TH-PO1046

Efficacy of tenapanor to treat hyperphosphatemia in patients on hemodialysis

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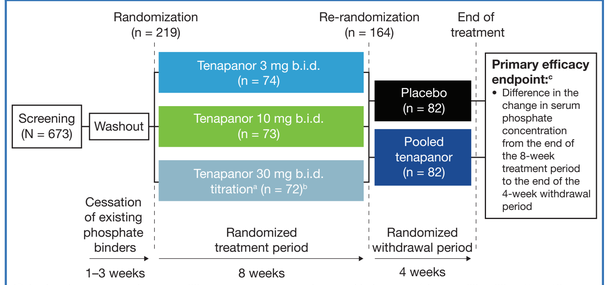
Background

- Tenapanor is a minimally absorbed, orally administered, small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3).
- Tenapanor, administered twice daily as a small tablet, reduces absorption of gastrointestinal sodium[1] and phosphate.[2,3]
  - The precise mechanism of reducing absorption of gastrointestinal phosphate is under investigation. It is thought to involve reduction of paracellular phosphate transport, without direct binding to phosphate or any direct effect on sodium-dependent phosphate transport protein 2B (NaPi2b, also known as NPT2b).[3]
- In a phase 2b study in patients undergoing hemodialysis, treatment with tenapanor for 4 weeks resulted in statistically significant reductions in serum phosphate concentrations relative to placebo in a dose-dependent manner.[4]
- Here, we present the efficacy results of the first phase 3 study of tenapanor in patients with hyperphosphatemia undergoing hemodialysis.
  - The safety and tolerability of tenapanor in this study are described in a separate poster (Block *et al.* Poster TH-PO1045).[5]

Methods

- This was a double-blind 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.
- Adults (18–80 years of age) with chronic kidney disease 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.
  - In the 30 mg b.i.d. group, weekly stepwise down-titration (30 → 20 → 15 → 10 → 3 mg b.i.d.) was permitted during the first 4 weeks based on gastrointestinal tolerability (hereafter referred to as 'tenapanor 30 mg b.i.d. titration').
- At the end of the 8-week randomized treatment period, patients entered a 4-week withdrawal period, in which they were randomized to:
  - remain on their dose of tenapanor (data from all three dose groups during the withdrawal period were pooled, hence this group is hereafter referred to as the 'pooled tenapanor group')
  - receive placebo instead of tenapanor.
- 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.
  - The responder population was defined as patients achieving a decrease in serum phosphate concentration of at least 1.2 mg/dL during the randomized treatment period.

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; [c]primary endpoint was in the 'responder population' (defined as all patients with a reduction in serum phosphate concentration of at least 1.2 mg/dL during the randomized treatment period).
b.i.d., twice daily.

Table 1. Patient demographics and baseline characteristics (safety population).

Characteristic	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)
Age, years	55.7 ± 11.5	57.4 ± 10.8	54.2 ± 10.9
Sex, n (%)			
Male	46 (62)	34 (47)	48 (68)
Race, n (%)			
White	30 (41)	25 (34)	30 (42)
Black or African American	40 (54)	45 (62)	40 (56)
Other[a]	4 (5)	3 (4)	1 (1)
Ethnicity, n (%)			
Hispanic or Latino	13 (18)	8 (11)	18 (25)
Body mass index, kg/m^2	32.5 ± 8.5	33.6 ± 8.5	33.4 ± 8.1
Time since first hemodialysis, years	12.3 ± 13.3	13.1 ± 11.2	12.1 ± 12.1
Serum phosphate, mg/dL (post-washout)	7.40 ± 1.57	7.46 ± 1.69	7.62 ± 1.43

Unless otherwise indicated, data are mean ± standard deviation.
[a]Includes Asian, American Indian or Alaskan native, native Hawaiian or Pacific Islander and other.
b.i.d., twice daily.

