Poster TH-PO164

Sustained Phosphate Reduction Assessed by Serum Phosphate Area Under the Curve With Tenapanor Is Associated With Reduced Fibroblast Growth Factor 23 in Patients With Chronic Kidney Disease and Hyperphosphatemia on Dialysis

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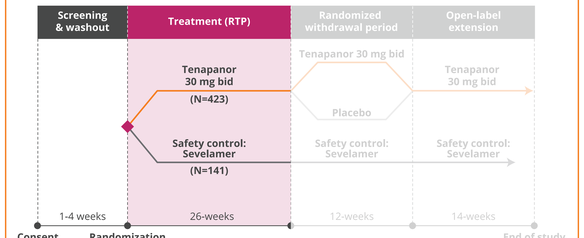
Introduction

- The Kidney Disease Improving Global Outcomes Chronic Kidney Disease—Mineral and Bone Disorder Clinical Practice guidelines (2017) recommend that strategies for managing hyperphosphatemia should be based on the use of serial measurements of serum phosphate (serum P).[1]
- More recently, average serum P area under the curve (AUC) has been identified as a more robust predictor of outcomes than other methods for estimating serum P control.[2,3]
  - Measuring serum P AUC indicates both the degree to which serum P is increased above the upper target range (4.5 mg/dL) and for how long it has been out of range during a specific time period.[3]
- Intact fibroblast growth factor 23 (iFGF23) is increased in end-stage kidney disease and is associated with increased cardiovascular mortality, but it is often not well correlated to single-point estimates of serum P.[4,5]
- Tenapanor is approved to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders (PBs) or who are intolerant of any dose of PB therapy.[6]
- In the randomized, phase 3 PHREEDOM trial (NCT03427125), tenapanor monotherapy reduced serum P with acceptable safety in patients with end-stage kidney disease receiving maintenance dialysis.[7]
- Here, we calculated the average daily serum P AUC from the serum P measurements taken during the phase 3 PHREEDOM trial of tenapanor to assess whether better long-term serum P control is associated with lower iFGF23.

Methods

- The Ardelyx-supported PHREEDOM study was a 52-week, phase 3 trial of tenapanor as monotherapy for hyperphosphatemia in adults on maintenance dialysis.
- The design and methods for PHREEDOM have been described previously[7]; briefly:
  - PHREEDOM enrolled adult patients receiving maintenance dialysis with serum P ≥6.0 and <10.0 mg/dL and a ≥1.5 mg/dL increase in serum P after PB washout.
  - During the open-label randomized treatment period (RTP), eligible patients were randomized (3:1) to receive tenapanor 30 mg orally twice a day (bid) or sevelamer carbonate as a safety control.
- Our analysis was performed on the intent-to-treat (ITT) analysis set comprising the 407 patients treated with tenapanor who met all eligibility criteria and had at least 1 post-baseline serum P measurement during the 26-week RTP (**Figure 1**).
  - For each patient in the ITT analysis set, the last observed value (LOV) after baseline during the RTP was mapped to the End of RTP – LOV analysis visit. Values mapped to the End of RTP – LOV analysis visit differ from values mapped to week 26, which only applied to patients with an observed value at the week 26 visit.

Figure 1: Study Design of the 26-Week RTP of PHREEDOM[7]



N=number of randomized patients. bid, twice a day; RTP, randomized treatment period.

- We examined correlations between average daily serum P AUC above 4.5 mg/dL during the 26-week RTP and iFGF23 at the end of the RTP, along with summaries of changes in iFGF23 in accordance with 4 serum P AUC categories:
  - Total serum P AUC was calculated by plotting serum P (y axis) against time (x axis) and solving for the total surface area of all trapezoids and/or triangles created across the amount of time spent above serum P >4.5 mg/dL.[2,3]
  - The average daily serum P AUC was then derived as the total serum P AUC divided by the number of study days between the baseline serum P assessment and the last serum P assessment of the RTP.
  - For the summaries of changes in iFGF23 related to average daily serum P AUC, the serum P AUC data were categorized by the extent to which they exceeded the upper target range of 4.5 mg/dL, as follows: >0-0.5 mg/dL, >0.5-1.0 mg/dL, >1.0-2.0 mg/dL, and >2.0 mg/dL.

Results

Patients

- Baseline demographics and disease characteristics for the ITT analysis set (N=407) are presented in **Table 1**.

Table 1: Baseline Demographics and Disease Characteristics (ITT Analysis Set)

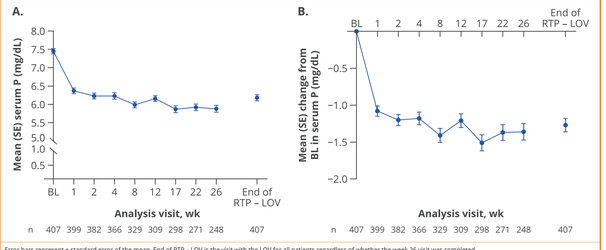
	Tenapanor (N=407)
Age, mean (SD), y	57.8 (12.7)
Male, n (%)	258 (63.4)
Race, n (%)	
American Indian or Alaska Native	11 (2.7)
Asian	21 (5.2)
Black or African American	187 (45.9)
Native Hawaiian or other Pacific Islander	2 (0.5)
White	185 (45.5)
Other	1 (0.2)
Ethnicity, n (%)	
Non-Hispanic or non-Latino	292 (71.7)
Hispanic or Latino	113 (27.8)
Not reported or unknown	2 (0.5)
BMI,[a] mean (SD), kg/m²	31.2 (7.4)
Type of dialysis, n (%)	
Hemodialysis	365 (89.7)
Peritoneal dialysis	42 (10.3)
Duration of dialysis treatment, mean (SD), mo	53.4 (50.8)
BL serum P level, mean (SD), mg/dL	7.45 (1.43)
BL iFGF23, median (range), pg/mL	6417.5 (21.0-66000.0)

[a]n=405.
BL, baseline; BMI, body mass index; iFGF23, intact fibroblast growth factor 23; ITT, intent-to-treat; P, phosphate.

