CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213931Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Summary Review for Regulatory Action

Table 1. Administrative Application Information

Category	Application Information
Application type	Resubmission
Application number(s)	213931
Priority or standard	Standard
Submit date(s)	4/17/2023
Received date(s)	4/17/2023
PDUFA goal date	10/17/2023
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	See DARRTS signature page
Established name	Tenapanor
(Proposed) trade name	XPHOZAH
Pharmacologic class	Sodium/hydrogen exchanger 3 (NHE3) inhibitor
Code name	AZD1722/RDX5791
Applicant	Ardelyx, Inc.
Dose form/formulation(s)	Tablets/10 mg, 20 mg, 30 mg
Dosing regimen	Twice daily
Applicant proposed indication(s)/population(s)	for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis who have had an inadequate response or intolerance to a phosphate binder therapy
Proposed SNOMED indication	20165001 | Hyperphosphatemia (disorder)|
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy
Approved SNOMED indication	20165001 | Hyperphosphatemia (disorder)|

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1. Glossary

AC	advisory committee
AE	adverse event
BID	twice daily
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CI	confidence interval
CSR	clinical study report
DMC	data monitoring committee
EOP2	end-of-phase 2
EPC	established pharmacologic class
ER	exposure-response
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
IND	investigational new drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intention-to-treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRHD	maximum recommended human dose
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PT	preferred term
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TID	three times daily
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

On June 29, 2020, FDA received a New Drug Application (NDA) for tenapanor for the control of serum phosphorus (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. On July 28, 2021, the Division issued a Complete Response (reproduced in the Appendix) citing concerns that the magnitude of the treatment effect of tenapanor was small and of unclear clinical significance. The letter further noted that there was well established precedent for accepting serum phosphorus as a surrogate endpoint and basis for approval in this therapeutic area, there was no precedent for accepting treatment effects of the magnitude seen in this development program.

On December 3, 2021, the Applicant submitted a request for formal dispute resolution to the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN). In his denial of the appeal (reproduced 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.

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 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 Response action which 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. If the Applicant chose not to withdraw the appeal and respond to the CR action, then Dr. Stein intended to proceed with an Advisory Committee meeting.

On November 16, 2022, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the tenapanor application. Following that meeting, Dr. Stein granted the appeal. In his appeal granted letter dated December 27, 2022 (reproduced in the Appendix), Dr. Stein stated the following: "In summary, I conclude that the benefit risk assessment for tenapanor is not favorable as initial therapy but is favorable when the prescribed dialytic, nutritional, and maximally tolerated pharmacological therapy does not provide adequate phosphate-lowering. I

direct the Division to work with you to develop a label with this indication." On April 17, 2023, the Applicant resubmitted their application for tenapanor. Based on guidance from Dr. Stein, tenapanor will be approved for the following indication and usage: "XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy."

II. Efficacy and Safety Evaluation

2. Efficacy Evaluation

See FDA's Multi-disciplinary Collaborative Review dated July 28, 2021, as well as Dr. Joffe's appeal denial letter dated February 4, 2022 and Dr. Stein's appeal granted letter dated December 27, 2022 (both reproduced in the Appendix) for a discussion of the data supporting efficacy.

In his appeal granted letter, Dr. Stein indicated that prior to the Complete Response submission, the Applicant should request a meeting with the Division and provide a background package that included a list of all new analyses that were provided as background to, presented at, discussed at, or referenced at the Advisory Committee meeting, as well as a listing of all completed trials not provided in the NDA. On February 13, 2023, the Division met with the Applicant to discuss the data that would be included in the resubmission. With regard to the data supporting efficacy, it was agreed that the Applicant would submit the new analyses that were presented at the Advisory Committee Meeting, as well as the clinical study reports for studies TEN-02-401(Study 401) and TEN-02-402 (Study 402), two studies that were completed following FDA's initial review. As the Applicant's appeal was granted based on the existing efficacy data, the Division reviewed the clinical study reports of Studies 401 and 402 to confirm that the results, as reported by the Applicant, did not raise any new concerns related to the data supporting efficacy. As a whole, the efficacy findings in these studies were consistent with the findings reported in the studies submitted in the initial marketing application. Key findings from these studies are summarized below; for further information on these studies, see the Appendix.

Key findings from Studies 401 and 402

- Study 401 was a long-term, open-label study that assessed the efficacy of tenapanor alone or in combination with sevelamer to achieve a serum phosphorous (s-P) ≤4.5 mg/dL and ≥2.5 mg/dL in adult patients with chronic kidney disease (CKD) on dialysis. The trial also evaluated the ability of tenapanor, when added to sevelamer in patients taking sevelamer at study entry, to reduce the sevelamer pill number from baseline. Patients were enrolled from the open-label extension study phase of Study TEN-02-301 (Study 301) and treated for up to 18 months. Based on the Applicant's analyses, the addition of tenapanor for patients already on sevelamer further reduced s-P by a least squares (LS) mean of 0.60 mg/dL (95% CI: 0.2 – 1.0) at the endpoint visit, a magnitude similar to that seen in study TEN-02-202 (Study 202). The average pill number (consisting of all pills taken to target this level of phosphorous control) was approximately 8 pills at the start of the study and 8 pills at the end of the study.

- Study 402 was a randomized, open-label study that evaluated whether use of tenapanor as core therapy (alone or in combination with phosphate binders) could achieve a target s-P level of ≤5.5 mg/dL for the treatment of hyperphosphatemia. A secondary objective of the study was to evaluate the effect of tenapanor on reducing daily phosphorous-lowering pill burden (defined by the Applicant as the number of pills and total pill weight) when patients were started on or transitioned to tenapanor from their current phosphate binder therapy. Among patients enrolled in the trial, approximately 39% had a s-P ≤5.5 mg/dL at the end of a 10-week open label treatment period. The median total phosphorous-lowering pill number decreased by one to four pills depending on the strategy used when initiating tenapanor. The open-label design, lack of a control arm and lack of a run-in period to assess for phosphate binder adherence at baseline limits interpretation of these findings.

3. Safety Evaluation

See FDA's Review dated July 28, 2021, for a discussion of the safety findings in Study 301, TEN-02-201 (Study 201), and Study 202.

The safety analyses of studies reviewed in the original marketing application identified diarrhea as the most common adverse reaction, resulting in dose reductions and treatment discontinuations in a significant proportion of tenapanor-treated patients. The safety findings raised concerns about tolerability related to diarrhea and potential complications, such as dehydration and clinically significant electrolyte losses. Thus, the safety analyses that follow focus on the findings for diarrhea and temporally related adverse events in Studies 401 (N=172) and 402 (N=333), which were not completed at the time of the original NDA submission.

For Study 401, the safety dataset included all patients who completed Study 301 and chose to enroll in the 14-month open-label extension. All baseline data for Study 401 were taken from the End of Treatment visit for Study 301. Study 401 included two arms, which were based on treatment assignment in Study 301. Patients from the tenapanor arm in Study 301 were given the option for add-on therapy of sevelamer based on their serum phosphorus following a protocol-specified dose titration schedule. Patients from the 301 sevelamer arm were taking sevelamer and given tenapanor as add-on, and the sevelamer dose was then adjusted based on their serum phosphorus following a protocol-specified dose titration schedule. Treatment-emergent adverse events (TEAEs) included those that occurred on treatment, plus one day if tenapanor was withdrawn due to an AE. TEAEs that occurred in Study 301 and continued in Study 401 were excluded by the Applicant, as they were not considered treatment-emergent for Study 401. AE reported terms were coded using MedDRA Version 23.1.

For Study 402, the safety dataset included all patients who received at least one dose of study drug. All patients in the study received tenapanor in both the 10-week open-label treatment period (Part A) and the optional 16-week open-label extension period (Part B). In Cohort 1 (straight switch), patients discontinued phosphate binders and were immediately started on tenapanor 30 mg twice daily (BID) at Visit 2 (Day 1) and were allowed to add phosphate binders based on s-P at Visit 4 (week 2) according to protocol; in Cohort 2, patients taking phosphate binders initiated add-on tenapanor 30 mg BID at Visit 2 (Day1) and the phosphate binder dose was decreased by at least 50% with an option to change the dosing regimen from TID to BID or QD. Cohort 3 enrolled phosphate binder naïve patients based on their serum phosphorus to receive tenapanor 30 mg BID at Visit 2 (Day 1). Treatment-emergent adverse events included

those that occurred on treatment, plus one day if tenapanor was withdrawn due to an AE. Adverse event terms were coded using MedDRA Version 24.0.

Of note, since completion of FDA's initial review, postmarketing safety surveillance identified drug hypersensitivity as a safety signal for the tenapanor product approved for irritable bowel syndrome (Ibsrela). The postmarketing safety signal is being evaluated. For this NDA, safety analyses of the phase 2 and 3 clinical trials did not detect a safety signal; the narrow FMQs related to hypersensitivity reactions were balanced between treatment arms and there were no serious reports related to hypersensitivity (**Table 14** in Appendix).

3.1 Diarrhea

Study 401

As expected, diarrhea was the most common AE in Study 401 and was reported more frequently in those patients started on tenapanor for the first time (301 Sevelamer arm; 46%) than those who were taking tenapanor at the end of Study 301 (301 Tenapanor arm; 12%; **Table 2**). Severe cases of diarrhea and cases resulting in discontinuation were also reported at a higher incidence in the 301 Sevelamer arm (5%, respectively) compared with the 301 Tenapanor arm (1%, respectively). Approximately 25% of the 301 Sevelamer arm required dose reduction because of tenapanor-associated diarrhea.

Diarrhea-Related AEs

Diarrhea was not reported as a serious adverse event (SAE). However, there was one diarrhea-related SAE of colitis reported in the 301 Tenapanor arm. Subject (b) (6) (41-year-old male) was hospitalized for colitis on study day 62, presenting with a 3-day history of abdominal pain and diarrhea (reported as non-serious). Tenapanor was interrupted, the patient was treated and discharged 2 days later with referral for colonoscopy. No previous history of colitis was reported, and relevant concomitant medications included loperamide. The patient resumed tenapanor and completed the study. There were no other reports of colitis in Study 401.

Hyponatremia

Hyponatremia was reported as non-serious in two patients. In one case, ongoing diarrhea may have contributed to the event of hyponatremia though other factors likely also played a role. A 66-year-old female in the 301 Sevelamer arm (Subject (b) (6)) was hospitalized for small bowel obstruction (reported SAE) on study day 161. The patient presented with abdominal pain, diarrhea, generalized weakness, dehydration, hypotension, and hyponatremia after a 2-day history of nausea, vomiting, and 5- months of on-going moderate diarrhea. The hyponatremia was reported as mild, and no sodium levels were reported. CT of the abdomen and pelvis revealed a small bowel obstruction with transition point likely within a right lateral hernia (strangulation could not be excluded) and focal gastric cardia wall thickening possibly secondary to gastritis. Treatment with sevelamer was discontinued and tenapanor was interrupted for 8 months due to the small bowel obstruction and resultant small bowel resection. The patient resumed treatment and completed the study.

Dehydration

Dehydration was reported in 3 patients (2 events reported as nonserious in the 301 Sevelamer arm and 1 reported as nonserious in the 301 Tenapanor arm). One patient (Subject (b) (6)) in the 301 Sevelamer arm experienced moderate dehydration that was temporally related to diarrhea

(see discussion of event under "Hyponatremia"). The other cases were not reported as diarrhea related.

GI Hemorrhage

There were four patients with GI hemorrhage (3 events were reported as serious in the 301 Tenapanor arm and 1 event was reported as non-serious in the 301 Sevelamer arm.) Two of the patients in the 301 Tenapanor arm experienced GI hemorrhage that was temporally related to diarrhea. Subject (b) (6) (58-year-old male) was hospitalized for GI bleeding on study day 50, with a four-day history of melena and on-going intermittent mild diarrhea since study day 1. Small intestinal bleeding was discovered and treated. The patient resumed tenapanor and completed the study. Prior concomitant medications included warfarin which was discontinued due to the GI bleed. Subject (b) (6) (68-year-old female) was hospitalized for GI bleeding on study day 11, following a four-day history of melena associated with mild diarrhea, weakness, fatigue, and cold intolerance (diarrhea reported as a non-serious AE). Bleeding in the second and third portions of the duodenum was discovered and treated. The patient resumed tenapanor and completed the study.

Other Findings

There were no reports of severe diarrhea or diarrhea-related AEs in the tenapanor-treated patients who died.

The most common SAE was hyperkalemia, reported more frequently in the 301 Sevelamer arm (6.6%) than in the 301 Tenapanor arm (0.9%). The cases were attributed to non-compliance with dialysis, diet, or other reasons not related to tenapanor.

Table 2. Diarrhea, Safety Population, Study 401

Preferred Term[2,3]	TEN-02-301 Sevelamer Arm[1] (initially tenapanor-naïve) (+ tenapanor add-on) N=61 n (%)	TEN-02-301 Tenapanor Arm (+/- sevelamer add-on) N=111 n (%)	Risk Difference (95% CI)
Diarrhea[4]	28 (45.9)	13 (11.7)	34.2 (20.3,48.1)
AE Severity[5]			
Mild	18 (29.5)	5 (4.5)	25.0 (12.9, 37.1)
Moderate	14 (23.0)	9 (8.1)	14.8 (3.1, 26.6)
Severe	3 (4.9)	1 (0.9)	4.0 (1.7, 9.7)
Moderate or Severe AE	17 (27.9)	10 (9.0)	18.9 (6.4, 31.3)
SAE	0 (0.0)	1 (0.9)	-0.9 (-0.01, 2.7)
Action Taken with Drug			
Discontinuation	3 (4.9)	1 (0.9)	4.0 (-1.7, 9.7)
Interruption	4 (6.6)	1 (0.9)	5.7 (-0.8, 12.1)
Dose Reduction	15 (24.6)	4 (3.6)	21.0 (9.6, 32.3)
Other Diarrhea-Related AEs			
Hyponatremia	1 (1.6)	1 (0.9)	0.7 (-2.9, 4.4)
Dehydration	2 (3.3)	1 (0.9)	2.4 (-2.4, 7.2)
GI Hemorrhage	1 (1.6)	3 (2.7)	-1.1 (-5.5, 3.3)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio, JMP
[1] All patients were tenapanor naïve at the start of the study and tenapanor was added on.
[2]Treatment-emergent adverse event defined as any event that occurred on treatment (after the first dose of drug up to end of treatment) plus one day. AEs from TEN-02-301 that continued in TEN-02-401 were excluded by the Applicant, as they were not considered treatment-emergent for TEN-02-401.
[3] Coded as MedDRA PT; MedDRA Version 23.1
[4] At least one episode; Includes PTs enteritis, gastroenteritis, colitis, frequent bowel movement
[5] Includes first episode only; Severity definitions were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

Study 402

Diarrhea was the most common AE in Study 402 and was reported in a similar proportion of patients in Cohort 1 (40%) and Cohort 2 (42%). Among the small cohort of patients who were naïve to phosphate binders and were started on tenapanor (Cohort 3), diarrhea was reported in 30% of patients. The incidence of severe cases of diarrhea and cases resulting in discontinuation were similar in Cohorts 1 and 2; Cohort 1: 3%, 5%, respectively and Cohort 2: 5%, 5%, respectively. Approximately 18% of patients in Cohorts 1 and 2 required dose reduction because of tenapanor-associated diarrhea. See **Table 3** for further information.

Diarrhea-related AEs

Diarrhea-related SAEs were rare, with only one SAE of diarrhea reported in Cohort 2. Subject (b) (6) (51-year-old male) was hospitalized for intractable vomiting and diarrhea on study day 55. Tenapanor was interrupted, the patient was treated and returned home the next day. The patient resumed tenapanor and completed the study. There were no SAEs of colitis in Study 402.

Hyponatremia

There were no reports of hyponatremia in Study 402.

Dehydration

Dehydration was reported in one patient in Cohort 1; the event was temporally related to diarrhea. Subject (b) (6) (66-year-old male) experienced diarrhea and dehydration (both reported as non-serious on study day 6). Per the provided information, the patient reported several nightly episodes of diarrhea despite the use of antidiarrheals. The tenapanor dose was reduced, and the AEs were reported to have resolved after 3 weeks.

GI hemorrhage

There were four TEAEs of GI hemorrhage (2 serious and one non-serious in Cohort 1 and one non-serious in Cohort 2.) Two of the events were temporally related to diarrhea. Subject (b) (6) (59-year-old male) in Cohort 1, who reported on-going mild diarrhea since study day 1, was hospitalized for a gastrointestinal bleed on study day 186. During hospitalization, the subject's hemoccult was positive and upper and lower GI endoscopies showed acute gastritis and diverticulosis but no active bleeding. The patient was treated with 2 units of red blood cells and signed out against medical advice. Treatment with tenapanor was resumed and the patient completed the study on tenapanor and phosphate binder. Subject (b) (6) (55-year-old male) in Cohort 2 experienced rectal hemorrhage (reported as non-serious) on study day 31 after reporting moderate watery diarrhea starting on study day 4. The tenapanor dose was initially reduced for the diarrhea and tenapanor was interrupted for the rectal hemorrhage and resumed four days later. The patient completed the study on tenapanor and phosphate binder.

Other Findings

There were no reports of severe diarrhea or diarrhea-related AEs in the tenapanor-treated patients who died.

Other than COVID-19, the most commonly reported SAE was hyperkalemia, which was reported at a similar incidence in Cohorts 1, 2 and 3 (2%, 1%, and 3%, respectively). Most cases were attributed to non-compliance with dialysis, or other reasons not related to tenapanor.

Table 3. Diarrhea, Safety Population, Study 402

	10-Week OL Treatment Period		
Preferred Term[1,2]	**Cohort 1 Tenapanor (switched to tenapanor ± PB add-on) N=151 n (%)**	**Cohort 2 Tenapanor (↓PB dose 50% + tenapanor) N=152 n (%)**	**Cohort 3 Tenapanor (PB naïve + tenapanor) N=30 n (%)**
Diarrhea[3]	61 (40.4)	64 (42.1)	10 (33.3)
AE Severity[4]			
Mild	29 (19.2)	26 (17.1)	4 (13.3)
Moderate	31 (20.5)	34 (22.4)	5 (16.7)
Severe	4 (2.6)	7 (4.6)	1 (3.3)
Moderate or Severe AE	34 (22.5)	40 (26.3)	6 (20.0)
SAE	0	1 (0.7)	0
Action Taken with Drug			
Discontinuation	8 (5.3)	7 (4.6)	0
Interruption	1 (0.7)	0	0
Dose Reduction	28 (18.5)	27 (17.8)	4 (13.3)
Other Diarrhea-Related AEs			
Hyponatremia	0	0	0
Dehydration	1 (0.7)	0	0
GI Hemorrhage	3 (2.0)	1 (0.7)	0

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 10-week treatment period.
[2] Coded as MedDRA PT, Version 24.0
[3] At least one episode; Includes PTs gastroenteritis, gastroenteritis viral, frequent bowel movements
[4] Includes first episode only; Severity definitions were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PB, phosphate binder; PT, preferred term

Incidence and Exposure-Adjusted Event rate for Different Use Settings

In response to a request from the Division, the Applicant provided a summary table containing information on the incidence and exposure-adjusted event rate (per 100 patient-years) for all cases of diarrhea, serious cases of diarrhea, severe cases of diarrhea, and discontinuations due to diarrhea for the following use settings: (1) tenapanor administered as monotherapy, (2) phosphate binder added to background tenapanor therapy, and (3) tenapanor added to background phosphate binder therapy. As shown in **Table 15** (see the Appendix), the exposure-adjusted event rate for diarrhea leading to drug discontinuation was numerically lower when tenapanor was added to background phosphate binder than when used as monotherapy (exposure-adjusted event rate per 100 patient years of 14.9 and 28.5, respectively), suggesting that tenapanor may be better tolerated when used in combination with phosphate binder therapy.

