FDA Briefing Document

NDA# 213931

Drug name: Tenapanor hydrochloride

Applicant: Ardelyx, Inc.

Cardiovascular and Renal Drugs Advisory Committee Meeting

November 16, 2022

Division of Cardiology and Nephrology/Office of Cardiology, Hematology, Endocrinology and Nephrology

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the magnitude of tenapanor's effect on serum phosphorus and its benefits versus risks to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
AE	adverse event
bid	twice daily
BRF	Benefit-Risk Framework
CKD	chronic kidney disease
ESKD	end-stage kidney disease
EAS	efficacy analysis set
ESRD	end-stage renal disease
FAS	full analysis set
FDA	Food and Drug Administration
GI	gastrointestinal
ITT	intention-to-treat
LOCF	last observation carried forward
LS	least squares
MMRM	mixed model repeated measures
NDA	New Drug Application
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
OL	open-label
qd	four times daily
RT	randomized treatment
RW	randomized withdrawal
s-P	serum phosphorus
SAE	serious adverse event

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA or *the Agency*) is convening this Advisory Committee (AC) meeting to discuss the clinical meaningfulness of tenapanor's effect on serum phosphorus (s-P) and whether tenapanor's benefits outweigh its risks in adults with chronic kidney disease (CKD) on dialysis when used as (1) monotherapy and (2) in combination with a phosphate binder for the treatment of hyperphosphatemia.

1.2 Context for Issues to Be Discussed at the AC

Hyperphosphatemia is common in patients with CKD on dialysis and to date, four major classes of phosphate binders have been approved in the United States for the control of s-P in adults with CKD on dialysis. Gastrointestinal (GI) side effects are seen with all approved agents, the pill burden can be high, and adherence can be challenging. As such, there is unmet need for effective, safe and well-tolerated treatments for hyperphosphatemia. Ideally such treatments would have a low pill burden.

All currently marketed products for the control of s-P in patients with CKD on dialysis were approved based on their effects on a surrogate endpoint, changes in s-P levels. In epidemiologic studies, elevated s-P levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with CKD. In patients on dialysis, higher s-P levels have also been associated with increased mortality. To date, however, there are no data from outcome studies demonstrating that lowering s-P levels in these patients improves clinical outcomes such as cardiovascular events or mortality. Based on the existing data, FDA has accepted treatment effects on s-P as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with CKD on dialysis. Although the FDA has not stipulated that applicants demonstrate a treatment effect larger than some threshold, it has indicated that the magnitude of the treatment effect should be clinically relevant. It has also stated that if the magnitude of the effect is significantly smaller than that of currently approved products, then applicants will need to address the clinical relevance. In the studies that established the efficacy and safety of products currently approved for the control of s-P, these therapies lowered s-P levels by ~1.5 to 2.2 mg/dL.

1.3 Brief Description of Issues for Discussion at the AC

Initial FDA Review

On June 29, 2020, FDA received a New Drug Application (NDA) for tenapanor for the control of s-P in adults with CKD on dialysis. Tenapanor is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3, an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. In contrast to currently approved agents for controlling s-P, which bind phosphate in the GI tract, thereby decreasing absorption, tenapanor reduces sodium absorption and decreases phosphate absorption by reducing phosphate permeability through the paracellular pathway.

To support the efficacy of tenapanor as monotherapy for reducing s-P in patients with CKD on dialysis, the Applicant conducted two studies (Studies TEN-02-201 and TEN-02-301). The Applicant also submitted the results of a third study (Study TEN-02-202) to support use in combination with existing phosphate-binder treatment. In both monotherapy studies, tenapanor's efficacy in reducing s-P was assessed in a randomized, double-blind, placebo-controlled withdrawal period. In Study TEN-02-201, which compared different dosing strategies, an 8-week double-blind randomized treatment (RT) period preceded the 4-week randomized withdrawal (RW) period; in Study TEN-02-301, which included an active comparator, a 26-week open-label (OL), RT period preceded the 12-week RW period. In both studies, the primary efficacy analysis during the RW period was based on the Efficacy Analysis Set, a subset of the intent-to-treat (ITT) population, which was intended to enrich for a responder population. Specifically, the efficacy analysis set (EAS) limited the primary efficacy analysis to patients who achieved a reduction of ≥1.2 mg/dL in serum phosphorus level in the RT period prior to RW.

Among the patients randomized to tenapanor in the 26-week OL treatment period of Study TEN-02-301, approximately 60% finished the 26-week treatment period and were rerandomized to receive tenapanor or placebo during the 12-week RW period. The most common reason for early withdrawal from the OL treatment period was diarrhea. Of the 219 patients who were randomized into the 8-week treatment period of Study TEN-02-201, approximately 75% completed the 8-week treatment period and entered the 4-week RW period. Of those who entered the RW period, approximately half were excluded from the EAS used for the primary analysis in Studies TEN-02-301 and TEN-02-201.

Among these trials, the largest treatment effect was observed in the EAS of Study TEN-02-301. In Study TEN-02-301, the point estimate of the treatment difference in the LS mean change in serum phosphorus from baseline to the end of the 12-week RW period was −1.4 mg/dL based on the EAS. However, the enrichment strategy did not appear to reliably identify patients who would have a larger treatment response to tenapanor. The FDA review team further concluded that analyses based on the ITT population of the RW periods in Studies TEN-02-201 and TEN-02-301 provided perhaps the best estimates of the average treatment effect in the subset of patients that are likely to tolerate tenapanor and remain on therapy. The magnitude of the mean treatment effect in this population (−0.7 mg/dL in both studies) appeared to be less than that observed with approved agents (~1.5 to 2.2 mg/dL). In Study TEN-02-202, which evaluated tenapanor use in combination with existing phosphate binder treatment, the magnitude of the treatment effect was similar to that observed in the monotherapy trials, −0.7 mg/dL.

Because focusing on the mean effect ignores the fact that some patients may have a larger and clinically relevant response to treatment, further exploratory analyses were conducted to characterize the treatment effect. These analyses explored whether it might be possible to individualize therapy based on a patient's response to treatment (i.e., assess for a response in a patient at some early time point and discontinue treatment in patients who do not appear to have an adequate response). These exploratory analyses suggested that if such a strategy were tested, it would need to take into consideration the variability in serum phosphorus measurements.

Complete Response Letter

On July 28, 2021, the Division issued a Complete Response letter (reproduced in Section 5.3 in the Appendix) stating the following:

> "Although we agree that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis, the magnitude of the treatment effect is small and of unclear clinical significance. In some diseases, we have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate and changes in clinical outcomes. In this disease state, we do not have such data. And, while there is well established precedent for accepting serum phosphorus as a surrogate endpoint and basis for approval in this therapeutic area, there is no precedent for accepting treatment effects of the magnitude seen in this development program.
>
> For this application to be approved, you will need to conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on a clinical outcome thought to be caused by hyperphosphatemia in CKD patients on dialysis. We note that, in principle, it may be possible to individualize treatment based on a patient's early response to a drug that lowers serum phosphorus levels (i.e., assess for a response at some early time point and only continue treatment in patients who have a clinically relevant response); however, such a strategy would need to be prospectively tested and would also likely need to be based on multiple measurements of serum phosphorus over time to distinguish the treatment effect from intrasubject variability."

Post-Action Meeting

On October 1, 2022, the Division met with the Applicant in response to a request from the Applicant to gain further clarity on the issues that led to the issuance of the Complete Response letter.

- In response to a question from the Applicant regarding the degree to which considerations of comparative effectiveness played a role in its decision, the Division stated that in considering what might constitute a clinically relevant treatment effect, it considered the precedent set by previously approved treatments and the existing data supporting the use of s-P as a surrogate endpoint. The Division also noted that while there is no formal requirement related to comparative effectiveness, being much less effective than existing therapy means that a drug will delay or possibly prevent many patients reaching goals set by their clinicians.
- In response to a question for the Applicant regarding the Division's perspective on the level of s-P reduction that it considers clinically relevant and the basis upon which the Division has come to consider this threshold to predict clinical outcomes in patients with CKD on dialysis, the Division stated that its thinking on this matter is informed by the precedent set by previously approved treatments and the existing data supporting the use of s-P as a surrogate endpoint, as described in its Complete Response letter. The Division further noted that there is an ongoing multicenter, cluster-randomized trial in patients undergoing maintenance hemodialysis to evaluate whether the current standard approach of targeting s-P levels of <5.5 mg/dL as compared with less stringent control of s-P (to target levels of >6.5 mg/dL) alters clinical outcomes (a hierarchical composite outcome of time to all-cause mortality and all-cause hospitalization among patients with ESRD

undergoing hemodialysis). The Division observed that this study would likely contribute to the understanding of s-P reduction as a surrogate endpoint.

- In response to a question from the Applicant regarding the Division's views on the utility of obtaining advice from an Advisory Committee on the clinical significance of tenapanor's reduction of s-P in CKD patients on dialysis alone or in combination with phosphate binders, the Division agreed that there might be merit to taking the issue to an Advisory Committee and indicated that it would look into the issue further. In a Post-meeting Note to the Applicant, the Division indicated that it had reached out to others within the Agency for guidance, had given further thought to the topics that might be discussed at a potential Advisory Committee meeting, and had considered whether such a meeting would be likely to alter the Division's conclusion about the approvability of the application based on the existing data. The Division stated that it continued to believe that the recommendations set forth in the Complete Response letter are an appropriate path forward to resolving the identified deficiencies and did not believe that a discussion with an Advisory Committee would alter its conclusions regarding the approvability of the application based on the existing data. Furthermore, the Division continued to believe that without additional data to address the identified deficiencies, a resubmission likely would not constitute a complete response. Thus, if the Applicant continued to disagree with the Division's conclusion, the Applicant may submit a request for Formal Dispute Resolution (FDR). As described in FDA's Guidance for Industry and Review Staff, Formal Dispute Resolution: Sponsor Appeals Above the Division Level (November 2017), as part of an original appeal or at any point in the FDR process, a sponsor can request that a scientific dispute be reviewed by an appropriate Advisory Committee. The deciding official reviewing the appeal would determine whether to grant or deny the request for Advisory Committee review.

First Formal Dispute Resolution Request

On December 3, 2021, the Applicant submitted a request for formal dispute resolution to the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN). Formal dispute resolution is a mechanism for an applicant to obtain formal review of any FDA decision by raising the matter with the supervisor of the employee who made the decision. In his denial of the appeal (reproduced in Section 5.3 in the Appendix), Dr. Hylton Joffe, Director of OCHEN, stated that based on the data available to the Division at the time of the Complete Response letter, he was unable to conclude that tenapanor's overall clinical benefit is meaningful and outweighs its risks. As a path forward, he recommended that the Applicant submit a Complete Response to their NDA that provided the additional information and analyses described in his Appeal Denial letter. He further indicated that if the Applicant submitted a Complete Response with the requested information and it still raised concerns regarding the adequacy of the data to establish a meaningful effect with benefits that outweigh the risks, the Division would consider whether a public meeting of the Cardiovascular and Renal Drugs Advisory Committee would be appropriate to provide further input on the issue during the review cycle.

Second Formal Dispute Resolution Request

On February 18, 2022, the Applicant submitted a request for formal dispute resolution to the Office of New Drugs. Dr. Peter Stein, Director of the Office of New Drugs, reviewed the request and on April 15, 2022, issued an interim appeal response (reproduced in Section 5.3 in the Appendix) indicating that additional input was needed to reach a decision. Therefore, he intended to direct the Division to bring

the tenapanor application to a Cardiovascular and Renal Drugs Advisory Committee meeting. However, he also noted that there was another potential pathway for the Applicant to consider. As indicated in the OCHEN Appeal Denial letter, there were additional analyses that could be included in a response to the Complete Reponse action and could lead to reconsideration by the Division. If the Applicant wanted the Division to consider these analyses, the Applicant could withdraw this appeal and submit them in response to the Complete Response action.

1.4 Draft Points for Consideration

The Applicant is seeking approval of tenapanor to control s-P in adults with CKD on dialysis. As you review this briefing document, consider the following issues:

- Based on the existing data, FDA has accepted treatment effects on s-P as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with CKD on dialysis. Although the FDA has not stipulated that applicants demonstrate a treatment effect larger than some threshold, it has indicated that the magnitude of the treatment effect should be clinically relevant. It has also stated that if the magnitude of the effect is significantly smaller than that of currently approved products, then applicants should address the clinical relevance. In the studies that established the efficacy and safety of products currently approved for the control of s-P, these therapies lowered s-P levels by ~1.5 to 2.2 mg/dL.
- The Applicant's development program evaluated tenapanor's effect on s-P when administered (1) as monotherapy and (2) in combination with existing phosphate binder treatment. What is the magnitude of tenapanor's treatment effect on s-P in both settings?
- Do you consider the magnitude of the treatment effect on s-P in CKD patients on dialysis to be clinically meaningful? If so, what is the basis for this conclusion? Do you consider it clinically meaningful as monotherapy? In combination with existing phosphate-lowering therapy?
- Diarrhea was the most common adverse reaction in clinical trials of tenapanor in patients with CKD on dialysis. Consider this risk from a safety and tolerability perspective.
- Consider whether tenapanor's benefits outweigh its risks for the control of s-P in adults with CKD on dialysis when administered (1) as monotherapy and (2) used in combination with other agents.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Hyperphosphatemia is a common complication in patients with CKD on dialysis and is defined as an elevated level of s-P (>4.5 mg/dL). In epidemiologic studies, elevated s-P levels have been associated with increased risks of secondary hyperparathyroidism; vascular, valvular, and other soft-tissue calcification; and cardiovascular morbidity and mortality in patients with CKD. Based on these data, as well as biological plausibility, FDA has accepted treatment effects on s-P as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with CKD on dialysis. However, data from randomized controlled trials demonstrating that treatments that lower serum phosphorus improve patient outcomes are lacking. There is also uncertainty about what should constitute the "target" serum phosphorus level in the dialysis population. As such, clinical practice guidelines recommend lowering elevated serum phosphorus levels toward the normal range and grade

the strength of the recommendation as "level 2" ("we suggest") and the quality of supporting evidence as "low"[1].

In most adults with CKD who are on hemodialysis in the United States, thrice weekly intermittent hemodialysis and dietary restriction of foods and drinks high in phosphorus are not sufficient to control hyperphosphatemia. GI phosphate binders are widely used to control s-P levels in adults with CKD on dialysis. To date, four major classes of agents have been approved for this use in the United States—calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-based binding agents. Common adverse reactions include GI side effects, such as constipation, diarrhea and nausea. Also, the pill burden can be high, since patients may need to take multiple pills with each meal . As such, there is an unmet need for well-tolerated treatments that can effectively control s-P. Ideally, such treatments would have a low pill burden.

2.2 Pertinent Drug Development and Regulatory History

Tenapanor is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3, an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. In contrast to currently approved agents for controlling s-P, which bind phosphate in the GI tract, thereby decreasing absorption, tenapanor reduces sodium absorption and decreases phosphate absorption by reducing phosphate permeability through the GI paracellular pathway.

Over the course of product development, there were a number of discussions with the Applicant about the design of the tenapanor development program and the data needed to demonstrate efficacy and safety. Discussions pertinent to the focus of this briefing document are summarized below.

- In November 2017, the Agency provided feedback on the protocol and statistical analysis plan for the Applicant's phase 3 Study TEN-02-301. In its Advice Letter, the Agency advised the Applicant that "If the size of the effect of tenapanor on serum phosphorus is significantly smaller than the size of the effect of currently approved phosphate binders, then you will need to address the clinical relevance of the effect size of your product on serum phosphorus."
- In December 2018, the Agency issued an Advice Letter in response to a request for feedback on Study TEN-02-202, which evaluated the efficacy of tenapanor as adjunctive therapy to phosphate binder treatment in ESRD subjects with hyperphosphatemia. In response to the Applicant's questions regarding whether the results of Study TEN-02-202 could support additional labeling claims, the Agency stated: "Assuming the trial is well-conducted and the size of the treatment effect is clinically relevant, we agree that the results could be described in labeling."

[1] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.

- In March 2020, a meeting was held with the Applicant to discuss the planned NDA submission for tenapanor for the control of serum phosphorus in adults with CKD on dialysis. The discussion focused on the clinical relevance of the magnitude of the treatment effect on s-P. According to the minutes:

  "The Agency indicated that it has accepted serum phosphorus as a surrogate endpoint and basis for approval for products intended to treat hyperphosphatemia in patients with chronic kidney disease on dialysis. The evidence supporting its use as a surrogate endpoint includes biologic plausibility and epidemiologic data; but, to date, there is no evidence from outcome studies demonstrating that a treatment's effect on serum phosphorus predicts its effect on clinical outcomes." The Agency clarified, however, that while it has accepted serum phosphorus as a surrogate endpoint, a treatment effect of any magnitude is not considered sufficient to support approval.

  The Agency indicated that the Applicant should address the clinical relevance of the magnitude of the treatment effect observed in their development program in their NDA submission. The Agency stated that it is interested in the evidence supporting the conclusion that the magnitude of the treatment effect is clinically relevant, as opposed to "expert opinion." The Agency also stated that showing a marked treatment effect in patients with more marked elevations in s-P level at baseline could be compelling.

3 Summary of Issues for the AC

3.1 Efficacy Issues

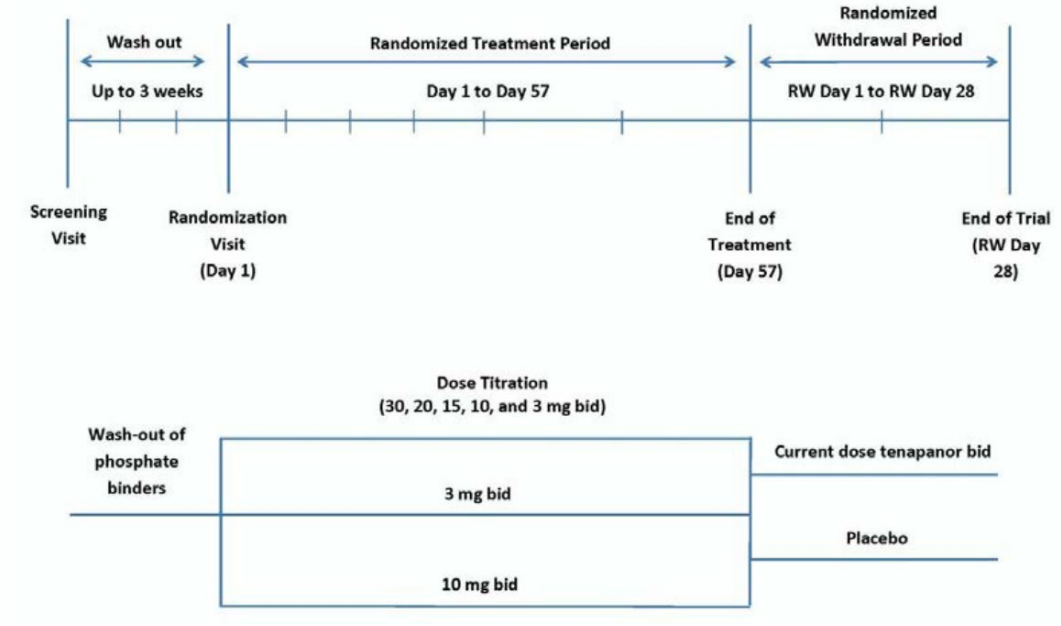
3.1.1 Sources of Data for Efficacy

The ability of tenapanor to lower s-P when administered as monotherapy in adult subjects with CKD on dialysis was evaluated in two randomized, multicenter studies (the phase 2b Study TEN-02-201, and the phase 3 Study TEN-02-301). Both studies were conducted in the United States and included an initial treatment period followed by a randomized, double-blind, placebo-controlled withdrawal period. A third study (Study TEN-02-202) evaluated the efficacy of tenapanor as adjunctive therapy to phosphate-binder treatment. Overviews of the designs of Studies TEN-02-201, TEN-02-301, and TEN-02-202 are provided below.

Design of Study TEN-02-201

Study TEN-02-201 was a phase 2b, multicenter, randomized, double-blind, study that evaluated the efficacy, safety, and tolerability of different dosing regimens of tenapanor in treating hyperphosphatemia in ESRD patients on hemodialysis. The study included a screening visit; a wash-out period of up to 3 weeks, during which existing phosphate-lowering medication was withheld; an 8-week RT period, in which all groups received tenapanor, blinded to treatment (3 mg twice daily [bid], 10 mg bid, or a titration regimen); and a 4-week placebo-controlled RW period, during which subjects were rerandomized 1:1 to their current tenapanor treatment or to placebo. The study design is shown in Figure 1.

Figure 1. Schematic of Design of Study TEN-02-201



Source: Study TEN-02-201 Protocol version 3, dated May 27, 2016.

