66000.0)	5888.2 (28.1-66000.0)
cFGF23, median (range), RU/mL	10014.1 (391.3-117840.0)	10042.0 (677.7-110640.0)
iPTH, median (range), pg/mL	363.0 (31-1731)	356.0 (16-1422)
Calcium, mean (SD), mg/dL	8.4 (0.8)	8.4 (0.8)
Concomitant calcimimetic, n (%)	41 (9.8)	18 (13.1)
Concomitant vitamin D and analogs, n (%)	53 (12.6)	27 (19.7)
Concomitant calcium supplements, n (%)	2 (0.5)	5 (3.6)

[a]Includes Asian, Native American or Alaskan, Native Hawaiian or Other Pacific Islander, and other.
BMI, body mass index; cFGF23, C-terminal fibroblast growth factor 23; ESKD, end-stage kidney disease; iFGF23, intact fibroblast growth factor 23; iPTH, intact parathyroid hormone; RU, reference unit; sP, serum phosphate.

Incidence of TEAEs During the RTP

- During the 26-week RTP, 80.4% of patients on tenapanor and 64.2% of patients on sevelamer reported a TEAE (**Table 2**).
  - The lower overall incidence of TEAEs observed in the sevelamer arm may have been confounded by the large proportion of patients (63.5%) who had received sevelamer prior to study entry.
- The most common TEAE was diarrhea (tenapanor, 53.0%; sevelamer, 7.3%).
- The overall incidence of serious TEAEs was lower in the tenapanor vs sevelamer arm (17.4% vs 23.4%).
  - Pneumonia was the only serious TEAE reported in ≥3% of patients in either treatment arm (tenapanor, 0.7%; sevelamer, 3.6%).
  - Three patients in the tenapanor arm experienced a total of 4 drug-related serious TEAEs (diarrhea, n=2; dehydration, n=1; nodal arrythmia, n=1). No drug-related serious TEAE was reported in the sevelamer arm.
- The overall incidence of TEAEs leading to hospitalization was lower in the tenapanor vs sevelamer arm (17.4% vs 23.4%).
- A higher proportion of patients treated with tenapanor vs sevelamer experienced a TEAE leading to study drug discontinuation (24.3% vs 1.5%).
  - The low overall incidence of TEAEs leading to study drug discontinuation with sevelamer may be due to the large proportion of patients treated with sevelamer prior to study entry.
- One patient died due to a TEAE. This death (respiratory failure) occurred in the tenapanor arm and was considered unrelated to tenapanor.

Table 2. Incidence of TEAEs During the RTP (Safety Population)

	Tenapanor (N=419)	Sevelamer (N=137)
Any TEAE[a]	337 (80.4)	88 (64.2)
Diarrhea	222 (53.0)	10 (7.3)
Hyperphosphatemia	27 (6.4)	3 (2.2)
Hypertension	15 (3.6)	7 (5.1)
Fall	11 (2.6)	10 (7.3)
Cough	9 (2.1)	9 (6.6)
Fluid overload	8 (1.9)	7 (5.1)
AV fistula thrombosis	6 (1.4)	7 (5.1)
Pneumonia	4 (1.0)	7 (5.1)
Serious TEAE[b]	73 (17.4)	32 (23.4)
Pneumonia	3 (0.7)	5 (3.6)
TEAE leading to study drug discontinuation	102 (24.3)	2 (1.5)
TEAE leading to hospitalization	73 (17.4)	32 (23.4)
TEAE leading to death	1 (0.2)[c]	0

Data are n (%).
[a]Preferred terms reported in ≥5% of patients in either treatment arm are presented. [b]Preferred terms reported in ≥3% of patients in either treatment arm are presented. [c]Death was due to respiratory failure and was considered unrelated to tenapanor.
AV, arteriovenous; RTP, randomized treatment period; TEAE, treatment-emergent adverse event.