Safety Evaluation Conclusion

Interpretation of the safety data from Studies 401 and 402 is limited since the studies did not include a placebo or active-control arm. Nevertheless, the findings appear to be consistent with findings in the studies reviewed as part of the original marketing application. Diarrhea was the most common adverse reaction. Across the clinical trials, diarrhea was reported in up to 53% of patients. The majority of these events were reported to be mild-to-moderate in severity and

resolved over time, or with dose reduction. Severe diarrhea was reported in 5% of patients and was associated with dehydration and hyponatremia in less than 1% of patients.

III. Appendices

4. Advisory Committee Summary

On November 16, 2022, the Cardiovascular and Renal Drugs Advisory Committee was convened to discuss tenapanor for the control of serum phosphorus levels in adults with CKD on dialysis. The committee was asked to comment on whether the size of the treatment effect on serum phosphorus is clinically meaningful and whether tenapanor's benefits outweigh its risks. The text below is abstracted from the Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting.

- The Committee agreed that the data indicate that tenapanor has a measurable effect on serum phosphorus but also noted that tenapanor appeared to be less effective than approved phosphate binders. Several members noted the pill burden associated with existing treatments and opined there may be a role for tenapanor as monotherapy in a subset of patients, for example, for those who do not appear to tolerate existing treatment and who respond to tenapanor. However, one member noted that he had not seen any data indicating that patients who do not tolerate existing treatments can tolerate tenapanor and also achieve adequate control with tenapanor as monotherapy.
- Several members voiced concern about the limitations of the data supporting the use of serum phosphorus as a surrogate for clinical outcomes, and specifically the absence of data from randomized controlled trials supporting its use as a surrogate. Members also noted that the community did not have strong evidence to know what target phosphorus levels should be, however a trial was underway to address the issue. Given the existing data, members indicated that it was difficult to comment on the clinical meaningfulness of the magnitude of tenapanor's effect. Several members highlighted the importance of patient choice and shared decision making and also noted that dialysis patients were highly monitored.
- The Committee voted 9 (yes) to 4 (no) that tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered as monotherapy. Those members who voted "Yes" recognized an underserved sub-population who are unable to tolerate current treatments and noted that tenapanor will provide additional options for the subgroup of patients who can tolerate tenapanor and achieve adequate response. Members also noted the importance of patient choice and preference in a setting where data are limited as relates to clinical benefit. Those who voted "No" voiced concern about clinical benefit, noting that the surrogate endpoint had not been adequately validated with clinical outcomes, the modest treatment effect on serum phosphorus, and that it didn't seem likely that a sizeable population would achieve adequate control with monotherapy given the size of the treatment effect.

- The Committee voted 10 (yes) to 2 (no), with one abstention, that tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered in combination with phosphate binder treatment. Those members who voted "Yes" generally thought there was likely to be greater use in this setting and that there was more support for use in this setting, particularly in patients with more severe hyperphosphatemia. These members also noted the importance of having tools to individualize care. The members who voted "No", voiced concern about the nature of the data supporting serum phosphorus as a surrogate endpoint, the modest treatment effect, and the need for better data to guide the management of hyperphosphatemia in clinical practice.

5. Summary of Regulatory History

See Summary of Regulatory Action as well as FDA's Multi-disciplinary Collaborative Review dated July 28, 2021.

6. Efficacy Assessment Additional Information and Assessment

Study 401

Study 401 was a long-term, open-label study to evaluate the ability of tenapanor alone or in combination with sevelamer to achieve a s-P within the population reference range (s-P ≤4.5 mg/dL and ≥2.5 mg/dL) in adult patients with CKD on dialysis with hyperphosphatemia (s-P >4.5 mg/dL at baseline). The study also evaluated the addition of tenapanor to adult patients taking sevelamer on the percentage reduction in the sevelamer dose. Patients who completed the one-year study TEN-02-301 were eligible to enroll and baseline data were taken from Study 301 "End of Treatment" visit. Patients enrolled from the 301 Sevelamer arm initiated tenapanor while continuing their previous sevelamer regimen; their sevelamer dose was then titrated based on their s-P following a protocol-specified dose titration schedule. Patients previously on tenapanor in Study 301 continued tenapanor and were given sevelamer in addition based on their s-P following a protocol-specified dose titration schedule. In both arms, tenapanor was also adjusted based on s-P levels (if the patient was not on sevelamer) and/or GI tolerability.

Dose Titration Guidance

Tenapanor Arm

To start, patients on the tenapanor arm (from Study301) had sevelamer added based on their baseline s-P as described below:

- s-P ≥2.5 and ≤4.5 mg/dL: no changes
- s-P >4.5 and ≤5.0 mg/dL: one 800 mg tablet daily (QD) added
- s-P >5.0 and ≤5.5 mg/dL: one 800 mg tablet twice daily (BID) added
- s-P >5.5 mg/dL: one 800 mg tablet three times daily (TID) added

At subsequent visits, the sevelamer dose was increased in a stepwise manner based on subsequent s-P levels as follows:

- s-P >4.5 and ≤5.0 mg/dL: one 800 mg tablet added to the existing regimen

- s-P >5.0 and ≤5.5 mg/dL: two 800 mg tablets added to the existing regimen
- s-P >5.5 mg/dL: three 800 mg tablets each day (800 mg TID) added to the existing regimen.

The maximum dose of sevelamer allowed was based standard of care, the sevelamer package insert, and the Investigator's experience with each patient.

If the s-P was <2.5 mg/dL at any visit, the sevelamer dose was lowered by one 800 mg tablet TID or BID or QD based on the investigator's experience with each patient or as per the package insert. For patients that were not on sevelamer, the tenapanor dose was lowered by one 10 mg tablet BID or 10 mg QD (for those only taking tenapanor 10 mg BID).

Sevelamer Arm
Patients from the Study 301 Sevelamer arm had tenapanor added based on their baseline s-P as described below. Investigators adjusted the tenapanor dose based on the most recent s-P laboratory data and/or GI tolerability in 10 mg increments to a minimum of 10 mg QD or a maximum of 30 mg BID, not more than once daily.

- s-P >2.5 and ≤3.5 mg/dL: three 10 mg tablets of tenapanor QD were added and the sevelamer dose could be lowered by one 800 mg tablet TID.
- s-P >3.5 and ≤4.5 mg/dL: three 10 mg tablets of tenapanor QD were added
- s-P >4.5: three 10 mg tablets of tenapanor BID were added

If the s-P was >4.5 mg/dL at the next visit, the tenapanor dose was increased to a maximum of 30 mg BID. If the tenapanor dose was already maxed, sevelamer was increased by at least one 800 mg tablet at the largest meal and up to one 800 mg tablet TID; investigators had flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert.

If the s-P was <2.5 mg/dL at any visit, sevelamer dose was lowered by one 800 mg tablet TID; Investigators had flexibility to dose sevelamer BID or QD based on their experience with each patient or as per package insert. If the patient was not taking sevelamer, then tenapanor could be lowered by one 10 mg tablet BID (or 10mg QD if the patient was only on tenapanor 10 mg BID).

Entry Criteria
Patients were eligible if they completed Study 301 and excluded if they were scheduled for a living donor kidney transplant, planned to change to different method of dialysis or home dialysis

Baseline Demographic/Clinical Characteristics/Patient Disposition

As depicted in **Table 4**, in the Safety Analysis Set, approximately 64% of patients were male, 50% were Black of African American, 44% were Caucasian, and 30% identified as Hispanic of Latino. The mean age was 57 years, the mean baseline weight was 89 kg, and the mean BMI was 31 kg/m^2. Approximately 92% of patients were on hemodialysis (HD). The mean baseline serum phosphorous level was 5.8 mg/dL and the mean baseline parathyroid hormone (PTH) level was 399 pg/mL.

Table 4. Baseline Demographic and Clinical Characteristics, Safety Population, Study 401

Characteristic	TEN-02-301 Tenapanor Arm N=111	TEN-02-301 Sevelamer Arm N=61	Total N=172
Sex, n (%)			
Male	65 (58.6)	44 (72.1)	109 (634)
Female	46 (41.4)	17 (27.9)	63 (36.6)
Age, years			
Mean (SD)	56.0 (12.1)	58.5 (14.0)	56.7 (12.9)
Age groups (years), n (%)			
<45	17 (15.3)	11 (18.0)	28 (16.3)
≥45 to <65	66 (59.5)	30 (49.2)	96 (55.8)
≥65	28 (25.2)	20 (32.8)	48 (27.9)
Race, n (%)			
White	44 (39.6)	31 (50.8)	75 (43.6)
Black/African American	59 (53.2)	27 (44.3)	86 (50.0)
Others	8 (7.2)	3 (4.9)	11 (6.4)
American Indian or Alaska Native	7 (6.3)	0 (0.0)	7 (4.1)
Asian	1 (0.9)	3 (4.9)	4 (2.3)
Ethnicity, n (%)			
Hispanic	31 (27.9)	20 (32.8)	51 (29.7)
Non-Hispanic	80 (72.1)	41 (67.2)	121 (70.3)
Type of dialysis n (%)			
Hemodialysis	105 (94.6)	53 (86.9)	158 (91.9)
Peritoneal dialysis	6 (5.4)	8 (13.1)	14 (8.1)
Baseline sP level (mg/dL)			
Mean (SD)	5.8 (1.5)	5.8 (1.6)	5.8 (1.5)

Source: CSR TEN-02-401; verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

As shown in **Table 5**, there were higher rates of withdrawal in the sevelamer arm (26 patients, 43%) which added on tenapanor as compared to the tenapanor arm (22 patients, 20%) which added on sevelamer. Approximately half of the withdrawals (14 patients) in the sevelamer arm were for non-specific reasons (i.e., "Withdrawal by patient", "Other"), while three patients withdrew due to an adverse event. Death rates were similar between both arms.

Table 5. Patient Disposition, Study 401, Enrolled Patients

Category	TEN-02-301 Sevelamer Arm (N=61)	TEN-02-301 Tenapanor Arm (N=111)
Enrolled, n (%)	61	111
Completed the study, n (%)	35 (57.4)	89 (80.2)
Withdrew prior to completing the study, n (%)	26 (42.6)	22 (19.8)
Primary reason for early withdrawal from the study, n (%)		
Death	6 (9.8)	8 (7.2)
Withdrawal by patient	8 (13.1)	4 (3.6)
Adverse event	3 (4.9)	3 (2.7)
Physician decision	2 (3.3)	0 (0.0)
Protocol deviation	1 (1.6)	0 (0.0)
Other	6 (9.8)	7 (6.3)
Primary reason for early withdrawal from the study was related to COVID-19	1 (1.6)	1 (0.9)
Safety Analysis Set [1], n (%)	61 (100.0)	111 (100.0)
FAS [2], n (%)	60 (98.4)	111 (100.0)
Reason excluded from FAS, n (%)		
Did not have at least 1 post-treatment sP measurement	1 (1.6)	0 (0.0)
FAS (sP >4.5) [3], n (%)	42 (68.9)	92 (82.9)
FAS (sP ≥5.5) [4], n (%)	34 (55.7)	62 (55.9)

Source: CSR TEN-02-401; verified by FDA
Abbreviations: FAS, full analysis set; N, number of subjects in treatment group; n, number of subjects with given characteristic; sP, serum phosphorus

Results

The following results were reported by the Applicant; all results are descriptive (i.e., did not undergo testing under a prespecified plan to control type 1 error).

The overall s-P reference response rate (defined as achieving an s-P ≤4.5 mg/dL and ≥2.5 mg/dL) was 33.3% (57/171): 35.0% (21/60) for patients from the 301 Sevelamer arm and 32.4% (36/111) for patients from the 301 Tenapanor arm (**Table 6**) at the endpoint visit (defined as the visit with the last observed s-P assessment during the study, up to Month 18). At the end of the study, there was a LS mean reduction of 0.60 (95% CI: 1.0 – 0.2) mg/dL in s-P levels in the 301 Sevelamer arm compared to baseline (**Table 7**).

Table 6. Analysis of s-P Reference Response at the Endpoint Visit (Primary Efficacy Endpoint), Study 401, Full Analysis Set

Analysis Visit Statistic	TEN-02-301 Sevelamer Arm (N=60)	TEN-02-301 Tenapanor Arm (N=111)	Total (N=171)
Endpoint Visit [1]			
sP response rate, n/N′ (%)	21/60 (35.0)	36/111 (32.4)	57/171 (33.3)
Asymptotic 95% Wald CI	22.9, 47.1	23.7, 41.1	26.3, 40.4

Source: CSR TEN-02-401; not verified by FDA
Abbreviations: FAS, full analysis set; N, number of subjects in treatment group; n, number of subjects with given characteristic; sP, serum phosphorus

Table 7. Analysis of Change from Baseline in s-P (mg/dL) at the Endpoint Visit Using ANCOVA, Study 401, Full Analysis Set

Category Statistic	TEN-02-301 Sevelamer Arm (N=60)
Baseline [1]	
n	60
Mean (SD)	5.79 (1.630)
Change from baseline to Endpoint Visit [2]	
LS mean (SE)	-0.60 (0.203)
95% CI LS mean	(-1.00, -0.20)

Source: CSR TEN-02-401; not verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; LS, least squared; SE, standard error; CI, confidence interval

The study also assessed if the addition of tenapanor to the sevelamer arm reduced the sevelamer pill number. As shown in **Table 8**, patients were on a mean of approximately eight sevelamer pills at baseline which decreased to a mean of approximately six sevelamer pills at the end of the study. With tenapanor added, the mean total number of pills taken to lower s-P was unchanged from baseline.

Table 8. Change in Sevelamer Daily Dose at the Endpoint Visit from Baseline, Study 401, Full Analysis Set

	301 Sevelamer Arm (N=60)	
Analysis Visit	**Baseline**	**Endpoint Visit**
Sevelamer Daily Dose, tablets		
Mean (SD)	8.2 (3.8)	6.3 (3.9)
Median	8.5	6.0

Source: Based on information provided in CSR TEN-02-401; not verified by FDA
Abbreviations: FAS, full analysis set; N, number of subjects in treatment group; SD, standard deviation

Conclusion
The magnitude of s-P reduction (0.6 mg/dl) seen in the sevelamer arm that had tenapanor added on is similar to that seen in previous studies, even after accounting for the small reduction in the mean sevelamer pill number. The overall number of pills taken to reduce serum phosphorous (i.e., phosphorous binders plus tenapanor) per day remained the same (when assuming the tenapanor dose could be represented with a single 10, 20, or 30 mg tablet BID).

Study 402

Study 402 was a randomized, open-label, two-part study that evaluated whether patients with CKD on dialysis (both phosphate binder naïve or previously on phosphate binders) could achieve a target s-P level of ≤5.5 mg/dL when using tenapanor as the core therapy (alone or with phosphate binders) for the treatment of hyperphosphatemia. A secondary objective of the study was to evaluate the effect of tenapanor on reducing daily phosphorous-lowering pill burden (defined by the Applicant as the number of pills and total pill weight) when patients were started on or transitioned to tenapanor from their current phosphate binder therapy. The study consisted of a screening visit, a 10-week open-label treatment period (Part A) and an optional 16-week open-label extension period (Part B). The discussion below focuses on the 10-week open-label treatment period and the effect of tenapanor on reducing daily phosphorous-lowering pill number.

Treatment Assignment
Patients who were previously on phosphate binders were randomized to Cohort 1 or Cohort 2 while patients who were phosphate binder naïve were enrolled under Cohort 3 as below:

- Cohort 1 (Straight Switch) – Patients discontinued all phosphate binders and were started on tenapanor 30 mg BID.
- Cohort 2 (50% Reduction) – Patients decreased their phosphate binder dose by at least 50% (rounded down) and were started on tenapanor 30 mg BID. Phosphate binder therapy could be switched from TID to BID or daily dosing if needed.
- Cohort 3 (Binder Naïve) – Phosphate binder naïve patients were initiated on tenapanor 30 mg BID.

Patients were enrolled/randomized on Day 1 and started tenapanor immediately with no washout period.

Dose Titration
Phosphate binders were allowed to be added and/or up-titrated if needed based on s-P levels starting at Week 2 up to the maximum labeled dose TID. Recommended dose adjustments based on s-P levels are detailed below:

- If the patient's s-P assessed at Week 2 was >5.5 mg/dL, one phosphate binder pill QD (added to the largest meal of the day) or BID (taken with tenapanor) was added.
- If the patient was taking a phosphate binder and his/her s-P was <5.0 mg/dL, one or two phosphate binder pills were removed from the patient's daily regimen.

- If the patient was not taking phosphate binders and his/her s-P was ≤3.5 mg/dL, the tenapanor dose was decreased by 10 mg BID (or 10 mg BID if the patient was taking tenapanor 10 mg BID).

Entry Criteria

The study enrolled adult patients with CKD on hemodialysis (HD) for at least three months or chronic maintenance peritoneal dialysis (PD) for a minimum of six months. The standard Kt/V had to be ≥1.2 at the most recent measurement. Patients must have been on a phosphate binder regimen TID taking a minimum of 6 pills per day of Renvela, Auryxia, or PhosLo and/or a minimum of three pills a day for Fosrenol or Velphoro. Patients on phosphate binders had to have an s-P level >5.5 mg/dL and ≤10 mg/dL at the most recent visit while phosphate binder naïve patients had to have an s-P > 4.5 mg/dL and ≤10 mg/dL. Patients were excluded if their serum parathyroid hormone (PTH) exceeded 1200 pg/mL, had a history of inflammatory bowel disease or irritable bowel syndrome with diarrhea, or was scheduled for a living donor kidney transplant or planned to relocate to another dialysis center during the study.

Baseline Demographics, Clinical Characteristics, and Patient Disposition

In the Safety Analysis Set of the 10-week Treatment Period, approximately 68% of patients were male, 44% were Black or African American, 44% were Caucasian, and 28% identified as Hispanic or Latino. The mean age was 53 years, the mean pre-dialysis baseline weight was 94 kg, and the mean baseline BMI was 32 kg/m^2. Approximately 81% of patients were on HD and the mean dialysis duration was 4 years and 6 months. The mean baseline serum phosphorous level was 7.1 mg/dL and the mean baseline PTH level was 402 pg/mL. Of note, key baseline characteristics were generally balanced between Cohorts 1 and 2 while Cohort 3 (a smaller cohort of phosphate binder naïve patients) had a lower baseline mean serum phosphorous of 6.1 mg/dL and a lower mean dialysis duration of 19 months (**Table 9**).