Results

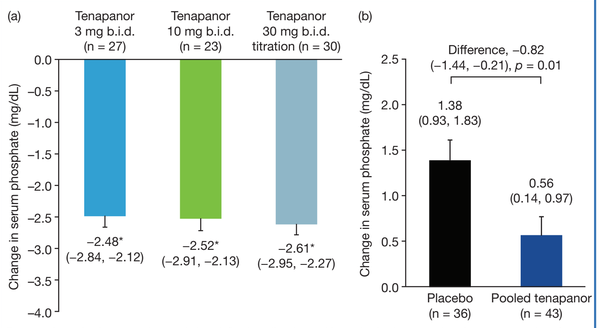
Patient disposition

- In total, 219 patients met the study entry criteria and were randomly assigned to treatment, 164 (75%) of whom completed the 8-week treatment period and were re-randomized at the start of the 4-week withdrawal period (Figure 1).
  - A total of 55 (25%) patients discontinued during the randomized treatment period; the principal reasons for discontinuation were adverse events (31%) and hyperphosphatemia (18%).
- Of the 164 patients entering the randomized withdrawal period, 152 (93%) completed it.
- Patient demographics and baseline characteristics were generally well balanced across treatment groups for both the randomized treatment (Table 1) and randomized withdrawal periods.

Serum phosphate – responder population

- In total, 80 patients achieved a reduction in serum phosphate concentration of at least 1.2 mg/dL during the 8-week treatment period and were included in the responder population.
  - Least-squares mean (LSM) reductions in serum phosphate concentration from baseline to week 8 in the responder population were in the range 2.48–2.61 mg/dL for the three dose groups (all $p < 0.001$ vs baseline; Figure 2a).
- Between the end of the 8-week randomized treatment period and the end of the 4-week randomized withdrawal period, there was an increase in serum phosphate concentration in both the pooled tenapanor and placebo groups (Figure 2b).

Figure 2. Change in serum phosphate concentration in the responder population from baseline to the end of the 8-week randomized treatment period (a) and from the end of the 8-week randomized treatment period to the end of the 4-week randomized withdrawal period (b).



Data are shown for the responder population, defined as all patients with a reduction in serum phosphate concentration of at least 1.2 mg/dL during the randomized treatment period; data are LSM change (95% confidence interval) in serum phosphate concentration and error bars show standard error, from an analysis of covariance with treatment and pooled investigator sites as factors and baseline (in a) or end of 8-week treatment period (in b) serum phosphate concentration as a covariate.
*$p < 0.001$ vs baseline.
b.i.d., twice daily; LSM, least-squares mean.

- The LSM change (95% confidence interval [CI]) in serum phosphate concentration was 0.56 (0.14, 0.97) mg/dL in the pooled tenapanor group and 1.38 (0.93, 1.83) mg/dL in the placebo group.
- The difference in the LSM (primary efficacy endpoint) was −0.82 (−1.44, −0.21) mg/dL, which was statistically significant ($p = 0.01$).

Serum phosphate – intent-to-treat population

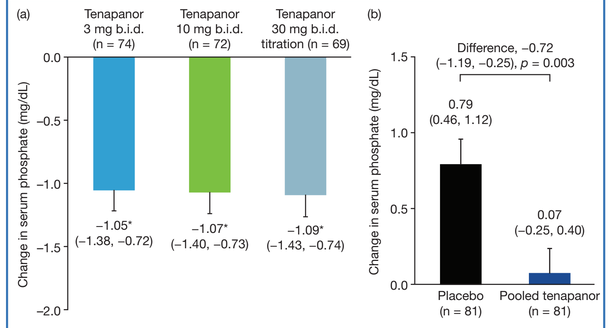
- Significant reductions in serum phosphate concentration from baseline to the end of the 8-week randomized treatment period of approximately 1.1 mg/dL were achieved in all three tenapanor dose groups ($p < 0.001$ vs baseline; Figure 3a).
- Approximately 30% of patients in each group achieved a serum phosphate goal (< 5.5 mg/dL) at the end of the 8-week treatment period (Table 2).
- At the end of the 4-week randomized withdrawal period, the LSM change (95% CI) in serum phosphate concentration from the end of the 8-week randomized treatment period was 0.07 (−0.25, 0.40) mg/dL in the pooled tenapanor group and 0.79 (0.46, 1.12) mg/dL in the placebo group (Figure 3b).
  - The difference in the LSM was −0.72 (−1.19, −0.25) mg/dL ($p = 0.003$).

