TH-PO1045

Gastrointestinal tolerability of tenapanor to treat hyperphosphatemia in patients on hemodialysis

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Background

- Hyperphosphatemia is a common complication of chronic kidney disease (CKD) stage 5D and is associated with morbidity and mortality.[1]
- The use of phosphate binders for the treatment of patients with hyperphosphatemia is commonly associated with gastrointestinal side effects including diarrhea, nausea, vomiting, dyspepsia, constipation, abdominal pain and abdominal bloating.[2]
- Tenapanor is a minimally absorbed, orally administered, small-molecule inhibitor of sodium/hydrogen exchanger isoform 3 (NHE3) and inhibits the absorption of gastrointestinal sodium and phosphate.[3,4]
- In a phase 2b placebo-controlled study in patients undergoing hemodialysis, treatment with tenapanor for 4 weeks reduced serum phosphate concentrations relative to placebo, with diarrhea being the most common adverse event.[5]
- Here, we present the safety and tolerability results of the first phase 3 study of tenapanor in patients with hyperphosphatemia undergoing hemodialysis.
  - The efficacy of tenapanor in this study is described in a separate poster (Block *et al.* Poster TH-PO1046).[6]

Methods

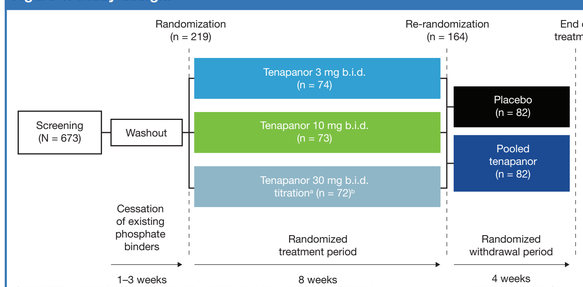
- This was a double-blind, parallel-group study with an 8-week randomized treatment period followed by a 4-week randomized placebo-controlled withdrawal period (ClinicalTrials.gov identifier: NCT02675998) (Figure 1).
  - The study was conducted in accordance with the Declaration of Helsinki at 32 sites in the USA, with all patients providing written informed consent.
  - The primary efficacy endpoint, based on the responder population, was the difference between the pooled tenapanor and placebo groups in the change in serum phosphate concentration from the end of the 8-week treatment period to the end of the 4-week withdrawal period.
- Adults (18–80 years of age) with CKD stage 5D (hemodialysis) who were receiving at least three daily doses of phosphate-binder medication were eligible for inclusion.
- Following a 1–3-week washout of phosphate binders, patients who had serum phosphate concentrations of 6.0–10.0 mg/dL and an increase of at least 1.5 mg/dL from screening were randomized 1:1:1 to receive a single tablet of tenapanor 3 mg, 10 mg or 30 mg twice daily (b.i.d.) for 8 weeks.
  - Patients initiated on tenapanor 30 mg b.i.d. were allowed to down-titrate weekly (stepwise 30 → 20 → 15 → 10 → 3 mg b.i.d.) during the first 4 weeks, on the basis of gastrointestinal tolerability (hereafter referred to as 'tenapanor 30 mg b.i.d. titration').
- After 8 weeks of tenapanor treatment, patients were re-randomized 1:1 to remain on their dose of tenapanor or to receive placebo for 4 weeks.
- Patients recorded daily bowel movement frequency and form (Bristol Stool Form Scale [BSFS][7]) using an electronic diary.
  - Reporting of increased bowel movement frequency or loosening of stool, regardless of the magnitude of the effect, was classified as the adverse event (AE) of 'diarrhea'.
- Safety and tolerability analyses included all patients who received at least one dose of study drug.

Results

Study participants

- In total, 219 patients were randomized; 218 patients received at least one dose of study drug, 164 entered the 4-week randomized withdrawal period and 152 completed the study (Figure 2).
  - The most common reasons for discontinuation of study treatment were AEs and hyperphosphatemia.

Figure 1. Study design.