Key analysis populations are defined below:

- Intention-to-treat (ITT) analysis set for the 4-week RW period: All subjects who met the study entry inclusion/exclusion criteria, completed the 8-week RT period and entered the 4-week RW period.
- EAS: All ITT subjects who met the study entry inclusion and exclusion criteria, completed the 8-week RT period, achieved at least a 1.2 mg/dL reduction in s-P from baseline to the end of the 8-week RT period and entered the 4-week RW period.

The primary efficacy analysis was to be based on the EAS (i.e., an enriched population) using the last-observation-carried-forward (LOCF) approach for handling missing data. The primary efficacy variable was the change in s-P from the end of the 8-week RT period to the end of the 4-week RW period or the endpoint visit for this period, which was defined as the last visit during the 4-week RW period. The primary efficacy model was to be an analysis of covariance (ANCOVA) model with terms for pooled investigator site, treatment group, and baseline s-P (defined as the value at the end of the RT period) as the covariates.

Design of Study TEN-02-301

Study TEN-02-301 was a phase 3 study in ESRD patients on hemodialysis and peritoneal dialysis that had a 26-week, OL active-controlled treatment period then a 12-week, placebo-controlled, RW period followed by a 14-week OL safety extension. The key features of the OL treatment period and RW period were as follows:

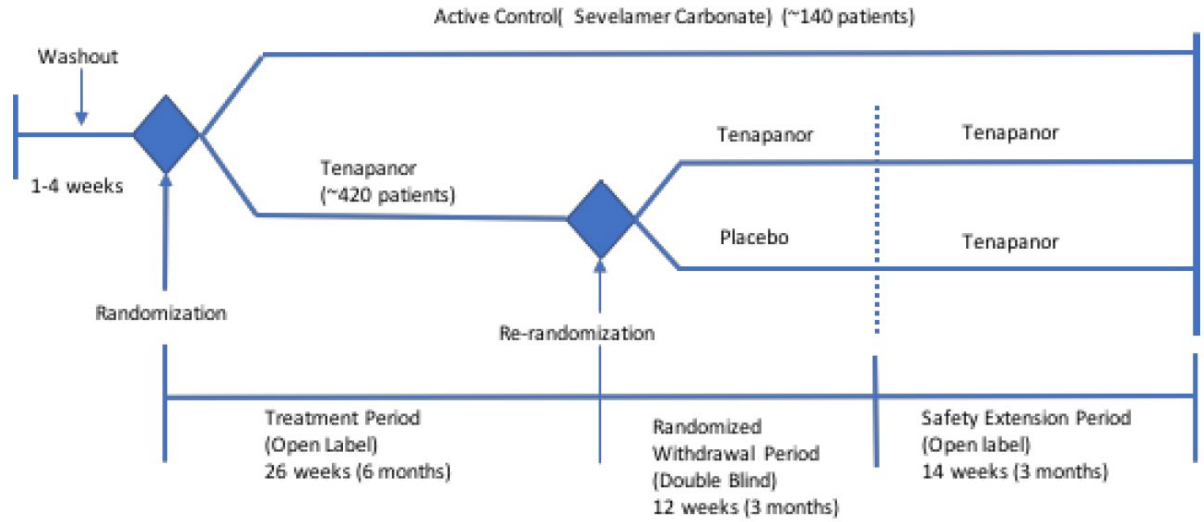
- OL RT Period: Subjects who met all the inclusion/exclusion criteria were randomized 3:1 to either receive tenapanor or sevelamer carbonate (an approved phosphate binder) after 1, 2, or 3 weeks of wash-out if they had a s-P level of at least 6.0 mg/dL and not more than 10.0 mg/dL, and had an increase in s-P of at least 1.5 mg/dL versus pre wash-out (Visit 1, screening visit). Those randomized

to take sevelamer carbonate were to be dosed based on the FDA-approved labeling. Subjects randomized into the tenapanor group were to take tenapanor for 26 weeks; after this period, subjects in the tenapanor arm were to enter a placebo-controlled RW period. During the OL treatment period, subjects randomized to tenapanor were to initiate treatment at the highest recommended dose (30 mg taken twice daily). During the 26-week treatment period, the dose of tenapanor could be down- or up-titrated (to a maximum dose of 30 mg bid) in a stepwise fashion based on s-P levels and/or GI tolerability. Dose titration was to occur in 10 mg bid increments (e.g., from 30 mg bid to 20 mg bid, and from 20 mg bid to 10 mg bid). Subjects were to take tenapanor prior to breakfast and dinner. On dialysis days, subjects on hemodialysis were not to take study drug at the meal prior to dialysis and instead take it before another meal. If a meal was skipped, the dose was to be taken with another meal during the day or at around the time that the meal would have been consumed.

- RW Period: At the end of the 26-week treatment period, subjects in the tenapanor group only were to be randomized 1:1 to either remain on the tenapanor dose they were taking on day 183 (Visit 13) or receive placebo for 12 weeks.

The study design is shown in Figure 2.

Figure 2. Schematic of Design of Study TEN-02-301



Source: Study TEN-02-301 Protocol version 4, dated May 30, 2018.

Key analysis populations are defined below:

- ITT Analysis set for the 26-week RT period: All subjects who met the study entry inclusion/exclusion criteria, received at least one dose of tenapanor, and had at least one post-treatment s-P measurement during the 26-week RT period. Subjects randomized to the sevelamer carbonate (active control) group were not included in this ITT analysis set.
- ITT Analysis set for the 12-week RW period: All subjects who met the study entry inclusion/exclusion criteria, completed the 26-week RT period, entered the 12-week RW period, received at least one

dose of tenapanor, and had at least one post-treatment s-P measurement during the 12-week RW period.

- EAS: All ITT subjects who met the study entry inclusion/exclusion criteria, received at least one dose of tenapanor during the 26-week RT period, completed the 26-week RT period, achieved a reduction of ≥1.2 mg/dL in s-P level from baseline to the end of the 26-week RT period and entered the 12-week RW period.

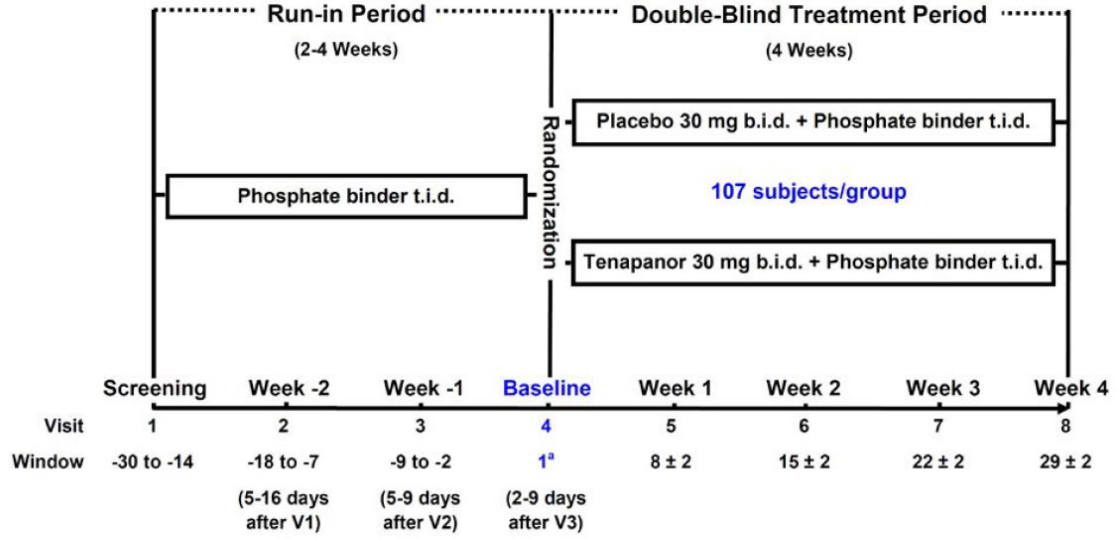
The primary efficacy analysis was to be based on the EAS using the LOCF approach. The primary efficacy endpoint was the change in s-P from the end of the 26-week RT period to the endpoint visit of the 12-week RW period, where the endpoint visit was defined as the last visit with an s-P assessment during the 12-week RW period. The primary efficacy model was an ANCOVA model that included treatment and pooled site as fixed effects and baseline s-P at the start of the RW period (defined as the value at the end of the RT period) as a continuous covariate. An sensitivity analysis using a mixed model repeated measures (MMRM) approach was to be performed.

Design of Study TEN-02-202

The primary objective of Study TEN-02-202, a randomized, double-blind, placebo-controlled study, was to evaluate the effect of tenapanor on the change in s-P level when tenapanor is administered orally twice daily for 28 days as adjunctive therapy to ESRD subjects with hyperphosphatemia on stable phosphate-binder therapy.

This study consisted of a Screening Visit; a Run-in Period of at least 2 weeks and up to 4 weeks, during which existing phosphate-binder treatment was maintained; and a 4-week Double-Blind Treatment Period, during which subjects were randomized at a 1:1 ratio to receive tenapanor at a dose of 30 mg twice daily (bid; three 10 mg tablets each time) or placebo while continuing their existing phosphate-binder treatment. The dose of phosphate binder was to remain unchanged throughout the study (from Screening to the end of study). An overview of the study design is shown in Figure 3.

Figure 3. Design of Study TEN-02-202



Source: Study TEN-02-202 Protocol version 2, dated January 22, 2019.

Key analysis populations are defined below:

- ITT Population: Comprised all randomized subjects.
- Full analysis set (FAS): Included all ITT subjects with at least one postbaseline s-P measurement during the study.

The primary efficacy endpoint was the change from baseline in s-P level at Week 4. An MMRM approach was used for the primary efficacy analysis. The MMRM analysis included the interactive response technology-recorded phosphate-binder type (sevelamer or non-sevelamer), s-P level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (Week 1 through Week 4), and Treatment-by-Visit interaction as fixed effects. Baseline s-P level and Baseline-by-Visit were included as covariates, and subject as a random effect. A sensitivity analysis using MMRM in the per-protocol population was also to be performed.

3.1.2 Efficacy Summary

3.1.2.1 Study TEN-02-201

Subject Disposition

In Study TEN-02-201, 219 subjects were randomized to one of three dosing regimens of tenapanor in the 8-week RT period, 164 of whom (75%) completed the 8-week RT period and entered the 4-week RW period. Of these 164 subjects, 82 subjects were randomized to the placebo group, and 82 subjects were randomized to the tenapanor group. The most common reason for early withdrawal from the 8-week RT period was related to GI adverse events (AEs) (mainly diarrhea). Of the 164 subjects who entered the 4-week RW period, 12 (7.3%) withdrew from the study prior to completing the 4-week RW period; the most common reasons for withdrawal were hyperphosphatemia (5 subjects) and AE (3 subjects). Eighty subjects met the criteria for inclusion in the EAS (37% of those randomized into the study; 49% of those who entered the 4-week RW period). Of these 80 subjects, 76 (95%) completed the 4-week RW period, 34 in the placebo group and 42 in the three tenapanor groups. Additional disposition information for the 4-week RW period is provided in Table 1.

Table 1. Subject Disposition—8-Week RT Period and 4-Week RW Period, Study TEN-02-201

Parameter	Placebo n (%)	All Tenapanor n (%)	Total n (%)
Randomized to 8-week RT period[1]		219 (100)	219 (100)
Completed 8-week RT period[1]		164 (74.9)	164 (74.9)
Entered 4-week RW period[2]	82 (100)	82 (100)	164 (100)
Completed 4-week RW period[2]	74 (90.2)	78 (95.1)	152 (92.7)
Withdrew prior to completing 4-week RW period[2]	8 (9.8)	4 (4.9)	12 (7.3)
Primary reason for early withdrawal from 4-week RW period[2]			
Hyperphosphatemia	3 (3.7)	2 (2.4)	5 (3.0)
Adverse event	2 (2.4)	1 (1.2)	3 (1.8)
Protocol deviation	1 (1.2)	0 (0.0)	1 (0.6)
Hypophosphatemia	1 (1.2)	0 (0.0)	1 (0.6)
Physician decision	0 (0.0)	1 (1.2)	1 (0.6)
Withdrawal by subject	1 (1.2)	0 (0.0)	1 (0.6)

Parameter	Placebo n (%)	All Tenapanor n (%)	Total n (%)
Efficacy analysis set[2]	37 (45.1)	43 (52.4)	80 (48.8)
Reason excluded from efficacy analysis set[2]			
Did not achieve a reduction of 1.2 mg/dL in serum phosphorus level from baseline to the end of the 8-week RT period	45 (54.9)	39 (47.6)	84 (51.2)
Safety analysis set[2,3]	82 (100)	82 (100)	164 (100)

Source: Study TEN-02-201 Clinical Study Report, Table 5.
[1] Percentages were calculated using the number of subjects randomized to the 8-week RT period as the denominator.
[2] Percentages were calculated using the number of subjects entering the 4-week RW period as the denominator.
[3] All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set.
Abbreviations: RT, randomized treatment; RW, randomized withdrawal

Key Efficacy Results

Table 2 shows the results for the primary efficacy endpoint in the EAS. The LOCF approach was used as the primary efficacy analysis. The least-squares (LS) mean change in s-P from the end of the 8-week RT period to the end of the 4-week RW period was 1.4 mg/dL in the placebo group and 0.6 mg/dL in the pooled tenapanor group, resulting in a LS mean treatment difference between the pooled tenapanor group and the placebo group of −0.8 mg/dL (p=0.01). A sensitivity analysis using the MMRM method showed a treatment effect estimate of −0.9 (p=0.0068).

The results of analyses using the ITT analysis set for the 4-week RW period, which included all 164 subjects who entered the 4-week RW period, were similar to those based on the 80 subjects in the EAS. The LS mean change in s-P from the end of the 8-week RT period to the end of the 4-week RW period in the ITT population was 0.8 mg/dL for the placebo group and 0.1 mg/dL for the pooled tenapanor group. The LS mean of the treatment difference between the tenapanor group and the placebo group was −0.7 mg/dL (p=0.003). MMRM analysis yielded a treatment effect estimate of −0.8 (p=0.0012). Therefore, the enriched population in this study (those with a ≥1.2 mg/dL reduction in s-P during the RT period) did not have a meaningfully higher reduction in s-P with tenapanor relative to placebo in the RW period. Analyses based on tenapanor dose did not suggest a clear dose-response relationship for efficacy. Additional information is provided in the Appendix.

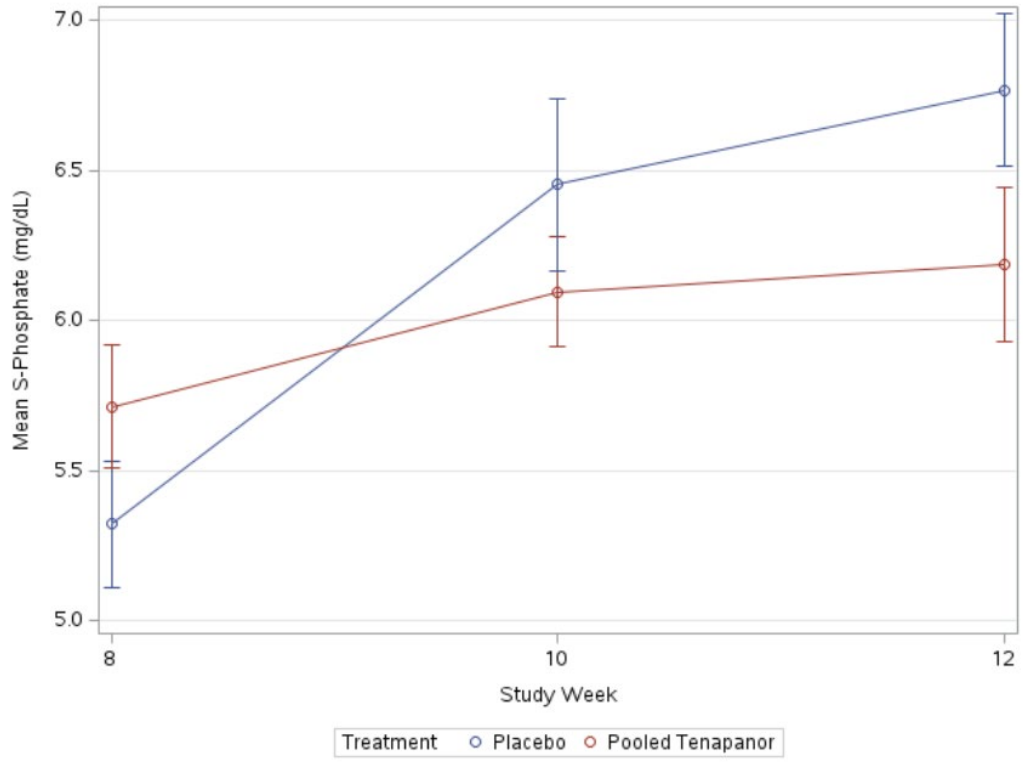
Table 2. Change in Serum Phosphorus (mg/dL) From the End of the 8-Week RT Period to the End of the 4-Week RW Period, Efficacy Analysis Set, Study TEN-02-201

	Tenapanor Versus Placebo	
Parameter	Placebo (N=37)	All Tenapanor (n=43)
End of the 8-week RT period[1]	5.3 (1.29)	5.7 (1.34)
Change from baseline to the end of the 4-week RW period[2]		
LS Mean (SE)[3]	1.4 (0.23)	0.6 (0.21)
LS Mean difference (SE) (versus placebo)		−0.8 (0.31)
95% CI LS Mean difference (versus placebo)		(−1.4, −0.2)
p-Value		0.01

Source: Study TEN-02-201 Clinical Study Report, Table 8.
[1] The end of the 8-week RT period was defined as the last assessment during the 8-week RT period.
[2] The end of the 4-week RW period was defined as the last assessment during the 4-week RW period.
LS means, SE, 95% CIs, and p-values were from an ANCOVA model with treatment and pooled Investigator site as factors and end of the 8-week RT period value as a covariate.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least-squares; RT, randomized treatment; RW, randomized withdrawal; SE, standard error

Figure 4 shows the mean s-P (mg/dL) values during the 4-week RW period for the EAS. The mean s-P in the placebo arm increased from 5.3 mg/dL at the end of the 8-week RT period to 6.8 mg/dL at the end of the 4-week RW period. The mean s-P in the tenapanor arm increased from 5.7 mg/dL at the end of the 8-week RT period to 6.2 mg/dL at the end of the 4-week RW period.

Figure 4. Mean ± Standard Error Serum Phosphorus (mg/dL) for the 4-Week Randomized Withdrawal Period, Efficacy Analysis Set, Study TEN-02-201



Source: Study TEN-02-201 Clinical Study Report, Figure 2 and FDA statistical reviewer: adeff.xpt, SAS.

3.1.2.2 Study TEN-02-301

Subject Disposition

In the phase 3 Study TEN-02-301, 564 subjects were randomized into the 26-week treatment period (423 to tenapanor and 141 to sevelamer carbonate). Of the 423 subjects randomized to tenapanor, 167 (39%) withdrew before completing the 26-week RT period. Of these subjects, 67 subjects in the tenapanor group (16%) withdrew due to diarrhea and 22 (5%) withdrew for hyperphosphatemia. Two hundred fifty-five tenapanor-treated subjects (60%) completed the 26-week RT period and were rerandomized 1:1 to remain on their current tenapanor dose or receive placebo during the 12-week RW period. A total of 131 subjects met the criteria for inclusion in the EAS (31% of the subjects originally randomized to tenapanor; 51% of the subjects randomized into the RW period); 116 (89%) of subjects in the EAS completed the 12-week RW period, 61 in the placebo group and 55 in the tenapanor group. Additional disposition information for the 26-week RT period and the 12-week RW period is provided in Table 3 and Table 4, respectively.