Table 2. Other endpoints (intent-to-treat population).

8-week randomized treatment period			
Endpoint	**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)**
Proportion of patients achieving serum phosphate goal at end of period (< 5.5 mg/dL), n (%)	24 (32)	23 (32)[a]	20 (29)[b]
Serum parathyroid hormone, pmol/L			
Baseline, mean ± SD	427 ± 233	391 ± 282	381 ± 203
Change from baseline to end of treatment, LSM (95% CI)[c]	1 (−39, 41)	7 (−33, 47)	−25 (−65, 16)
Serum fibroblast growth factor 23, pg/mL			
Baseline, median (range)	3510 (46–71 584)	4675 (123–166 330)	7461 (623–61 745)
Change from baseline to end of treatment, LSM (95% CI)[c]	−1203 (−2985, 579)	−771 (−2544, 1002)	−2168 (−3991, −345)*
4-week randomized withdrawal period			
Endpoint		**Placebo (n = 82)**	**Pooled tenapanor (n = 82)**
Serum parathyroid hormone, pmol/L			
End of 8-week treatment period, mean ± SD		394 ± 259	403 ± 260
Change from end of 8-week randomized treatment period to end of 4-week randomized withdrawal period, LSM (95% CI)[d]		24 (−9, 56)	4 (−29, 36)
Serum fibroblast growth factor 23, pg/mL			
End of 8-week treatment period, median (range)		3073 (64–46 713)	4151 (52–39 469)
Change from end of 8-week randomized treatment period to end of 4-week randomized withdrawal period, LSM (95% CI)[d]		2429 (845, 4013)	892 (−682, 2467)

[a]n = 72; [b]n = 69; [c]LSM change and 95% CI are from an analysis of covariance model with treatment and pooled investigator site as factors and baseline concentration as a covariate; [d]LSM change and 95% CI are from an analysis of covariance model with treatment and pooled investigator site as factors and end of 8-week treatment period concentration as a covariate.
*$p = 0.02$ vs baseline.
b.i.d., twice daily; CI, confidence interval; LSM, least-squares mean; SD, standard deviation.

Figure 3. Change in serum phosphate concentration in the intent-to-treat population from baseline to the end of the 8-week randomized treatment period (a) and from the end of the 8-week randomized treatment period to the end of the 4-week randomized withdrawal period (b).



Data are LSM change (95% confidence interval) in serum phosphate concentration and error bars show standard error, from an analysis of covariance with treatment and pooled investigator sites as factors and baseline (in a) or end of 8-week treatment period (in b) serum phosphate concentration as covariates.
*$p < 0.001$ vs baseline.
b.i.d., twice daily; LSM, least-squares mean.

Other endpoints – intent-to-treat population

- Serum parathyroid hormone concentrations were broadly similar across groups and no significant changes were noted in either of the two treatment periods (Table 2).
- There was some variability in median serum fibroblast growth factor 23 (FGF23) concentrations at baseline (Table 2).
  - A significant reduction from baseline to the end of the 8-week treatment period ($p = 0.02$) was observed in the tenapanor 30 mg b.i.d. titration group.
  - At the end of the 4-week randomized withdrawal period, there was no significant difference in the mean change in FGF23 concentration between the pooled tenapanor and placebo groups.

Conclusions

- In this phase 3 randomized trial of tenapanor treatment in patients with hyperphosphatemia undergoing hemodialysis, there was a statistically significant difference between tenapanor and placebo in the change in serum phosphate concentration over the 4-week randomized withdrawal period in the responder population, which was the primary efficacy endpoint.
- Tenapanor provided statistically significant reductions from baseline in serum phosphate concentration over 8 weeks of treatment in all three dose groups.
- Tenapanor, with its novel mechanism of action involving reduction of paracellular phosphate transport without direct binding to phosphate, provides a potential new treatment option for reducing serum phosphate in patients with hyperphosphatemia undergoing hemodialysis.

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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