[a]Patients initially receiving tenapanor 30 mg b.i.d. were allowed to down-titrate weekly (stepwise 30 → 20 → 15 → 10 → 3 mg b.i.d.) during the first 4 weeks of the randomized treatment period, based on gastrointestinal tolerability.
[b]One patient did not receive any dose of study drug and was excluded from analyses.
b.i.d., twice daily.

- Patient demographics and baseline characteristics were generally well balanced across cohorts. The mean age of participants (standard deviation) was 55.8 (11.1) years and 58.7% were men.
- The final twice-daily doses in the tenapanor 30 mg b.i.d. titration cohort were: 30 mg in 18 patients (52.9%), 20 mg in 7 patients (20.6%), 15 mg in 4 patients (11.8%), 10 mg in 2 patients (5.9%) and 3 mg in 3 patients (8.8%).
- Mean compliance with study treatment was more than 90% for all cohorts throughout the study.

General safety and tolerability

- Tenapanor was well tolerated, with the most common AEs being gastrointestinal in nature (Table 1).
  - The most common AEs were diarrhea and hyperphosphatemia, experienced by 86 patients (39.4%) and 12 patients (5.5%) in the randomized treatment period, respectively.
  - The most common AE leading to study drug discontinuation was diarrhea (n = 18). No patients discontinued owing to diarrhea during the randomized withdrawal period.
  - One patient receiving tenapanor 3 mg b.i.d. died during the study owing to sudden cardiac death, which was not considered to be related to study treatment.
- There were few serious AEs (SAEs) reported across all cohorts and no SAEs were reported in patients receiving tenapanor during the randomized withdrawal period.
  - The most common SAEs were fluid overload (n = 3) and pneumonia (n = 3) during the randomized treatment period and fluid overload (n = 2) during the randomized withdrawal period.

Gastrointestinal adverse events

- A summary of the gastrointestinal AEs reported during the study is shown in Table 2.
  - During the randomized treatment period, diarrhea was experienced by 29.7% of patients receiving tenapanor 3 mg b.i.d., 41.1% of patients receiving tenapanor 10 mg b.i.d. and 47.9% of patients receiving tenapanor 30 mg b.i.d. titration.
  - Most cases of diarrhea were mild or moderate in severity.

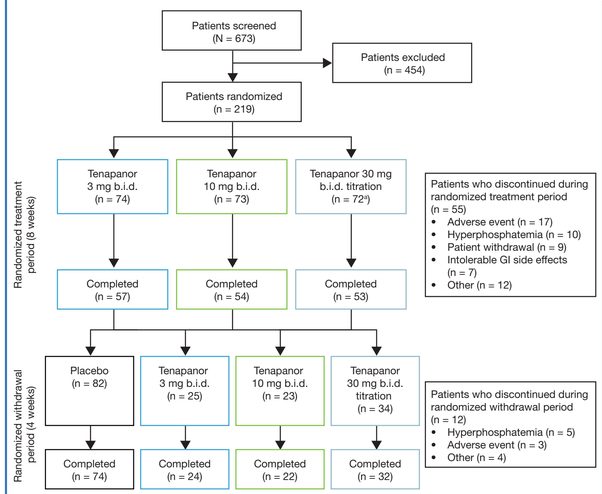
Table 1. Summary of adverse events.