Table 9. Baseline Demographic and Clinical Characteristics, Safety Population, Study 402

Characteristic	Cohort 1 Tenapanor N=151	Cohort 2 Tenapanor N=152	Cohort 3 Tenapanor N=30	Total N=333
Sex, n (%)				
Male	107 (70.9)	102 (67.1)	18 (60.0)	227 (68.2)
Female	44 (29.1)	50 (32.9)	12 (40.0)	106 (31.8)
Age, years				
Mean (SD)	52.3 (11.1)	52.3 (12.2)	55.4 (16.5)	53.0 (12.1)
Age groups (years), n (%)				
<45	37 (24.5)	36 (23.7)	7 (23.3)	80 (24.0)
≥45 to <65	92 (60.9)	87 (57.2)	14 (46.7)	193 (58.0)
≥65	22 (14.6)	29 (19.1)	9 (30.0)	60 (18.0)
Race, n (%)				
White	64 (42.4)	62 (40.8)	20 (66.7)	146 (43.8)
Black/African American	66 (43.7)	71 (46.7)	9 (30.0)	146 (43.8)
Others	20 (13.2)	17 (11.2)	1 (3.3)	38 (11.4)
American Indian or Alaska Native	3 (2.0)	6 (3.9)	1 (3.3)	10 (3.0)
Asian	13 (8.6)	3 (2.0)	0 (0.0)	16 (4.8)
Ethnicity, n (%)				
Hispanic	42 (27.8)	38 (25.0)	13 (43.3)	93 (27.9)
Non-Hispanic	114 (75.0)	109 (72.2)	17 (56.7)	240 (72.1)

Characteristic	Cohort 1 Tenapanor N=151	Cohort 2 Tenapanor N=152	Cohort 3 Tenapanor N=30	Total N=333
Type of dialysis, n (%)				
Hemodialysis	119 (78.8)	124 (81.6)	25 (83.3)	268 (80.5)
Peritoneal dialysis	32 (21.2)	28 (18.4)	5 (16.7)	65 (19.5)
Dialysis Duration, months				
Mean (SD)	58 (52)	57 (50)	19 (21)	54 (50)
Baseline sP level (mg/dL)				
Mean (SD)	7.1 (1.0)	7.2 (1.1)	6.1 (0.8)	7.1 (1.1)

Source: CSR TEN-02-402; verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

As depicted in **Table 10**, approximately 85% of patients finished Part A. Approximately 5% of patients discontinued due to an AE and another 6% withdrew for unspecified reasons.

Table 10. Patient Disposition, Study 402, Randomized Cohort

	Randomized Cohort			
Category	Cohort 1	Cohort 2	Cohort 1/2	Cohort 3
Screened - n				
Screen failure - n (%) [1]				
Patients randomized or enrolled	151	152	303	30
Patients who completed 10-Week Treatment Period (Part A) - n (%) [2]	127 (84.1)	133 (87.5)	260 (85.8)	25 (83.3)
Premature discontinuation from Part A [2]	24 (15.9)	19 (12.5)	43 (14.2)	5 (16.7)
Primary reason of discontinuation - n (%) [2]				
Adverse Event	7 (4.6)	8 (5.3)	15 (5.0)	1 (3.3)
Death	3 (2.0)	1 (0.7)	4 (1.3)	0 (0.0)
Hyperphosphatemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophosphatemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Physician Decision	0 (0.0)	1 (0.7)	1 (0.3)	1 (3.3)
Sponsor Decision	2 (1.3)	0 (0.0)	2 (0.7)	1 (3.3)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	12 (7.9)	5 (3.3)	17 (5.6)	2 (6.7)
Protocol Deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	4 (2.6)	4 (1.3)	0 (0.0)
Premature study discontinuation related to COVID-19 - n (%) [2]	1 (0.7)	2 (1.3)	3 (1.0)	0 (0.0)

Source: CSR TEN-02-402; verified by FDA
Abbreviations: n, number of subjects with given characteristic; sP, serum phosphorus

Results

The following results were reported by the Applicant; all results are descriptive (i.e., did not undergo testing within a plan that controlled control type 1 error).

As shown in **Table 11** patients in Cohort 1 had a mean (SD) decrease in s-P of 0.9 (1.7) mg/dL from baseline, Cohort 2 had a mean (SD) decrease in s-P of 1.0 (1.8) mg/dL from baseline, and Cohort 3 had a mean (SD) decrease in s-P of 0.9 (1.5) at the end of Part A. Among all enrolled patients, approximately 39% of patients had a s-P ≤5.5 mg/dL, with a numerically higher proportion in Cohort 3 (63%) and a lower proportion across Cohorts 1 and 2 (36%) (**Table 12**). Of note, the median baseline s-P was numerically lower in Cohort 3 (6.0 mg/dL) as compared to the other Cohorts (median of 7.0 mg/dL) and 23% of patients in Cohort 3 had a s-P < 5.5 mg/dL at baseline.

Table 11. Summary of Serum Phosphorous (mg/dL) and Change from Baseline in Serum Phosphorous at Part A Endpoint, Study 402, Full Analysis Set

Analysis Visit Statistic	Cohort 1 N=151	Cohort 2 N=152	Cohort 3 N=30	Total N=333
Baseline				
n	151	152	30	333
Mean (SD)	7.1 (1.0)	7.2 (1.1)	6.1 (0.8)	7.1 (1.1)
Median	7.0	7.0	6.0	6.8
Min, Max	5.6, 10.0	5.6, 10.0	4.6, 7.6	4.6, 10.0
Change from Baseline to Part A Endpoint				
n	151	152	30	333
Mean (SD)	-0.9 (1.7)	-1.0 (1.8)	-0.9 (1.5)	-0.9 (1.7)
Median	-1.0	-0.8	-1.1	-0.9
Min, Max	-5.2, 3.6	-7.9, 3.7	-3.4, 3.1	-7.9, 3.7

Source: Based on information provided in CSR TEN-02-402; not verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects analyzed at timepoint; SD, standard deviation

Table 12. Summary of Serum Phosphorous Response at Baseline and Part A Endpoint, Study 402, Full Analysis Set

Response Endpoint Analysis Visit Statistic	Randomized Cohort Cohort 1 (N=151)	Randomized Cohort Cohort 2 (N=152)	Randomized Cohort Cohort 1/2 (N=303)	Cohort 3 (N=30)	Total (N=333)
s-P Response (<=5.5 mg/dL)					
Baseline [1]					
n/N` (%)	0/151 (0.0)	0/152 (0.0)	0/303 (0.0)	7/30 (23.3)	7/333 (2.1)
95% CI	0, 2.41	0, 2.4	0, 1.21	9.93, 42.28	0.85, 4.28
Part A Endpoint					
n/N` (%)	52/151 (34.4)	58/152 (38.2)	110/303 (36.3)	19/30 (63.3)	129/333 (38.7)
95% CI	26.9, 42.6	30.41, 46.38	30.88, 42	43.86, 80.07	33.48, 44.2

Source: CSR TEN-02-402; not verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; s-P, serum phosphorus

Table 13 shows the changes in total phosphorous-lowering medication pill numbers from baseline to the Part A endpoint. At baseline, patients in Cohorts 1 and 2 were on a median of seven phosphorous-lowering pills. At the end of 10 weeks, the total number of phosphorous-lowering pills decreased by a median of 4 pills in Cohort 1 and 1 pill in Cohort 2.

Table 13. Summary of Change from Baseline in Phosphorous-Lowering Medication Pill Number at Part A Endpoint, Full Analysis Set (Cohorts 1 and 2), Study 402

Analysis Visit Statistic	Cohort 1 N=151	Cohort 2 N=152
Baseline		
n	147	148
Mean (SD)	8.8 (3.8)	9.3 (4.0)
Median	7	7
Part A Endpoint Change from Baseline		
n	146	148
Mean (SD)	-3.5 (4.6)	-1.6 (4.2)
Median	-4	-1

Source: Based on information provided in CSR TEN-02-402; not verified by FDA
Abbreviations: N, number of subjects in treatment group; n, number of subjects at given timepoint; SD; standard deviation

Conclusion
The study was designed to assess whether use of tenapanor as core therapy (alone or in combination with phosphate binders) could achieve a target s-P level of ≤5.5 mg/dL for the treatment of hyperphosphatemia. Among patients enrolled in the trial, approximately 39% had a s-P ≤5.5 mg/dL at the end of the 10-week open-label treatment period. The median total phosphorous-lowering pill number decreased by one to four pills depending on the strategy used when initiating tenapanor. The open-label design, lack of a control arm and lack of a run-in period to assess for phosphate binder adherence at baseline limits interpretation of these findings.

7. Safety Assessment Additional Information and Assessment

Table 14. Adverse Events by Hypersensitivity-Related FMQ, Safety Population, Study 301 and Integrated CKD on Dialysis Analysis Set

Study 301 - Initial 26 weeks	**Tenapanor**	**Phosphate Binder**	
N	419	137	
FMQ Narrow n (%)			
Anaphylactic Reaction	0	0	
Angioedema	0	0	
Pruritis	8 (1.9)	3 (2.2)	
Rash	0	1 (0.7)	
Urticaria	0	1 (0.7)	
Integrated CKD on Dialysis Safety Analysis Set- Initial 12 weeks[1]	**Tenapanor**	**Phosphate Binder**	**Placebo**
N	934	256	69
FMQ Narrow n (%)			
Anaphylactic Reaction	0	0	0
Angioedema	0	1 (0.4)	0
Pruritis	18 (1.9)	2 (0.8)	3 (4.3)
Rash[2]	3 (0.3)	0	0
Urticaria	0	0	0

[1]Includes safety data collected up to the first 12 weeks of treatment; all 4 weeks of treatment for D5611C00001, D5613C00001, and TEN-02-202; and all 12 weeks of treatment for TEN-02-201 (excluding safety data collected during the randomized withdrawal period from patients who received placebo) and TEN-02-301 (the first 12 weeks of treatment during the randomized open label treatment period).

[2]PTs also included in the Pruritis FMQ

Table 15. Incidence of and Exposure-Adjusted Event rate (per 100 pt-yrs) for all Cases of Diarrhea, Serious Cases of Diarrhea, Severe Cases of Diarrhea, and Discontinuations Due to Diarrhea under Various Settings

	Placebo, Phosphate Binder, and Tenapanor Administered as Monotherapy [1]						Phosphate Binder Added to Background Tenapanor Therapy		Tenapanor Added to Background Phosphate Binder Therapy
	Placebo (N=69) n (%) E	Phosphate Binder (N=256) n (%) E	Tenapanor 2-30 mg (N=257) n (%) E	Tenapanor 60 mg (N=578) n (%) E	Tenapanor 90-120 mg (N=45) n (%) E	Tenapanor Overall (N=880) n (%) E	TEN-02-301 Tenapanor Arm in TEN-02-401 with Any PB (N=101) n (%) E	TEN-02-402 Cohorts 1 & 3 with Any PB (N=11) n (%) E	Tenapanor + PB Arm in TEN-02-202 & TEN-02-301 Sevelamer Arm in TEN-02-401 & TEN-02-402 Cohort 2 (N=330) n (%) E
Total Patient-Years	5.25	129.38	35.24	305.50	3.26	344.00	124.83	36.70	114.35
Patients with Any									
Diarrhea	8 (11.6) 152.3	22 (8.6) 17.0	90 (35.0) 255.4	313 (54.2) 102.5	27 (60.0) 828.7	430 (48.9) 125.0	9 (8.9) 7.2	44 (37.3) 119.9	141 (42.7) 123.3
Serious Diarrhea	1 (1.4) 19.0	0	1 (0.4) 2.8	2 (0.3) 0.7	0	3 (0.3) 0.9	0	0	1 (0.3) 0.9
Severe Diarrhea	1 (1.4) 19.0	0	11 (4.3) 31.2	36 (6.2) 11.8	4 (8.9) 123.0	51 (5.8) 14.8	1 (1.0) 0.8	4 (3.4) 10.9	14 (4.2) 12.2
Diarrhea Leading to Drug Discontinuation [2]	0	3 (1.2) 2.3	24 (9.3) 68.1	87 (15.1) 28.5	0	111 (12.6) 32.3	1 (1.0) 0.8	4 (3.4) 10.9	17 (5.2) 14.9

N = number of patients in the corresponding treatment group. N = number of patients with the event of interest. % = 100 × n / N. PB = Phosphate Binder.
E = exposure-adjusted event rate = 100 × n / total patient-years, where total patient-years = total treatment exposure in days for the N patients / 365.25. The treatment exposure in days = treatment end date in a study – treatment start date in the same study + 1 for all patients unless specified otherwise.

[1] Including patients from the CKD on Dialysis Safety Analysis Set pooled from study-level safety analysis sets of studies D5611C00001, D5613C00001, TEN-02-201, TEN-02-202 (Placebo + PB Arm only), and TEN-02-301, as well as patients on tenapanor monotherapy throughout the TEN-02-402 study. Tenapanor dose groups were categorized using the pooling strategy for the Integrated Summary of Safety in the original NDA submission. For patients who completed the TEN-02-301 study and continued on tenapanor monotherapy throughout the TEN-02-401 study, the treatment exposure in days = treatment end date in TEN-02-401 – treatment start date in TEN-02-301 + 1. For studies TEN-02-301 and TEN-02-201, diarrhea events that occurred under the placebo treatment during the randomized withdrawal period were categorized based on the initial tenapanor dose received at the beginning of the randomized treatment period.

[2] Including patients who reported any treatment-emergent diarrhea event with "Drug Withdrawn" as the action taken with study drug (for monotherapy groups) or tenapanor (for other groups) recorded on the AE electronic case report form (eCRF). Specifically for the TEN-02-402 study, patients with any treatment-emergent diarrhea event indicated as the primary AE leading to study discontinuation on the End of Study eCRF were also included.

8. Labeling Summary of Considerations and Key Additional Information

The Prescribing Information (PI) was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner. A high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI is provided below.

Under Indications and Usage;

- Phrasing of the benefit has been revised from (b) (4) to 'to reduce serum phosphorus.'
- The indication has been revised, following instructions from Dr. Stein to restrict the indication to 'add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.'

Under Dosage and Administration;

- Language has been added to instruct patients not to take tenapanor prior to a hemodialysis session as patients may experience diarrhea. Patients were given similar instructions in the trials.

Under Drug Interactions;

- A subsection has been added to advise separating administration of tenapanor and kayexalate by 3 hours.

Under Clinical Studies;

- This section has been revised to provide a concise summary of the key information supporting effectiveness that practitioners should consider when making decisions about use.
- The review team did not agree with the Applicant's proposal (b) (4) (b) (4) (b) (4). Instead, the section will discuss the results in the intent-to-treat population. Concern was also raised that including these results would be misleading with respect to efficacy when the drug is used as indicated in labeling.

9. Postmarketing Requirements and Commitments

None.

10. Applicant-FDA Communications

The Complete Response letter, Dispute Appeal Denial, and Dispute Appeal Granted issued by FDA to the Applicant (as mentioned in Sections I and II) are appended in the following pages.

25 Pages Have Been Withheld As Duplicate Copy Of The "Complete Response Letter, Dispute Appeal Denial, and Dispute Appeal Granted" dated July 28, 2021, February 4, 2022, and December 27, 2022, respectively, Which Are Located In The Other Action Letters and Administrative and Correspondence Documents Review Section Of This NDA Approval Package

11. Review Team Acknowledgements

Table 16. Reviewers of Summary Assessment

Role	Name(s)
Clinical Reviewer Efficacy	Austin Hu, MD
Clinical Reviewer Safety	Selena DeConti, PharmD, MPH
Associate Director Labeling	Michael Monteleone, MS, RAC
Deputy Division Director for Safety	Mary Ross Southworth, PharmD
Deputy Division Director (signatory)	Aliza Thompson, MD, MS

Table 17. Additional Reviewers of Resubmission

Office or Discipline	Name(s)
OPQ	Joseph Leginus, Suong Tran, Dan Berger, Nancy Waites, Feiyan Jin, Rebecca Moody, Grafton Adams, Theodore Carver
Pharmacology/Toxicology	Victor Long, Xuan Chi
Clinical Pharmacology	Li Wang, Harisudhan Thanukrishnan
OPDP	Charuni Shah, Sapna Shah
OSE/DMEPA	Tayler Nalesnik, Nicole Iverson, Christina Topper, Hina Mehta, Danielle Harris
Regulatory Project Manager	Sabry Soukehal

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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AUSTIN H HU
10/17/2023 02:04:27 PM

MICHAEL V MONTELEONE
10/17/2023 02:28:27 PM

MARY R SOUTHWORTH
10/17/2023 02:29:45 PM

Clinical Pharmacology Review

NDA or BLA Number	213931
Link to EDR	\\CDSESUB1\evsprod\NDA213931\0036
Submission Date	05/17/2023
Submission Type	NDA resubmission
Brand Name	XPHOZAH
Generic Name	Tenapanor
Dosage Form and Strength	Tablets/10 mg, 20 mg, 30 mg
Route of Administration	Oral
Dosage and Administration	The recommended dosage is 30 mg orally twice daily before the morning and evening meals. Decrease the dose as needed to manage gastrointestinal tolerability.
Proposed Indication	Control of serum phosphorus in adult patients with chronic kidney disease on dialysis who have had an inadequate response or intolerance to a phosphate binder therapy
Applicant	Ardelyx, Inc.
OCP Review Team	Li Wang, Ph. D. (primary reviewer) and Harisudhan Thanukrishnan, Ph. D. (secondary reviewer)

1. EXECUTIVE SUMMARY

Tenapanor (XPHOZAH) is a sodium hydrogen exchanger 3 (NHE3) inhibitor indicated for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis who have had an inadequate response or intolerance to a phosphate binder therapy. The original NDA package was submitted on June 20, 2020. A Complete Response Letter was issued on July 28, 2021, as the magnitude of tenapanor's effect in reducing serum phosphorous in chronic kidney disease patients on dialysis was small and of unclear clinical significance. The Applicant resubmitted the NDA on May 17, 2023, after proposing to limit use of tenapanor to patients with an inadequate response or intolerance to existing phosphate binder therapy.

There is a paragraph shown below in Section 12.3 Pharmacokinetics of the Prescribing Information (PI). The Clinical Pharmacology Review Team was asked to review the relevant dataset and clinical study reports (CSR) to confirm the accuracy of the text prior to inclusion in the PI.

In vitro study:

In Study RDX5791-PK-011.00, the Applicant conducted an *in vitro* binding study between tenapanor and phosphate binders including sevelamer carbonate, calcium carbonate, calcium acetate, and a potassium binder (sodium polystyrene sulfonate). The amount of binder used in the in vitro studies was based upon the predicted amount of binder present in the lumen of the gut after a typical dose of each binder. Sevelamer-1.6 mg/mL based on a 2.4 g dose; Calcium acetate-1 mg/mL based on a 2 x 667 mg dose (two tablets); Calcium carbonate- 2.4 mg/mL based on a 2 x 600 mg dose (two tablets) and Sodium polystyrene sulfonate-10 mg/mL based on a 15 g dose. The binders were incubated with tenapanor (1-100 µM) in simulated intestinal

binding buffer for 2 h at 37°C. The results showed that tenapanor interacts in vitro with sevelamer carbonate (% bound ~74-86%) and sodium polystyrene sulfonate (% bound ~ 26-31%), but neither calcium carbonate nor calcium acetate.

Reviewer comment:

The statement that tenapanor showed binding in vitro with sevelamer carbonate but did not show potential to bind with calcium carbonate and calcium acetate is valid.

Clinical Studies:

In Study D5611C00006, subjects received either tenapanor at 14 mg twice daily for 4 days (Treatment 1) or tenapanor at 14 mg BID in addition to sevelamer carbonate at 800 mg three times daily with meals for 4 days (Treatment 2). As tenapanor is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3 and leads to reduced sodium absorption and decreased phosphate absorption, any interference on pharmacodynamic effect of tenapanor will influence the Sodium excretion in feces.