Correlations Between Serum P AUC and iFGF23

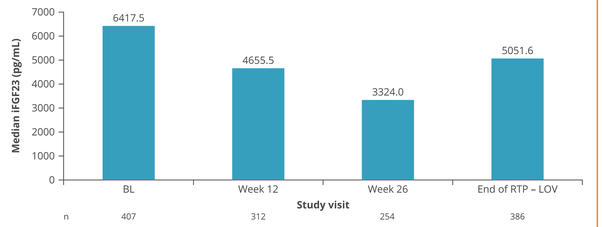
- For the 407 tenapanor-treated patients in the ITT analysis set, mean serum P reduced from 7.45 mg/dL at baseline to 6.18 mg/dL at the end of the RTP (**Figure 2A**), resulting in a mean change from baseline of 1.27 (SD: 1.83) mg/dL (**Figure 2B**).
- At the end of the RTP, the median iFGF23 was reduced from 6417.5 (range: 21.0-66000.0) pg/mL at baseline to 5051.6 (range: 26.9-66000.0) pg/mL (**Figure 3**); the median relative change from baseline was −23.2%.
- Analysis of the relationship between average daily serum P AUC and iFGF23 at the end of the RTP indicated a positive correlation between the 2 measures (ρ=0.499, *P*<0.001; **Figure 4**).

Figure 2: Mean Serum P (A) and Mean Change From Baseline in Serum P (B) During the RTP (ITT Analysis Set)



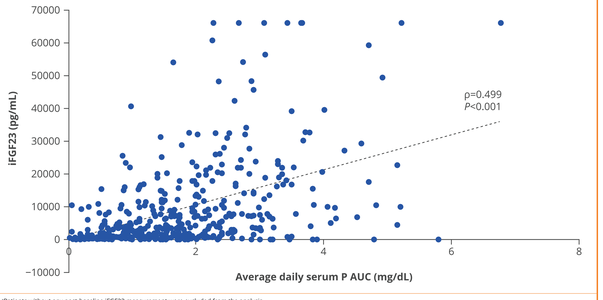
Error bars represent ± standard error of the mean. End of RTP – LOV is the visit with the LOV for all patients regardless of whether the week 26 visit was completed.
BL, baseline; ITT, intent-to-treat; LOV, last observed value; P, phosphate; RTP, randomized treatment period.

Figure 3: Median iFGF23 During the RTP (ITT Analysis Set)



BL, baseline; iFGF23, intact fibroblast growth factor 23; ITT, intent-to-treat; LOV, last observed value; RTP, randomized treatment period.

Figure 4: Correlation Between Average Daily Serum P AUC and iFGF23 at the End of the RTP – LOV (ITT Analysis Set)[a]

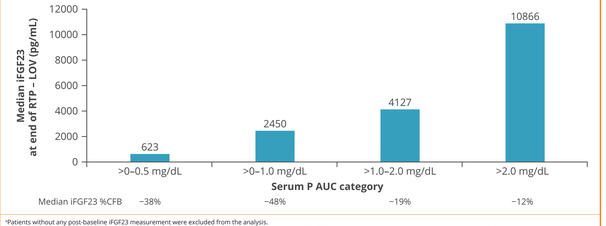


[a]Patients without any post-baseline iFGF23 measurement were excluded from the analysis.
AUC, area under the curve; iFGF23, intact fibroblast growth factor 23; ITT, intent-to-treat; LOV, last observed value; P, phosphate; RTP, randomized treatment period.

Changes in iFGF23 by Serum P AUC Category

- **Figure 5** shows the average daily serum P AUC and iFGF23 at the end of the RTP by serum P AUC category. An increasing trend in median iFGF23 was seen across the 4 serum P AUC categories: >0-0.5 mg/dL, >0.5-1.0 mg/dL, >1.0-2.0 mg/dL, and >2.0 mg/dL.
  - Greater median percent reductions from baseline in iFGF23 were seen in serum P AUC categories representative of better serum P control (>0–0.5 mg/dL and >0.5–1.0 mg/dL) than categories representative of worse serum P control (>1.0-2.0 mg/dL and >2.0 mg/dL).

Figure 5: Median iFGF23 and iFGF23 Change From Baseline at the End of the RTP – LOV by Serum P AUC Category (ITT Analysis Set)[a]



[a]Patients without any post-baseline iFGF23 measurement were excluded from the analysis.
[b]CFB, percent change from baseline; AUC, area under the curve; iFGF23, intact fibroblast growth factor 23; LOV, last observed value; P, phosphate; ITT, intent-to-treat; RTP, randomized treatment period.

Conclusions

Better serum P control with tenapanor, as measured by serum P AUC, was associated with lower iFGF23 and greater reduction in iFGF23 at the end of tenapanor treatment.

These findings may provide additional explanation for the relationship between serum P AUC and cardiovascular mortality reported in observational cohort studies.

Disclosures

This study was supported by Ardelyx, Inc. Simon Higgins, Yang Yang, David Rosenbaum, and David Spiegel are employees of Ardelyx, Inc. Kevin J. Martin is a paid consultant for Ardelyx, Inc., and participates in the data safety monitoring board or advisory board for Applied Therapeutics, LG Chem, and Renibus.

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Acknowledgments

Medical writing support for the development of this poster, under the direction of the authors, was provided by Ashfield MedComms, an Inizio company, and funded by Ardelyx, Inc.

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