Table 3. Subject Disposition—26-Week RT Period, Study TEN-02-301

Parameter	Sevelamer Carbonate N=141 n (%)	All Tenapanor N=423 n (%)	Total N=564 n (%)
Randomized to 26-week RT period	141 (100)	423 (100)	564 (100)
Completed 26-week RT period	117 (83.0)	256 (60.5)[2]	373 (66.1)
Withdrew prior to completing 26-week RT period	24 (17.0)	167 (39.5)	191 (33.9)
Primary reason for withdrawal from 26-week RT period			
Adverse event	2 (1.4)	77 (18.2)	79 (14.0)
Death	3 (2.1)	7 (1.7)	10 (1.8)
Hyperphosphatemia[1]	1 (0.7)	22 (5.2)	23 (4.1)
Hypophosphatemia[1]	0 (0.0)	5 (1.2)	5 (0.9)
Lost to follow-up	1 (0.7)	3 (0.7)	4 (0.7)
Physician decision	1 (0.7)	9 (2.1)	10 (1.8)
Withdrawal by subject	10 (7.1)	34 (8.0)	44 (7.8)
Protocol deviation	0 (0.0)	1 (0.2)	1 (0.2)
Other	6 (4.3)	9 (2.1)	15 (2.7)

Source: Study TEN-02-301 Clinical Study Report, Table 4.
[1] Withdrawal reasons were separated to adverse event.
[2] One subject completed the RT period but did not enter the RW period due to physician decision.
Abbreviations: GCP, good clinical practices; RT, randomized treatment

Table 4. Subject Disposition—12-Week RW Period, Study TEN-02-301

Parameter	Placebo n (%)	All Tenapanor n (%)	Total n (%)
Randomized to 26-week RT period[1]		423 (100)	423 (100)
Completed 26-week RT period[1]		256 (60.5)	256 (60.5)
Entered 12-week RW period[2]	127 (100)	128 (100)	255 (100)[4]
Completed 12-week RW period[2]	99 (78.0)	99 (77.3)	198 (77.6)
Withdrew prior to completing 12-week RW period[2]	28 (22.0)	29 (22.7)	57 (22.4)
Primary reason for early withdrawal from 12-week RW period[2]			
Adverse event	0 (0.0)	3 (2.3)	3 (1.2)
Death	1 (0.8)	1 (0.8)	2 (0.8)
Hyperphosphatemia[3]	14 (11.0)	7 (5.5)	21 (8.2)
Hypophosphatemia[3]	2 (1.6)	1 (0.8)	3 (1.2)
Lost to follow-up	0 (0.0)	2 (1.6)	2 (0.8)
Physician decision	3 (2.4)	3 (2.3)	6 (2.4)
Withdrawal by subject	2 (1.6)	8 (6.3)	10 (3.9)
Other	4 (3.1)	3 (2.3)	7 (2.7)
Not reported	2 (1.6)	1 (0.8)	3 (1.2)
ITT analysis set[2]	123 (96.9)	120 (93.8)	243 (95.3)
Reason excluded from ITT analysis set[2]			
Did not meet inclusion/exclusion criteria	2 (1.6)	3 (2.3)	5 (2.0)
Did not receive tenapanor or placebo or did not have at least 1 post-treatment serum phosphorus measurement	1 (0.8)	4 (3.1)	5 (2.0)
Serious GCP breach	1 (0.8)	1 (0.8)	2 (0.8)

Parameter	Placebo n (%)	All Tenapanor n (%)	Total n (%)
Efficacy analysis set[2]	68 (53.5)	63 (49.2)	131 (51.4)
Reason excluded from efficacy analysis set[2]			
Was not included in ITT analysis set	4 (3.1)	8 (6.3)	12 (4.7)
Did not achieve a reduction of 1.2 mg/dL in serum phosphorus level from period-level baseline to the end of the treatment period	55 (43.3)	57 (44.5)	112 (43.9)
Safety analysis set[2]	126 (99.2)	125 (97.7)	251 (98.4)

Source: Study TEN-02-301 Clinical Study Report, Table 5 and FDA reviewer.
[1] Percentages were calculated using the number of subjects randomized to the 26-week RT period as the denominator.
[2] Percentages were calculated using the number of subjects entering the 12-week RW period as the denominator.
[3] Withdrawal reasons were separated to adverse event.
[4] One subject completed the RT period but did not enter the RW period due to physician decision.
Abbreviations: GCP, good clinical practices; ITT, intent-to-treat; RT, randomized treatment; RW, randomized withdrawal

Key Efficacy Results

Table 5 shows the results for the primary efficacy variable in the EAS. The LS mean change in s-P from the period-level baseline (i.e., the last measurement of the 26-week treatment period) to the end of the 12-week RW period was 0.4 mg/dL for the tenapanor group and 1.8 mg/dL for the placebo group. Relative to placebo, the LS mean difference in s-P level change from the period-level baseline to the end of the 12-week RW period was −1.4 mg/dL for the tenapanor group (p<0.0001) using the LOCF approach. The MMRM analysis yielded a similar estimate, −1.3 mg/dL (p<0.0001).

Table 5. Analysis of Change From Period-Level Baseline in Serum Phosphorus (mg/dL) at the End of the 12-Week RW Period, Efficacy Analysis Set, Study TEN-02-301

	Tenapanor Versus Placebo	
Parameter	Placebo (N=68)	All Tenapanor (n=63)
Baseline at the 12-week RW period[1]	5.1 (1.25)	5.2 (1.13)
Change from baseline to the end of the 12-week RW period[2]		
LS Mean (SE)[3]	1.8 (0.20)	0.4 (0.20)
LS Mean difference (SE) (versus placebo)		−1.4 (0.28)
95% CI LS Mean difference (versus placebo)		(−1.9, −0.8)
p-Value		<0.0001

Source: Study TEN-02-301 Clinical Study Report, Table 10.
[1] For the 12-week RW period, baseline at the RW period was defined as the last measurement collected prior to the first dose of study drug during the 12-week RW period.
[2] The end of the 12-week RW period was defined as the last assessment during the 12-week RW period.
[3] LS means, SE, 95% CIs, and p-values were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; RW, randomized withdrawal; SE, standard error

Table 6 shows the results for the primary efficacy variable using the ITT analysis set. Estimates of the treatment effect based on the ITT analysis set of 243 patients (57% of the patients originally randomized to tenapanor) were considerably smaller than those based on the EAS of 131 patients (31% of patients originally randomized to tenapanor). The LS mean difference in the change in s-P from the period-level baseline to the end of the 12-week RW period in the ITT analysis set was −0.7 mg/dL (p=0.0020). MMRM analysis yielded a treatment effect estimate of −0.7 mg/dL (p<0.001).

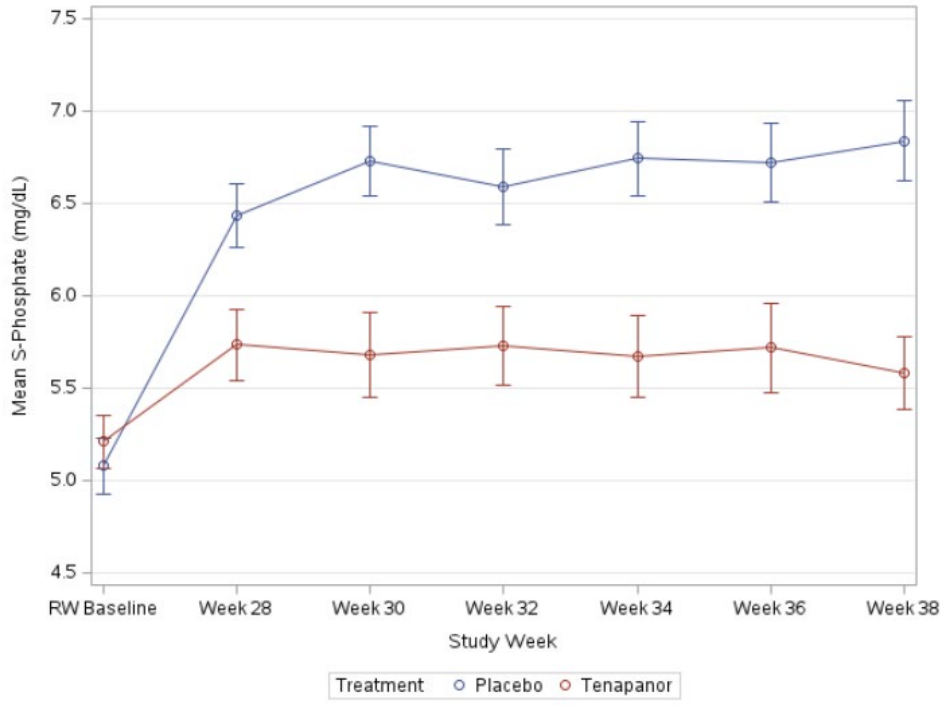
Table 6. Analysis of Change From Period-Level Baseline in Serum Phosphorus (mg/dL) at the End of the 12-Week RW Period, Intention-to-Treat Analysis Set, Study TEN-02-301

	Tenapanor Versus Placebo	
Parameter	**Placebo (N=123)**	**All Tenapanor (n=120)**
Baseline at the 12-week RW period[1]	5.8 (1.44)	5.9 (1.48)
Change from baseline to the end of the 12-week RW period[2]		
LS Mean (SE)[3]	0.9 (0.15)	0.2 (0.15)
LS Mean difference (SE) (versus placebo)		−0.7 (0.21)
95% CI LS Mean difference (versus placebo)		(−1.1, −0.2)
p-Value		0.002

Source: Study TEN-02-301 Clinical Study Report, Table 11.
[1] For the 12-week RW period, baseline at the RW period was defined as the last measurement collected prior to the first dose of study drug during the 12-week RW period.
[2] The end of the 12-week RW period was defined as the last assessment during the 12-week RW period.
[3] LS means, SE, 95% CIs, and p-values were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.
Abbreviations: CI, confidence interval; LS, least squares; RW, randomized withdrawal; SE, standard error

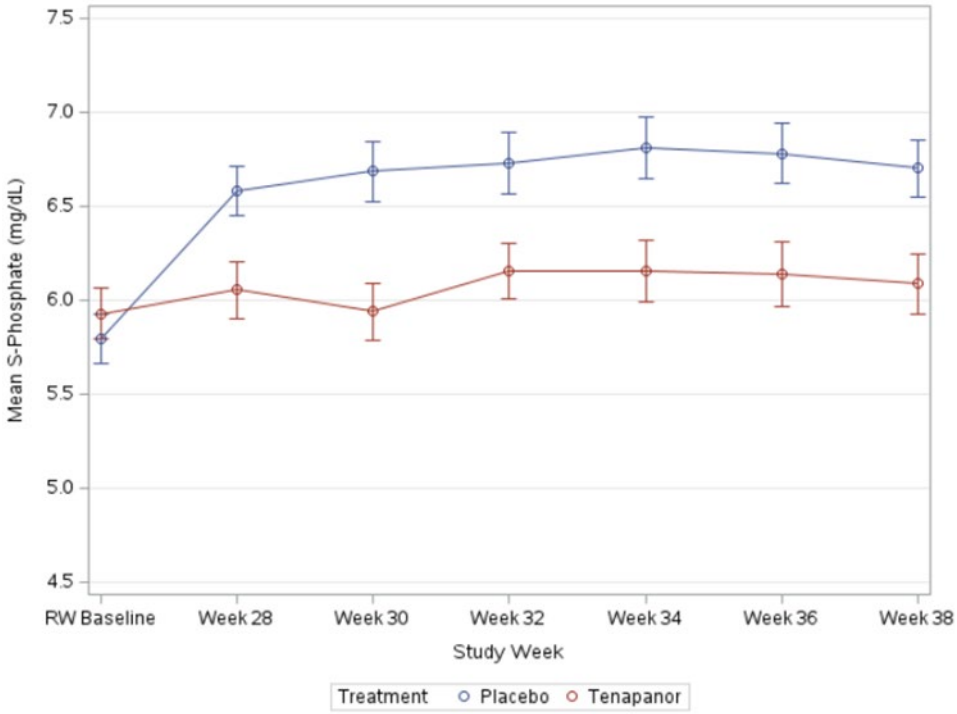
Figure 5 and Figure 6 show the mean s-P (mg/dL) values during the 12-week RW period for the EAS and the ITT populations, respectively. For the EAS, the mean s-P in the placebo arm increased from 5.1 mg/dL at the RW period baseline to 6.8 mg/dL at the end of the 12-week RW period; the mean s-P in the tenapanor arm increased from 5.2 mg/dL at the RW period baseline to 5.6 mg/dL at the end of the 12-week RW period. The difference in the change from baseline between the two groups was around −1 to −1.4 mg/dL in the EAS. However, for the ITT population, the difference in the change from baseline between the two arms was smaller, i.e., around −0.7 mg/dL.

Figure 5. Mean ± Standard Error Serum Phosphorus (mg/dL) in the 12-Week Randomized Withdrawal Period, Efficacy Analysis Set, Study TEN-02-301



Source: FDA Statistical reviewer; Study TEN-02-301, adeff.xpt, SAS.

Figure 6. Mean ± Standard Error Serum Phosphorus (mg/dL) in the 12-Week Randomized Withdrawal Period, Intention-to-Treat Analysis Set, Study TEN-02-301



Source: FDA Statistical reviewer; Study TEN-02-301, adeff.xpt, SAS.

3.1.2.3 Study TEN-02-202

Subject Disposition

In Study TEN-02-202, 236 subjects with CKD on dialysis and stable phosphate-binder therapy were randomized to receive tenapanor (n=117) or placebo bid (n=119) while continuing their established phosphate-binder regimen. One subject did not have at least one postbaseline s-P measurement in the tenapanor arm and was excluded from the FAS. Of the 235 subjects in the FAS, 229 subjects completed the 4-week study, 112 (96.6%) in the tenapanor arm and 117 (98.3%) in the placebo arm.

Key Efficacy Results

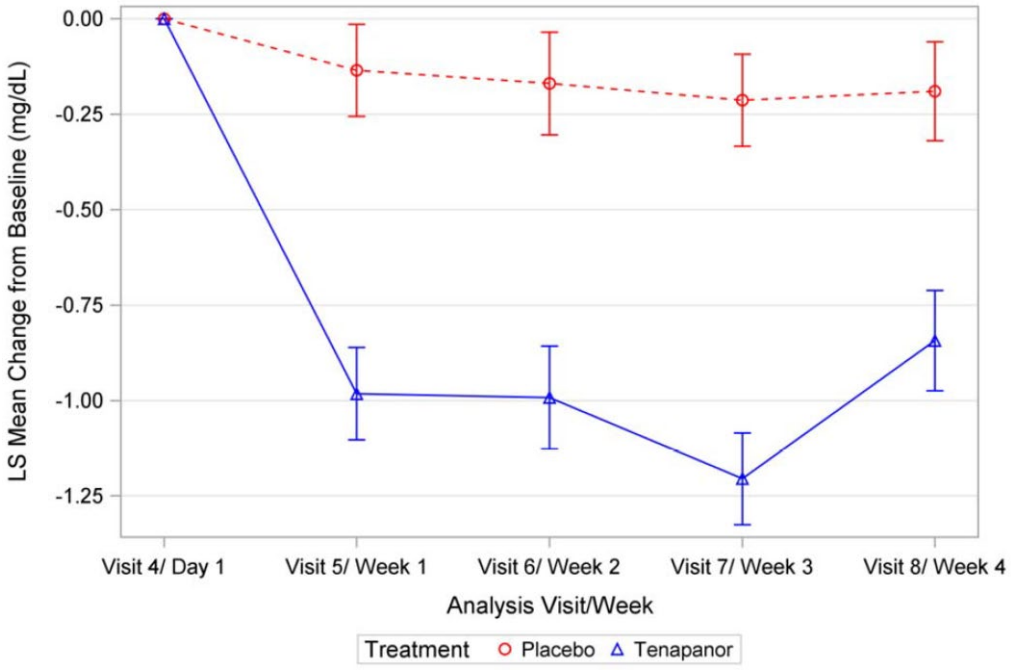
The primary efficacy endpoint was the change from baseline in s-P level at Week 4 in the FAS. Table 7 shows a summary of s-P levels and the primary analysis results using MMRM. The LS mean reduction in s-P level from baseline to Week 4 was −0.8 mg/dL in the tenapanor group and −0.2 mg/dL in the placebo group, resulting in a statistically significant treatment effect of −0.7 mg/dL (p=0.0004). Figure 7 presents the LS mean change in s-P from baseline over the course of the study for the FAS.

Table 7. Change From Baseline in Serum Phosphorus (mg/dL) at Week 4, Full Analysis Set, Study TEN-02-202

	Tenapanor Versus Placebo	
Paremeter	**Placebo (N=119)**	**Tenapanor (N=116)**
Baseline[1]	6.9 (1.37)	6.7 (1.32)
Change from baseline to Week 4[2]		
LS Mean (SE)[3]	−0.2 (0.13)	−0.8 (0.13)
LS Mean difference (SE) (versus placebo)		−0.7 (0.18)
95% CI LS Mean difference (versus placebo)		(−1.0, −0.3)
p-Value		0.0004

Source: Study TEN-02-202 Clinical Study Report, Table 6.
[1] Baseline was defined as the measurement collected at Visit 4 (day 1). If missing, the last measurement prior to the first dose of study medication was used.
[2] The Week-4 value was the measurement collected at Visit 8.
[3] LS means, SEs, CIs, and p-values were from a MMRM model with change from baseline as the dependent variable and IRT-recorded phosphate-binder type (sevelamer or non-sevelamer), serum phosphorus level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (Week 1 through Week 4), and treatment-by-visit interaction as fixed effects; baseline serum phosphorus level and baseline-by-visit as covariates; and subject as a random effect.
Abbreviations: CI, confidence interval; IRT, interactive response technology; LS, least squares; MMRM, mixed model repeated measures; SE, standard error

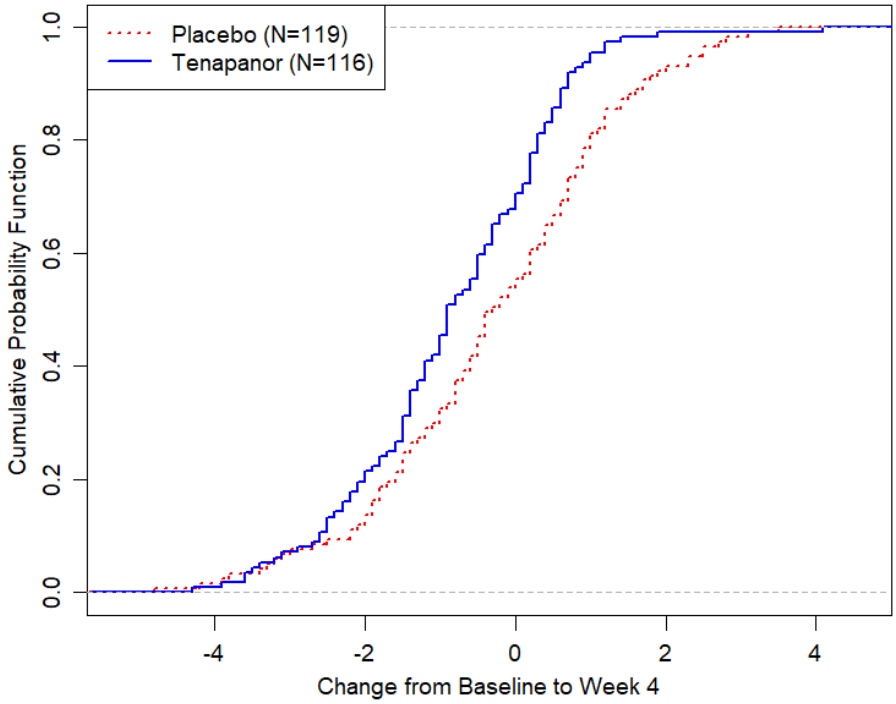
Figure 7. Least Squares Mean Change ± Standard Error in Serum Phosphorus (mg/dL) From Baseline Over Time, Full Analysis Set, Study TEN-02-202



Source: Study TEN-02-202 Clinical Study Report, Figure 2.
[1] The LS means and SEs were from an MMRM model with change from baseline as the dependent variable, IRT-recorded phosphate-binder type (sevelamer or non-sevelamer), serum phosphorus level at Visit 3 (<7.5 mg/dL or ≥7.5 mg/dL), treatment, visit (Week 1 through Week 4), and treatment-by-visit interaction as fixed effects, Baseline serum phosphorus level and baseline-by-visit as covariates, and subject as a random effect.
Abbreviations: IRT, interactive response technology; LS, least-squares; SE, standard error; MMRM, mixed model repeated measures

The cumulative distribution plots for change in s-P from baseline to Week 4 in the two arms are provided in Figure 8.

Figure 8. Cumulative Distribution of Change in Serum Phosphorus (mg/dL) From Baseline to Week 4 in Tenapanor Versus Placebo, Full Analysis Set, Study TEN-02-202



Source: FDA Statistical reviewer; Study TEN-02-202, adeff.xpt, R.
Subjects with missing s-P levels were not included in the plot.

3.1.3 Efficacy Issues in Detail

3.1.3.1 Magnitude of Treatment Effect When Used as Either Monotherapy or Used with Phosphate Binders

Issue: Although the Agency has accepted s-P as a surrogate endpoint and basis for approval for products intended to treat hyperphosphatemia in patients with CKD on dialysis, a treatment effect of any magnitude is not considered sufficient to support approval. A key review issue for this application was the magnitude of the treatment effect.

Assessment: In both monotherapy studies (TEN-02-201 and TEN-02-301), the primary efficacy analysis during the RW period was based on the EAS, a subset of the ITT population intended to enrich for a responder population. Specifically, the EAS limited the primary efficacy analysis to subjects who achieved a reduction of ≥1.2 mg/dL in s-P level in the RT period prior to the RW period. In Studies TEN-02-301 and TEN-02-201, approximately one-half of the subjects who entered the RW period were excluded from the EAS used for the primary analysis because their s-P lowering response did not meet the EAS criterion. Of those subjects who were initiated on tenapanor at the start of the trial, less than one-third were included in the EAS for Study TEN-02-301 and less than 40% were included in the EAS used for Study TEN-02-201.