Reviewer comment:

Since there was no significant difference in the amount of excreted fecal sodium between Treatments 1 and 2, the statement that tenapanor at 14 mg BID in a clinical study showed an absence of a pharmacodynamic drug interaction with sevelamer carbonate is valid and needs to be reflected in the proposed label.

The Applicant also utilized the results from Study TEN-02-202 to demonstrate drug-drug interaction (DDI) potency. However, the Applicant used serum phosphorus level as the indicator for DDI assessment.

Reviewer comment:

As serum phosphorus is also the efficacy endpoint for tenapanor and co-administered phosphate binder, the potential additive effect on serum phosphorus from tenapanor and co-administered phosphate binder is likely to diminish the DDI potency. (b) (4) (b) (4).

Recommendations

1. The Office of Clinical Pharmacology (OCP/DCEP) has reviewed the relevant study reports and suggest the following text in Section 12.3 of the PI.

(b) (4)

2. The reference to Sodium polystyrene sulfonate (SPS) should be separated out as it is not a phosphate binder. In addition, it is recommended that Applicant provide advice to mitigate interaction with SPS under Section 7 of PI and include supporting rationale.

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LI WANG
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND ASSESSMENT AND EVALUATION

Application Number*:	NDA 213931
Supporting Document Number/s:	0049 (NDA 211801)
CDER Receipt Date:	11/06/2020
Sponsor:	Ardelyx Inc.
Product:	Xphozah (Tenapanor Hydrochloride)
Pharmacologic Class:	Sodium/hydrogen exchanger 3 (NH3) inhibitor (Class not established)
Indication:	Control of serum phosphorous levels in adult patients with CKD on dialysis who had an inadequate response or intolerance to phosphate binder therapy
Therapeutic area:	Nephrology
Clinical Review Division:	Division of Cardiology and Nephrology (DCN)
Pharm/Tox Division	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
Reviewer:	Victor Long, Pharm.D., Ph.D.
Supervisor/Team Leader:	Xuan Chi, M.D., Ph.D.
Project Manager:	Sabry Soukehal
Purpose of Review:	Study Report Review Labeling Review
Alternative Assays:	N/A
Reviewer Completion Date:	September 21, 2023

Template Version: Sep 11, 2020

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1 Background

1.1 Regulatory History

Tenapanor was approved in September 2019 under NDA 211801 for irritable bowel disease with constipation. The approval came with a black box warning for risk of severe dehydration in pediatric patients and a contraindication for use in patients less than 6 years old based on results of two dose range finding studies in juvenile rats. In the NDA approval letter (September 12, 2019), as part of a postmarketing requirement, the Agency required the applicant to submit a 60-day GLP juvenile animal toxicology study in rats with dose initiation on PND21 to potentially support initiation of trials in pediatric subjects 6 and older. For the indication under NDA 211801, the Division of Gastroenterology (DG) waived the pediatric study requirement for ages 0 to < 6 years of age because the necessary pediatric studies are impossible or highly impracticable in this age group. The same applicant (Ardelyx, Inc.) has submitted NDA 213931 for tenapanor with the new indication of controlling serum phosphorous levels in patients with CKD who either 1) had an inadequate response to phosphate binders or 2) could not tolerate phosphate binders. In the labeling of NDA 213931, under section 8.4, the applicant added results from the 60-day juvenile study and its corresponding DRF study. The 60-day study was previously reviewed by Dr. Yolanda Branch under NDA 211801 (see previous reviews referenced below) but the DRF was never fully reviewed.

1.2 Relevant INDs, NDAs, BLAs or DMFs

NDA 211801
IND 108732

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 108732	Dinesh Gautam	March 12, 2020	Reference made to DRF study as supporting the doses for proposed juvenile rat toxicology study (Study #20301378)
NDA 211801	Yolanda Branch	February 15, 2023	Review of Study# 20301378

3 Studies Submitted

3.1 Studies Reviewed

2050TOX: A 21-Dat Oral Dose Range-Finding Toxicity Study in Post-Weaning Juvenile Rats

9 Reproductive and Developmental Toxicology

9.4 Juvenile Animal Studies+

9.4.1 Study Title: A 21-Day Oral Dose Range Finding Toxicity Study in Post-Weaning Juvenile Rats

Study no.:	2050TOX
Study report location:	EDR
Conducting laboratory and location:	Aredlyx, Inc., Fremont, CA
Duration:	21 days
GLP compliance:	No
Drug, lot #, and % purity:	Tenapanor Hydrochloride ((b) (4) Lot 17LV045D.HQ00006.4F; Ardelyx Lot 16)

Scientific Justification for Study:
In an 8-week repeat dose toxicity study (00775063) in juvenile rats treated with once-daily oral gavage doses of tenapanor at 0.03, 0.1, or 0.3 mg/kg/day from postnatal day (PND) 5 through 61, test article related mortality/moribundity was observed at 0.3 mg/kg/day. The no-observed-adverse-effect-level (NOAEL) was 0.1 mg/kg/day. Exposure at the NOAEL could not be determined because all plasma concentrations were below the limit of quantitation. The Agency noted that that although dehydration-related deaths were observed with tenapanor starting postnatal day 5 (approximately equivalent to a 1-month-old infant), there was no toxicology available in older animals to support contraindication of tenapanor for patients (b) (4) years old. The applicant was permitted to use data from DRF studies in the labeling to justify a black box warning for dehydration and contraindication in patients less than 6 years old while completing the Agency's postmarketing requirement of a 60-day GLP JAS study starting on PND21. The DRF study prior to the 60-day study is reviewed below.

JAS Specific Toxicity:
Dehydration/Diarrhea resulting in mortality

Methods

Doses:	0, 0.1, 1, and 5 mg/kg/day
Frequency of dosing:	Once Daily
Number/Sex/Group:	6 animals/sex/group
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.1 % (w/v) Tween 80 in DI H20
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Sprague Dawley
Age at start of experiment:	PND21
Period of development studied:	PND21 to PND42 (human equivalent of 2 to 12 years old)

Dosing Solution Analysis: Concentration data obtained from three batches (2 different aliquots)
- QC accuracy within ±15% of nominal concentrations
- CV% < 2%
- Correlation coefficient of calibration curves = 1
- No peaks detected in vehicle

Observations and Results

Mortality

There were multiple unscheduled deaths in the study at PND 21 and PND22, following the first 5 mg/kg/day dose. These included 4 males and 2 females that were either found dead or euthanized in extremis. As a result, the 5 mg/kg/day group was terminated early. An additional two males dosed at 1 mg/kg/day were found dead at PND22, but the remaining animals survived until scheduled necropsy. Abnormal fur was observed in all tenapanor-treated groups until necropsy and watery feces was observed at doses ≥1 mg/kg/day starting at approximately 4 hours post dose and lasting until Day 18 (PND 38). At 1 mg/kg/day, body weights were reduced in both sexes by approximately 20% beginning on Day 2 and gradually recovered to 86 and 94% of male and female controls, respectively, by the end of the study. This weight loss correlated to large decreases in food consumption beginning on Day 2 (up to 64% in males and 40% of females) with similar increases in water consumption (up to 69% in makes and 41% in females starting on Day 2. ALT was increased approximately 1.5x in both sexes at Day 22 (PND42). Macroscopic findings at necropsy included slightly enlarged cecum in 5/6 females dosed at 0.1 mg/kg/day and enlarged, fluid-filled cecum in all surviving animals of both sexes dosed at 1 mg/kg/day. Histopathology was not conducted in this DRF study. Trough plasma concentrations of tenapanor and AZ13792925 (major metabolite) were below the quantitative limit for all dose groups on Day 22.

11 Nonclinical Discussion

The trough plasma concentration indicated low systemic exposure of tenapanor in this study which is consistent with the previous JAS. The MTD of tenapanor was 1 mg/kg/day for females and used as the basis as the high dose for Study No. 20301378. A NOAEL for that study could not be established due to decreased tibial growth at the lowest dose (0.1 mg/kg/day) in both sexes. The previous review used 0.1 mg/kg/day as a “tolerated dose” to calculate safety margins of 0.03X to 0.3X. Along with the DRF study reviewed above and second pivotal JAS (reviewed by Dr. Branch), the proposed labeling contains result summaries for two previous DRF toxicity studies and the pivotal JAS as approved in NDA 211801. The totality of data demonstrates that doses greater than 1 and 5 mg/kg/day produce mortality in female and male rats, respectively, at ages less than PND 25 (approximately 4-5 years old). Meanwhile, lower doses (0.1 mg/kg/day) could be administered from PND21 to PND80 (adolescence) without adverse toxicity in either sex. In conclusion, the juvenile nonclinical data supports the applicant’s stated contraindication in the labeling for patients < 6 years old.

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MULTI-DISCIPLINARY COLLABORATIVE REVIEW

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	213931
Priority or standard	Standard
Submit date(s)	6/26/2020
Received date(s)	6/29/2020
PDUFA goal date	7/29/2021
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	See DARRTS signature page
Established name	Tenapanor hydrochloride
(Proposed) trade name	XPHOZAH
Pharmacologic class	Sodium/hydrogen exchanger 3 (NHE3) inhibitor
Code name	AZD1722/RDX5791
Applicant	Ardelyx, Inc.
Dose form/formulation(s)	Tablets/10 mg, 20 mg, 30 mg
Dosing regimen	Twice daily
Applicant proposed indication(s)/population(s)	Control of serum phosphorus in adult patients with chronic kidney disease on dialysis
Proposed SNOMED indication	20165001 | Hyperphosphatemia (disorder)|
Regulatory action	Complete response
Approved indication(s)/population(s) (if applicable)	Not applicable
Approved SNOMED indication	Not applicable

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BCRP	breast cancer resistance protein
BE	bioequivalence
BID	twice daily
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CYP450	cytochrome P450
DDI	drug-drug interaction
DMC	data monitoring committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCTD	electronic common technical document
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EOP2	end-of-phase 2
EPC	established pharmacologic class
ER	exposure-response
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
IC_{50}	half maximal inhibitory concentration

ICH	International Conference on Harmonization
IND	investigational new drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intention-to-treat
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MOA	mechanism of action
MRHD	maximum recommended human dose
NDA	new drug application
NHE3	sodium/hydrogen exchanger 3
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OATP	organic anion transporting polypeptides
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFDD	patient-focused drug development
P-gp	p-glycoprotein 1
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	periodic safety update report
PT	preferred term
QD	once daily
QTc	Corrected QT interval
REMS	risk evaluation and mitigation strategy
RT	randomized treatment
RW	randomized withdrawal
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration

TK	toxicokinetic
TQT	thorough QT
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

Background
Tenapanor is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. On June 29, 2020, FDA received an NDA for tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis.

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 serum phosphorus in adult patients with CKD on dialysis: calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. Common adverse reactions include gastrointestinal side effects; risks of calcium-based binders also include hypercalcemia and accumulation of calcium leading to vascular calcification. Pill burden is also high, and compliance is an issue. As such, there is unmet need for safe and well-tolerated treatments that achieve effective control of serum phosphorus with a low pill burden.

Of note, all currently approved agents for controlling serum phosphorus in patients with CKD on dialysis lower serum phosphorus by binding phosphate in the gastrointestinal tract, thereby decreasing absorption. Tenapanor exerts its effect on serum phosphorus via a different mechanism. By inhibiting NHE3, tenapanor reduces sodium absorption and decreases phosphate absorption by reducing phosphate permeability through the paracellular pathway.

Overview of development program and serum phosphorus as a surrogate endpoint
To support efficacy as monotherapy for reducing serum phosphorus in patients with CKD on dialysis, the Applicant submitted the results of two randomized, multi-center trials (TEN-02-201 and TEN-02-301). Both trials were conducted in the United States and included an initial treatment period followed by a randomized, double-blind, placebo-controlled withdrawal period. The Applicant 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.

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

Efficacy

As previously noted, both monotherapy trials included an initial treatment period followed by 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 subjects who achieved a reduction of ≥ 1.2 mg/dL in serum phosphorus level in the treatment period prior to randomized withdrawal.

As discussed in the body of this review, of the 423 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 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.[1] Subgroup analyses and analyses of the distribution of the responses did not suggest a "responder" population with a substantially larger response to treatment.[2] In exploratory analyses of the 26-week active

[1] In Study TEN-02-201, the LS mean treatment difference between the pooled tenapanor group and the placebo group was -0.82 mg/dL in the Efficacy Analysis Set (i.e., similar to the results obtained using the ITT population), suggesting that the approach used to enrich the Efficacy Analysis Set for patients with a greater response to treatment was not effective in doing so.

[2] Given the small size of the treatment effect, a question that was raised during internal discussions was whether it might to 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). FDA conducted exploratory analyses of the data from the 26-week treatment period of Study TEN-02-301 to assess whether the available data indicate that such a strategy might be viable. Results of this analysis suggest

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.

In sum, the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis; however, 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.

Safety

Tenapanor is minimally absorbed and diarrhea was the most common adverse reaction in clinical trials of tenapanor in patients with CKD on dialysis. During the 26-week open-label, randomized, active control treatment period of trial TEN-02-301, diarrhea was reported in 226 patients (54%) treated with tenapanor as compared to 11 patients (8%) treated with the active control. Approximately 36% of tenapanor treated patients had at least one adverse event of moderate diarrhea and 6% had at least one adverse event of severe diarrhea. In comparison, in the control arm, 4% of patients reported adverse events of moderate diarrhea and no patient reported a severe adverse event of diarrhea. In the majority of cases, diarrhea occurred soon after initiation of treatment, and resolved with continued treatment; however, 16% of tenapanor-treated diarrhea cases required discontinuation and 32% required dose reduction, compared with one discontinuation and no dose reductions in the comparator group. In contrast to the monotherapy trials, 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 (3% tenapanor vs 2% placebo); however, dose reductions were reported in 27% of patients in the tenapanor arm (as compared to only 4% of patients in the placebo arm). Such data suggest that tolerability may be improved when tenapanor is used in combination with phosphate binder treatment, though dose adjustments for tolerability may still be needed.

In sum, diarrhea, occasionally severe, was the most common adverse reaction in tenapanor-treated patients with CKD on dialysis. From a safety perspective, such a risk can be adequately addressed via labeling.

that if such a strategy were tested, it would likely need to be based on multiple assessments, as opposed to a single measurement at an early time point.

Conclusion and Recommendation

Tenapanor is effective in reducing serum phosphorus levels in patients with CKD on dialysis; however, the magnitude of the treatment effect is small and of unclear clinical significance. As such, the application should not be approved. 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 discontinue treatment in patients who do not appear to have an adequate 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. Alternatively, the Applicant could conduct an adequate and well-controlled trial demonstrating that tenapanor reduces the risk of a clinical outcome thought to be caused by hyperphosphatemia.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hyperphosphatemia is common in patients with chronic kidney disease (CKD) on dialysis and is defined as elevated levels of phosphorus in the blood (normal range of serum phosphorus: 2.5 mg/dL to 4.5 mg/dL). • Epidemiologic data and biological plausibility suggest that treating hyperphosphatemia could improve patient outcomes; 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 levels in the dialysis population.[3] 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".[4]	Hyperphosphatemia is common in patients with CKD on dialysis. Epidemiologic data and biologic plausibility suggest that treating hyperphosphatemia should improve patient outcomes; however, to date, there are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus predicts its effect on clinical outcomes such as cardiovascular events or mortality.

[3] An open-label, multicenter, cluster-randomized trial in ~4400 patients with kidney failure undergoing maintenance hemodialysis is currently evaluating whether the current standard approach of targeting serum phosphate levels of <5.5 mg/dL as compared with less stringent control of serum phosphate (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).

[4] Source: 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. 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;" (3) implication for policy: "The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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 US for the control of serum phosphorus in adult patients with CKD on dialysis: calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. Common adverse reactions include gastrointestinal side effects; risks of calcium-based binders also include hypercalcemia and accumulation of calcium leading to vascular calcification. Pill burden is also high and compliance is an issue.	There is unmet need for safe and well-tolerated treatments that achieve effective control of serum phosphorus with a low pill burden.

Benefit	To support efficacy as monotherapy for reducing serum phosphorus in patients with CKD on dialysis, the Applicant submitted the results of two randomized, multi-center trials (TEN-02-201 and TEN-02-301). Both trials were conducted in the United States and included an initial treatment period followed by a randomized, double-blind, placebo-controlled withdrawal period. The Applicant 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. • In both studies TEN-02-201 and TEN-02-301, the primary efficacy analysis during the randomized withdrawal 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 limited the primary efficacy analysis to subjects who achieved a reduction of ≥ 1.2 mg/dL in serum phosphorus level in the randomized treatment period prior to randomized withdrawal. Approximately half of the patients who entered the randomized withdrawal period were excluded from the efficacy analysis set used for the primary analysis in Studies TEN-02-301 and TEN-02-201. • In Study TEN-02-201, the treatment difference between pooled tenapanor and placebo was 0.82 mg/dL in the 4-week randomized withdrawal period based on efficacy analysis set and 0.72 mg/dL based the ITT analysis set. In Study TEN-02-301, the LS mean change in serum phosphorous from baseline to the end of the 12-week randomized withdrawal period was 1.37 mg/dL based on the Efficacy Analysis Set and 0.66 mg/dL based on the ITT analysis set. In Study TEN-02-202, which evaluated use in use in combination with existing phosphate binder treatment, the size of the treatment effect was similar─ 0.65 mg/dL. • 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 analysis are challenging to interpret.[5]	The submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis; however, the magnitude of the treatment effect appears to be small (both in absolute terms and relative to approved drugs) and the clinical relevance is unclear.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Tenapanor is minimally absorbed. Diarrhea was the most common adverse reaction in clinical trials of tenapanor in patients with CKD on dialysis. • During the 26-week randomized, active control treatment period of trial TEN-02-301, diarrhea was reported in 54% of tenapanor-treated patients as compared to 8% treated with the active control. Patients in the tenapanor group reported at least one adverse event of mild (16%), moderate (36%), or severe (6%) diarrhea, versus 6%, 4%, and 0, respectively, for patients in the active control group. Specific baseline patient characteristics that may predict severity were not identified. Approximately 16% of tenapanor-treated patients required discontinuation because of diarrhea, which was rarely reported in the active control group. Significant rates of diarrhea adverse reactions were also reported in other trials of tenapanor in patients with CKD on dialysis. • In contrast to the monotherapy trials, 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 (3% tenapanor vs 2% placebo).	Diarrhea, occasionally severe (6% of patients), was the most common adverse reaction in tenapanor-treated patients with CKD on dialysis. From a safety perspective, this risk can be adequately addressed through labeling. In clinical trials in which tenapanor was administered as monotherapy, a significant proportion of tenanor-treated patients discontinued treatment because of adverse events of diarrhea. Available data suggest that tolerability may be improved when tenapanor is used in combination with phosphate binder treatment.

Conclusions Regarding Benefit-Risk

Tenapanor's treatment effect on serum phosphorus appears to be modest and smaller than that seen in the development programs that supported the approval of marketed products for the proposed indication. As such, a key issue is the clinical significance of the drug's effect on serum phosphorus in patients with CKD on dialysis. From a safety perspective, diarrhea, sometimes severe, was the most common adverse reaction in tenapanor-treated patients with CKD on dialysis. Although this risk can be adequately addressed and mitigated through labeling, in clinical trials of tenapanor administered as monotherapy, a significant proportion of tenapanor-treated patients discontinued treatment because of adverse events of diarrhea, suggesting that poor tolerability may limit chronic use as monotherapy.