Randomized treatment period	Tenapanor 3 mg b.i.d. (n = 74)	Tenapanor 10 mg b.i.d. (n = 73)	Tenapanor 30 mg b.i.d. titration (n = 71)
Any AE	39 (52.7)	51 (69.9)	49 (69.0)
Treatment-related AE	24 (32.4)	38 (52.1)	33 (46.5)
AE leading to study discontinuation	8 (10.8)	16 (21.9)	11 (15.5)
AE leading to death	1 (1.4)	0 (0.0)	0 (0.0)
SAE	11 (14.9)	5 (6.8)	5 (7.0)
AEs by system organ class[a]			
Blood and lymphatic system disorders	2 (2.7)	2 (2.7)	0 (0.0)
Cardiac disorders	3 (4.1)	2 (2.7)	3 (4.2)
Gastrointestinal disorders	24 (32.4)	35 (47.9)	40 (56.3)
General disorders and administration site conditions	7 (9.5)	5 (6.8)	3 (4.2)
Infections and infestations	11 (14.9)	5 (6.8)	8 (11.3)
Injury, poisoning and procedural complications	5 (6.8)	11 (15.1)	5 (7.0)
Investigations	3 (4.1)	2 (2.7)	1 (1.4)
Metabolism and nutrition disorders	4 (5.4)	10 (13.7)	9 (12.7)
Musculoskeletal and connective tissue disorders	2 (2.7)	1 (1.4)	2 (2.8)
Nervous system disorders	4 (5.4)	1 (1.4)	1 (1.4)
Renal and urinary disorders	2 (2.7)	1 (1.4)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	3 (4.1)	3 (4.1)	5 (7.0)
Skin and subcutaneous tissue disorders	3 (4.1)	4 (5.5)	2 (2.8)
Vascular disorders	0 (0.0)	4 (5.5)	3 (4.2)

Randomized withdrawal period	Placebo (n = 82)	Tenapanor 3 mg b.i.d. (n = 25)	Tenapanor 10 mg b.i.d. (n = 23)	Tenapanor 30 mg b.i.d. titration (n = 34)
Any AE	21 (25.6)	4 (16.0)	7 (30.4)	12 (35.3)
Treatment-related AE	5 (6.1)	0 (0.0)	1 (4.3)	0 (0.0)
AE leading to study discontinuation	5 (6.1)	0 (0.0)	1 (4.3)	1 (2.9)
AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE	4 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
AEs by system organ class[a]				
Cardiac disorders	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (4.9)	0 (0.0)	0 (0.0)	2 (5.9)
General disorders and administration site conditions	1 (1.2)	0 (0.0)	0 (0.0)	2 (5.9)
Infections and infestations	2 (2.4)	2 (8.0)	1 (4.3)	2 (5.9)
Injury, poisoning and procedural complications	4 (4.9)	2 (8.0)	0 (0.0)	2 (5.9)
Investigations	2 (2.4)	1 (4.0)	0 (0.0)	2 (5.9)
Metabolism and nutrition disorders	7 (8.5)	0 (0.0)	1 (4.3)	3 (8.8)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	1 (4.0)	3 (13.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (2.4)	0 (0.0)	1 (4.3)	0 (0.0)

Data are presented as n (%).
[a]Data shown for system organ classes for which two or more patients in any group experienced an AE.
AE, adverse event; b.i.d., twice daily; SAE, serious adverse event.

Figure 2. Patient flow diagram.



[a]One patient did not receive any dose of study drug and was excluded from analyses.
b.i.d., twice daily; GI, gastrointestinal.

Bowel movement frequency and stool form

- Mean bowel movement frequency was within the normal range for healthy individuals[8] in all groups throughout the study (Figure 3a).
  - Across all patients, mean bowel movement frequency increased by 2.8/week from baseline (week −1) to the end of the randomized treatment period.
  - At the end of the randomized withdrawal period, mean bowel movement frequency was higher in patients receiving tenapanor (12.3–14.2/week) than in those receiving placebo (11.5/week).
- Mean BSFS score increased by 0.8 from baseline during the randomized treatment period and mean BSFS score was 0.4–0.9 points higher in patients receiving tenapanor than in those receiving placebo at the end of the randomized withdrawal period (Figure 3b).