Among the trials, the largest mean treatment effect was observed in the EAS of Study TEN-02-301. The LS mean difference between the tenapanor and placebo arms in the 12-week RW period was −1.4 mg/dL in the EAS and a more modest reduction of −0.7 mg/dL in the broader ITT analysis set. However, such a strategy did not appear to reliably identify patients who would have a larger treatment response to

tenapanor as reflected by the lack of an enrichment effect with the same strategy in Study TEN-02-201. In Study TEN-02-201, the mean treatment difference between tenapanor and placebo was −0.8 mg/dL in the 4-week RW period based on the EAS and −0.7 mg/dL based on the broader ITT analysis set.

Analyses based on the ITT population of the RW periods in Study TEN-02-201 and Study TEN-02-301 provide perhaps the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on therapy. The magnitude of the treatment effect in this broader subset (-0.7 mg/dL in both studies) appears to be less than that observed with approved agents (~1.5 to 2.2 mg/dL). When used in combination with phosphate binders, the magnitude of the treatment effect was similar to that seen when used as monotherapy.

Review Team Conclusion: We expect that tenapanor's average treatment effect on s-P when used in patients who tolerate and remain on therapy is about 0.7 mg/dL. The magnitude of the treatment effect appears to be less than that observed with approved agents.

3.1.3.2 Identifying a Responder Population

Issue: Focusing on the mean effect ignores the fact that some patients may have a larger and clinically relevant response to treatment. Moreover, in principle, it may be possible to individualize treatment based on a patient's early response to treatment (i.e., assess for a response at some early time point and continue treatment only in patients who have a clinically relevant response). Exploratory analyses were conducted to assess whether it might be possible to individualize treatment based on a patient's early response to tenapanor.

Assessment: Ideally, the strategy used to identify patients with a meaningful response to tenapanor would identify these patients early in the course of treatment, so that patients with a poor response can switch to a more effective therapy.

The FDA review team conducted exploratory analyses based on the 26-week RT period of Study TEN-02-301 to explore further whether such a strategy might be effective. Specifically, these analyses assessed how likely the subjects who achieved a ≥1.2 mg/dL reduction in s-P in the early weeks (early responders) were to maintain a reduction of s-P ≥1.2 mg/dL at subsequent visits, such as Week 26. In FDA's exploratory analyses, less than one-half of these "early responders" in the tenapanor arm sustained a reduction of s-P ≥1.2 mg/dL at Week 26 (Table 8). In addition, among these "early responders", less than a third achieved a s-P level <5.5 mg/dL at Week 26. Because the initial RT period of Study TEN-02-301 did not include a placebo-control, the results for tenapanor should be interpreted with caution. The results for the active control (sevelamer) group are provided in the Appendix. Note that Study TEN-02-301 was not designed to compare the efficacy of the two products.

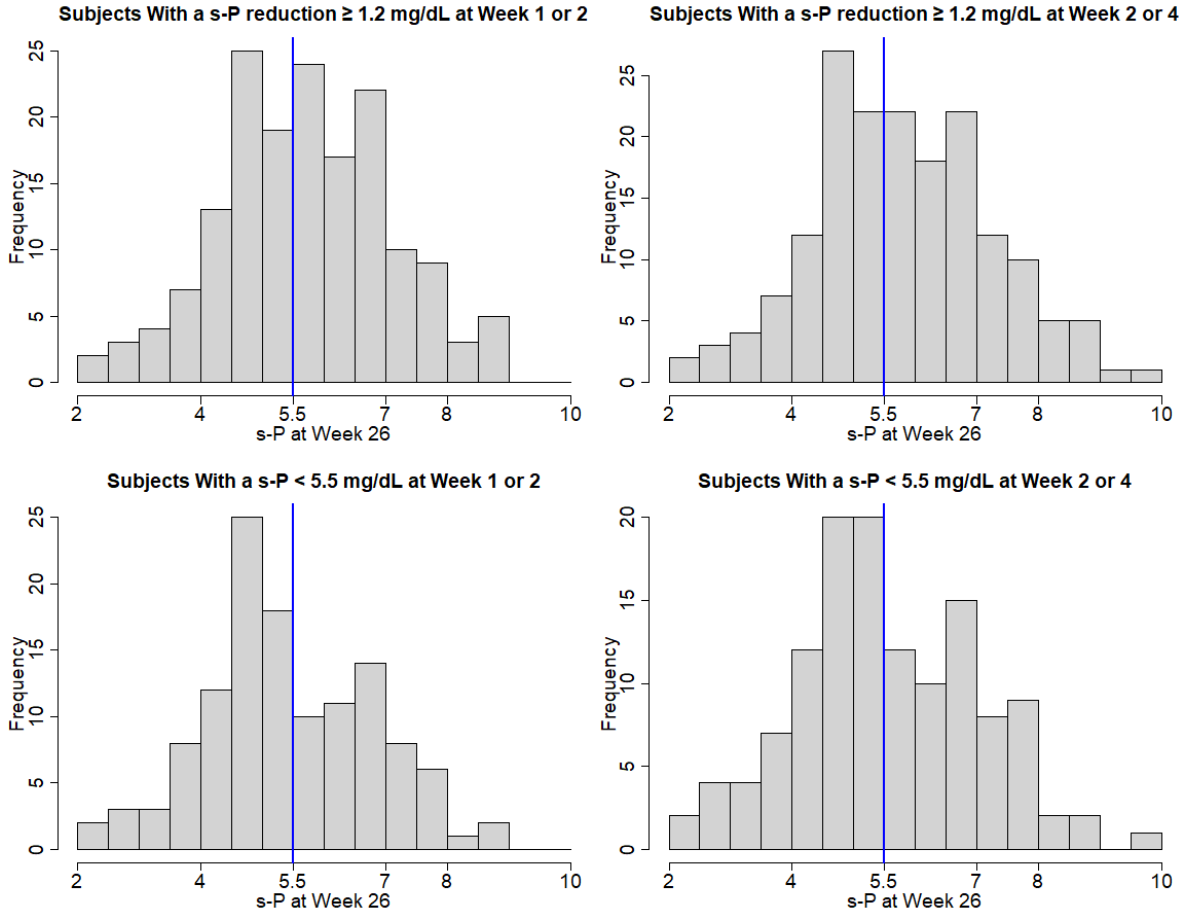
Table 8. Percentage of Subjects With a ≥1.2 mg/dL Reduction in Serum Phosphorus at Week 26 or Serum Phosphorus Concentration <5.5 mg/dL at Week 26 Among Subjects With a ≥1.2 mg/dL Reduction in Serum Phosphorus in Early Weeks, Tenapanor Arm, Study TEN-02-301

	Subjects Reached a s-P Reduction ≥1.2 mg/dL at Week 1 or Week 2		Subjects Reached a s-P Reduction ≥1.2 mg/dL at Week 2 or Week 4		
Group	**Yes (N=250)**	**No (N=157)**	**Yes (N=258)**	**No (N=149)**	**N=407***
Week 26 a s-P reduction ≥1.2 mg/dL	110 (44%)	24 (15%)	116 (45%)	16 (12%)	134 (33%)
Week 26 s-P <5.5 mg/dL	68 (27%)	32 (20%)	72 (28%)	28 (19%)	100 (25%)

Source: FDA Statistical reviewer; Study TEN-02-301, adeffads.xpt, SAS.
Subjects with missing s-P at a particular week were treated as not reaching a s-P reduction ≥1.2 mg/dL or not reaching a target s-P level of 5.5 mg/dL (worst-case imputation approach).
* Intent-to-treat population for the RT period (subjects who met inclusion/exclusion criteria, received at least one dose of tenapanor, had at least one post baseline serum phosphate measurement, and did not have a serious GCP breach.
Abbreviation: s-P, serum phosphorus

Figure 9 shows the distribution of s-P at Week 26 for those who had an s-P reduction ≥1.2 mg/dL in the early weeks (top panels) and for those who reached an s-P <5.5 mg/dL in the early weeks (bottom). The distribution of s-P at Week 26 is wide, with a considerable proportion of patients having a Week 26 s-P above 5.5 mg/dL despite the subjects meeting the threshold s-P response in the early weeks.

Figure 9. Distributions of Serum Phosphorus at Week 26 in Subjects With an s-P Reduction ≥1.2 mg/dL (Top Panels) or Reaching an s-P <5.5 mg/dL (Bottom Panels) in Early Weeks, 26-Week RT Period, Study TEN-02-301



Source: FDA Statistical reviewer; Study TEN-02-301, adeffads.xpt, SAS, R.
Subjects with missing s-P levels were not included in the distributions.
Abbreviations: RT, randomized treatment; s-P, serum phosphorus

Review Team Conclusion: In principle, it may be possible to individualize treatment based on a patient's early response to tenapanor. However, further data are needed to support the efficacy of such a strategy. If such a strategy were to be implemented, it would likely need to take into consideration the variability in s-P measurements.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

FDA's safety evaluation primarily focused on Study TEN-02-301, which employed the dosing regimen proposed in the labeling and included the longest period of controlled safety data (an initial 26-week OL treatment period with an active comparator). Study TEN-02-301 included periods with different designs and, for the purpose of safety analyses, these different periods of the study were analyzed separately. For adverse events (AEs) of special interest and any AEs that warranted further evaluation, separate analyses of the data from Studies TEN-02-201 and TEN-02-202 were also performed. Because the studies submitted in support of efficacy and safety differed in key aspects of study design, the review

team concluded that analyses of pooled study data would be challenging to interpret, and, for the most part, such analyses were not conducted.

3.2.2 Safety Summary

Tenapanor is minimally absorbed and, with the exception of diarrhea and tolerability issues resulting in discontinuation of tenapanor and dose reductions, safety analyses did not raise significant concerns.

3.2.3 Key Safety Issue

3.2.3.1 Diarrhea

Diarrhea was a predefined adverse event of special interest and was to be classified by investigators as mild, moderate, or severe using the following scale:

- Mild—The patient experiences symptoms but these are easily tolerated or managed without specific treatment.
- Moderate—The patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
- Severe—The patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

Table 9 provides an overview of the diarrhea AEs reported in the initial treatment periods of the phase 2b and 3 studies. Over half (54%) of tenapanor-treated subjects in Study TEN-02-301 reported diarrhea during the initial 26-week treatment period, compared to 8% of those treated with sevelamer (Table 9). During these 26 weeks, approximately 40% of the tenapanor-treated subjects reported at least one moderate or severe diarrhea event versus 3% of subjects treated with sevelamer. In Study TEN-02-201, which lacked a comparator arm during the initial 8-week treatment period and included doses lower than those proposed in labeling, diarrhea was reported in 39% of tenapanor-treated subjects during the initial 8-week period and was classified as moderate to severe in 22% of tenapanor-treated subjects. In Study TEN-02-202, in which tenapanor and placebo were administered in combination with a phosphate binder, diarrhea was reported in 43% of tenapanor-treated subjects as compared to 7% of those treated with placebo; these events were classified as moderate to severe in 24% of subjects in the tenapanor arm versus 2% of those in the placebo arm.

Serious adverse events (SAEs) of diarrhea were reported in three (0.5%) subjects in the tenapanor arm versus none in the phosphate-binder arm of Study TEN-02-301. Subject (b) (6) reported severe diarrhea within 3 days of starting tenapanor and reported several bouts of severe diarrhea after tenapanor was discontinued on day 6; the subject withdrew from the study on day 15. Subject (b) (6) was hospitalized on study day 36 with dehydration, severe nodal arrhythmia, bradycardia, hyponatremia, and acidosis after several weeks of diarrhea. Subject (b) (6) was hospitalized with dehydration on day 6 of the study due to severe diarrhea that started after the first dose. In Study TEN-02-201, there was one SAE of diarrhea reported with tenapanor. Subject (b) (6) presented to an emergency department on study day 36, with a 3-day history of severe abdominal pain, nausea, and intractable diarrhea. Tenapanor was withdrawn and the patient recovered. No SAEs of diarrhea were reported during TEN-02-202.

In Study TEN-02-301, 65 (16%) of tenapanor-treated subjects discontinued study drug because of diarrhea and 135 (32%) had a dose reduction because of diarrhea, as compared with one and zero subjects, respectively, in the control arm. In Study TEN-02-201, discontinuations or dose reductions due to diarrhea were reported in 8% and 10%, respectively, of tenapanor-treated subjects. Discontinuations due to diarrhea were uncommon in Study TEN-02-202, in which tenapanor was administered with a phosphate binder, though dose reductions for diarrhea were not (27% of subjects in the tenapanor arm compared to 4% of subjects in the placebo arm).

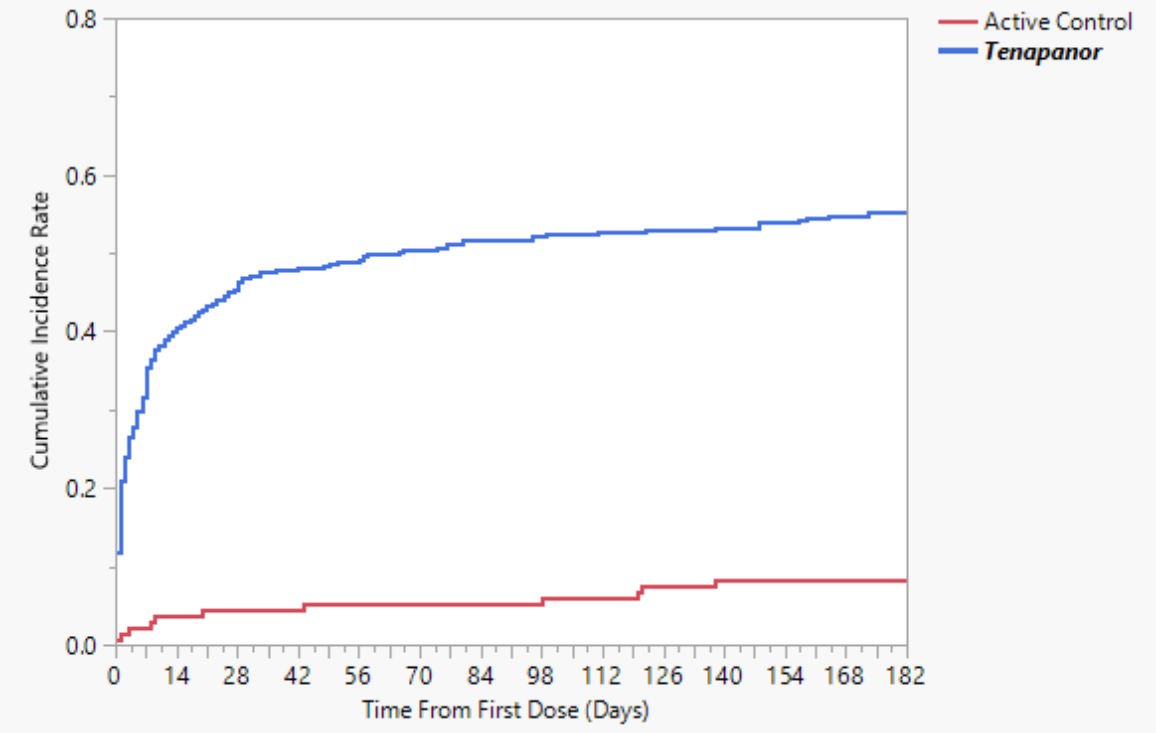
Table 9. Diarrhea, Safety Population, Studies TEN-02-301, TEN-02-201, and TEN-02-202, Initial Treatment Periods

	TEN-02-301 26-Week OL			TEN-02-201 8-Week PG	TEN-02-202 4-Week		
Preferred Term[1,2]	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Risk Difference (95% CI)	Tenapanor N=218 n (%)	Tenapanor + PB N=117 n (%)	Placebo + PB N=119 n (%)	Risk Difference (95% CI)
Diarrhea[3]	226 (53.9)	11 (8.0)	45.9 (38.4, 51.8)	86 (39.4)	50 (42.7)	8 (6.7)	36.0 (25.5,45.6)
Diarrhea AE severity[4]							
Mild	61 (14.6)	7 (5.1)	9.5 (3.6, 14.0)	40 (18.3)	22 (18.8)	6 (5.0)	13.8 (5.6, 22.3)
Moderate	140 (33.4)	4 (2.9)	30.5 (24.4, 35.5)	43 (19.7)	24 (20.5)	2 (1.7)	18.8 (11.2, 27.1)
Severe	25 (6.0)	0	6.0 (2.7, 8.7)	4 (1.8)	4 (3.4)	0	3.4 (−0.4, 8.4)
Moderate or severe	165 (39.3)	4 (2.9)	36.4 (30.1, 41.4)	47 (21.5)	28 (23.9)	2 (1.7)	22.2 (14.2, 30.8)
Diarrhea SAE	3 (0.7)	0 (0.0)	0.7 (−0.1, 1.5)	1 (0.5)	0	0	0
Action taken with drug due to diarrhea							
Discontinuation	65 (15.5)	1 (0.7)	14.8 (10.3, 18.6)	18 (8.3)	4 (3.4)	2 (1.7)	1.7 (−3.0, 6.9)
Interruption	6 (1.4)	0	1.4 (−1.4, 3.0)	2 (0.9)	2 (1.7)	0	1.7 (−1.7, 6.0)
Dose reduction	135 (32.2)	0	32.2 (27.1, 36.8)	21 (9.6)	31 (26.5)	5 (4.2)	22.3 (13.4, 31.3)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio, JMP.
[1] Treatment-emergent adverse event.
[2] Coded as MedDRA PT.
[3] At least one episode; includes the PTs gastroenteritis, colitis, defecation urgency, and gastroenteritis viral.
[4] Includes first episode only; severity definitions were predefined by the Applicant and classified by the investigator as mild, moderate, or severe.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event; PB, phosphate binder; PG, parallel group; PT, preferred term; RW, randomized withdrawal; SAE, serious adverse event

In Study TEN-02-301, the majority of diarrhea events in the tenapanor group occurred in the first 7 days of dosing (Figure 10). Diarrhea lasted for a mean duration of 41 days (median 13 days) and was recurrent (two or more episodes reported) in 14% of tenapanor-treated versus 2% of phosphate binder-treated subjects. Concomitant antidiarrheals during treatment were reported in a higher proportion of tenapanor-treated subjects (34%) versus phosphate-binder treated subjects (19%).

Figure 10. Kaplan–Meier Plot of Subjects Reporting First Occurrence of Diarrhea, Safety Population, Study TEN-02-301, 26-Week Treatment Period



Source: Reviewer's analysis; adsl.xpt, adae.xpt; JMP.

Common AEs in Study TEN-02-301 that were temporally associated with diarrhea AEs included vomiting, nausea, and abdominal pain. Other relevant temporally associated AEs included rectal hemorrhage and colitis (details are provided in the Appendix). Syncope and fall were not temporally associated with diarrhea. There were no reports of severe diarrhea or diarrhea-related AEs in the tenapanor-treated subjects who died.

Hyponatremia was reported in five subjects in the tenapanor group; all during the initial treatment period of Study TEN-02-301. None was reported in the phosphate-binder group. There was one serious report of hyponatremia temporally related to diarrhea (summarized above); the subject was hospitalized and withdrew from the study. Three of the remaining four subjects reported moderate diarrhea during the study, but not temporally linked to the hyponatremia event. Two of these five subjects completed the study.

Baseline subject characteristics (such as age, weight, and serum phosphorus) predictive of the severity of diarrhea were not identified (Figure 13 in the Appendix).