[5] The pivotal monotherapy trials had an initial treatment period, followed by a placebo-controlled randomized withdrawal period. As such, one cannot compare tenapanor's effect in patients with more marked elevations at baseline or the distribution of responses in the initial treatment period of these trials to a placebo control.

II. Interdisciplinary Assessment

3. Introduction

In June 2020, Ardelyx submitted a new drug application (NDA dated June 26, 2020, received June 29, 2020) for Tenapanor hydrochloride 10 mg, 20 mg, and 30 mg Tablets for the control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis. Tenapanor hydrochloride (proposed proprietary name: (b) (4)) is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. Inhibition of NHE3 by tenapanor results in reduced sodium absorption, leading to decreased phosphate absorption through the paracellular pathway. Tenapanor (50 mg tablets; proprietary name IBSRELA®) was approved for the treatment of irritable bowel syndrome with constipation in 2019 but, to date, has not been marketed for this indication.

Disease Background

Hyperphosphatemia is a common complication in patients with CKD on dialysis and is defined as elevated levels of phosphorus in the blood (normal range: 2.5-4.5 mg/dL). 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 morbidity and mortality in patients with chronic kidney disease.

In most patients with chronic kidney failure in the US, thrice weekly intermittent hemodialysis and dietary restriction of foods and drinks high in phosphorus are not sufficient to control hyperphosphatemia and gastrointestinal phosphate binders are widely used to control serum phosphorus levels in adult patients with chronic kidney disease on dialysis. To date, four major classes of agents have been approved for this use in the US- calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. Common adverse reactions include gastrointestinal side effects and risks of calcium-based binders include hypercalcemia and accumulation of calcium leading to vascular calcification. Pill burden is also high.

Regulatory History

There were a number of interactions with the Applicant over the course of the development program; see the appendix for further discussion of the regulatory history. A key review issue for this application is the size of the treatment effect on serum phosphorus. While the Agency 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, a treatment effect of any size is not considered sufficient to support approval. At the preNDA meeting, the Agency advised the Applicant to address the clinical relevance of the size of the treatment effect observed in their development program in their NDA submission. The Agency also noted that data indicating that the product has a marked treatment effect in patients with more marked elevations at baseline could be compelling.

Key review issues:
Key review issues included the magnitude of the treatment effect on serum phosphorus, both in absolute terms and relative to other treatments, and the product's safety and tolerability profile.

3.1. Approach to the Review

Tenapanor's clinical development program included biopharmaceutical studies, human pharmacokinetic and pharmacodynamic studies, drug-drug interaction studies, and efficacy and safety studies. The table below provides an overview of key studies. The efficacy evaluation, which was conducted by Shen Xiao[6] and Fanhui Kong, focused on studies TEN-02-201, -202, and -301. Selena DeConti reviewed the data supporting safety.

[6] Dr. Xiao left the Agency during the review period and the remaining clinical portions of the review were completed by Dr. Thompson.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Tenapanor

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
TEN-02-201	02675998	Multicenter, Randomized, Double-Blind, Parallel Group Study with Placebo-Controlled, Randomized Withdrawal Period	3, 10 mg/bid /oral	Change of phosphorus from the end of treatment to the end of the RW period	8-week treatment; 4-week withdrawal	219	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	41 sites in US
TEN-02-202	03824587	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Tenapanor as Adjunctive Therapy to Phosphate Binder Therapy in End-Stage Renal Disease (ESRD) Patients with Hyperphosphatemia	30 mg/bid/oral can be modified to 10 mg bid	Change of phosphorus from baseline to the end of treatment	4-week	236	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	46 sites in US
TEN-02-301	03427125	A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis	10 mg bid/oral titration up to 30 mg bid	Change of phosphorus from the end of treatment to the end of the RW period	26-week treatment; 12-week withdrawal	564	End-Stage Renal Disease Patients on Hemodialysis/Peritoneal dialysis (ESRD-HD/PD)	104 sites in US
D5613C00001	02081534	A Phase 2b, Randomized, Double blind, Placebo-controlled, Parallel-group, Multicenter Dose finding Study to evaluate the Efficacy, Safety and Tolerability of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	1 mg, 3 mg, 10 mg, and 30 mg bid and 3 mg and 30 mg qd/oral	Change of phosphorus from baseline to the end of treatment	4-week	150	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	17 sites in US; 14 sites in Poland, 7 sites in Slovakia, 9 sites in UK

		Studies to Support Safety						
D5610C00001	01847092	An Exploratory Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Design Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of AZD1722 in CKD Patients with Type 2 Diabetes Mellitus and Albuminuria	15 mg bid up or down titration to 5mg or 60 mg/oral	Change of phosphorus from baseline to the end of treatment	12-week	154	type 2 diabetes mellitus with albuminuria	43 sites in US; 5 sites in Germany
D5611C00001	01764854	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel Design Study to Evaluate the Pharmacodynamics, Safety, and Tolerability of AZD1722 in End-Stage Renal Disease Patients on Hemodialysis	Up to 45 mg bid/oral	Change of phosphorus from baseline to the end of treatment	4-week	90	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	14 sites in US
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
TEN-02-401 (ongoing)	03988920	A Long-Term, Open Label Study to Evaluate the Ability of Tenapanor Alone or in Combination with Sevelamer to Treat to Goal Serum Phosphorus in Patients with End-Stage Renal Disease on Dialysis (NORMALIZE)	Dose titrated up to 30mg bid/oral	Change of phosphorus from baseline to the end of treatment	18-month	150-200	End-Stage Renal Disease Patients on Hemodialysis/Peritoneal dialysis (ESRD-HD/PD)	40-60 sites in US
7791-001	03864458	A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose-finding Study of KHK7791 in Hyperphosphatemia Patients on Hemodialysis	5, 10, 30 mg bid, and 30 mg down titration group/oral	Change of phosphorus from baseline to the end of treatment	6-week	200	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	Conducted in Japan (number of sites are not clear)
7791-002	03864445	A Phase 2, Randomized, Double-blind, Placebo-controlled, Phosphate Binder-combination Study of KHK7791 in Hyperphosphatemia Patients on Hemodialysis	30 mg bid titrated lower to 5 mg bid/oral	Change of phosphorus from baseline to the end of treatment	6-week	40	End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD)	Conducted in Japan (number of sites are not clear)
7791-003	03831607	A Phase 2, Open-label, single-arm Phosphate Binder Switch Study of	30 mg bid titrated lower to 5 mg bid/oral	Achievement of at least 30% decrease in the mean of the	26-week	60	End-Stage Renal Disease Patients on Hemodialysis	Conducted in Japan (number of sites are not clear)

		KHK7791 in Hyperphosphatemia Patients on Hemodialysis		total number of phosphate binders and KHK7791 tablets prescribed daily			(ESRD-HD)	

4. Patient Experience Data

No patient experience data were submitted.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Mechanism of action	Tenapanor is a locally acting inhibitor of Sodium/hydrogen exchanger 3 (NHE3). By inhibiting NHE3 on the apical surface of the enterocytes, it blocks paracellular absorption of phosphate in the gut mucosa, leading to lower serum phosphorus levels in patients with chronic kidney disease on dialysis.
Active moieties	Tenapanor is the active moiety. The major metabolite (M1) is inactive against NHE3.
QT prolongation	No clinically relevant effects on the QTc interval were observed at 3 times the mean maximum exposure of M1 at the recommended dosage.
General Information	
Bioanalysis	Tenapanor, M1, digoxin, enalapril, enalaprilat, and warfarin (R- and S-Warfarin) concentrations in human plasma were measured by validated LC-MS/MS methods.
Healthy subjects versus patients	The plasma C_{max} at steady state of M1 in dialysis patients is nearly equal to that observed in healthy subjects. Tenapanor is minimally absorbed and most of the plasma samples are below the limit of quantification.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	The geometric mean concentrations of M1 at steady state on Day 85 and Day 183 following 30 mg BID tenapanor administration are 10.4 ng/mL and 8.97 ng/mL, respectively (TEN-02-301).
Range of effective dose(s) or exposure	10-30 mg BID
Maximally Tolerated Dose or Exposure	In multiple studies (TEN-02-301, TEN-02-202, and TEN-02-201), the highest administered dose was 30 mg BID.
Dose proportionality	Not applicable
Accumulation	Not applicable
Time to achieve steady-state	4-5 days for M1
Bridge between to-be marketed and clinical trial formulations	Bioequivalence between the tenapanor formulation used in Study TEN-02-201 and the to-be-marketed tenapanor formulation, which was also used in Studies TEN-02-202 and TEN-02-301, was established in Study TEN-02-106 based on urine sodium excretion as the pharmacodynamic endpoint at doses of 10 and 30 mg.
Absorption	
Bioavailability	Not evaluated
T_{max}	The median (range) T_{max} of M1 is 4 (4-24) hours.
Food effect (Fed/fasted) Geometric least square mean and 90% CI	Food effect on the PK of M1 was not evaluated. Administration of tenapanor 5 to 10 minutes before a meal increased the 24-hour stool sodium excretion compared to administration of tenapanor in the fed or fasting condition.
Distribution	
Volume of distribution	Not estimated
Plasma protein binding	Not estimated
Drug as substrate of transporters	Tenapanor is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3.

Characteristic	Drug Information
Elimination	
Mass balance results	Following administration of a single 15 mg radiolabeled ^{14}C-tenapanor dose to healthy subjects, approximately 70% of the radioactivity was excreted in feces within 120 hours post-dose and 79% within 240 hours post-dose, mostly as the parent drug accounting for 65% of dose within 144 hours post-dose. Approximately 9% of the administered dose was recovered in urine, primarily as metabolites. M1 is excreted in urine unchanged accounting for 1.5% of dose within 144 hours post-dose.
Half-life	The geometric mean (CV%) of $t_{1/2}$ of M1 is 25.4 h (9.52).
Metabolic pathway(s)	Tenapanor is metabolized primarily by CYP3A.
Primary excretion pathways (% dose)	See mass balance results above. The majority of the radioactivity is accounted for in feces as unabsorbed drug.
Intrinsic Factors and Specific Populations	
Body weight	Not evaluated
Age	Not evaluated
Renal impairment	The mean plasma concentrations of M1 in subjects with eGFR <15 mL/min was 2.55 ng/ml (n=5), in comparison to 7.99 ng/mL (n=12) in healthy subjects following similar doses. The absolute exposures of M1 are generally very low in both healthy subjects and in subjects with renal impairment. Efficacy and safety data for the proposed indication is from patients with CKD on dialysis.
Hepatic impairment	Geometric mean C_{max} of tenapanor, C_{max} of M1 and AUC of M1 were approximately 53%, 27.0% and 35.4% higher following administration of tenapanor to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function, respectively. These changes are not likely to be clinically relevant due to the overall low exposures of tenapanor and M1 in both groups and the lack of pharmacological activity of M1.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Tenapanor inhibits CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A. M1 inhibits CYP2D6 and CYP3A. However, the likelihood of a clinically relevant DDI effect of tenapanor is low as tenapanor is minimally absorbed and the exposure of M1 is low.
Inhibition/induction of transporter systems	Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1, while enalapril is a substrate of OATP2B1. Following administration of a single 20 mg enalapril dose with tenapanor (30 mg BID) at steady state, the mean AUC and C_{max} of enalapril was decreased by 64% and 69%, respectively, in healthy subjects. The mean AUC and C_{max} of enalaprilat was decreased by 52% and 68%, respectively, in healthy subjects.
Immunogenicity (for Biologics)	
Bioanalysis	Not applicable
Incidence	Not applicable
Clinical impact	Not applicable

5.1. Nonclinical Assessment of Potential Effectiveness

Tenapanor is an inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3). By inhibiting NHE3 on the apical surface of enterocytes, tenapanor reduces the uptake of sodium from the lumen of the gastrointestinal tract, resulting in increased luminal fluid. Mechanistic studies suggest that passive paracellular absorption is reduced and that there is modulation of the intercellular tight junctions manifested experimentally as increased transepithelial electrical resistance (TEER), resulting in reduced paracellular phosphate permeability.

Affinity for the primary target was evaluated in vitro by testing AZD1722 in opossum kidney cells transiently expressing rat or human NHE3. The IC_{50}s were determined to be 7.9 nM for rat NHE3 and 0.5nM for human NHE3.

In vivo, urinary excretion of sodium and phosphate was evaluated in healthy Sprague-Dawley rats treated with AZD1722, lanthanum carbonate (Fosrenol, a phosphate binder that reduces absorption of phosphate), or a combination of AZD1722 and lanthanum carbonate mixed in a standard laboratory diet for 7 consecutive days. Blood samples were collected during this time period for analysis of plasma phosphorus and creatinine. Urine and feces were collected during a 17-hour period in metabolic cages on day 7. The dose of AZD1722 was constant at 0.013 g/kg chow, corresponding to a daily intake of 0.72 mg/kg on day 4 and 0.81 mg/kg on day 7. Urine sodium and phosphorous excretion were decreased in animals treated with AZD1722. Fosrenol decreased the excretion of phosphorous only. The sponsor interpreted the decreased urinary sodium and phosphorous to indicate a decrease in gastrointestinal absorption. Other, similar, pharmacology studies were conducted and also showed decreased urinary sodium and phosphorous excretion and variability of plasma phosphorous. The multiplicity of mechanisms for maintaining physiologic phosphorous levels in healthy animals complicates interpretation of the plasma phosphorus data.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

The recommended dose of tenapanor is 30 mg orally twice daily (BID) before the morning and evening meals. The dose can be adjusted to 20 mg or 10 mg orally twice daily as needed to maintain serum phosphorus at target levels or manage gastrointestinal tolerability. The dosing regimen proposed for labeling was based on the results of the phase 2 study (D5613C00001) and further evaluated in phase 3 trials (TEN-02-201, TEN-02-202, and TEN-02-301).

The dose selected for the pivotal trials is supported by the results of a phase 2 study (D5613C00001). In Study D5613C00001, there were seven parallel treatment groups, with six on tenapanor treatment and one on placebo. The tenapanor doses were 1 mg, 3 mg, 10 mg, and

30 mg BID and 3 mg and 30 mg QD. All subjects received 4 weeks of treatment, which was considered sufficient to stabilize effects on serum phosphorus after reduced gut uptake. Serum phosphorus were measured weekly. Safety assessments included physical examination, blood pressure and pulse rate, clinical laboratory evaluations, ECGs, and adverse event monitoring. In this study, serum phosphorus levels decreased in a dose-dependent manner.[7] In addition, a BID dosing regimen showed greater serum phosphorus reduction than QD dosing (Figure 1).

Based on the results of this study, doses of 3-30 mg BID were selected for further evaluation in the pivotal trials.

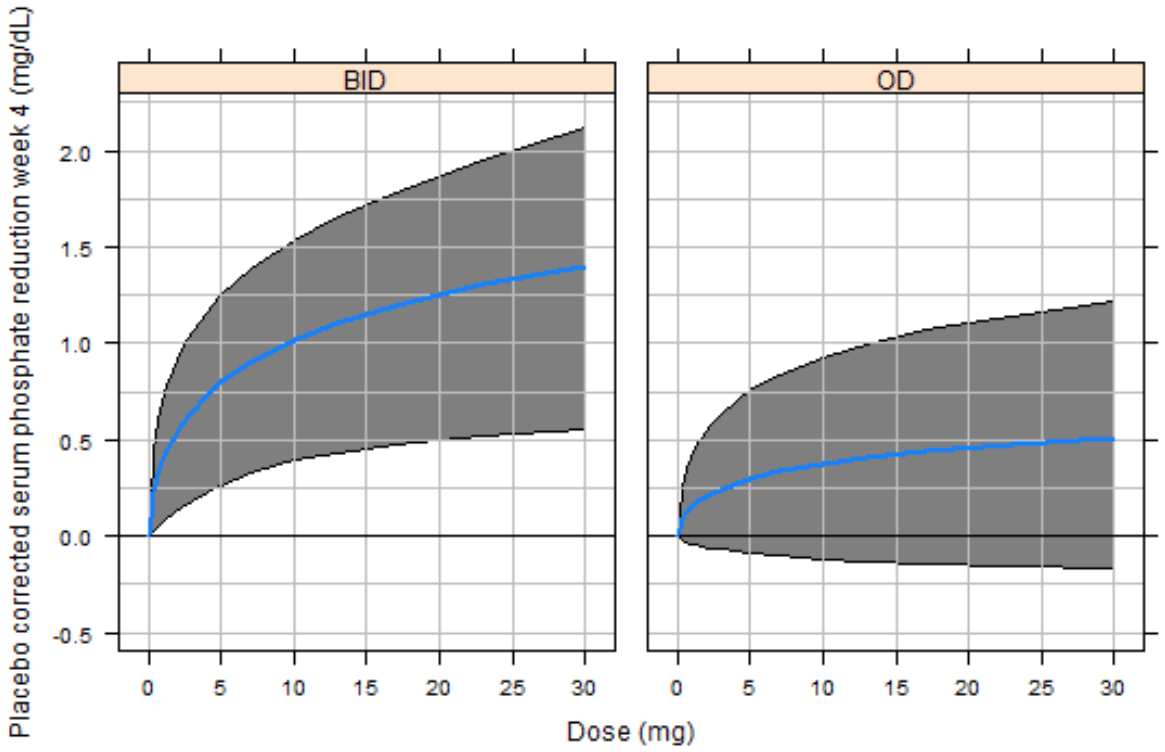


Figure 1. Model Predicted Placebo-Corrected Dose Response for BID and QD Dosing for Tenapanor Doses 0 to 30 mg, D5613C00001

Source: Clinical Study Report: D5613C00001 (Figure 3; page 35)
Note: Grey area represents the 95% CI.
Abbreviations: BID, twice daily; CI, confidence interval; OD, once daily; QD, once daily

[7] Of note, in both studies D5613C00001 and TEN-02-201, a dose-response relationship was also observed for gastrointestinal AEs (i.e., a greater proportion of patients experienced such AEs at higher as compared to lower doses).

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

The ability of tenapanor to lower serum phosphorus when administered as monotherapy in adult patients with CKD on dialysis was evaluated in two randomized, multi-center trials (TEN-02-201 and TEN-02-301). Both trials were conducted in the United States and included an initial treatment period followed by a randomized, double-blind, placebo-controlled withdrawal period. An overview of the design of TEN-02-301 and TEN-02-201 is provided below. A third trial (TEN-02-202) evaluated the efficacy of tenapanor as adjunctive therapy to phosphate binder therapy and is described in the appendix.

TEN-02-201

Title of Study: An 8-Week, Multicenter, Randomized, Double Blind, Parallel Group Study with a 4-week, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Efficacy, Safety and Tolerability of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis.

Trial Dates and Amendments: The trial was initiated on January 20, 2016 and was completed on January 6, 2017. The original study protocol (Edition 1, dated November 24, 2015) was amended twice following study initiation─ on March 3, and May 27, 2016. The May 2016 amendment included changes to the primary endpoint and sample size based on feedback given by the FDA at an EOP2 meeting in May 2016.