Exposure-Adjusted Incidence of TEAEs During the RTP

- During the RTP, the mean (SD) duration of exposure to study drug was 137.2 (67.9) days for tenapanor and 171.4 (35.3) days for sevelamer, with data available for a total of 157.4 and 64.3 patient-years, respectively (**Table 3**).
- The exposure-adjusted incidence rate for any TEAE was 214.1 per 100 patient-years in the tenapanor arm and 136.9 per 100 patient-years in the sevelamer arm.
- The exposure-adjusted incidence rate for a serious TEAE was similar for tenapanor and sevelamer (46.4 and 49.8 per 100 patient-years, respectively).

Table 3. Exposure-Adjusted Incidence of TEAEs During the RTP (Safety Population)

	Tenapanor (N=419)	Sevelamer (N=137)
Observed patient-years	157.4	64.3
Exposure-adjusted incidence rate of any TEAE per 100 patient-years[a]	214.1	136.9
Diarrhea	141.1	15.6
Hyperphosphatemia	17.2	4.7
Fluid overload	5.1	12.4
Pneumonia	3.2	10.9
Fall	8.9	15.6
AV fistula thrombosis	3.8	10.9
Cough	5.7	14.0
Hypertension	9.5	10.9
Exposure-adjusted incidence rate of a serious TEAE per 100 patient-years[b]	46.4	49.8
Pneumonia	1.9	7.8
Exposure-adjusted incidence rate of a TEAE leading to study drug discontinuation	64.8	3.1
Exposure-adjusted incidence rate of a TEAE leading to hospitalization	46.4	49.8
Exposure-adjusted incidence rate of a TEAE leading to death	0.6	0

[a]Preferred terms reported in ≥5% of patients in either treatment arm are presented. [b]Preferred terms reported in ≥3% of patients in either treatment arm are presented.
AV, arteriovenous; RTP, randomized treatment period; TEAE, treatment-emergent adverse event.

Conclusions

The most common TEAE in the PHREEDOM study was diarrhea.

A lower proportion of patients treated with tenapanor vs sevelamer experienced a serious TEAE while the exposure adjusted rates were similar.

The overall incidence of TEAEs leading to hospitalization was lower in the tenapanor arm than in the sevelamer arm while the exposure adjusted rates were similar.

Overall, this safety analysis of the PHREEDOM study confirms that tenapanor has acceptable safety and tolerability profiles in patients with CKD on maintenance dialysis.

Disclosures

Arnold Silva receives research support from Ardelyx, Inc., AstraZeneca, Reata, ProKidney, Diamedica, Novartis, Boehringer Ingelheim, Retrophin, Goldfinch Bio, Akebia, Bayer, Fibrogen, and Gilead Sciences; consulting fees from Ardelyx, Inc., Reata, ProKidney, Boehringer Ingelheim, Novartis, and Bayer; and speaker honoraria from Aurinia, Bayer, and Boehringer Ingelheim. German T. Hernandez receives research support from Apellis, Vertex, NovoNordisk, Bayer, Alexion, Morphosys AG, Ardelyx, Inc., Boehringer Ingelheim, Akebia, Otsuka, Cara Therapeutics, Janssen, Bristol Myers Squibb, AstraZeneca, Travere Therapeutics, Novartis, Chinook, Kezar Life Sciences, Renibus Therapeutics, Goldfinch Bio, Gilead Sciences, KBP Biosciences, Dynavax, Complexa, Aurinia, Baxter, Pharmacosmos, Relypsa (now Vifor), Cormedix, Biogen, Genentech-Roche; honoraria from Otsuka, Alexion, AstraZeneca, Travere Therapeutics, Akebia, Bayer, Relypsa (now Vifor), and Aurinia; and is a joint venture partner at DaVita Kidney Care. David Spiegel, David Rosenbaum, Susan Edelstein, Yang Yang, Suling Zhao, and Laura Williams are employees of Ardelyx, Inc.

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