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Tenapanor Plus Phosphate Binder Reduces Interdialytic Weight Gain in Patients With Chronic Kidney Disease on Hemodialysis: Post Hoc Analysis of the AMPLIFY Study

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Background

- Chronic volume overload is common in patients with chronic kidney disease on hemodialysis (HD), and both excessive interdialytic weight gain (IDWG) and large ultrafiltration volumes are associated with adverse outcomes such as hypertension, cardiovascular events, intradialytic hypotension, as well as all-cause and cardiovascular mortality.[1-3]
- Tenapanor is a first-in-class, investigational phosphate absorption inhibitor (PAI). Preclinical studies have shown that tenapanor blocks paracellular phosphate absorption 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.[4] Inhibition of NHE3 by tenapanor also leads to increased stool sodium and water content in animals and humans.[4,5]
  - In 2 phase 3 trials (NCT02675998 and NCT03427125), tenapanor met the primary efficacy endpoint for serum phosphate-lowering and was generally well tolerated in patients with hyperphosphatemia undergoing maintenance dialysis.[6,7]
  - In the phase 3, randomized, double-blind, placebo-controlled AMPLIFY trial (NCT03824587), tenapanor also improved control of hyperphosphatemia in patients on maintenance dialysis when used in combination with phosphate binders compared with placebo plus phosphate binders.[8]
- IDWG is driven by both sodium intake and non–sodium-driven water intake from liquids and food. Based on its mechanism of action, tenapanor may decrease IDWG by reducing intestinal sodium absorption and increasing stool sodium excretion.
- In a previous phase 2 study (NCT01764854), tenapanor treatment increased stool sodium and weight compared with placebo in patients undergoing HD; however, no significant change in IDWG was observed over the 4-week study in a limited sample size (n=16 inpatients; n=72 outpatients).[9]
- The AMPLIFY study provided a large patient population with a blinded placebo control to readdress this question. We performed a post hoc analysis of pre-HD weights in patients from AMPLIFY to assess the hypothesis that patients treated with tenapanor in combination with phosphate binders had decreased IDWG and approached their target dry weight, as reflected by a pre-HD weight decrease compared with patients treated only with phosphate binders.

Methods

- The AMPLIFY study design has been reported previously.[8]
  - Briefly, the trial enrolled adult patients who had received maintenance HD thrice weekly for ≥3 months or maintenance peritoneal dialysis for ≥6 months, had a Kt/V ≥1.2 at most recent assessment before screening, and had been prescribed and were taking ≥1 phosphate binder ≥3 times daily with a dose that was unchanged in the 4 weeks before screening.
  - Patients were required to have serum phosphate ≥5.5 to ≤10 mg/dL at screening and at the end of a 2- to 4-week run-in period despite phosphate binder treatment.
  - Patients were excluded if they had clinical signs of hypovolemia at screening or parathyroid hormone concentration >1200 pg/mL.
  - Patients were randomized to add tenapanor twice a day (bid; starting at a dose of 30 mg bid) or placebo to their treatment regimen for 4 weeks, with randomization stratified by type of phosphate binder and serum phosphate concentration at the end of the run-in period.
  - There was no washout.
- Pre-HD weights were recorded at baseline and at week 4 after a short interdialytic interval.
- Analyses of IDWG in AMPLIFY were performed on patients receiving HD in the safety population, which included all randomized patients with ≥1 dose of study drug (tenapanor or placebo).

Results

Patients

- Of the 236 patients included in the safety population, 212 patients were on HD (105 assigned to tenapanor plus phosphate binder, 107 assigned to placebo plus phosphate binder).
- Baseline demographics and disease characteristics in patients on HD were generally similar between treatment groups (**Tables 1 and 2**).

Pre-HD weight change

- At week 4, mean pre-HD weight decreased with tenapanor and increased with placebo, and the least-squares (LS) mean percent change in pre-HD weight differed significantly between tenapanor and placebo groups (LS mean difference: −0.81%, *P*=0.0284; **Table 3**).
- At week 4, the proportion of patients with any decrease in pre-HD weight was greater in the tenapanor group than in the placebo group (*P*=0.0126 Cochran-Mantel-Haenszel test; **Figure 1**).
- Pre-HD weight decreased in a greater number of patients from the tenapanor group and increased in a greater number from the placebo group (**Figure 2**).

Table 1. Baseline Demographics and Disease Characteristics of Patients on HD From the AMPLIFY Trial

	Tenapanor + phosphate binder (n=105)	Placebo + phosphate binder (n=107)
Age, mean years (SD)	55.4 (12.4)	54.1 (13.0)
Sex, n (%)		
Male	60 (57.1)	69 (64.5)
Female	45 (42.9)	38 (35.5)
Race, n (%)		
Black or African American	50 (47.6)	46 (43.0)
White	49 (46.7)	54 (50.5)
Asian	2 (1.9)	4 (3.7)
Other[a]	4 (3.8)	3 (2.8)
Ethnicity, n (%)		
Not Hispanic or Latino	69 (65.7)	76 (71.0)
Hispanic or Latino	36 (34.3)	30 (28.0)
Unknown	0	1 (0.9)
BMI, mean kg/m² (SD)	33.7 (7.9)	30.7 (8.4)
Duration since ESRD diagnosis, median years (range)	3.6 (0.4-23.4)	3.2 (0.3-25.3)
Duration since first dialysis, median months (range)	43.2 (5.6-280.8)	36.8 (4.9-231.2)
Baseline sP, mean mg/dL (SD)	6.6 (1.3)	6.9 (1.4)
Baseline sP category, n (%)		
<7.5 mg/dL	80 (76.2)	72 (67.3)
≥7.5 mg/dL	25 (23.8)	35 (32.7)
Baseline iFGF23, pg/mL, mean (SD)	12,918.1 (14,441.7)	15,359.7 (16,623.5)
Most recent Kt/V, mean (SD)	1.5 (0.3)	1.6 (0.4)

Data reported for patients on HD from the safety analysis set, which included all randomized patients.
[a]American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other.
BMI, body mass index; ESRD, end stage renal disease; HD, hemodialysis; iFGF23, intact fibroblast growth factor 23; Kt/V, a measure of dialysis adequacy; sP, serum phosphate.