Study Design:

Overview of Trial Design: TEN-02-201 was a phase 2b, 8-week, multicenter, randomized, double-blind, parallel group study with a 4-week, placebo-controlled, randomized withdrawal period to evaluate the efficacy, safety and tolerability of tenapanor to treat hyperphosphatemia in end-stage renal disease patients on hemodialysis. The primary objective of the study was to compare the effect of tenapanor versus placebo by comparing the difference in the change in serum phosphorus from the end of the 8-week treatment period to the end of the 4-week randomized withdrawal period or the endpoint visit for this period, between the pooled tenapanor treatments and placebo.

The trial included a screening visit, a wash out period of up to 3 weeks, during which existing phosphate lowering medication was withheld, an 8-week treatment period, in which all groups received tenapanor, blinded to treatment (3 mg bid, 10 mg bid, or titration regimen), and a 4-week placebo-controlled, randomized withdrawal period, during which subjects were re-randomized 1:1 to either remain on their current tenapanor treatment or placebo.

A schematic of the trial design is shown below.

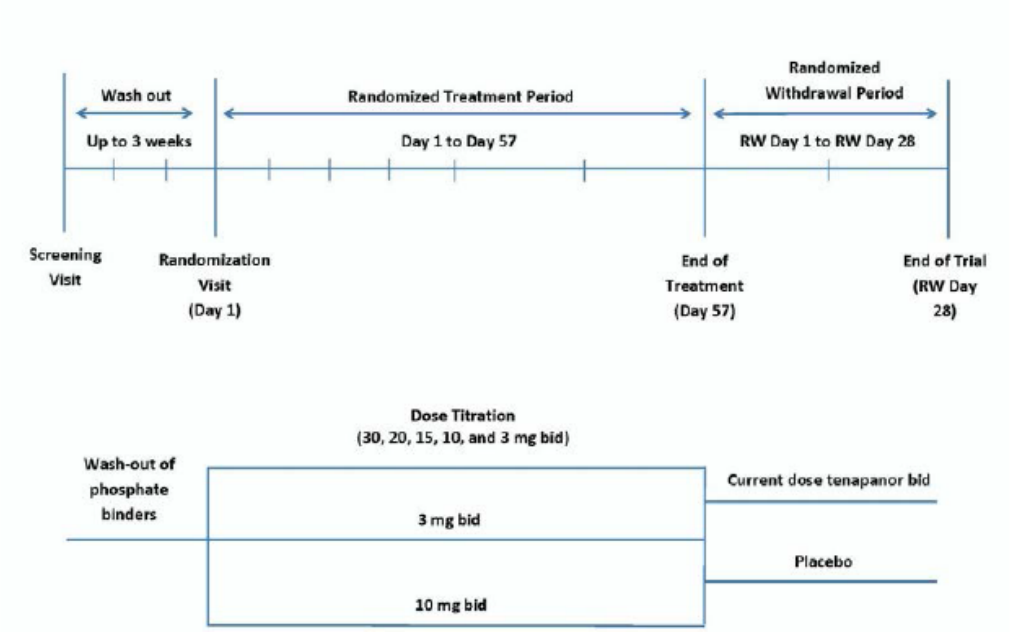


Figure 2. Schematic of design of TEN-02-201

Source: Protocol TEN-02-201 dated 27 May 2016

Efficacy Endpoints: The primary efficacy variable was specified as the change in serum phosphorus from the end of the 8-week treatment period to the end of the 4-week randomized withdrawal period or the endpoint visit for this period. The primary efficacy analysis was to be based on the difference between the pooled tenapanor treatments and placebo treatment group.

Sample Size Considerations: For the primary efficacy analysis, a sample size of 39 subjects in the pooled tenapanor treatments and placebo group provided 90% power to detect a difference in the change in serum phosphorus from the end of the 8-week treatment period to the end of the 4-week randomized withdrawal period or the endpoint visit for this period, between the pooled tenapanor treatments and placebo with at least a 75% effect size. The 75% effect size was based on a minimum of a 1.5 mg/dL difference between placebo and the combined tenapanor treatments and a common standard deviation of no greater than 2.0 mg/dL. A sample size of 200 allowed for a 20% dropout rate, (meaning 20% of subjects would not complete the 8-week treatment period) and assumed at least 50% of subjects would be considered responders in the 8-week treatment period, i.e., a subject who achieved at least a 1.2 mg/dL reduction from baseline to the end of the 8-week treatment period.

TEN-02-301

Study Title: A 26-Week, Phase 3, Open Label Study with a 12-Week, Placebo-Controlled, Randomized Withdrawal Period Followed by an Open Label Long Term Safety Extension to

Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis and Peritoneal Dialysis

Trial Dates and Amendments: The trial was initiated on January 31, 2018 and was completed on February 17, 2020. The original study protocol (Edition 1, dated July 24, 2017) was amended twice prior to trial initiation. Following trial initiation, the protocol was amended once (Edition 4, dated May 30, 2018). The changes that were made in this amendment do not impact the ability to interpret the results of the trial.

Study Design:

Overview of Trial Design: Study TEN-02-301 was a 26-week, open-label active-controlled study with a 12-week, placebo-controlled, randomized withdrawal period followed by an open-label long-term safety extension to evaluate the safety and efficacy of tenapanor to treat hyperphosphatemia in end-stage renal disease patients on hemodialysis and peritoneal dialysis. The stated primary objectives of the trial were

- to evaluate the safety and tolerability of tenapanor for the treatment of hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD) and on Peritoneal Dialysis (ESRD-PD) when administered twice daily for up to 52 weeks.
- to compare the phosphorus lowering effect between tenapanor and placebo based on the change in serum phosphorus (s-P) from the end of the 26-week treatment period to the end of the up to 12- week randomized withdrawal period or the endpoint visit for this period in the responder population (efficacy analysis set).

In brief, the trial included a screening visit, a phosphate binder-free wash-out period of up to four weeks, a randomized, active-controlled open-label treatment period, a placebo-controlled, randomized withdrawal period, followed by an open label safety extension period for a total treatment period of up to 52 weeks. Key features of the open-label treatment period and randomized withdrawal period were as follows:

- Open-label treatment period: Patients who met all the inclusion/exclusion criteria were to be randomized 3:1 to either receive tenapanor or sevelamer carbonate. Those randomized into the active control group were to take sevelamer carbonate based on standard of care using the package insert for guidance for a 52-week study period. Patients randomized into the tenapanor group were to take tenapanor for 26-weeks; after this period, patients in the tenapanor arm were to enter at a placebo-controlled randomized withdrawal period (see below).

  During the open-label treatment period, patients 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 titrated or up titrated (to a maximum dose of 30 mg bid) in a stepwise fashion based on serum-phosphorus 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). Patients were to take tenapanor prior to breakfast and dinner. On dialysis days, patients on HD 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.

- Randomized Withdrawal Period: At the end of the 26-week treatment period, patients 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 up to an additional 12 weeks.

A schematic of the trial design is shown below.

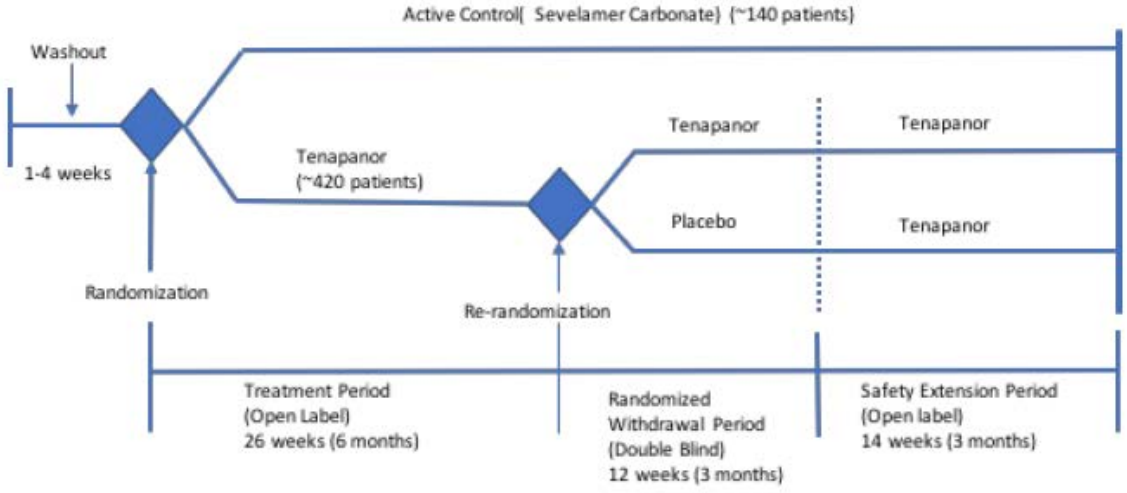


Figure 3. Schematic of Design of TEN-02-301
Source: Protocol TEN-02-301

Efficacy Endpoints: The primary efficacy endpoint was the change in serum phosphorus level from the end of the 26-week treatment period to the endpoint visit of the randomized withdrawal period, where the endpoint visit of the randomized withdrawal period was defined as the last visit with a serum phosphorus assessment during the randomized withdrawal period. The primary efficacy analysis was to be based on the difference between the tenapanor and placebo groups in the efficacy analysis set, which included all patients who met the study entry inclusion/exclusion criteria, received at least 1 dose of tenapanor during the 26-week treatment period, completed the 26-week treatment period, and achieved a reduction of >1.2 mg/dL in serum phosphorus level from baseline to the end of the 26-week treatment period. Key secondary endpoints (i.e., prespecified endpoint that were to be tested within plans to control overall type 1 error) also assessed effects on serum phosphorus.

Sample Size Considerations: For the primary efficacy analysis, a sample size of 146 patients (73 patients/group) in the 12-week randomized withdrawal period was expected to provide more than 95% power to detect a difference between tenapanor and placebo treatment in the change in serum phosphorus from the end of the 26-week treatment period to the end of the 12-week randomized withdrawal period or the endpoint visit for this period, between the tenapanor treatment and placebo. This calculation was based on a two-sample t-test with a two-sided significance level of α=0.05, an assumed treatment difference of 1.0 mg/dL and a common standard deviation of 1.6 mg/dL. A trial sample size of 560 allowed for a 30% dropout rate (meaning 30% of patients would not complete the 26-week treatment period) and assumed at

least 50% of patients in the tenapanor group would be considered responders in the 26-week treatment period, i.e., patients who achieved at least a 1.2 mg/dL reduction from baseline to the end of the 26-week treatment period.

6.2.2. Eligibility Criteria

Key entry criteria for studies TEN-02-301 and TEN-02-201 included the following:

Inclusion Criteria:

- Age ≥ 18 years (TEN-02-201 also specified an upper age limit of 80 years);
- Chronic maintenance hemodialysis 3× per week for at least 3 months (TEN-02-301 also permitted enrollment of patients on chronic maintenance peritoneal dialysis for a minimum of 6 months);
- Stable vascular access as assessed by Investigator;
- Kt/V≥ 1.2 (TEN-02-301) or 1.3 (TEN-02-201) at most recent measurement prior to screening;
- Prescribed and taking at least 3 doses of phosphate binder per day. The prescribed dose should have been unchanged during the last 3 weeks prior to screening;
- Serum phosphorus levels between 4.0 and 8.0 mg/dL (TEN-02-301) or between 4.0 and 7.0 mg/dL (TEN-02-201) at screening analyzed at the central laboratory used in the study.
    - Additional Criteria for Study TEN-02-301 for randomization into the open-label treatment phase: Patients must have serum phosphorus levels of at least 6.0 mg/dL but not more than 10.0 mg/dL and have had an increase of at least 1.5 mg/dL versus pre wash-out value after 1, 2 or 3 weeks wash-out of phosphate binders.
    - Additional Criteria for Study TEN-02-201 for enrollment: For randomization in the study, after 1 week wash-out of phosphate binders, subjects must have serum phosphorus level of at least 9.0 mg/dL but not more than 10.0 mg/dL and have had an increase of at least 1.5 mg/dL versus pre wash-out value. For randomization in the study, after 2 or 3 weeks wash-out of phosphate binders, subjects must have serum phosphorus level of at least 6.0 mg/dL but not more than 10.0 mg/dL and have had an increase of at least 1.5 mg/dL versus pre wash-out value.
    - If on any vitamin D or calcimimetics regimen, the dose should have been unchanged for the last 4 weeks prior to screening (Inclusion criterion for TEN-02-201 but not TEN-02-301)

Exclusion Criteria:

- Severe hyperphosphatemia defined as serum phosphorus greater than 10.0 mg/dL on phosphate-binders at any time point during clinical routine monitoring for the 3 preceding months before screening visit;
- Serum/plasma parathyroid hormone >1200 pg/mL based on the most recent value from the subject's medical records;
- Clinical signs of hypovolemia at randomization as judged by the Investigator;

- History of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome;
- Scheduled for living donor kidney transplant, change to peritoneal dialysis, home HD or plan to relocate to another center during the study period;
- Diarrhea or loose stools during the week before randomization defined as Bristol stool form scale (BSFS) ≥ 6 and frequency ≥ 3 for 2 or more days;
- Life expectancy < 12 months (TEN-02-301) or < 6 months (TEN-02-201);
- Persistent metabolic acidosis defined as serum carbon dioxide <18 mmol/L from two consecutive measurements during screening and washout periods (Criterion for TEN-02-201 but not TEN-02-301)

6.2.3. Statistical Analysis Plan

Study TEN-02-201

The original Statistical Analysis Plan (SAP, Version 1.0) was dated November 24, 2015. The study was initially designed as a phase 2 clinical trial; however, after the trial was started, the FDA recommended that the sponsor schedule an End-of-Phase 2 meeting to discuss the design of the development program. Based on FDA feedback at the EOP2 meeting on May 9, 2016, the primary endpoint was changed to the difference between pooled tenapanor groups and placebo in the responder population (subjects with ≥ 1.2 mg/dL decrease from baseline to the end of the 8-week treatment period) from the end of the 8-week Randomized Treatment period (RT period) to the end of the 4-week randomized withdrawal period (RW period) and the sample size was increased to 200. The TEN-02-201 Protocol (Edition 3, 27 May 2016) and SAP (Version 3, 27 May 2016) were amended based on the change in the primary endpoint.[8]

Datasets:

The SAP defined the following key datasets:

- ITT Analysis Set: All subjects who met the study entry inclusion/exclusion criteria, received at least one dose of study drug, and had at least one serum phosphate assessment during the 8-week RT period.
- Efficacy Analysis Set: All subjects who met the study entry inclusion and exclusion criteria, completed the 8-week RT period and achieved at least a 1.2 mg/dL reduction in S-Phosphate from baseline to the end of the 8-week RT period.

Efficacy Analyses

[8] In an advice letter to the Sponsor dated June 26, 20216, FDA indicated that without knowing exactly what information was available from the trial at the time the primary endpoint was changed and absent review of the final trial data, it was difficult to provide a definitive answer as to whether Study TEN-02-201 would be considered an adequate and well-controlled trial. FDA further stated that assuming statistically significant effects on serum phosphorus levels were observed in both the randomized withdrawal phases of Study TEN-02-301 and Study TEN-02-201 and consistent and supportive findings in the 8-week treatment phases of Study TEN-02-201 and Study TEN-02-301, the development program, as a whole, would provide the data needed to support effectiveness.

The primary efficacy analysis was to be based on the Efficacy Analysis Set. The primary efficacy variable was the change in S-Phosphate 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. The primary efficacy analysis was to compare the primary efficacy endpoint between the pooled tenapanor treatments and placebo in the efficacy analysis set using an analysis of covariance (ANCOVA) model with terms for pooled investigator site, treatment group, and baseline as covariates. Baseline for this analysis was defined as the S-phosphorus value at the end of the 8-week RT period. The change from baseline to each assessment time was the dependent variable. The least-squares (LS) means were presented for the change from baseline values for each treatment group with the p-value (for the 8-week RT period) and 95% CI. For the 4-week RW period, the difference of LS means for the change from baseline values between the pooled tenapanor treatments and placebo group was also presented with the p-value and 95% CI. Sensitivity analyses were carried out for the primary efficacy analysis to assess the influence of early termination during the 4-week RW period.

All other efficacy analyses were to be descriptive (i.e., there was no prespecified plan to control for multiplicity). All efficacy analyses for the 8-week RT period were carried out using the ITT Analysis Set. All efficacy analyses for the 4-week RW period were carried out using the Efficacy Analysis Set and ITT Analysis Set. The ITT Analysis Set for the 4-week RW period included all ITT subjects who completed the 8-week RT period.

Study TEN-02-301
The Statistical Analysis Plan v1.1 was dated January 4, 2018 and revised to v2.0 on December 21, 2018 based on the study Protocol Edition No. 4 on May 30, 2018. The primary analysis of the primary endpoint remained unchanged in the SAP v2.0.

Datasets:

The SAP defined the following key datasets:

- ITT Analysis Set for the 26-week Randomized Treatment period (RT period): All subjects who met the study entry inclusion/exclusion criteria, received at least 1 dose of tenapanor, and had at least 1 post-treatment s-P measurement during this study 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 Randomized Withdrawal Period (RW period): All subjects who met the study entry inclusion/exclusion criteria, received at least 1 dose of study drug (tenapanor or placebo), and had at least 1 post-treatment s-P measurement during this study period.
- Efficacy Analysis Set: All ITT subjects who meet 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, and achieved a reduction of ≥1.2 mg/dL in s-P level from baseline to the end of the 26-week RT period.
- Safety Analysis Set for the 26-week RT Period: All subjects who received at least 1 dose of study drug (tenapanor or sevelamer carbonate) during this study period. The Safety analysis set for the 12-week RW period included all subjects who received at least 1 dose of study drug (tenapanor, placebo, or sevelamer carbonate) during this study period.

Efficacy Analyses

The primary efficacy analysis and applicable key secondary efficacy analyses were to be based on the Efficacy Analysis Set. The primary efficacy endpoint was the change in s-P level from Visit 13 to the endpoint visit of the RW period; for subjects who completed the RW period, the endpoint visit was to be Visit 19. For subjects who prematurely discontinued the RW period, the endpoint visit was to be the last visit with an s-P assessment during the RW period. The primary analysis was to compare the mean changes of the primary endpoint using an ANCOVA model based on the last observation carried forward (LOCF), with treatment and pooled site as fixed effects, and baseline s-P level of the RW period as a continuous covariate. The LS mean difference in Week 12 s-P change between the tenapanor and placebo groups, along with the 95% confidence interval (CI) and p-value were also to be reported. Given a total of 80 to 105 sites in the United States, investigational sites were to be pooled based on geographic region and number of subjects randomized at the site to balance sample sizes among pooled sites. Pooled sites were to be added to all applicable statistical models as a factor.

All other efficacy analyses were to be descriptive (i.e., there was no prespecified plan to control for multiplicity). Continuous secondary endpoints were to be analyzed using a mixed-effects model for repeated measures (MMRM). For secondary endpoints analyzed using analysis of covariance (ANCOVA) as well as all binary response endpoints, missing data were to be imputed using the last- observation-carried-forward (LOCF) approach.

Data Sources

The Applicant's electronic data sources were stored under \\CDSESUB1\evsprod\NDA213931\0001. Data sources include all material reviewed, i.e., study reports, analysis data sets in ADAM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets were stored under \\CDSESUB1\evsprod\NDA213931\0001\m5\datasets\. The analysis programs were also stored in the same directory.