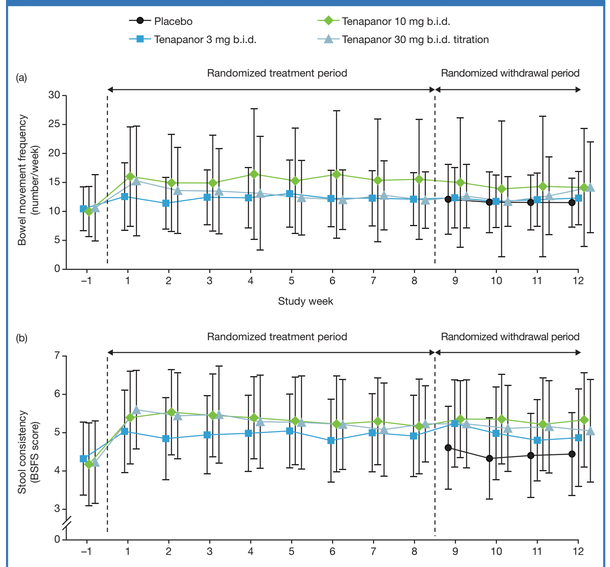
Table 2. Gastrointestinal adverse events.

Randomized treatment period	Tenapanor 3 mg b.i.d. (n = 74)	Tenapanor 10 mg b.i.d. (n = 73)	Tenapanor 30 mg b.i.d. titration (n = 71)
Gastrointestinal disorders by preferred term[a]			
Diarrhea	22 (29.7)	30 (41.1)	34 (47.9)
Mild	9 (12.2)	11 (15.1)	14 (19.7)
Moderate	12 (16.2)	16 (21.9)	17 (23.9)
Severe	1 (1.4)	3 (4.1)	3 (4.2)
Vomiting	2 (2.7)	3 (4.1)	3 (4.2)
Flatulence	2 (2.7)	3 (4.1)	2 (2.8)
Abdominal discomfort	1 (1.4)	4 (5.5)	1 (1.4)
Abdominal distension	0 (0.0)	1 (1.4)	2 (2.8)
Abdominal pain	0 (0.0)	3 (4.1)	0 (0.0)
Abdominal pain upper	2 (2.7)	1 (1.4)	0 (0.0)
Frequent bowel movements	0 (0.0)	3 (4.1)	0 (0.0)
Nausea	2 (2.7)	1 (1.4)	0 (0.0)
Defecation urgency	0 (0.0)	2 (2.7)	0 (0.0)

Randomized withdrawal period	Placebo (n = 82)	Tenapanor 3 mg b.i.d. (n = 25)	Tenapanor 10 mg b.i.d. (n = 23)	Tenapanor 30 mg b.i.d. titration (n = 34)
Gastrointestinal disorders by preferred term[a]				
Diarrhea	2 (2.4)	0 (0.0)	0 (0.0)	1 (2.9)
Mild	1 (1.2)	0 (0.0)	0 (0.0)	1 (2.9)
Moderate	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Food poisoning	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)

Data are presented as n (%).
[a]Data shown for AEs that were experienced by more than 2% of patients in any group.
AE, adverse event; b.i.d., twice daily.

Figure 3. Bowel movement frequency (a) and stool consistency (b).



Placebo, n									74	72	71	64	
Tenapanor													
3 mg b.i.d., n	71	68	68	63	61	58	58	54	52	23	25	24	23
10 mg b.i.d., n	68	70	70	68	63	58	57	55	53	22	22	22	21
30 mg b.i.d. titration, n	65	65	61	60	55	53	53	49	49	30	29	28	28

Data are presented as mean ± standard deviation. BSFS scores are weekly averages.
b.i.d., twice daily; BSFS, Bristol Stool Form Scale.

Conclusions

- Overall, tenapanor was well tolerated in patients with hyperphosphatemia undergoing hemodialysis.
  - The most common AE was diarrhea.
- Tenapanor treatment was associated with stool softening and more frequent bowel movements that, on average, remained within the normal range with regard to both frequency and form.[7,8]
- These findings reflect the pharmacodynamic mechanism of action of tenapanor, which increases stool sodium and water content,[4] and may indicate a potential benefit to patients receiving hemodialysis, some of whom experience constipation.

References

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Disclosures

Geoffrey A Block serves as a consultant to Ardelyx and he and his practice have received ownership interest in Ardelyx. David P Rosenbaum and Andrew Yan are employees of and have ownership interest in Ardelyx. Paul Korner is a former employee of and has ownership interest in Ardelyx. Glenn M Chertow is a consultant to and has received ownership interest in Ardelyx.

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