4 Benefit-Risk Framework

Benefit-Risk Framework

	Evidence and Uncertainties
Analysis of Condition	• Hyperphosphatemia is common in patients with CKD on dialysis and is defined as an elevated level of s-P (>4.5 mg/dL). • In epidemiologic studies, elevated s-P levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft-tissue calcification and cardiovascular disease in patients with CKD. In patients on dialysis, higher s-P levels have also been associated with increased mortality. While such epidemiologic data and biological plausibility suggest that treating hyperphosphatemia could improve patient outcomes, data from randomized controlled trials demonstrating that treatments that lower serum phosphorus improve patient outcomes are lacking. There is also uncertainty about what should constitute the "target" s-P level in the dialysis population. As such, clinical practice guidelines recommend lowering elevated s-P levels toward the normal range and grade the strength of the recommendation as "level 2" ("we suggest") and the quality of supporting evidence as "low."[1,2]
Current Treatment Options	• In patients with CKD on hemodialysis, hyperphosphatemia is treated with thrice weekly intermittent hemodialysis, dietary restriction of foods and drinks high in phosphorus, and gastrointestinal phosphate binders. • To date, four major classes of phosphate binders have been approved in the United States for the control of s-P in adults with CKD on dialysis: calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-based binding agents. In the studies that established the efficacy of these products for the control of s-P, the mean reductions in s-P levels ranged from ~1.5 to 2.2 mg/dL. Gastrointestinal side effects are seen with all approved agents, the pill burden can be high, and adherence can be challenging.
Benefits	• The primary efficacy analysis in both monotherapy studies (Studies TEN-02-201 and TEN-02-301) was based on a subset of the intent-to treat population intended to enrich for a responder population. Specifically, the primary efficacy analysis was limited to subjects who achieved a reduction of ≥1.2 mg/dL in s-P level in the RT period prior to the RW period. In both studies, approximately one-half of the subjects who entered the RW period were excluded from the primary analysis because their s-P lowering response did not meet the enrichment criterion. • In the trials, the largest mean treatment effect was observed in the enriched population of Study TEN-02-301 (−1.4 mg/dL). However, the enrichment strategy used in Study TEN-02-301 did not appear to reliably identify patients who would have a larger treatment response to tenapanor as reflected by the lack of an enrichment effect with the same strategy in Study TEN-02-201. Analyses based on the broader intent-to-treat population of the placebo-controlled RW periods of these monotherapy trials appear to provide the best estimate of the average treatment effect in patients who are likely to tolerate tenapanor and remain on therapy. The magnitude of the treatment effect in this broader subset (0.7 mg/dL) appears to be less than that observed with approved agents (~1.5 to 2.2 mg/dL). When used in combination with phosphate binders, the magnitude of the treatment effect was similar to that seen when used as monotherapy.

	Evidence and Uncertainties
	• The clinical significance of the magnitude of the treatment effect is unclear. In some diseases, we have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate endpoint and changes in clinical outcomes. In this disease state, we do not have such data. Although the FDA has not stipulated that applicants demonstrate a treatment effect larger than some threshold, it has indicated that the magnitude of the treatment effect should be clinically relevant. While there is well established precedent for accepting serum phosphorus as a surrogate endpoint and basis for approval in this therapeutic area, there is no precedent for accepting treatment effects of the magnitude seen in this development program. • Because focusing on the mean effect ignores the fact that some patients may have a larger and clinically relevant response to treatment, further exploratory analyses were conducted to characterize the treatment effect. These analyses explored whether it might be possible to individualize therapy based on a patient's response to treatment (i.e., assess for a response in a patient at some early time point and discontinue treatment in patients who do not appear to have an adequate response). These exploratory analyses suggested that if such a strategy were tested, it would need to take into consideration the variability in serum phosphorus measurements.
Risks and Risk Management	• Tenapanor is minimally absorbed. Diarrhea was the most common adverse reaction in clinical studies of tenapanor in adults with CKD on dialysis. • Over half (54%) of tenapanor-treated subjects in Study TEN-02-301 reported diarrhea during the initial 26-week treatment period, compared with 8% of those treated with the sevelamer active control. During these 26 weeks, approximately 40% of the tenapanor-treated subjects reported at least one moderate or severe diarrhea event versus 3% of subjects treated with sevelamer. In Study TEN-02-301, 16% of tenapanor-treated subjects discontinued study drug because of diarrhea and 32% had a dose reduction because of diarrhea. Such data suggest that tolerability may limit the ability of patients to adhere to long-term treatment. • Although the incidence of serious adverse events of diarrhea was low (0.5%) in the tenapanor arm, the risks of severe diarrhea and its potential sequelae (e.g., dehydration, hypotension, falls, ischemia) must be considered where there is a reasonable expectation of wider use in the real-world setting, i.e., a more diverse patient population that is not as closely monitored as in a clinical trial setting. • In contrast to the monotherapy studies, discontinuations due to diarrhea were uncommon in the 4-week placebo-controlled treatment period of Study TEN-02-202, which assessed use in combination with existing phosphate-binder treatment.

Abbreviations: CKD, chronic kidney disease; RT, randomized treatment; RW, randomized withdrawal; s-P, serum phosphorus

[1] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.

[2] According to the Reference Key for the guideline, the implications of a level 2 recommendation are as follows: (1) Implications for patients: "The majority of people in your situation would want the recommended course of action, but many would not; " (2) implications for clinicians: "Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences;" and (3) implication for policy: "The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

5 Appendix

5.1 Additional Efficacy Information

Study TEN-02-201

Of the 82 subjects in the tenapanor arm that entered the RW period, 25 were in the 3 mg daily group, 23 were in the 10 mg daily group, and 34 were in the dose-titration group. A total of 43 (52%) tenapanor-treated subjects was included in the EAS: 11 (44%) from the 3 mg daily group, 13 (57%) from the 10 mg daily group, and 19 (56%) from the dose-titration group.

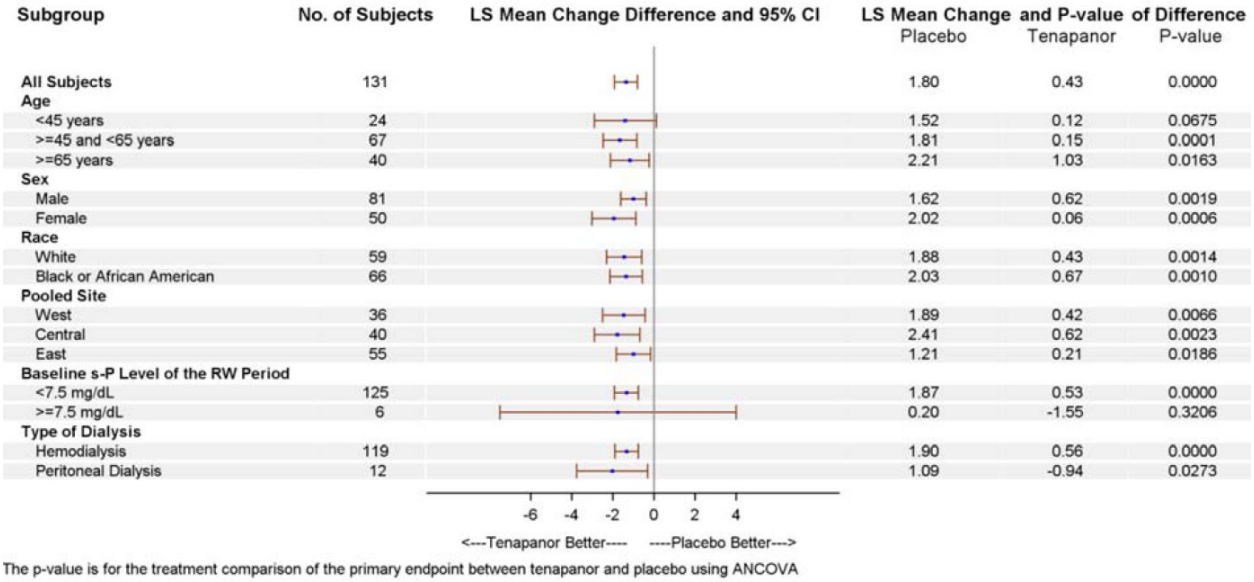
We conducted exploratory analyses on the EAS using an ANCOVA model with pre-specified covariates to assess the effect of the tenapanor dosing group on s-P. The LS mean changes in s-P in the 3 mg, 10 mg, and dose-titration arms compared with the placebo arm during the 4-week RW period were −1.0 mg/dL, −0.9 mg/dL, and −0.7 mg/dL, respectively. The corresponding results in the ITT population were −0.5 mg/dL, −0.7 mg/dL, and −0.8 mg/dL for the 3 mg, 10 mg, and dose-titration tenapanor groups, respectively. A clear dose-response relationship is not seen, however the small sample sizes of the treatment groups limit conclusions.

The dose-response in the 8-week RT period was also evaluated. The median change in s-P from baseline to the end of 8-week RT period in the ITT analysis set was −0.95 mg/dL, −0.85 mg/dL, and −1.2 mg/dL for the 3 mg, 10 mg, and dose-titration tenapanor groups, indicating a similar effect on s-P in the three dosing arms. The findings suggests that it may be better to start at a lower tenapanor dose (where tolerability is better) and titrate up rather than to start high and titrate down, as proposed by the Applicant.

Study TEN-02-301

Subgroup analyses using the EAS on the 12-week RW period are shown in Figure 11**.**

Figure 11. Subgroup Analyses of Change From RW Baseline in Serum Phosphorus (mg/dL) at the End of the 12-Week RW Period, Efficacy Analysis Set, Study TEN-02-301



The p-value is for the treatment comparison of the primary endpoint between tenapanor and placebo using ANCOVA

Source: Study TEN-02-301 Clinical Study Report, Figure 4.
Abbreviation: RW, randomized withdrawal

The results for the responder analysis for the sevelamer active control arm in the 26-week RT period of Study TEN-02-301 are provided in Table 10.

Table 10. Percentage of Subjects with a ≥1.2 mg/dL Reduction in Serum Phosphorus at Week 26 or Serum Phosphorus Concentration <5.5 mg/dL at Week 26 Among Subjects With a ≥1.2 mg/dL Reduction in Serum Phosphorus in Early Weeks, Sevelamer Active Control Arm, Study TEN-02-301

	Subjects Reached a s-P Reduction ≥1.2 mg/dL at Week 1 or Week 2		Subjects Reached a s-P Reduction ≥1.2 mg/dL at Week 2 or Week 4		
	Yes (N=81)	No (N=56)	Yes (N=96)	No (N=41)	N=137*
Week 26 s-P reduction ≥1.2 mg/dL	53 (65%)	22 (39%)	62 (65%)	13 (32%)	75 (55%)
Week 26 s-P <5.5 mg/dL	35 (43%)	25 (45%)	42 (44%)	18 (44%)	60 (44%)

Source: FDA Statistical reviewer; Study TEN-02-301, adeffads.xpt, SAS.
Subjects with missing s-P at a particular week were treated as not reaching a s-P reduction ≥1.2 mg/dL (nonresponder) or a target s-P level of 5.5 mg/dL (worst-case imputation approach).
*Safety analysis set for the active control arm in the RT period.
Abbreviation: s-P, serum phosphorus

Study TEN-02-202

Additional exploratory analyses were performed in Study TEN-02-202, which included a placebo-control arm. In Study TEN-02-202, one of the prespecified key secondary analyses assessed the percentage of subjects who reached an s-P level <5.5 mg/dL at Week 4 in the two arms. This analysis showed that 34.5% and 20.2% (difference of 14.3%) of subjects had an s-P level below 5.5 mg/dL at Week 4 of the RT

period in the tenapanor and placebo arms, respectively. Similar analyses were performed on all weeks (Table 11.). The Applicant used the LOCF approach for missing data and obtained similar results.

Table 11. Number (n) and Proportion (%) of Subjects Reaching Serum Phosphorus <5.5 mg/dL by Week, Full Analysis Set, Study TEN-02-202

	Placebo N=119 (100%)	Tenapanor N=116 (100%)	Response Rate Difference % (Tenapanor Versus Placebo)
Serum phosphorus response: n (%)			
Baseline	13 (10.9)	23 (19.8)	8.9
Week 1	26 (21.8)	56 (48.3)	26.5
Week 2	28 (23.5)	46 (39.7)	16.2
Week 3	20 (16.8)	55 (47.4)	30.6
Week 4	24 (20.2)	40 (34.5)	14.3

Source: FDA Statistical reviewer; Study TEN-02-202, adeff.xpt, SAS.
Baseline was defined as the measurement collected at Visit 4 (day 1). If missing, the last measurement prior to the first dose of study medication was used.
Missing data during the 4 weeks were treated as not reaching the target s-P level of 5.5 mg/dL (worst-case imputation approach).
Abbreviation: s-P, serum phosphorus

Analyses were performed to assess how likely the subjects who achieved a s-P level <5.5 mg/dL at early weeks were to sustain the target s-P <5.5 mg/dL at a following week in the tenapanor and placebo arms (Table 12). Among those subjects who reached an s-P level of <5.5 mg/dL at Week 1, a similar percentage (46%) of tenapanor and placebo subjects had an s-P level of <5.5 mg/dL at Week 4.

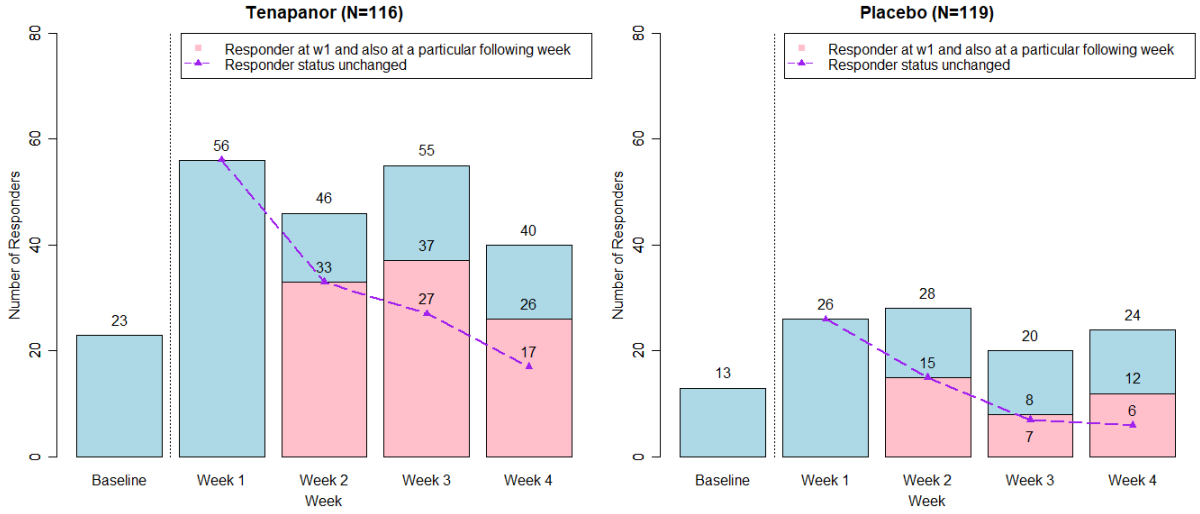
Table 12. Number and Percentage of Subjects Achieving a Serum Phosphorus <5.5 mg/dL by Week, Based on Subject's Serum Phosphorus Level at Week 1, Study TEN-02-202

	Serum Phosphorus <5.5 mg/dL at Week 1		Serum Phosphorus ≥5.5 mg/dL at Week 1	
Reaching <5.5 mg/dL Serum Phosphorus by Week	Placebo N=26 (%)	Tenapanor N=56 (%)	Placebo N=93 (%)	Tenapanor N=60 (%)
Week 2	15 (58%)	33 (59%)	13 (14%)	13 (22%)
Week 3	8 (31%)	37 (66%)	12 (13%)	18 (30%)
Week 4	12 (46%)	26 (46%)	12 (13%)	14 (23%)

Source: FDA Statistical reviewer; Study TEN-02-202, adeff.xpt, SAS.
Missing data during the 4 weeks were treated as not reaching the target s-P level of 5.5 mg/dL (worst-case imputation approach).

Further exploratory analyses were conducted to compare the response at Week 1 with those of the following weeks. Analyses were performed to assess how likely the subjects who achieved a s-P level <5.5 mg/dL at early weeks were to sustain the target s-P <5.5 mg/dL at a following week in the tenapanor and placebo arms (Table 12). Among those subjects who reached an s-P level of <5.5 mg/dL at Week 1, a similar percentage (46%) of tenapanor and placebo subjects had an s-P level of <5.5 mg/dL at Week 4. Figure 12 shows that by Week 4, only 30% of tenapanor-treated subjects (and 23% of placebo-treated subjects) who achieved an s-P of <5.5 mg/dL at Week 1 consistently sustained a s-P of <5.5 mg/dL at Weeks 2, 3, and 4.

Figure 12. Number of Subjects Reaching s-P Level <5.5 mg/dL at Each Week, Full Analysis Set, Study TEN-02-202



Source: FDA Statistical reviewer; Study TEN-02-202, adeff.xpt, R.
Missing data during the 4 weeks were treated as not reaching the target s-P level of 5.5 mg/dL (worst-case imputation approach).
Abbreviation: s-P, serum phosphorus

5.2 Additional Safety Information

Study TEN-02-301 General Safety

In the initial treatment period of Study TEN-02-301, 80% of tenapanor-treated subjects reported at least one AE compared to 64% of those treated with the active control, sevelamer. SAEs were reported in 17% of tenapanor-treated subjects compared to 23% of those treated with sevelamer. A greater proportion of subjects in the tenapanor group (24%) compared to the sevelamer group (2%) discontinued treatment due to an AE; AEs leading to dose reductions were also more common in the tenapanor arm. See Table 13 for an overview of AEs in the Study TEN-02-301 safety population.

Table 13. Overview of Adverse Events, Safety Population[1], Study TEN-02-301

	26-Week OL Treatment Period		
Event	**Tenapanor N=419 n (%)**	**Phosphate Binder[2] N=137 n (%)**	**Risk Difference (95% CI)**
Any AE[3]	337 (80.4)	88 (64.2)	16.2 (7.6, 25.2)
Moderate or severe AEs (grade 3-5)[4]	258 (56.8)	58 (42.3)	14.5 (4.9, 23.7)
SAE	73 (17.4)	32 (23.4)	-6.0 (-1.4, 14.4)
SAEs with fatal outcome	1 (0.2)[5]	0 (0.0)	0.2 (-2.5, 1.3)
AE leading to discontinuation	102 (24.3)	2 (1.5)	22.8 (17.4, 27.3)
AE leading to dose reduction	142 (33.9)	5 (3.6)	30.3 (24.0, 35.4)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio.
[1] Safety population defined as all subjects who received at least one dose of tenapanor during the study period.
[2] Active control group received sevelamer carbonate for the entire study period.
[3] Includes treatment-emergent AE defined as any event that occurred after the first dose of drug up to end of the 12-week RW treatment period.
[4] Moderate: Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities. Severe: Events interrupt the subject's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up.
[5] Sixty-six-year-old male subject died of respiratory failure on study day 30; his last dose of tenapanor was on study day 8 when he presented to the emergency department after dialysis. The subject was noted to have severe malnutrition. A chest X-ray revealed cardiomegaly, congestion, and bilateral pneumothorax; findings that were concerning for congestive heart failure/volume overload. The subject was treated with ant biotics, lung catheters, and remained hospitalized until transitioned to hospice and death. His medical history included malnutrition, HIV/AIDS, and hypertension.
Abbreviations: AE, adverse event; CI, confidence interval; ED, emergency department; N, number of subjects in group; n, number of subjects with at least one event; OL, open-label; RW, randomized withdrawal; SAE, serious adverse event

The most commonly reported AEs during the initial 26-week treatment period were diarrhea (54% tenapanor versus 8% sevelamer) and hyperphosphatemia (6% tenapanor versus 3% sevelamer), which were also the most commonly reported reasons for discontinuations (Table 14).