Data Quality

Per the clinical study report (CSR), the Sponsor held meetings to prepare investigators for the study and standardize performance. They hired clinical research associates to conduct periodic on-site visits to ensure adherence to the protocol, review case report forms and site source documents for accuracy and completeness of information, examine site records for documentation of study drug receipt and administration, observe the progress of the study, and review investigator files for required documents.

Sites accessed the electronic data capture (EDC) system and entered data into the eCRF. The sponsor used specifically designed computer-generated checks, as well as manual edit checks, to identify data entry errors or other data inconsistencies.

According to the CSR, data were reviewed on an ongoing basis. When flagged, necessary requests for clarifications or corrections were sent to the investigator via data queries within the EDC system. After all queries were resolved and appropriate corrections or clarifications were made to the database, the database was considered clean.

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

Patient Disposition

Study TEN-02-201

In Study TEN-02-201, 673 subjects were screened, of which 219 (33%) subjects were randomized into the 8-week RT period. In total, 164 (75%) of these subjects completed the 8-week RT period and entered the 4-week RW period. The proportion was similar across the study groups: 57 (77%) subjects in the 3 mg BID tenapanor group, 54 (74%) subjects in the 10 mg BID tenapanor group, and 53 (74%) subjects in the tenapanor dose-titration group. Of the subjects entering the 4-week RW period, 12 (7%) subjects withdrew from the study prior to completing the 4-week RW period. The most common reasons for early withdrawal from the 4-week RW period were hyperphosphatemia (5 subjects) and adverse event (3 subjects).

As previously noted, the primary efficacy analysis was to be based on the Efficacy Analysis Set, defined as subjects who met the study entry inclusion and exclusion criteria, completed the 8-week treatment period and achieved at least a 1.2 mg/dL reduction in S-Phosphate from baseline to the end of the 8-week treatment period. Of the 164 subjects who entered the 4-week RT period, 80 (49%) patients met the criteria for inclusion in the efficacy subset. Of these 80 patients, 76 (95%) completed the 4-week RW period, 34 in the placebo group and 42 in the three tenapanor groups.

See the table below for additional information on subject disposition.

Table 6. Subject Disposition, 4-Week Randomized Withdrawal Period, TEN-02-201

Category	Placebo	Tenapanor 3 mg BID	Tenapanor 10 mg BID	Tenapanor Dose-Titration	Overall
Entered RW period- n (%)	82 (100.0)	25 (100.0)	23 (100.0)	34 (100.0)	164 (100.0)
Completed RW period (4 weeks) - n (%)	74 (90.2)	24 (96.0)	22 (95.7)	32 (94.1)	152 (92.7)
Withdrew prior to completing RW period - n (%) [1]	8 (9.8)	1 (4.0)	1 (4.3)	2 (5.9)	12 (7.3)
Primary reason of early withdrawal from RW period					
Hyperphosphatemia - n (%)	3 (3.7)	0 (0.0)	1 (4.3)	1 (2.9)	5 (3.0)
Adverse event - n (%)	2 (2.4)	0 (0.0)	0 (0.0)	1 (2.9)	3 (1.8)
Protocol deviation - n (%)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hypophosphatemia - n (%)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Physician decision - n (%)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.6)
Withdrawn by subject - n (%)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Safety Analysis Set - n (%) [1]	82 (100.0)	25 (100.0)	23 (100.0)	34 (100.0)	164 (100.0)
Efficacy Analysis Set - n (%) [2]	37 (45.1)	11 (44.0)	13 (56.5)	19 (55.9)	80 (48.8)
Reasons excluded from Efficacy Analysis Set					
Did not achieve at least a 1.2 mg/dL reduction in serum phosphorus from baseline to end of the 8-week RT period - n (%)	45 (54.9)	14 (56.0)	10 (43.5)	15 (44.1)	84 (51.2)

1. All subjects who received at least 1 dose of study drug were included in the Safety Analysis Set.
2. Subjects must have met study entry inclusion and exclusion criteria, completed the 8-week RT period, and achieved at least a 1.2 mg/dL reduction in serum phosphorus from baseline to the end of the 8-week RT period to be included in the Efficacy Analysis Set.

Source: Table 5 of the Clinical Study Report for TEN-02-301

Study TEN-02-301

A total of 1559 subjects were screened, and 564 subjects were randomized into the 26-week treatment period (423 to tenapanor and 126 to sevelamer carbonate). As shown in Table 7, 167 (39%) subjects in the tenapanor group withdrew early from the 26-week treatment period, as compared to 24 (17%) in the sevelamer carbonate group. The primary reason for early withdrawal was an adverse event (2 subjects in the sevelamer carbonate group and 77 in the tenapanor group). Of the 77 subjects who withdrew for an adverse event in the tenapanor group, 67 (87%) withdrew because of diarrhea.

Table 7. Patient Disposition, 26-Week Treatment Period, All Screened Subjects, TEN-02-301

	Sevelamer Carbonate N=141 n (%)	All Tenapanor N=423 n (%)	Total N=564 n (%)
Completed 26-Week treatment period [1]	117 (83.0%)	256 (60.5%)	373 (66.1%)
Withdrew prior to completing the 26-Week treatment period	24 (17.0%)	167 (39.5%)	191 (33.9%)
Primary reason for withdrawal from 26-week treatment period [1]			
Adverse event	2 (1.4%)	77 (18.2%)	79 (14.0%)
Death	3 (2.1%)	7 (1.7%)	10 (1.8%)
Hyperphosphatemia	1 (0.7%)	22 (5.2%)	23 (4.1%)
Hypophosphatemia	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%)

1. Percentages were calculated using the number of patients entering the 26-week treatment period (i.e., all randomized patients) as the denominator.
Source: Table 4 of the Clinical Study Report forTEN-02-301

As previously noted, 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 or receive placebo. The disposition of patients who entered the 12-week RW period is shown in Table 8. A total of 57 (22.4%) patients withdrew prior to completing the 12-week RW period. The most common primary reason for early withdrawal was hyperphosphatemia.

Table 8. Patient Disposition, 12-Week Randomized Withdrawal Period, All Randomized Subjects, TEN-02-301

	Placebo N=127 n(%)	All Tenapanor N=128 n(%)	Total N=255 n(%)
Entered RW period [1]	127	128	255
Completed RW period [2]	99 (78.0%)	99 (77.3%)	198 (77.6%)
Withdrew prior to completing RW period [2]	28 (22.0%)	29 (22.7%)	57 (22.4%)
Primary reason for early withdrawal from RW period [2]			
Adverse event	0 (0.0%)	3 (2.3%)	3 (0.8%)
Death	1 (0.8%)	1 (0.8%)	3 (0.8%)
Hyperphosphatemia	14 (11.0%)	7 (5.5%)	21 (5.6%)
Hypophosphatemia	2 (1.6%)	1 (0.8%)	3 (0.8%)
Lost to follow-up	0 (0.0%)	2 (1.6%)	2 (0.5%)
Physician decision	3 (2.4%)	3 (2.3%)	8 (2.2%)
Withdrawal by subject	2 (1.6%)	8 (6.3%)	10 (2.7%)
Other	4 (3.1%)	3 (2.3%)	9 (2.4%)
Not reported [3]	2 (1.6%)	1 (0.8%)	3 (0.8%)

1. Percentages were calculated using the number of patients entering the 26-week treatment period (i.e., all randomized patients) as the denominator.
2. Percentages were calculated using the number of patients entering the 12-week RW period as the denominator.
3. The reason for early withdrawal from the RW period was not recorded for patients who discontinued early from both the RW period and the safety extension period.
Source: Table 5 of the Clinical Study Report TEN-02-301

Demographics:

The baseline demographics and disease characteristics were, in general, well-balanced between treatment arms in Studies TEN-02-201 and TEN-02-301 and were similar across trials.

In the randomized treatment period of Study TEN-02-201, 59% of patients were male, 57% were Black or African American, 39% were White and the majority of patients were not Hispanic or Latino (82%). The mean age was 56 years, the mean baseline weight was 96 kg, and the mean BMI was 33 kg/m^2. The mean baseline serum phosphorus level was 7.5 mg/dL and the mean baseline PTH value prior to study entry was 433 pg/mL.

In the Safety analysis set of the 26-week treatment period of Study TEN-02-301, the majority of patients were male (64%), White (47%) or Black/African American (46%), and not Hispanic or Latino (72%). The mean age at screening was 58 years, the mean baseline weight was 90 kg, and mean baseline BMI was 31 kg/m^2. The majority of patients (90%) in the Safety analysis set of the 26-week treatment period were receiving HD, with the remainder (10%) receiving PD. The mean baseline serum phosphorus level was 7.4 mg/dL and mean baseline intact PTH level was

417 pg/mL. The demographics of patients who participated in the randomized withdrawal portion of the trial were similar.

Table 9. Baseline Demographic and Clinical Characteristics, 26-week Treatment Period, Safety Population, TEN-02-301

Characteristic Category/Statistic	Sevelamer Carbonate (N=137)	All Tenapanor (N=419)	Total (N=556)
Sex, n (%)			
Male	91 (66.4%)	265 (63.2%)	356 (64.0%)
Female	46 (33.6%)	154 (36.8%)	200 (36.0%)
Age, years			
Mean (SD)	59.0 (12.6)	57.7 (12.6)	58.1 (12.6)
Age groups (years), n (%)			
<45	20 (14.6%)	65 (15.5%)	85 (15.3%)
≥45 to <65	72 (52.6%)	222 (53.0%)	294 (52.9%)
≥65	45 (32.8%)	132 (31.5%)	177 (31.8%)
Race, n (%)			
White	70 (51.1%)	189 (45.1%)	259 (46.6%)
Black/African American	60 (43.8%)	195 (46.5%)	255 (45.9%)
Asian	7 (5.1%)	21 (5.0%)	28 (5.0%)
Other	0 (0.0%)	14 (3.3%)	14 (2.6%)
Ethnicity, n (%)			
Hispanic or Latino	41 (29.9%)	115 (27.4%)	156 (28.1%)
Non-Hispanic or Latino	96 (70.1%)	302 (72.1%)	398 (71.6%)
Not reported	0 (0.0%)	2 (0.4%)	2 (0.4%)
Baseline height (kg) height at screening (cm)			
N	137	417	556
Mean (SD)	169.8 (10.9)	169.1 (10.5)	169.3 (10.6)
Baseline weight (kg)			
n	137	419	556
N			
Mean (SD)	90.4 (24.9)	89.8 (24.5)	89.9 (23.8)
Baseline BMI (kg/m^2)			
n	137	417	554
Mean (SD)	31.4 (9.9)	31.3 (7.5)	31.3 (8.2)

Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic
Source: Table 4 of the Clinical Study Report TEN-02-301

Efficacy Results

Study TEN-02-201

As previously noted, the primary efficacy variable in Study TEN-02-201 was the change in serum phosphorus 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. The primary efficacy analysis compared the primary efficacy endpoint between the pooled tenapanor treatments and placebo in the Efficacy Analysis Set. Of the 164 subjects who entered the 4-week RW period and were randomized to tenapanor (n=82) or placebo (n=82), 39 subjects in the tenapanor group and 45 in placebo group did not achieve a reduction of ≥1.2 mg/dL in serum phosphorus level from the baseline to the end of the treatment

period and hence were not included in the primary efficacy analysis. The baseline for the RT period is defined as the last measurement collected prior to the first dose of study medication. As such, the efficacy analysis set included a total of 80 patients, 43 in the tenapanor arm and 37 in the placebo arm.

Table 10 shows the results for the primary efficacy variable in the Efficacy Analysis Set; an LOCF analysis was used for the primary efficacy analysis. The LS mean change in serum phosphorus from the end of the 8-week RT period to the end of the 4-week RW period was 1.38 mg/dL in the placebo group and 0.56 mg/dL for the pooled tenapanor group, resulting in a LS mean treatment difference between the pooled tenapanor group and the placebo group of -0.82 mg/dL (p=0.01). The observed case analysis showed a treatment difference of -0.76 mg/dL (p=0.018) between the pooled tenapanor arm and the placebo arm and the MMRM analysis gave a treatment effect estimate of -0.77 (p = 0.0012).

The results of analyses using the ITT Analysis Set for the 4-week RW period, which included all subjects who entered the 4-week RW period, were similar to the results obtained using the Efficacy Analysis Set, suggesting that the approach used to enrich the Efficacy Analysis Set for patients with a greater response to treatment was not effective in doing so. The LS mean change in serum phosphorus from the end of the 8-week RT period to the end of the 4-week RW period was 0.79 mg/dL for the placebo group and 0.07 mg/dL for the pooled tenapanor group. The LS mean of the treatment difference between the pooled tenapanor group and the placebo group was -0.72 mg/dL (p =0.003). The MMRM analysis gave a treatment effect estimate of -0.86 (p = 0.0068).

Table 10. Change in Serum Phosphorus (mg/dL) From the End of the 8-Week Randomized Treatment Period to the End of the 4-Week Randomized Withdrawal Period, Efficacy Analysis Set, TEN-02-201

Timepoint Statistic	Placebo (N = 37)	Pooled Tenapanor (N = 43)
End of 8-week RT period [1]		
n	37	43
Mean (SD)	5.32 (1.285)	5.71 (1.341)
End of 4-week RW period [2]		
n	36	43
Mean (SD)	6.86 (1.488)	6.16 (1.621)
Change from end of 8-week RT period to end of 4-week RW period		
n	36	43
Mean (SD)	1.46 (1.421)	0.45 (1.401)
LS mean (SE) [3]	1.38 (0.228)	0.56 (0.208)
95% CI LS mean	(0.93, 1.83)	(0.14, 0.97)

Treatment Comparison	LS Means Difference (SE) [3]	LS Means Difference 95% CI [3]	p-value [3]
Pooled tenapanor vs placebo	-0.82 (0.310)	(-1.44, -0.21)	0.010

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.
3. Least-squares means, SE, 95% CIs, and p-values were from an ANCOVA model with treatment and pooled Investigator site as factors and end of 8-week RT period value as a covariate.

Source: Table 8 of the Clinical Study Report TEN-02-201

Figure 4 shows the mean serum phosphorus (mg/dL) values during the 4-week RW period for the Efficacy Analysis Set. The mean serum phosphorus 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 while the mean serum phosphorus in the tenapanor arm increased from 5.7 mg/dL at the end of 8-week RT period to 6.2 mg/dL at the end of the 4-week RW period.

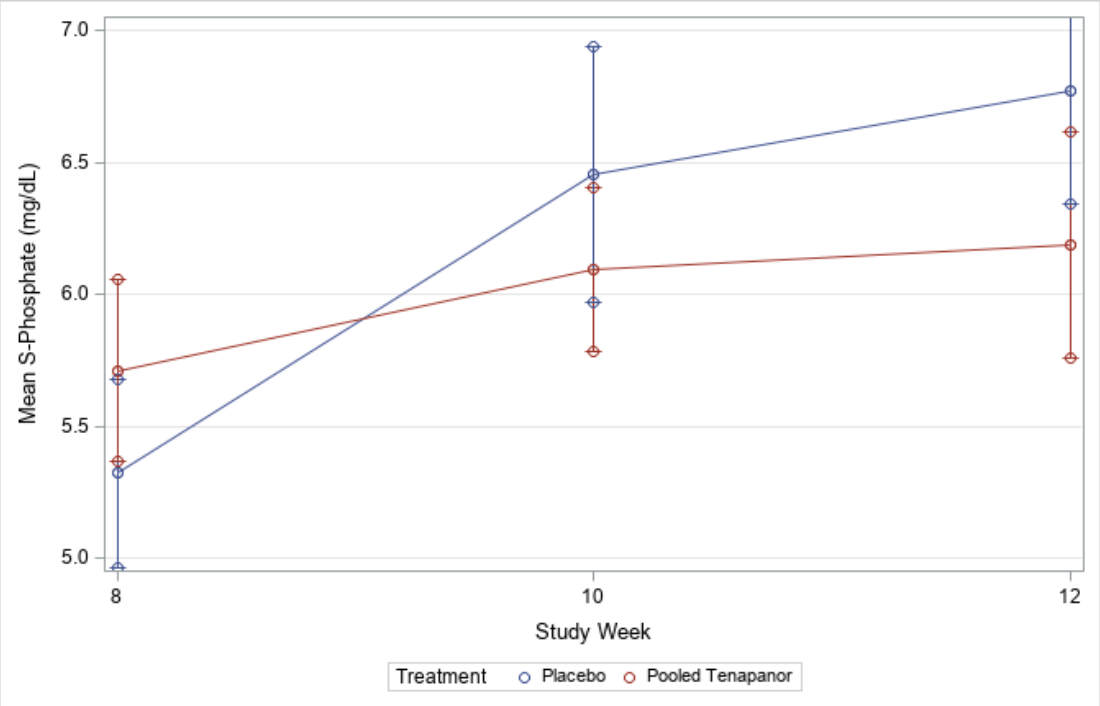


Figure 4. Mean Serum Phosphorus (mg/dL) for the 4-Week Randomized Withdrawal Period - Efficacy Analysis Set, TEN-02-201

Source: Figure 2 of the Clinical Study Report for TEN-02-201 and FDA Reviewer

Study TEN-02-301

The primary efficacy endpoint was the change in serum phosphorus level from Visit 13 to the endpoint visit of the RW period in Study TEN-02-301; the primary efficacy analysis was to be based on the Efficacy Analysis Set. Of the 423 subjects randomized to tenapanor in the 26-week RT period, 255 tenapanor-treated subjects (60%) finished the 26-week RT period and were re-randomized 1:1 to receive tenapanor (n=128) or placebo (n=127) during the 12-week RW period. Of these 255 subjects, 131 (51%) subjects, met the criteria for inclusion in the Efficacy Analysis set; 63 of these subjects were in the tenapanor arm and 68 were in the placebo arm. During the 12-Week RW period, 11% of subjects in the Efficacy Analysis Set withdrew before completion of the trial (7 placebo and 8 tenapanor).

Table 11 shows the results for the primary efficacy variable in the Efficacy Analysis Set; the primary efficacy analysis used an LOCF approach. Using the primary analysis method, the LS mean change in serum phosphorus 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 0.43 mg/dL for the tenapanor group and 1.80 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 -1.37 mg/dL for the tenapanor group ($p<0.0001$). The observed case analysis gave a treatment effect of -1.27 mg/dL ($p<0.0001$) and the MMRM analysis gave an estimate of -1.30 mg/dL $p < 0.0001$.

Table 11. Primary Analysis: Analysis of Change from Period-Level Baseline in Serum Phosphorus (mg/dL) at End of 12-Week Randomized Withdrawal Period Using ANCOVA, 12-Week Randomized Withdrawal Period, Efficacy Analysis Set, TEN-02-301

	Tenapanor vs. Placebo	
	Placebo (N=68)	**All Tenapanor (N=63)**
Baseline at the RW period [1]	5.08 (1.25)	5.21(1.13)
Change from baseline to the end of the 12-week period [2]		
LS Mean (SE)	1.80 (0.20)	0.43 (0.20)
95% CI LS mean	(1.41, 2.19)	(0.04, 0.83)
LS Mean difference (SE) (versus placebo)		-1.37 (0.28)
95% CI LS mean difference (versus placebo)		(-1.92, -0.82)
p-value		<0.0001

The LS means, SEs, 95% CIs, and p-value were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.

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. End of 12-week RW period was defined as the last assessment during the 12-week RW period.