Table 2. Phosphate Binder Type in Patients on HD From the AMPLIFY Trial

	Tenapanor + phosphate binder (n=105)	Placebo + phosphate binder (n=107)
Phosphate binder type, n (%)		
Sevelamer alone	44 (41.9)	42 (39.2)
Sevelamer carbonate	40 (38.1)	39 (36.4)
Sevelamer hydrochloride	4 (3.8)	3 (2.8)
Sevelamer + non-sevelamer	12 (11.4)	12 (11.2)
Calcium-based	24 (22.9)	23 (21.5)
Calcium acetate	22 (21.0)	21 (19.6)
Calcium carbonate	2 (1.9)	2 (1.9)
Iron-based	12 (11.4)	26 (24.3)
Sucroferric oxyhydroxide	4 (3.8)	16 (15.0)
Ferric citrate	8 (7.6)	10 (9.4)
Others	13 (12.4)	4 (3.7)
Lanthanum carbonate	2 (1.9)	1 (0.9)
Multiple non-sevelamer	11 (10.5)	3 (2.8)

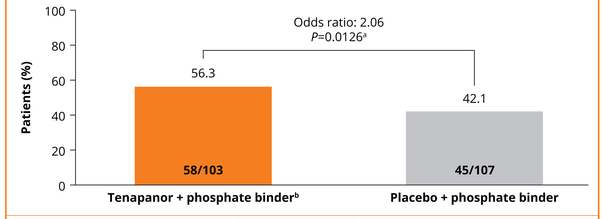
Data reported for patients on HD from the safety analysis set, which included all randomized patients.
HD, hemodialysis.

Table 3. Change in Pre-HD Weight From Baseline to Week 4

	Tenapanor + phosphate binder (n=103)[a]	Placebo + phosphate binder (n=107)
Baseline mean pre-HD weight, kg (SD)	96.2 (23.0)	90.0 (26.6)
Week 4 mean pre-HD weight, kg (SD)	95.8 (23.0)	90.2 (26.3)
LS mean pre-HD weight percent change from baseline, % (SE)	−0.24 (0.27)	0.57 (0.29)
LS mean difference in percent change between tenapanor and placebo at week 4, % (SE)[b]	−0.81 (0.37) *P*=0.0284	

[a]Pre-HD weight measurements at week 4 were not available for 2 patients in the tenapanor arm. [b]*P* value, LS means, and SEs were obtained from an ANCOVA model with sex, phosphate binder type, and treatment as factors and baseline pre-HD weight as a covariate. The analysis was performed for treated patients on HD with observed weight at baseline and week 4.
ANCOVA, analysis of covariance; HD, hemodialysis; LS, least-squares.

Figure 1. Proportion of Patients With Any Decrease in Pre-HD Weight at Week 4



[a]*P* value was obtained from Cochran–Mantel–Haenszel test controlling for sex and phosphate binder type. The analysis was performed for treated patients on HD with observed weight at baseline and week 4. [b]Pre-HD weight measurements at week 4 were not available for 2 patients in the tenapanor arm.
HD, hemodialysis.

Figure 2. Histogram of Pre-HD Weight Change at Week 4

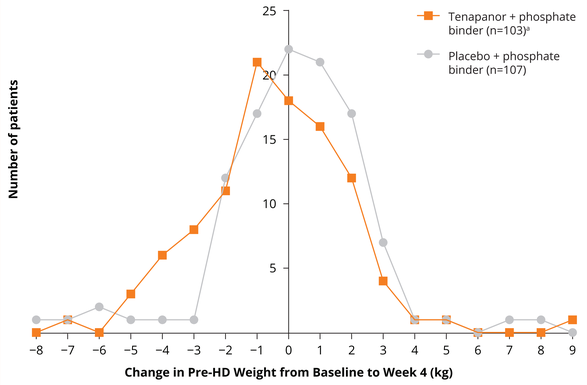


Figure shows data for treated patients on HD with observed weight at baseline and week 4.
[a]Pre-HD weight measurements at week 4 were not available for 2 patients in the tenapanor arm.
HD, hemodialysis.

Conclusions

- These results suggest that tenapanor may reduce IDWG in patients with chronic kidney disease on HD, possibly by increasing stool excretion of sodium and water.
- The potential for helping patients achieve target dry weight while controlling serum phosphate may be beneficial for patients on HD, particularly those who struggle to achieve target dry weight or have large IDWGs.
- Future clinical trials are needed to evaluate and confirm tenapanor's ability to reduce IDWG.

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Disclosures

Steven Fishbane served as a scientific advisor for Ardelyx, Inc. Stephen Z. Fadem is a principal investigator for Ardelyx, Inc. Yang Yang, Susan Edelstein, and David M Spiegel are employees of Ardelyx, Inc.

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