Table 14. Adverse Events Occurring in ≥3 Subjects and a 0.5% Higher Risk Difference in Tenapanor Than the Comparator, Safety Population, Study TEN 02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Adverse Event[1,2]	**Tenapanor N=419 n (%)**	**Sevelamer N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
Subjects with at least 1 TEAE	337 (80.4)	88 (64.2)	16.2 (7.6, 25.2)	58 (46.4)	70 (55.6)	−9.2 (−3.1, 21.1)
Diarrhea[4]	226 (53.9)	11 (8.0)	45.9 (38.4, 51.8)	6 (4.8)	3 (2.4)	2.4 (−2.7, 7.9)
Hyperphosphatemia[5]	27 (6.4)	4 (2.9)	3.5 (−1.3, 6.8)	7 (5.6)	15 (11.9)	−6.3 (−13.3, 0.6)
Acute respiratory failure[6]	13 (3.1)	1 (0.7)	2.4 (−1.1, 4.6)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Dyspnea[7]	11 (2.6)	1 (0.7)	1.9 (−1.6, 4.0)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Hypertensive emergency[8]	8 (1.9)	1 (0.7)	1.2 (−2.2, 3.1)	1 (0.8)	1 (0.8)	0 (0.0, 0.0)
Cardiac failure congestive[9]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Dehydration[10]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Gastrointestinal hemorrhage[11]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	1 (0.8)	2 (1.6)	−0.8 (−3.0, 4.9)
Hyponatremia	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Hypocalcemia	7 (1.7)	1 (0.7)	1.0 (−0.9, 2.8)	1 (0.8)	0 (0.0)	0.8 (−2.2, 4.4)
Flatulence	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Sinus congestion	4 (1.0)	0 (0.0)	1.0 (0.0, 1.9)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Osteomyelitis	7 (1.7)	1 (0.7)	0.9 (-0.9, 2.8)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Urinary tract infection	7 (1.7)	1 (0.7)	0.9 (-0.9, 2.8)	2 (1.6)	3 (2.4)	−0.8 (−3.5, 5.3)
Hypotension	10 (2.4)	6 (4.4)	−2.0 (−1.1, 7.0)	2 (1.6)	1 (0.8)	0.8 (−1.8, 3.5)
COPD	3 (0.7)	0 (0.0)	0.7 (−0.1, 1.5)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Coronary artery disease	3 (0.7)	0 (0.0)	0.7 (−0.1, 1.5)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Diabetic ketoacidosis	3 (0.7)	0 (0.0)	0.7 (−2.1, 2.1)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Hyperglycemia	3 (0.7)	0 (0.0)	0.7 (−0.1, 1.5)	1 (0.8)	1 (0.8)	0 (0.0, 0.0)
Pulmonary congestion	3 (0.7)	0 (0.0)	0.7 (−2.1, 2.1)	0 (0.0)	0 (0.0)	0 (0.0, 0.0)
Squamous cell carcinoma of skin	3 (0.7)	0 (0.0)	0.7 (−0.1, 1.5)	0 (0.0)	1 (0.8)	−0.8 (−2.2, 4.4)
Seizure	3 (0.7)	1 (0.7)	0 (0.0, 0.0)	1 (0.8)	0 (0.0)	0.8 (−2.2, 4.4)

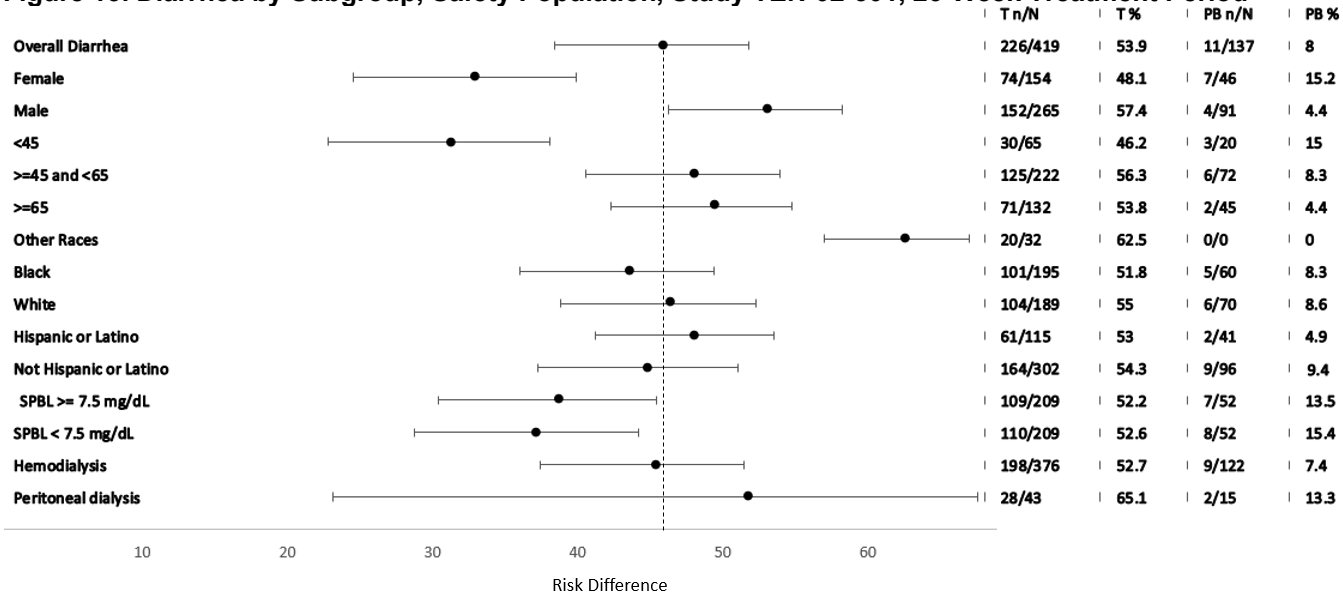
Source: Reviewer's analysis; adsl.xpt, adae.xpt; MAED.
[1] TEAE defined as any event that occurred after the first dose of drug up to the end of the 12-week RW treatment period.
[2] Coded as MedDRA PT.
[3] Placebo arm includes subjects rerandomized to placebo from tenapanor; all subjects had previously received tenapanor.
[4] Includes the PTs gastroenteritis, colitis, defecation urgency, and gastroenteritis viral.
[5] Includes the PTs blood phosphorus increased.
[6] Includes the PTs respiratory failure and respiratory distress.
[7] Includes the PT hypoxia.
[8] Includes the PT hypertensive crisis.
[9] Includes the PT cardiac failure.
[10] Includes PT hypovolemia.
[11] Includes the PTs rectal hemorrhage, hemorrhoidal hemorrhage, and upper gastrointestinal hemorrhage.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disorder; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event; OL, open-label; PT, preferred term; RW, randomized withdrawal; TEAE, treatment-emergent adverse event

Overall Deaths

Few deaths were reported during the initial 26-week treatment period in Study TEN-02-301 and the proportion was similar in the two groups (1.7% tenapanor and 2.2% sevelamer). One death in Study TEN-02-301 was reported as the outcome of the SAE respiratory failure and not considered related to tenapanor due to a significant medical history of underlying comorbidities. One death was reported in a tenapanor-treated subject during the initial 8-week treatment period in Study TEN-02-201 (no comparator) and no deaths were reported in Study TEN-02-202. Five additional deaths were reported in the Study TEN-02-401 OL extension at the time of the review, two in the tenapanor group (1.8%) and three in the phosphate-binder group (4.8%). The deaths were unlikely to be related to tenapanor; most subjects had multiple cardiovascular risk factors and died due to cardiovascular disease or sepsis, which are common causes of death in this patient population.

Details for Safety Issue: Diarrhea

Figure 13. Diarrhea by Subgroup, Safety Population, Study TEN-02-301, 26-Week Treatment Period



Source: Reviewer's figure; adsl.xpt, adae.xpt; JMP, Excel.
Abbreviation: SPBL, serum phosphorus at baseline

Other Findings

Common AEs that were temporally associated with diarrhea AEs included vomiting, nausea, and abdominal pain. Other relevant temporally associated events included dehydration, hyponatremia, rectal hemorrhage, hemorrhoidal hemorrhage, and colitis.

Dehydration was reported in five subjects in the tenapanor group in Study TEN-02-301. All of these events were reported in the first 60 days of the 26-week OL treatment period. In contrast, no events were reported in the sevelamer group (Table 15).

Table 15. Dehydration Adverse Events, Safety Population, Study TEN-02-301

Preferred Term[1,2]	26-Week OL Treatment Period Tenapanor N=419 n (%)	 Sevelamer N=137 n (%)	 Risk Difference (95% CI)
Dehydration[3]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)
Serious adverse event	1 (0.2)	0 (0.0)	0.2 (−2.5, 1.3)
Action taken with drug			
Discontinuation	2 (0.5)	0 (0.0)	0.5 (−2.3, 1.8)
Interruption	1 (0.2)	0 (0.0)	0.2 (−2.5, 1.3)
Dose Reduction	1 (0.2)	0 (0.0)	0.2 (−2.5, 1.3)
Temporally related to diarrhea	2 (0.5)	0 (0.0)	0.5 (−2.3, 1.8)
Sex			
Female	1 (0.2)	0 (0.0)	0.2 (−2.5, 1.3)
Male	4 (1.0)	0 (0.0)	1.0 (−1.8, 2.5)
Age			
≥45 to 65 years	2 (0.5)	0 (0.0)	0.5 (−2.3, 1.8)
>65 years	3 (0.7)	0 (0.0)	0.7 (−2.1, 2.1)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio, JMP.
[1] Treatment-emergent adverse event defined as any event that occurred after the first dose of drug up to end of the 12-week randomized treatment period.
[2] Coded as MedDRA preferred terms.
[3] Includes the PT hypovolemia.
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

In Study TEN-02-301, hyponatremia was reported in five subjects in the tenapanor group; all of these cases were reported in the initial 26-week OL treatment period. None was reported in the phosphate-binder group. There was one report of serious hyponatremia temporally related to diarrhea; the subject ((b) (6) discussed above) was hospitalized and withdrew from the study. Three of the other four subjects reported moderate diarrhea during the study, but not temporally linked to the hyponatremia event. Two of the five subjects in whom hyponatremia was reported completed the study. Although hyponatremia was not reported as an AE in the RW period, abnormalities in sodium levels (shift from normal to below normal) were observed at the end of the study period in a higher proportion of subjects randomized to tenapanor than placebo.

Two of the six cases of GI-related hemorrhage in the tenapanor arm were temporally associated with diarrhea; one subject reported rectal hemorrhage and one subject ((b) (6)) reported hemorrhoidal bleed on study day 3, for which the drug was permanently withdrawn. In the RW period, one subject in the tenapanor group and two in the placebo group reported GI hemorrhage; neither event was temporally related to diarrhea. As of the cut-off date for the provided data for the extension study TEN-02-401, two other tenapanor-treated subjects reported GI hemorrhage. Both were hospitalized and required a procedure to resolve. The majority of tenapanor-treated subjects experiencing GI-related hemorrhage reported gastric ulcers or had a history of GI comorbidities; all but one subject remained on treatment and completed the study.

Colitis was reported for two tenapanor-treated subjects in the 26-week treatment period of Study TEN-02-301 compared to none in the sevelamer group. No such cases were reported during the RW period. One of these subjects ((b) (6)) reported colitis (nonserious) on day 10 of the study, which progressed to worsening of colitis (serious AE) and dehydration on day 37. This subject also reported a significant history of concomitant GI comorbidities and completed the study. The remaining subject ((b) (6))

experienced severe colitis (reported as nonserious) on days 153 to 176 of the study, which resulted in a dose reduction; the subject discontinued the study on day 175.

5.3 Applicant–FDA Communications

The *Complete Response letter*, *Dispute Appeal Denial*, and *Dispute Appeal Interim Response* issued by FDA to the Applicant (as mentioned in Section 1.3) are appended in the following pages.

NDA 213931

COMPLETE RESPONSE

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory and Quality Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your new drug application (NDA) dated June 26, 2020, received June 29, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride 10 mg, 20 mg, and 30 mg tablets.

We acknowledge receipt of your major amendment dated April 28, 2021, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

To support efficacy as monotherapy for reducing serum phosphorus in patients with chronic kidney disease (CKD) on dialysis, you submitted the results of two randomized, multi-center trials (TEN-02-201 and TEN-02-301). You also submitted the results of a third trial — a randomized, double-blind, placebo-controlled trial (TEN-02-202), to support use in combination with existing phosphate binder treatment. All three studies evaluated tenapanor's efficacy in reducing serum phosphorus levels.

In epidemiologic studies, elevated serum phosphorus levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with CKD. In patients on dialysis, higher serum phosphorus levels have also been associated with increased mortality. To date, however, there are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus levels predicts its effect on clinical outcomes such as cardiovascular events or mortality. Nevertheless, the Division of Cardiology and Nephology, following the precedent set by the former Division of Metabolism and Endocrinology Products, treats serum phosphorus reduction as a valid surrogate in patients with CKD on dialysis. All currently marketed products for the control of serum

phosphorus in patients with CKD on dialysis were approved based on effects on serum phosphorus levels. In the trials conducted to support approval, these therapies lowered serum phosphorus levels by ~1.5 – 2.2 mg/dL.

In both monotherapy trials, tenapanor's efficacy in reducing serum phosphorus levels was assessed in a randomized, double-blind, placebo-controlled withdrawal period. In Study TEN-02-201, which compared different dosing strategies, an 8-week double-blind randomized treatment period preceded the randomized withdrawal phase; in Study TEN-02-301, which included an active comparator, a 26-week open-label, randomized treatment period preceded this phase. In both studies, the primary efficacy analysis during the randomized withdrawal period was to be based on the Efficacy Analysis Set, a subset of the intent-to-treat (ITT) population, which was intended to enrich for a responder population. Specifically, the Efficacy Analysis Set limited the primary efficacy analysis to patients who achieved a reduction of ≥ 1.2 mg/dL in serum phosphorus level in the treatment period prior to randomized withdrawal.

Among the patients randomized to tenapanor in the 26-week open-label treatment period of Study TEN-02-301, approximately 60% finished the 26-week treatment period and were re-randomized to receive tenapanor or placebo during the 12-week randomized withdrawal phase. Of the 219 patients who were randomized into the 8-week treatment period of Study TEN-02-201, approximately 75% completed the 8-week treatment period and entered the 4-week randomized withdrawal phase. Of those who entered the randomized withdrawal period, approximately half were excluded from the Efficacy Analysis Set used for the primary analysis in Studies TEN-02-301 and TEN-02-201.

Among the trials, the largest treatment effect was observed in the Efficacy Analysis Set of Study TEN-02-301. In Study TEN-02-301, the point estimate of the treatment difference in the LS mean change in serum phosphorus from baseline to the end of the 12-week randomized withdrawal period was 1.37 mg/dL based on the Efficacy Analysis Set. However, the clinical relevance of this estimand is unclear given that it was derived from a subset of the trial population. Analyses based on the ITT population of the randomized withdrawal periods in Study TEN-02-201 and Study TEN-02-301 provide perhaps the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on therapy. The sizes of the treatment effects in this subset were small─ 0.72 mg/dL and 0.66 mg/dL, respectively.

We further note that subgroup analyses and analyses of the distribution of the responses did not suggest a "responder" population with a substantially larger response to treatment. In exploratory analyses of the 26-week active controlled treatment period of Study TEN-02-301, tenapanor's effect size appeared to be larger in patients with more marked elevations at baseline; however, the effect size still appeared to be smaller than that observed with the active control, and, absent a placebo control, the results of these analyses are challenging to interpret. In Study TEN-02-202, which evaluated tenapanor use in combination with existing phosphate binder treatment, the

size of the treatment effect was similar to that observed in the monotherapy trials─ 0.65 mg/dL.

Although we agree that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis, the magnitude of the treatment effect is small and of unclear clinical significance. In some diseases, we have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate and changes in clinical outcomes. In this disease state, we do not have such data. And, while there is well-established precedent for accepting serum phosphorus as a surrogate endpoint and basis for approval in this therapeutic area, there is no precedent for accepting treatment effects of the magnitude seen in this development program.

For this application to be approved, you will need to conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on a clinical outcome thought to be caused by hyperphosphatemia in CKD patients on dialysis. We note that, in principle, it may be possible to individualize treatment based on a patient's early response to a drug that lowers serum phosphorus levels (i.e., assess for a response at some early time point and only continue treatment in patients who have a clinically relevant response); however, such a strategy would need to be prospectively tested and would also likely need to be based on multiple measurements of serum phosphorus over time to distinguish the treatment effect from intrasubject variability.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, November 23, 2020 which addresses the proposed proprietary name, Xphozah. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
07/28/2021 04:27:54 PM

NDA 213931

APPEAL DENIED

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory Affairs and Quality Assurance Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride tablets, 10 mg, 20 mg, and 30 mg.

I also refer to your December 3, 2021, request for formal dispute resolution received on December 3, 2021. The appeal concerned the Complete Response letter issued by Aliza Thompson, MD, MS, Deputy Director, Division of Cardiology and Nephrology, on July 28, 2021, for tenapanor for the control of serum phosphorus in adults with chronic kidney disease on dialysis.

I also acknowledge receipt of the requested additional clarifying information on January 7, 2022.

I have carefully reviewed the materials you submitted in support of your appeal, as well as pertinent portions of your NDA submission, FDA reviews, meeting minutes, decision memoranda, and the Complete Response letter. I have also consulted with Staff in the Division of Cardiology and Nephrology, the Division of Biometrics II in the Office of Biostatistics, and the Office of New Drug Policy.

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

You are seeking approval of tenapanor, an inhibitor of sodium/hydrogen exchanger isoform 3, for the control of serum phosphorus in adults with chronic kidney disease on dialysis. You have provided pivotal efficacy data from three controlled trials: Two trials with a run-in period followed by a placebo-controlled, randomized withdrawal period (Study 301 and Study 201) and one randomized, placebo-controlled trial evaluating tenapanor as add-on to phosphate binder therapy (Study 202). As noted in the Complete Response letter issued by the Division of Cardiology and Nephrology, the Division agrees that the submitted data in these three trials show that tenapanor can reduce serum phosphorus in chronic kidney disease patients on dialysis, and I am in agreement with this conclusion.

The crux of the issue is whether the magnitude of serum phosphorus reduction seen with tenapanor is clinically meaningful and, if it is, whether that benefit outweighs the risks of the drug. It is well established that the effect shown in adequate and well-controlled clinical investigations, must be, in FDA's judgment, clinically meaningful for drug approval.[1] In addition, FDA must also determine that the expected benefits of the drug outweigh its risks to patients. Both of these longstanding and widely recognized criteria must be met for approval. Below, I discuss my assessment of these issues and provide rationale for my determination.

As you and the Division note, epidemiological studies have shown an association between elevated serum phosphorus and an increased risk of vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with chronic kidney disease. In epidemiological studies, high serum phosphorus has been associated with increased mortality in patients on dialysis. In addition, as you and the Division both note, there are no completed randomized, controlled trials that have definitively demonstrated that lowering of serum phosphorus improves clinical outcomes, such as cardiovascular events or mortality in this population. The ongoing HiLo trial (NCT04095039) is evaluating whether the current standard approach of targeting serum phosphorus below 5.5 mg/dL improves all-cause mortality and all-cause hospitalization compared to less stringent control that targets serum phosphorus above 6.5 mg/dL among patients with end-stage renal disease undergoing hemodialysis. This study has an estimated completion date of April 2023 (ClinicalTrials.gov, accessed February 4, 2022). Nonetheless, treatment guidelines recommend lowering high serum phosphorus concentrations towards the normal range or below 5.5 mg/dL in patients with end-stage renal disease on dialysis. For example, the international Kidney Disease Improving Global Outcomes (KDIGO) 2017 guideline[2] notes that lowering serum phosphorus towards the normal range in this population is a level 2C recommendation (a suggestion based on low quality evidence).

That said, in certain instances FDA has accepted serum phosphorus as a surrogate endpoint and basis for traditional approval in patients with chronic kidney disease on dialysis when the effect on serum phosphorus was sufficiently large to be considered clinically meaningful with benefit that outweighed the risks. It is important to note, however, that even for accepted surrogate endpoints, a drug effect may be so small that it does not provide any meaningful clinical benefit or alters the benefit/risk assessment. It is challenging to define a minimum drug effect on serum phosphorus given that the relationship between phosphorus lowering and clinical benefit has not been established. The Division informed you during development that the magnitude of phosphorus lowering with tenapanor needed to be sufficient to reasonably conclude there would be

[1] See preamble to FDA final rule on accelerated approval (57 FR 58942, 58944 (December 11, 1992)); Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3rd Cir. 1986).
[2] KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017; 7: 1-59.

clinical benefit. For example, in an Advice letter dated November 9, 2017, the Division stated “If the size of the effect of tenapanor on serum phosphorus is significantly smaller than the size of the effect of currently approved phosphate binders, then you will need to address the clinical relevance of the effect size of your product on serum phosphorus.” As you have noted in your appeal, there are inherent limitations to cross-study comparisons with other approved phosphorus lowering therapies. Below I focus specifically on your program, which shows modest mean reductions in serum phosphorus with tenapanor.

For Study 301 and 201, your primary efficacy analyses focused on an enriched patient population defined as patients who completed the trial run-in period and had at least a 1.2 mg/dL improvement in serum phosphorus from the baseline to end of the run-in period. Your largest treatment effect was seen in Study 301 at the end of the subsequent randomized withdrawal period in this enriched population, which showed a LS mean difference for the change from baseline in serum phosphorus between tenapanor and placebo of 1.4 mg/dL, reflecting data for less than 25% of the patients who enrolled in the trial. However, your unenriched intent-to-treat analysis (reflecting data for about 45% of the patients enrolled in the trial, and which is expected to better reflect use in a general population that tolerates your drug) showed a LS mean treatment difference of 0.7 mg/dL. In Study 201, the LS mean treatment difference between tenapanor and placebo at the end of the randomized withdrawal period was 0.8 mg/dL in the enriched analysis population and 0.7 mg/dL in the unenriched intent-to-treat analysis population. In add-on-to-phosphate-binder Study 202, the LS mean treatment difference between tenapanor and placebo was 0.7 mg/dL. In summary, the preponderance of the data from these trials supports an expected overall mean treatment effect in the range of 0.7-0.8 mg/dL compared to placebo in a patient population like that enrolled in your clinical trials.

Furthermore, your efficacy results for the randomized withdrawal periods of Study 301 and 201 call into question the ability of your enrichment analysis approach to identify patients with larger responses to tenapanor. Specifically, while your enrichment analysis approach appears to have improved the treatment effect in the Study 301 placebo-controlled period (LS mean difference between tenapanor and placebo of 1.4 mg/dL for the enriched analysis population vs. 0.7 mg/dL for the unenriched analysis population), it appears not to have improved the treatment effect in the Study 201 placebo-controlled period (LS mean difference between tenapanor and placebo of 0.8 mg/dL for the enriched analysis population vs. 0.7 mg/dL for the unenriched analysis population). This finding in Study 201 illustrates that even having a greater than 1.2 mg/dL decline from baseline in serum phosphorus based on a single measurement does not necessarily translate into a larger treatment effect assessed when patients are subsequently randomized to continue tenapanor or switch to placebo. This finding raises questions about the feasibility of identifying patients who have greater responses to tenapanor in clinical practice and probably reflects to at least some degree challenges related to serum phosphorus variability in the context of the overall modest efficacy with your drug.

Taking these results in aggregate and noting that there is a considerable proportion of patients with a treatment response below these means, a substantial number of patients treated with tenapanor in clinical practice would be expected to have very small numerical reductions in serum phosphorus if they continued your drug versus comparable patients who chose to come off your drug. Whether the benefits of tenapanor in these patients is clinically meaningful and outweighs the risks (discussed below) is unclear.

What about the patients who experienced a reduction in serum phosphorus larger than the LS means? The analyses provided in your NDA do not adequately evaluate the magnitude of the serum phosphorus reductions among these patients. In Study 301, the analyses focus on the run-in period, which you note in your appeal is not appropriate for efficacy conclusions against sevelamer and, if you disregard the sevelamer data, is otherwise uncontrolled. In Study 201, the analyses also focus on the run-in period during which patients only received tenapanor. Uncontrolled analyses of serum phosphorus do not provide reliable conclusions on an endpoint that has considerable intra-patient variability.

Of more interest are responder analyses and analyses of distribution of response for tenapanor versus placebo during the randomized, placebo-controlled treatment periods of your three trials. In your appeal, you mention only one such analysis – an analysis of Study 202 responders (percentage of patients with serum phosphorus below 5.5 mg/dL) of 37% with tenapanor compared to 22% with placebo at the end of the Week 4 randomized, double-blind treatment period. However, this analysis has several limitations. First, as noted in the Interim Response to Appeal – Information Request letter, it is important to consider whether this difference in response rate is primarily driven by numerically small reductions from just above 5.5 mg/dL to just below 5.5 mg/dL. In your response, you provided a waterfall plot for the tenapanor responders but did not include the corresponding waterfall plot for the placebo responders. In addition, given the inherent intra-patient variability in serum phosphorus concentrations, additional analyses at other timepoints and across timepoints are needed to determine the extent and consistency of reductions in the tenapanor vs. placebo responders. It is possible that such analyses may show that there are patients who can have more sizeable, consistent reductions in serum phosphorus over time with tenapanor compared to placebo but without such analyses in hand this is an unanswered question. Because these analyses have not been previously submitted to the NDA prior to issuance of the Complete Response letter, I cannot request and consider these analyses as part of my decision on your Appeal.

Turning to safety, I acknowledge that tenapanor is minimally absorbed. However, that does not mean it is risk-free or has only minor risks. In Study 202, the incidence of reported diarrhea was 43% with tenapanor compared to 7% with placebo, with 22% of tenapanor-treated patients reporting moderate diarrhea and four patients (3.4%) reporting severe diarrhea. I also note that in this trial there was one tenapanor-treated patient with reported dehydration (Table 14.1.3.1) but I could not find additional details on this adverse event in the Clinical Study Report. Of note, analyses of adverse events

during the randomized, placebo-controlled period of this study may not adequately reflect longer term risks with combination therapy given the relatively short, randomized treatment duration of only four weeks.

In Study 301 and 201, the placebo-controlled periods only included patients who completed the run-in periods, reflecting a selected patient population that made it to the timepoint of randomization and who are more likely overall to tolerate tenapanor than a general population that is initially started on the drug. If we instead assess the safety data from the 26-week run-in period for Study 301, 24% of tenapanor-treated patients discontinued the drug due to adverse events (most commonly due to diarrhea) and 34% had a tenapanor dose reduction due to adverse events. During this run-in period involving more than 400 tenapanor-treated patients, 53% of the tenapanor-treated patients reported diarrhea and 6% (n=26) had diarrhea classified as severe by the investigator. In addition, there were 3 reported serious adverse events of diarrhea, including one subject ((b) (6) who was hospitalized with dehydration (and hyponatremia, nodal arrhythmia, bradycardia, and acidosis) after several weeks of moderate diarrhea and another subject ((b) (6) who was hospitalized with dehydration on Day 6 who had severe diarrhea that started after the first tenapanor dose. While it is challenging to determine conclusively drug relatedness for any specific adverse event, diarrhea (which could be severe) is consistent with tenapanor's mechanism of action and known safety profile. It is also important to note that patients in the target patient population can have significant comorbidities including atherosclerotic cardiovascular disease, which could make some patients particularly vulnerable to adverse effects stemming from severe diarrhea and dehydration, such as ischemia. Furthermore, the observed events described above occurred in the context of clinical trials, where a selective population of patients is managed in a tightly controlled setting. In contrast, in the real-world there is a reasonable expectation of wider use in a more diverse patient population that is not as closely monitored as in a clinical trial. The risks of severe diarrhea and its potential sequelae (e.g., dehydration, hypotension, falls, ischemia) in the context of real-world use must be weighed against any clinical benefit.

Lastly, as discussed above, it is unclear whether healthcare providers will be able to identify in clinical practice whether a patient is benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of tenapanor's modest mean effects. Although serum phosphorus is measured routinely in the patient population, the results are influenced by food intake, adherence to and timing of drug intake and dietary modifications, as well as diurnal variations.[2] Guidelines, therefore, recommend basing treatment decisions not on a single serum phosphorus result but rather on the trends of serial measurements. While a large treatment effect of a drug may be discernable beyond this variability, it is unclear whether the current treatment guideline strategy will allow reliable treatment decisions for continuing or stopping tenapanor given the overall modest mean treatment effects. This could lead to continued or indefinite treatment with tenapanor in a considerable number of patients who are not benefiting from the drug but who may still be exposed to the risks.

In summary, based on the data available to the Division at the time of the Complete Response letter, I am unable to conclude that tenapanor's overall clinical benefit is meaningful and outweighs its risks. As discussed above, given the modest mean treatment effect in the overall, unenriched patient population, there is a substantial proportion of patients who would be treated with tenapanor in clinical practice and who would have small numerical reductions in serum phosphorus if they continued your drug versus comparable patients who chose to come off your drug. Furthermore, as discussed above, the analyses included in your NDA do not adequately evaluate the distribution of response and responder analyses for tenapanor compared to placebo to understand fully the extent of the treatment effect and, importantly, whether there are patients who have a sustained, meaningful response over time. There are also potential safety concerns related to severe diarrhea and dehydration that cannot be dismissed when tenapanor is used in a wide population of patients on dialysis and must be weighed against the effectiveness of tenapanor, but this requires a better understanding of tenapanor's efficacy compared to placebo beyond the LS mean results. Lastly, there is the concern regarding the feasibility of healthcare providers being able to identify in clinical practice which patients are benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of tenapanor's modest mean effects. In a situation where the mean treatment effect of a drug is small and it is unclear if this reflects meaningful benefit that outweighs the risks, it may still be reasonable to approve a drug if one can readily identify patients with a meaningful response such that the drug can be continued in these patients and stopped in those with an inadequate or poor response. However, as discussed above, this has not been adequately demonstrated in your NDA.

As a path forward, I recommend that you submit a Complete Response to your NDA that provides the additional information and analyses described below to respond to these identified concerns.

Information and New Analyses Recommended in a Complete Response Submission:

1. Analyses that go beyond the LS mean results to assess the extent of serum phosphorus changes with tenapanor compared to placebo for Studies 301, 201, and 202, focusing on distribution of response and analyses of responders and non-responders. Given the intra-patient variability in serum phosphorus measurements in the context of the modest LS means, it is critical to conduct analyses that define responders as those who have consistently responded at more than a single timepoint and assess whether there is such an identifiable responder population.

   The analyses should be conducted on the randomized, placebo-controlled treatment periods, and include results for tenapanor and placebo. For Study 301 and 201 perform the analyses for the enriched and unenriched populations. For all analyses, baseline is the beginning of the randomized, placebo-controlled period. Clearly note the statistical population used for all analyses and how

missing data were handled. Examples of analyses include but do not need to be limited to the following:

Study 202:

- Distribution of responses (e.g., cumulative distribution plots) for tenapanor vs. placebo for change in serum phosphorus from baseline to the end of the randomized period. Include similar analyses for change in serum phosphorus from baseline to the other time points of the randomized period.

- Analyses showing the extent of change in serum phosphorus from baseline to the end of the randomized period (e.g., waterfall plots) for tenapanor and placebo responders (e.g., those who achieved serum phosphorus <5.5 mg/dL at the end of the randomized period, those who achieved serum phosphorus in the normal range at the end of the randomized period). Conduct similar analyses for the tenapanor and placebo non-responders. Conduct similar analyses from baseline to other time points of the randomized period.

- Responder analyses for tenapanor vs. placebo at each timepoint during the randomized period and at the end of the randomized period, where a responder is defined as having a certain reduction from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL reductions). Conduct a similar analysis of the percentage of patients who have a certain increase from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL increases).

- Analyses of the percentage of patients on tenapanor and placebo who consistently remained a responder beyond a single timepoint during the randomized period. For these persistent tenapanor and placebo responders, also assess their extent of serum phosphorus reduction. Conduct similar analyses for patients on tenapanor and placebo who consistently remained a non-responder throughout the randomized period. Examples of such analyses include:

    - Patients who consistently achieved serum phosphorus <5.5 mg/dL over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period.

    - Patients who consistently achieved serum phosphorus <5.5 mg/dL and who had >1 mg/dL decrease from baseline in serum phosphorus over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period. Similar analyses using other reductions instead of >1 mg/dL decrease from baseline in serum phosphorus (e.g., >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL decreases)

- Proportion of responders at an early timepoint in the randomized period who remained a responder at later timepoints.

- Similar analyses as above but for patients who consistently achieved serum phosphorus in the normal range over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period.

Study 301 and 201:

- Analyses assessing the distribution of change in serum phosphorus for tenapanor vs. placebo during the randomized, placebo-controlled withdrawal periods of Study 301 and 201.

- Analyses of the proportion of responders (e.g., those who achieved serum phosphorus <5.5 mg/dL, those who achieved serum phosphorus in the normal range) and non-responders for tenapanor and placebo at each time point of the randomized, placebo-controlled withdrawal period.

- Analyses showing the extent of change in serum phosphorus from baseline to the end of the randomized period (e.g., waterfall plots) for the tenapanor and placebo non-responders (e.g., those whose serum phosphorus was ≥5.5 mg/dL at the end of the randomized period, those whose serum phosphorus was above the upper limit of the normal range at the end of the randomized period). Conduct similar analyses for the tenapanor and placebo responders (e.g., those whose serum phosphorus was <5.5 mg/dL at the end of the randomized period, those whose serum phosphorus was within the normal range at the end of the randomized period). Also conduct similar analyses for other time points of the randomized period.

- Analyses of the percentage of patients on tenapanor and placebo at each timepoint during the randomized period and at the end of the randomized period who had a certain increase from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL increases). Conduct a similar analysis of the percentage of patients who had a certain decrease from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL decreases).

- Analyses of the percentage of patients on tenapanor and placebo who consistently remained a non-responder throughout the randomized, placebo-controlled periods. Conduct a similar analysis for consistent responders. For these consistent non-responders and consistent responders, also assess the extent of serum phosphorus change with

tenapanor vs. placebo. See the examples above for Study 202 and adapt them accordingly for Study 301 and 201.

2. Analyses of intra-patient variability over time in serum phosphorus concentrations in tenapanor and placebo-treated patients throughout the various treatment periods of Studies 301, 201, and 202.

3. A detailed assessment of how the benefits of tenapanor outweigh its risks based on these additional analyses in the context of the issues discussed in this Appeal Denied letter.

4. A detailed proposal for how to label your drug for prescribers for determining whether a patient is benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of the magnitude of tenapanor's treatment effects, taking into account the findings from the additional requested analyses described above as well as any other pertinent data in your NDA.

I have determined that this additional information and analyses are critical for determining whether tenapanor has clinically meaningful benefits that outweigh its risks. This new information and analyses have not been provided to the Division prior to the Complete Response action and, therefore, I am unable to consider the findings from such analyses as part of this appeal.

If you submit a Complete Response with this requested information and it still raises concerns regarding adequacy of the data to establish a meaningful effect with benefits that outweigh the risks, the Division will consider whether a public meeting of the Cardiovascular and Renal Drugs Advisory Committee would be appropriate to provide further input on this issue during the review cycle.

Questions regarding next steps as described in this letter should be directed to Sabry Soukehal, Regulatory Health Project Manager, at (240) 402-6187.

This constitutes the final decision at the Office of Cardiology, Hematology, Endocrinology and Nephrology level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Melissa Sage. Any questions concerning your appeal should be addressed to Melissa Sage at (301) 796-6449.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
02/04/2022 03:15:26 PM

NDA 213931

INTERIM APPEAL RESPONSE
INPUT NEEDED FROM ADVISORY COMMITTEE

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory and Quality Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride tablets for the control of serum phosphorus in adults with chronic kidney disease (CKD) on dialysis.

I also refer to your February 18, 2022, request for formal dispute resolution received on February 18, 2022. The appeal concerned the Complete Response letter issued by Aliza Thompson, MD, MS, Deputy Director, Division of Cardiology and Nephrology (DCN), on July 28, 2021.

I also refer to your request for formal dispute resolution, received on December 3, 2021, to the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN), and the denial of the appeal by Hylton Joffe, MMSc, MD on February 4, 2022.

I also refer to the meeting held between FDA and Ardelyx, Inc. on March 17, 2022, where the issues raised in your request for formal dispute resolution were discussed.

I have reviewed your appeal and conclude that additional input is needed to reach a decision. Accordingly, I intend to convene an Advisory Committee meeting and seek advice from the Cardiovascular and Renal Drugs Advisory Committee. We will notify you with additional details in the near future when the meeting is scheduled and work with you on the planning, as appropriate. The reasons for my decision to convene an Advisory Committee meeting, and an overview of the background issues, are outlined below.

Tenapanor is a small molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) intended for the treatment of hyperphosphatemia in patients with CKD on dialysis. The drug acts in the gastrointestinal (GI) tract to reduce absorption of luminal sodium, increasing luminal fluid. The reduced flux of sodium reduces paracellular phosphate absorption, and therefore increases GI phosphate loss, lowering serum phosphate levels.

The NDA for tenapanor included 3 adequate and well-controlled clinical trials to support the efficacy and safety of tenapanor in patients with CKD on dialysis with hyperphosphatemia, with two studies (TEN-02-201 and TEN-02-301) in monotherapy use, and one study (Study TEN-02-202) as add-on to phosphate binders. I will also discuss a small Phase 2 study that you reference in your FDRR letter. I will briefly review these studies in the following paragraphs.

Study TEN-02-201 was a 12-week dose-range finding, parallel group, randomized trial in patients with CKD on hemodialysis (HD). The trial included a wash-out period for patients already on phosphate binders, followed by a randomized 8-week dose comparison active treatment period with 3 different tenapanor dose arms with twice-daily dosing (3 mg, 10 mg, or dose-titration starting at 30 mg), and then a 4-week randomized withdrawal period comparing response at the patient's current tenapanor dose (from the 8-week treatment period) to response with placebo. The primary endpoint was the change from baseline in serum phosphate at the end of the randomized withdrawal period (with the baseline prior to entry into the randomized withdrawal period). The primary efficacy analysis population (the efficacy analysis set; EAS) were patients with at least a 1.2 mg/dL reduction from baseline at the end of the 8-week dose-comparison treatment period.

Overall, 218 patients were randomized into the dose-comparison controlled treatment period, balanced across the 3 tenapanor dose groups. During the 8-week dose-ranging period, about 25% of patients discontinued, many related to GI adverse events (particularly diarrhea). In this treatment period, reductions from baseline of about 1 mg/dL were seen across all 3 tenapanor treatment groups. This observation, however, provides limited information on tenapanor efficacy in lowering phosphate, as it fails to separate trial effects on serum phosphate concentrations from the effect of tenapanor. To argue for the value of such analyses, it might be suggested that in clinical practice, patients do not, of course, receive a placebo. However, unlike in practice, in a clinical trial, participants may well see decreases in phosphate with improved dietary adherence. Moreover, serum phosphate concentrations during the wash-out period were repeated to determine eligibility, with patients selected for study participation based upon protocol-specified elevations in serum phosphate concentrations; subsequent decreases, therefore, may reflect a regression to the mean phenomenon. In other words, decreases in serum phosphate in a clinical trial, absent a placebo control for comparison, are unreliable estimates of the extent of drug effect. Thus "trial" effect can only be sorted out from drug effect out with a placebo comparison.

Among the 82 patients entering the randomized withdrawal period, about half (43 patients) were included in the EAS. At the end of the randomized withdrawal period, the change from baseline in serum phosphate compared to placebo with tenapanor was -0.82 mg/dL in the EAS, similar to the reduction, of -0.72 mg/dL, relative to placebo in the overall randomized population entering this period. Thus, in this study, there was no meaningful enrichment of response—that is, even selecting patients who appeared to have a greater response to drug did not successfully identify higher responders.

Study TEN-02-301 was a 52-week randomized clinical trial in patients with CKD on hemodialysis who had hyperphosphatemia. Patients on dialysis already on phosphate binders entered a phosphate binder washout period, and those with elevated phosphate levels (6 to 10

mg/dL, and who had a rise in serum phosphate during wash-off, with re-screening allowed) entered a 26-week active treatment period, randomized (3:1) to either tenapanor (titrated doses) or sevelamer. At the end of this period, patients were then entered into a 12-week randomized withdrawal period. The primary endpoint was the change from baseline (entry into this period) at the end of the randomized withdrawal period. Overall, 564 patients were randomized into the 26-week active treatment period, with about 40% of tenapanor patients discontinuing, largely related to GI adverse events; 255 patients were randomized (1:1) to placebo or continuing their dose of tenapanor to enter the randomized withdrawal period. Among patients randomized to tenapanor, approximately 77% completed the treatment period. Thus, slightly fewer than about half of patients (0.60 x 0.77) entering the initial active-treatment period on tenapanor completed the randomized withdrawal period. Similar to the approach in Study TEN-02-201, the primary analysis was based upon a subset of patients entering the randomized withdrawal period, the EAS (defined the same as in Study TEN-02-201). Reduction in serum phosphate concentrations relative to placebo was -1.37 mg/dL in the EAS (p value of < 0.0001). Notably, in the overall population, the change from baseline was smaller, -0.66 mg/dL.

Study TEN-02-202 was a randomized, placebo-controlled trial in patients with CKD on dialysis with inadequately controlled hyperphosphatemia (phosphate ≥ 5.5 mg/dL at screening, with rescreening allowed) on phosphate binders. Patients were randomized (1:1) to the addition of tenapanor (30 mg BID) or placebo to ongoing phosphate binder therapy for a 4-week double-blind treatment period. Overall, 236 patients were randomized, with only 4.3% of patients not completing the double-blind period. The primary analysis showed that there was a -0.65 mg/dL change from baseline with tenapanor relative to placebo (p<0.001). The full response appeared to be achieved by Week 1 of treatment. A responder analysis showed that 22% and 37% (difference of 15%) of patients on placebo and tenapanor, respectively, had a decrease in phosphate to < 5.5 mg/dL at Week 4. Interestingly, the proportion achieving a serum phosphate < 5.5 mg/dL over the 4-week period was relatively unchanged from Week 1 to Week 4 in the placebo group but decreased from 49% at Week 1 to 37% at Week 4 in the tenapanor group.

In your FDRR letter, you discuss the results from a small Phase 2 study, Study D5613C00001. This was a randomized, placebo-controlled, dose-range finding study, evaluating once- and twice-daily doses of tenapanor from 1 mg to 30 mg. In this small study (about 25 patients per treatment group), model-predicted mean decreases relative to placebo of 1 mg/dL and 1.4 mg/dL (95% CI 0.55, 2.12 mg/dL), respectively, were reported for the 10 mg BID and 30 mg BID doses, respectively. Given the extent of patient discontinuation at the highest dose (about one-third of patients), and the wide confidence intervals around the estimated effect sizes, this study has significant limitations in providing a reliable estimate of treatment effect and does not substantially alter conclusions from the other studies discussed above regarding the extent of efficacy seen with tenapanor.

In the complete response letter dated July 28, 2021, considering the results across the adequate and well controlled studies, the Division cited the extent of reduction as insufficient to provide meaningful clinical benefit to patients. The Division acknowledged that they accept lowering of serum phosphate as a validated surrogate endpoint but consider that the *extent* of

effect is relevant to an approval decision. It is important to observe that the Division's perspective on this point has been consistent, having previously informed the company that a justification for an effect size smaller than seen with approved agents would be needed, noting that approved drugs provide reductions in serum phosphate concentrations in the 1.5-2.2 mg/dL range. Although the response from Study TEN-02-301 in the EAS was approximately 1.4 mg/dL, the Division was concerned that this extent of reduction may be difficult to identify in the clinical setting, given the variability of serum phosphate concentrations, and the many factors influencing these concentrations. Given their concern about the limited applicability of the EAS results, the Division concluded that "...the ITT analysis is the best estimate of the average treatment effect in…patients who are likely to tolerate tenapanor and remain on therapy. The sizes of treatment effects…were small—0.72 mg/dL and 0.66 mg/dL". The Division went on to note that there was "no precedent for accepting treatment effects of the magnitude seen in this development program." I will discuss later the rationale for the Division's view that the extent of phosphate reduction with tenapanor may not be clinically meaningful.

The company appealed this decision to OCHEN, and the appeal was denied by Dr. Hylton Joffe. Dr. Joffe acknowledged that the clinical trials had successfully demonstrated that tenapanor lowers serum phosphate, but also noted that to support approval, the effect size must be clinically meaningful and that the benefit must outweigh the risk. He pointed out that the Division had informed the sponsor in 2017 that "[i]f the size of the effect of tenapanor on serum phosphorus is significantly smaller than the size of the effect of currently approved phosphate binders, then you will need to address the clinical relevance of the effect size of your product on serum phosphorus." He noted that the effect size "may be so small that it does not provide any meaningful clinical benefit or alters the benefit/risk assessment." Dr. Joffe noted that the preponderance of study results showed an effect size of 0.7-0.8 mg/dL. Although he acknowledged the response in the enriched subset of patients in Study TEN-02-301, he contrasted this response to the response seen in Study TEN-02-201 where the same strategy showed no notable difference between the ITT results and those in the enriched subset of patients. Dr. Joffe also expressed doubts about the utility of the responder analyses in Study TEN-02-301 where there was no adequate control to provide a robust estimate of responders. He further noted that in Study TEN-02-202, where there was a placebo-control, the difference between treatment arms in the proportion of patients reaching serum phosphorus < 5.5 mg/dL was difficult to interpret based on the existing analyses included in your NDA. For example, he noted it is unclear whether this difference in response rate was primary driven by numerically small reductions from just above 5.5 mg/dL to just below 5.5 mg/dL when comparing the reductions with tenapanor to those with placebo. He also noted that additional analyses at other timepoints and across timepoints are needed to determine the extent and consistency of reductions in the tenapanor vs. placebo responders given the inherent intra-patient variability in serum phosphorus concentrations. Dr. Joffe concluded that there was insufficient information to support a conclusion that tenapanor offered clinically meaningful benefit to patients with CKD on dialysis who have hyperphosphatemia, and therefore recommended that you provide a number of further analyses of the trial results in a resubmission (response to the CR action), analyses that he considered might provide greater evidence to support the clinical value of tenapanor.

I will now review the assertions in your FDRR letter.

You argue that the additional analyses recommended by Dr. Joffe are not necessary to support a conclusion that there is substantial evidence of the effectiveness of tenapanor, and further that Dr. Joffe's conclusions regarding the efficacy of the drug were not correct. In support of this assertion, you point to the EAS results with the effect size of 1.4 mg/dL. You further note that Joffe's response does not recognize the distinct design of Study TEN-02-202 relative to Study TEN-02-301, and also point out that Dr. Joffe did not consider results from the small Phase 2 Study (D5613C00001), discussed above. I have already commented on the limitations of this Phase 2 study, but will briefly consider the other points below.

As I noted above, although the EAS in Study TEN-02-301 observed a reduction of 1.4 mg/dL relative to placebo, the ITT analysis from the randomized withdrawal period showed a more modest reduction of about 0.7 mg/dL. In contrast to these results from Study TEN-02-301, as Dr. Joffe points out, no greater response in the EAS relative to the ITT population was observed in Study TEN-02-201. In other words, the effect of enrichment—the ability of an initial greater response to predict a later greater response—was inconsistent between studies. It is also important to point out that when the Division references effect sizes of "1.5-2.2 mg/dL", these generally refer to placebo-corrected effect sizes in an ITT population, not results in an enriched population. I will discuss the results from other phosphate-lowering drugs below. Although I acknowledge that referencing results from other trials has limitations, studies of prior approved phosphate binders included similar patient populations (patients with CKD on dialysis washing off of phosphate binders) and study designs (using both prospective placebo-controlled and randomized withdrawal designs), and a laboratory analyte endpoint measured with standard assay methods.

In the paragraphs below, I will briefly discuss efficacy results from studies of these approved agents, including sucroferric oxyhydroxide (Velphoro), Lanthanum carbonate (Fosrenol), Ferric citrate (Auryxia), Sevelamer (Renagal), and calcium acetate (PhosLo).

For sucroferric oxyhydroxide (Velphoro) approximately 1059 patients with CKD on dialysis with hyperphosphatemia were randomized into an active-controlled 24-week treatment period. To establish the efficacy of the drug relative to control (a low dose of sucroferric oxyhydroxide considered to be minimally effective), the first 100 patients completing the active-treatment period *and* who had a serum phosphate concentration of < 5.5 mg/dL were re-randomized in a 1:1 ratio to continuing the sucroferric oxyhydroxide at the dose identified in the active-controlled period, or to a low dose of the drug (J Floege, AC Covic et al. Kidney Int 86:638-647, 2014). I note that this is an enrichment design with only patients tolerating the drug *and* achieving a serum phosphate < 5.5 mg/dL entered into the randomized withdrawal phase. In this randomized withdrawal period, a difference of approximately 1.5 mg/dL between the higher and low dose of sucroferric oxyhydroxide was observed (since the low dose likely provided some phosphate lowering this is a minimum estimate of drug effect). Notably, in the active-controlled period of this study, sucroferric oxyhydroxide provided approximately a 0.3 mg/dL greater extent of phosphate lowering relative to the sevelamer active control. This extent of greater efficacy was consistent with observations from a Phase 2 dose-range finding study of sucroferric oxyhydroxide that included a sevelamer control. In that same dose-range

finding study, sucroferric oxyhydroxide doses of 10-12.5 g/day provided approximately 1.5 mg/dL greater reduction in serum phosphate compared to the low dose of the drug (1.25 g/day), again, a minimum estimate of extent of phosphate lowering since the low dose likely had some effect to lower phosphate levels. Note that these latter results were *not* from an efficacy enriched population.

For lanthanum carbonate (Fosrenol), results from a placebo-controlled dose-ranging study and from a randomized withdrawal study (without efficacy enrichment) showed reductions of serum phosphate relative to placebo of about 2.0 mg/dL (prescribing information for Fosrenol; MS Joy, WF Finn, et al. Am J Kid Dis 42:96-107). For Ferric citrate (Auryxia), patients completing a 52-week active-controlled study period entered a randomized withdrawal period, without efficacy enrichment, with a 2.2 mg/dL difference observed after 4 weeks (prescribing information for Auryxia; JB Lewis, M Sika, et al. J Am Soc Nephrol 26:493-503, 2015). For sevelamer (Renagel), only a small placebo-controlled study (in 24 patients) was conducted; several active-controlled Phase 3 studies were conducted which showed reductions from baseline of about 2 mg/dL, similar to that seen with the calcium acetate active comparator (prescribing information for Renagel). For calcium acetate (PhosLo), a randomized withdrawal designed study, without enrichment for efficacy was conducted, showing a difference from placebo of approximately 1.9 mg/dL (5.9 mg/dL and 7.8 mg/dL in the calcium acetate and placebo groups, respectively) (prescribing information for PhosLo).

In summary, studies of the approved agents (sucroferric oxyhydroxide. lanthanum carbonate, ferric citrate, sevelamer, calcium acetate) have shown reductions compared to placebo or other control in the 1.5-2.2 mg/dL range, as referenced by the Division. It is reasonable to conclude, as the Division did, that tenapanor provides lesser reductions in serum phosphate (in the -0.65 to -0.8 mg/dL range in the ITT populations across studies TEN-02-201, -301, and -202) than observed with the approved phosphate-lowering agents. Therefore, concern about the clinical meaningfulness of the extent of reductions seen with tenapanor seems appropriate.

You argue that clinicians caring for patients with CKD on dialysis will make treatment decisions based on their patient's phosphate levels getting to goal (< 5.5 mg/dL) and not by the absolute extent of lowering. Since phosphate is a variable analyte—affected by dietary adherence, adherence to other phosphate-lowering therapy, prior dialysis response, and the variability of other biological phenomenon that regulate phosphate (e.g., FGF-23, PTH)—separating these influences from the effect of the drug may be difficult, especially for a drug with a modest effect size. Moreover, you assume that merely achieving the goal phosphate demonstrates the benefit of the drug. As previously pointed out by Dr. Joffe, small changes in phosphate may bring an individual from slightly above to slightly below 5.5 mg/dL, but not provide meaningful benefit to the patient. To counter what you consider an incorrect conclusion, you refer to the extensive responder analyses in Study TEN-02-301. As I have pointed out, these analyses have limited value as they are uncontrolled, and can be confounded by the trial effects I have already discussed. At our face-to-face virtual meeting, you referenced responder analysis results from the small Phase 2 study D5613C00001. I acknowledge a larger proportion of tenapanor-treated patients reached the phosphorus goal relative to placebo, but given the small study sample size and high drop-out rates, these estimates are not reliable. You point to the responder analyses from placebo-controlled Study TEN-02-201 where 15% more patients

achieved a goal phosphate level (< 5.5 mg/dL) compared to placebo; however, as noted, this difference is based upon a modest mean reduction in serum phosphate levels, therefore limiting the clinical meaningfulness of this difference in goal attainment.

At our meeting to discuss the FDRR, you also pointed to data submitted in a Clinical Information Amendment (1.11.3) supporting the ability to use early serum phosphate response to drug (Weeks 1, 2 or 4) as a predictor of sustained (Week 26) response. However, these results do not strongly support your contention. For example, less than half of patients (approximately 45%) who reached serum phosphate levels of < 5.0 mg/dL at one of these timepoints had a serum phosphate of < 5.5 mg/dL at Week 26. I acknowledge that these are conservative estimates, given how results from patients not reaching Week 26 were imputed.

As I noted, if a responder population—patients who would see a sustained greater response—can be reliably identified, this might support the clinical utility of tenapanor. I have already noted the discrepant effects of enrichment in Studies TEN-02-301 and TEN-02-201. You argue, however, that clinicians will continually monitor serum phosphate and only continue drugs that are effectively lowering phosphate levels. Yet, if one or another initial serum phosphate measurements after starting the drug shows a reduction, consistent with either variability of the analyte (for reasons outlined already above) or drug response, the drug may well simply be continued. Although you note that "routine monitoring to inform therapeutic approach" (FDRR page 9) is the "norm", this assumes that routine monitoring can reliably identify such patients based upon a stable response to drug, which is not necessarily the case here. Labeling that advised health care providers to discontinue tenapanor if at least a 1.2 mg/dL reduction is not initially observed might be a successful approach if the measurement was reasonably stable and consistently predictive of later response—but there is limited support for this approach. Indeed, the fact that no enrichment was seen in TEN-02-201 already suggests the limitations of the evidence for this approach. The Division, in fact, encouraged you to conduct further studies that might demonstrate that such an approach successfully identifies responder patients.

You then discuss drugs for other indications that have been approved with relatively small effect sizes, arguing that the Division's decision for tenapanor is inconsistent with regulatory precedent. You cite both drugs that target surrogate endpoints and those that are intended to treat symptomatic conditions. For example, you cite approvals of cholesterol-lowering drugs. For validated surrogate endpoints, in general, interventional trials have provided robust information on the outcome benefits to be obtained with reductions in the surrogate. For example, we know that even moderate reductions in cholesterol, hemoglobin A1C, and blood pressure can translate to measurable clinical benefit on important outcomes. Yet, even for drugs where there are data providing information on outcome improvements with lowering of the surrogate, some level of reduction may be considered as too small to provide a clinically meaningful outcome benefit to patients receiving the drug—and where this level is set must also consider the individual drug's risk profile. Such information on outcome benefits is not available for agents intended to reduce serum phosphate concentrations in patients with CKD on dialysis. This limitation makes it more challenging to identify an extent of effect that predicts a clinically meaningful outcome benefit—a point to which I will return below.

With respect to symptomatic therapies, such as Myrbetriq for overactive bladder, a reduction in the frequency of incontinence events of even a small extent is meaningful to patients suffering from this condition. In general, FDA looks to evidence that the extent of effect seen is meaningful to patients; not necessarily the entire treated patient population but results that support the conclusion that at least some patients will have meaningful improvements with the drug relative to placebo. In the case of Myrbetriq, (and Addyi (flibanserin)), the extent of improvement was clinically relevant to at least some patients who would be treated. For such drugs, patients can decide for themselves if they are seeing benefit, and, if so, continue the drug. Although there were patients treated with tenapanor who had what appeared to be a larger response, so too did some patients receiving placebo, reflecting the variability of the analyte and the challenges of separating effect of drug and other factors influencing serum phosphate levels.

As noted in the appeal denied letter from Dr. Joffe, substantial evidence of effectiveness requires persuasive evidence that the drug has the intended effect, usually demonstrated by showing statistically significant effects in two or more adequate and well controlled studies *and* an effect size that is clinically meaningful. Approval also requires a conclusion that the benefit of the drug outweighs its risks—an issue that I will also comment on below. There is no disagreement that tenapanor reduces serum phosphate concentrations in patients with CKD on dialysis who have elevated phosphate levels. The focus of the disagreement is whether the reductions observed with tenapanor are clinically meaningful, and, if clinically meaningful, whether the benefit offered by these reductions outweighs the risk of treatment with this drug.

With regard to the extent of reduction needed to support approval, you argue that the Division has not clearly provided an "intelligible decisional standard." You further note that an articulated standard is particularly important when "FDA has approved some products and not approved others." (FDRR page 11). You say that FDA must answer the "most important question: what standard—legal or scientific has the FDA applied in making its decision." You state that neither the CRL nor the prior appeal denied letter adequately lay out this standard.

As discussed already, FDA has accepted serum phosphate reduction as a validated surrogate endpoint to support an indication for the control of serum phosphate levels in patients with CKD on dialysis. The Division pointed out that the treatment of hyperphosphatemia in patients with CKD on dialysis is based upon epidemiological and animal model data, but direct evidence that *lowering* serum phosphate in such patients provides meaningful benefit is lacking. That is, there are no randomized interventional clinical trials that demonstrate improved patient outcomes with treatments that lower serum phosphate concentrations. Such information would inform the extent of clinical benefit to be obtained across the range of reductions in serum phosphate. Even though there is an absence of interventional studies establishing the benefit of phosphate reduction in improving clinical outcomes in patients with CKD on dialysis, accepting this endpoint as a validated surrogate was and is reasonable. Animal model studies provide biological plausibility for elevated phosphate to lead to vascular damage (and reduction to improve outcomes), and extensive epidemiological observational studies show a relationship between the severity of hyperphosphatemia and an increased occurrence of vascular events and reduced survival. Although animal data makes it *plausible* that lowering serum phosphate levels in patients with CKD on dialysis may provide clinical

benefit, effects seen in animal models do not, of course, always translate to a comparable benefit in humans. The observational data is also valuable; however, such data cannot distinguish between serum phosphate merely being a biomarker reflecting the severity of the homeostatic alterations and other vascular risk factors in patients with CKD, and not directly causal, or being the mediator of vascular risk; if the latter was the case, then reducing serum phosphate concentrations should lead to clinical outcome benefits, but if the former, benefit would not be seen.

Despite this uncertainty, given the available scientific evidence, and the often severe hyperphosphatemia and metabolic bone disease associated with uncontrolled hyperphosphatemia prior to the approval of phosphate binder drugs, it was reasonable for FDA to consider serum phosphate as a surrogate endpoint to support approval if sufficient reduction was demonstrated. It is worth noting that large interventional trials establishing the clinical value of lowering phosphate were not expected to be soon available when phosphate-lowering drugs were first approved. Even at present, although there are ongoing large outcome studies that will contribute important information to address this issue, these are not likely to read out in the near future. Approved phosphate binders do give health care providers tools that they can use to implement standard of care patient management recommendations such as from KDIGO (2017 CKD-Metabolic Bone Disease Guideline); it should be noted, however, that the quality of evidence supporting this recommendation was rated as low (C).

Having accepted serum phosphate lowering as a validated surrogate, the next consideration is the extent of reduction that can be considered clinically meaningful and support an approval decision. As already noted, a reduction that is merely statistically identifiable but not clinically meaningful does not provide substantial evidence of effectiveness. The Division has taken the position that, having approved a number of drugs to control hyperphosphatemia, the range of lowering provided by these drugs can be considered as a reasonable benchmark.

You argue that the appeal denial letter standard of “sufficiently large to be considered clinically meaningful” is “an unacceptable standard in light of its subjectivity.” I would point out, however, that this statement must be read in the context of prior statements by the Division pointing to the effect sizes seen across all other approved agents of at least 1.5 mg/dL (not based upon an enriched, efficacy analysis set, but in an ITT population). You then argue that the Division has not “articulated a basis for determining whether the magnitude of s-P reduction is…meaningful because there is no scientific basis upon which to do so.” (page 12 FDRR letter). You argue that the absence of such data prevents any quantitative cutpoint to support approval, and “any attempt to declare one is necessarily arbitrary.” The logical extension of your argument is that even, for example, a 0.2 mg/dL reduction in serum phosphate, absent outcome data, should be approvable. I disagree. Absent interventional study outcome data showing the relationship between the extent of phosphate lowering and the extent of clinical benefit, FDA must use its scientific judgement, recognizing that reductions below some cutpoint would be clinically trivial. My view is that the Division has done exactly that.

Although I think the Division has articulated a reasonable expectation for the extent of phosphate lowering needed to approve a new drug, my assessment is that additional input

from the Cardiovascular and Renal Drug Advisory Committee would be valuable in further considering what level of phosphate reduction is clinically meaningful—whether even the 0.7-0.8 mg/dL, as seen in the ITT analysis, may be considered acceptable to support approval—and if not, whether responders can be identified in practice given the variability in serum phosphate concentrations. The approval standard that FDA applied, in part, is whether the drug provides meaningful clinical benefit. Therefore, it seems appropriate to get further input on these issues from experts, including expert clinicians, in this area.

It is important to also respond to your detailed discussion of tenapanor safety, as you disagree with the concerns raised by Dr. Joffe that there are potential safety issues which must be considered. You correctly point out that in tenapanor clinical trials there were relatively few serious safety events related to the GI adverse events with tenapanor treatment. You also note that patients with CKD undergoing dialysis are carefully monitored and frequently seen by their health care providers so that early action can be taken if a patient does not tolerate tenapanor. However, I would point out that these patients are often fragile—typically older, with multiple co-morbidities, and generally with a limited expected survival. Approximately 55% of patients in the tenapanor group in Study TEN-02-301 had an adverse event of diarrhea in the first 3 months of the study, with 38% of having events (i.e., about two-thirds of all diarrhea events) assessed by investigators as either moderate (32%) or severe (6%) in intensity (compared to about 2% of patients with moderate intensity in the sevelamer group) (Table 14.3.1.4.2, page 1898 study report). A drug that induces such a high incidence of moderate or severe adverse events of diarrhea in a fragile patient population is likely to lead to serious safety events in practice—even in settings where there is regular monitoring by care providers. Based upon the trial data, I would expect such events to be infrequent, but when these occur, they may be severe. Indeed, it is a reasonable concern that patients with CKD on dialysis with moderate or severe diarrhea may become volume depleted and suffer venous or arterial thrombotic events or consequences of hypotension such as syncope and falls. My conclusion is that such risks, even if infrequent, must be set against the extent of benefit offered by tenapanor. I will add that since the adverse event occurs early, even if a responder approach is implemented with discontinuation of drug in patients without adequate phosphate reduction, all patients will likely be exposed to the risk, not just responders. This point must be considered in weighing benefit and risk.

I will direct the Division to bring the tenapanor application to a Cardiovascular and Renal Drugs Advisory Committee meeting.

However, I want to note that there is another potential pathway for you to consider. As outlined by Dr. Joffe, there are additional analyses (including analyses you presented at our face-to-face meeting that were not in the NDA submission) that could be included in a response to the CR action and could lead to reconsideration by the Division. If you would like the Division to consider these analyses, you could withdraw this appeal and submit them in response to the CR action. During its review of the resubmission, the Division may consider whether an AC meeting would be useful to their decision. If you chose not to withdraw this appeal and respond to the CR action, then I intend to proceed with an Advisory Committee meeting as outlined above, and I will respond to your appeal within 30 calendar days after the Advisory Committee meeting.

If you have any questions, call Cathryn Lee, MSN CRNP, at (301)796-1394.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER P STEIN
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