Source: Table 10 of the Clinical Study Report for TEN-02-301

Table 12 shows the results for primary efficacy variable using the ITT Analysis Set. As shown in the table, estimates for the treatment effect based on the ITT Analysis Set were much smaller than these based on the Efficacy Analysis Set. The LS mean change in serum phosphorus from the period-level baseline to the end of the 12-week RW period in the ITT Analysis Set was 0.22 mg/dL for the tenapanor group and 0.88 mg/dL for the placebo group, resulting in a LS mean difference between tenapanor and placebo in serum phosphorus change from period-level baseline to the end of the 12-week RW period of -0.66 mg/dL (p=0.0020). The observed case analysis gave a treatment effect estimate of -0.65 mg/dL (p=0.003) and the MMRM analysis gave a treatment effect estimate of -0.69 mg/dL ($p < 0.001$).

Table 12. Key Secondary Analysis: Analysis of Change from Period-Level Baseline in Serum Phosphorus (mg/dL) at End of 12-Week Randomized Withdrawal Period using ANCOVA, 12-Week Randomized Withdrawal Period, Intent-to-Treat Analysis Set, TEN-02-301

	Tenapanor vs. Placebo	
	Placebo (N=123)	All Tenapanor (N=120)
Baseline at the RW period [1]	5.80 (1.44)	5.93 (1.48)
Change from baseline to the end of the 12-week period [2]		
LS Mean (SE)	0.88 (0.15)	0.22 (0.15)
95% CI LS mean	(0.58, 1.17)	(-0.07, 0.51)
LS Mean difference (SE) (versus placebo)		-0.66 (0.21)
95% CI LS mean difference (versus placebo)		(-1.07, -0.24)
p-value		<0.0020

The LS means, SEs, 95% CIs, and p-value were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.

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.

Source: Table 11 of the Clinical Study Report for TEN-02-301

See "Review Issues Relevant to the Evaluation of Benefit" for information on efficacy findings in the 26-Week Treatment Period that preceded the 12-Week RW Period.

Subgroup analyses of change in serum phosphorus from Visit 13 to the endpoint visit of the randomized withdrawal period

Subgroup analyses were performed for the primary efficacy endpoint for age, sex, race, and geographic regions and were generally consistent across the prespecified subgroups. Figure 5 shows a forest plot of the LS mean difference in change from the period-level baseline in serum phosphorus to the end of the 12-week RW period for the Efficacy Analysis Set and subgroups of interest.

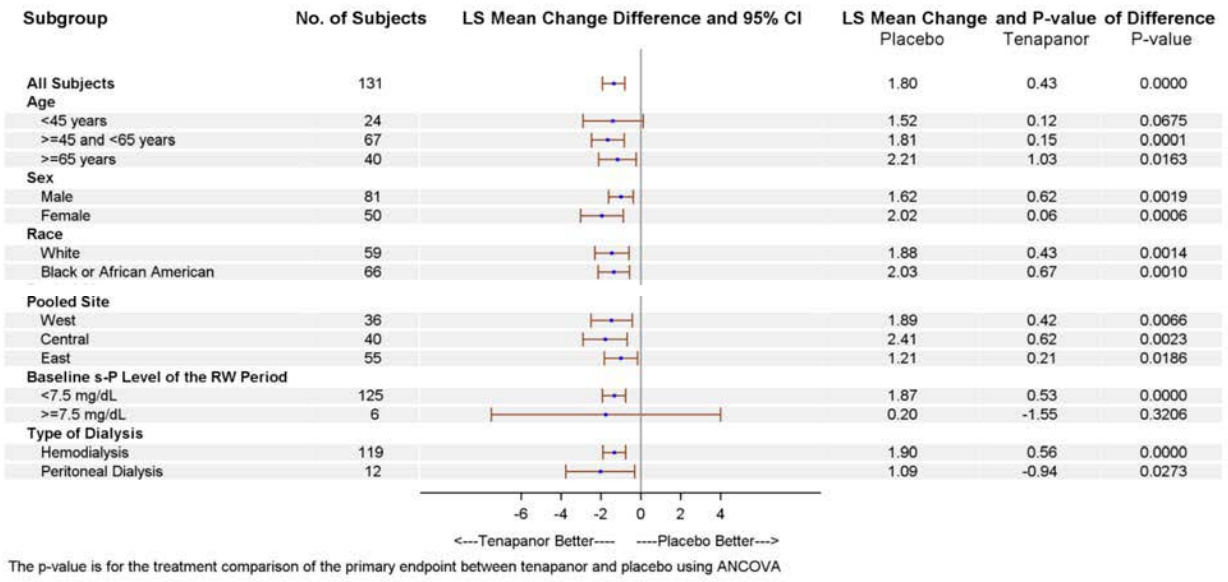


Figure 5. Subgroup Analysis: Forest Plot of LS Mean Difference in Change from Period-Level Baseline in Serum Phosphorus (mg/dL) at End of 12-Week Randomized Withdrawal Period, 12-Randomized Withdrawal Period, Efficacy Analysis Set, TEN-02-301

Source: Figure 4 of the Clinical Study Report for TEN-02-301

Analyses in patients with higher baseline serum phosphorous

Analyses were also conducted to explore whether patients with higher baseline serum phosphorus levels at the start had a larger treatment response. Because the proportion of patients who withdrew was substantially greater in the tenapanor as compared to the active control arm, it is challenging to obtain a reliable estimate of the treatment effect for tenapanor. Nevertheless, ANCOVA based on observed serum phosphorus changes at each visit provides some information on the treatment effect during the 26-week treatment period. As compared to patients with a baseline serum phosphorus < 7.5 mg/dL, patients with a baseline serum phosphorus ≥ 7.5 mg/dL had a larger treatment response in the 26-week randomized, active controlled treatment period of Study TEN-02-301. However, the size of the treatment effect on serum phosphorus was smaller in the tenapanor as compared to the active control arm. See the appendix for further discussion.

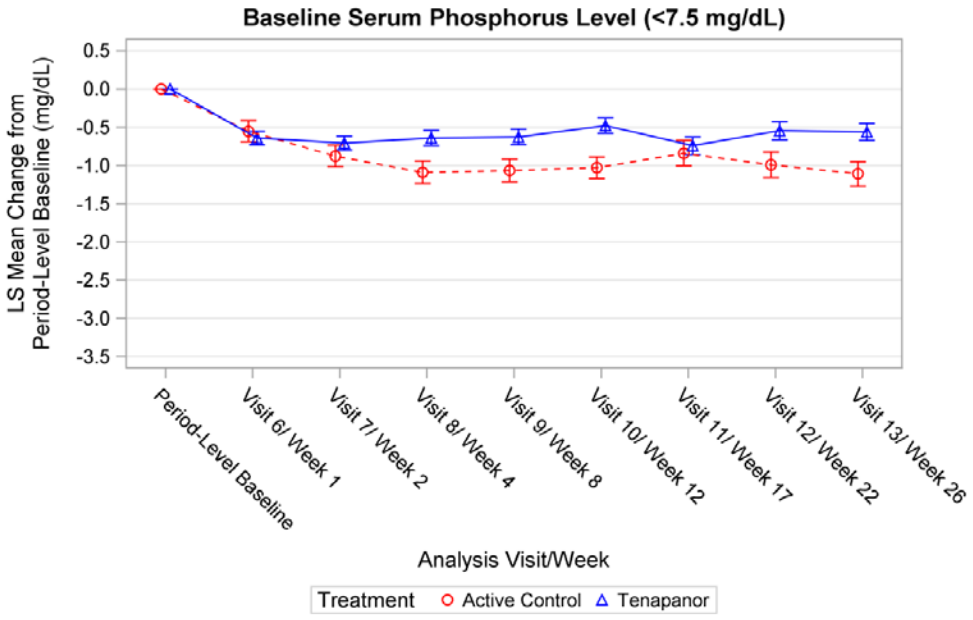


Figure 6. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm), TEN-02-301[1]

Source: Figure 14.2.4.3, Clinical Information Amendment, Module 1.11.3, TEN-02-301
[1]Analysis based on observed data only

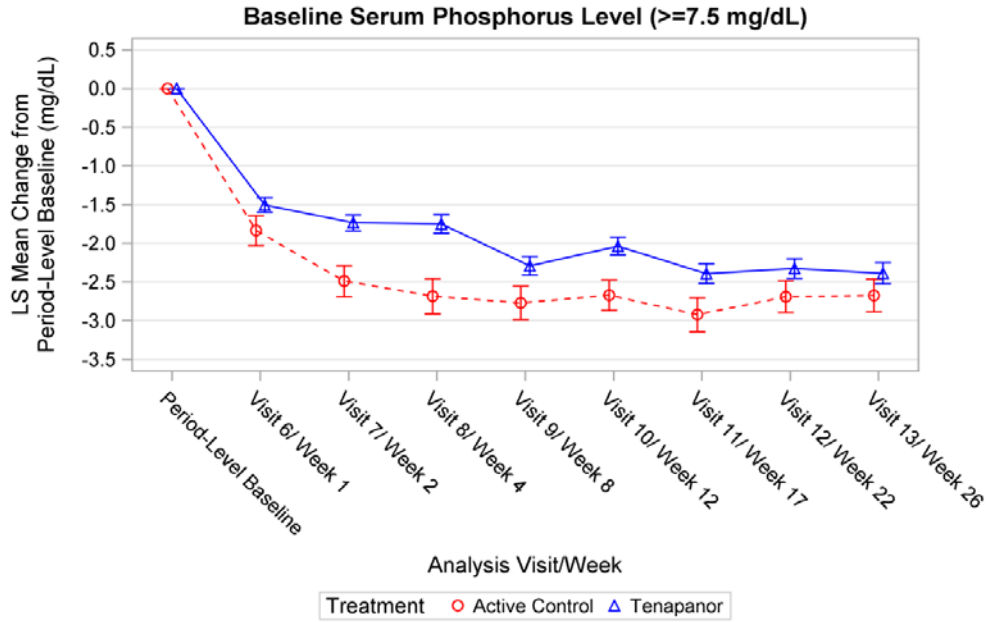


Figure 7. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm), TEN-02-301[1]

Source: Figure 14.2.4.3, Clinical Information Amendment, Module 1.11.3, TEN-02-301.
[1]Analysis based on observed data only

Analyses to assess for a responder population

Analyses of the distribution of the responses at Weeks 2 and 4 of the 26-week randomized, active controlled treatment period of Study TEN-02-301 did not suggest an obvious tenapanor "responder" population (i.e., a subpopulation with a substantially larger response to treatment). See below for the distribution at Week 2 (shown for both arms) and the appendix for the distribution at Week 4.

Figure 6. Histograms of Serum Phosphorus (mg/dL) Change from Baseline at Visit 7/Week 2 in the 26-Week Treatment Period Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)*

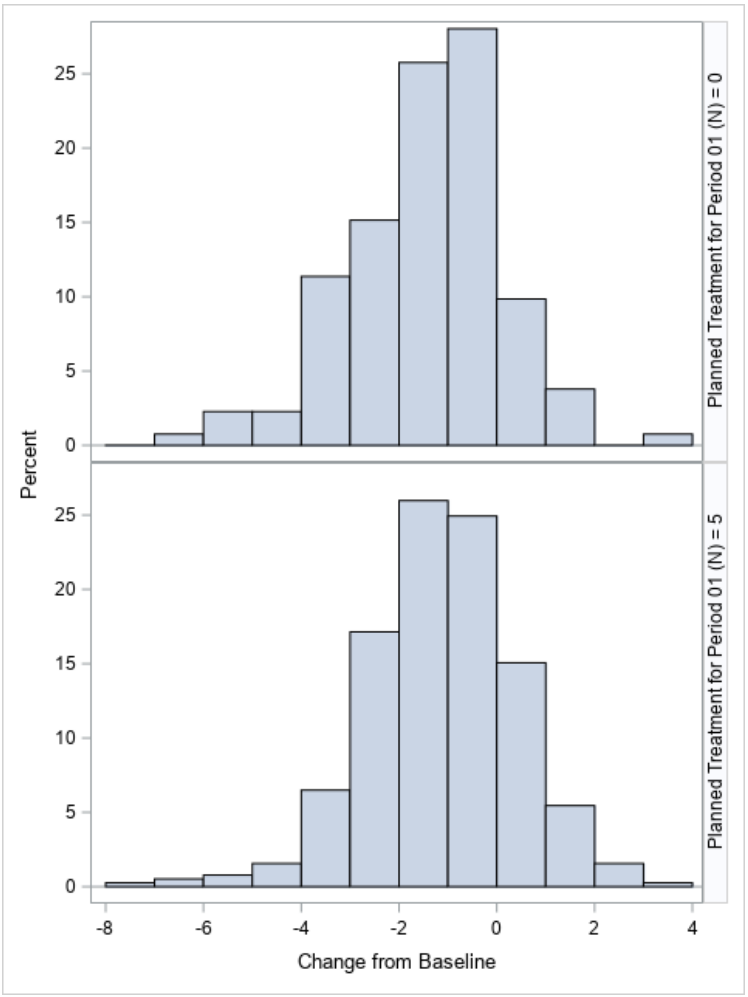


Figure 8. Histograms of Serum Phosphorus (mg/dL) Change from Baseline at Visit 7/Week 2, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm), TEN-02-301[1]

Source: Statistical Reviewer

[1]Top panel=tenapanor; bottom panel=active control. Subject withdrawal was highly unbalanced between the two treatment groups, with significantly more subjects withdrawing from the tenapanor as compared to the active control arm. As such, the distributions in the two arms cannot be directly compared.

6.4. Review Issues Relevant to the Evaluation of Benefit

While the Agency 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, a treatment effect of any size is not considered sufficient to support approval. A key review issue for this application was the magnitude of the treatment effect, both in absolute terms and relative to other treatments.

6.4.1. Magnitude of treatment effect when used as monotherapy and disposition of trial participants

Issue: Both Studies TEN-02-201 and TEN-02-301 used a randomized withdrawal design. In both studies, the primary efficacy analysis during the randomized withdrawal period was based on the Efficacy Analysis Set, a subset of the ITT population, that was intended to enrich for a responder population. Specifically, the Efficacy Analysis Set limited the primary efficacy analysis to subjects who achieved a reduction of ≥ 1.2 mg/dL in serum phosphorus level in the randomized treatment period prior to randomized withdrawal. This section addresses the efficacy findings in the context of the aforementioned trial design and disposition of patients in the trial.

Assessment:
Study TEN-02-301
A total of 564 subjects were randomized 1:3 into the 26-week treatment period (141 in sevelamer carbonate group, and 423 in tenapanor group) in Study TEN-02-301. Of the subjects randomized to tenapanor, 167 (39.5%) withdrew before completing the 26-week RT period. Among them, 67 subjects in tenapanor group withdrew due to diarrhea and 22 withdrew due to hyperphosphatemia. A total of 255 tenapanor-treated subjects finished the 26-week RT period and were re-randomized 1:1 to receive tenapanor (n=128) or placebo (n=127) during the 12-week RW period. The efficacy analysis set only included 131 of these subjects (63 in tenapanor arm and 68 in placebo arm). The LS mean change in s-P level from baseline to the end of the 12-week RW period was -1.37 mg/dL based on the Efficacy Analysis Set and -0.66 mg/dL based on the ITT analysis set.

Study TEN-02-201
In Study *TEN-02-201*, only 164 (74.9%) of the 219 subjects completed the 8-week RT period in which subjects were assigned to 3mg, 10 mg or dose-titration tenapanor group. 12 (7.3%) out of the 164 subjects withdrew from the study prior to completing the 4-week RW period. The most common reasons for the early withdrawal from the 4-week RW period were hyperphosphatemia (5 subjects) and adverse event (3 subjects). This study has a much shorter RW period compared

with Study 301, so the early withdrawal rate in the RW period in this study was not as high as in Study 301. The withdrawal rate was still very high in the 8-week RT period.

Of the 164 subjects who entered the randomized withdrawal period in Study TEN-02-201, only 80 subjects met the responder criteria and were included in the efficacy analysis set. The treatment difference between pooled tenapanor and placebo was -0.82 mg/dL in the 4-week RW period based on the Efficacy Analysis Set and -0.72 mg/dL based the ITT analysis set.

Conclusion:
Approximately half of the subjects who entered the RW period were excluded from the efficacy analysis set used for the primary analysis in Studies TEN-02-301 and TEN-02-201. Of those subjects who were initiated on tenapanor at the start of the trial, less than a third were included in the efficacy analysis set for TEN-02-301 and less than 40% were included in the efficacy analysis set used for TEN-02-201.

Among the trials, the largest treatment effect was observed in the Efficacy Analysis Set of Study TEN-02-301. The clinical relevance of this estimand is unclear given that it was derived from a subset of the trial population. Moreover, even if such a strategy could be implemented in clinical practice, the treatment effect obtained with this strategy was modest. Analyses based on the ITT population of the RW periods of 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 size of the treatment effect in this subset was small─ 0.72 mg/dL and 0.66 mg/dL, respectively.

6.4.2. Magnitude of Treatment Effect Relative to Other Therapies

Issue: To date, four major classes of agents have been approved for the proposed indication in the US- calcium-based binders, sevelamer-based products, lanthanum carbonate and iron-based binding agents. In the trials conducted to support approval, these therapies lowered serum phosphorus levels by ~1.5 – 2.2 mg/dL. Cross trial comparisons are, however, challenging to interpret. Study TEN-02-301 included an active control to support safety assessments (i.e., because of concern that the safety data from the trial would not be interpretable without the inclusion of a control arm in the initial treatment period). As such, the trial was not optimally designed to provide comparative efficacy data.[9] Nevertheless, exploratory analyses were conducted.

[9] For example, the protocol stipulated that patients randomized to the active control group should take the active control "based on standard of care using the package insert for guidance" (as opposed to providing guidance to adjust therapy to target specific goals). As another example: The SAP defined the ITT Analysis Set for the 26-week randomized treatment period as all subjects who met the study entry inclusion/exclusion criteria, received at least 1 dose of tenapanor, and had at least 1 post-treatment serum phosphorus measurement during this study period; subjects randomized to the sevelamer carbonate (active control) group were not included in this ITT analysis set.

Assessment: A total of 564 subjects were randomized 1:3 (141 to sevelamer carbonate and 423 to tenapanor) in the 26-week open-label treatment period of Study TEN-02-301. Of these subjects, 24 (17.0%) subjects in the sevelamer carbonate group and 167 (39.5%) subjects in the tenapanor group withdrew early from the 26-week treatment period.

Table 13 presents the results based on an observed case analysis using ANCOVA. The LS mean change in serum phosphorus from baseline to the end of the 26-week RT period was -1.37 mg/dL for the tenapanor group and -1.80 mg/dL for the sevelamer carbonate group. The treatment comparison between tenapanor and sevelamer carbonate showed a LS mean difference of 0.43 mg/dL favoring sevelamer carbonate (p=0.0064). As previously noted, subject withdrawal was highly unbalanced between the two treatment groups, with significantly more subjects withdrawing from the tenapanor as compared to the sevelamer treatment arm. As such, the results are heavily influenced by the approach taken to impute missing data. Given the limitations in trial design (see footnote on prior page) and the imbalance in withdrawal rates, it is challenging to provide a reliable estimate of the treatment effect that can be used to compare efficacy.

Table 13. Analysis of Change from Baseline in Serum Phosphorus (mg/dL) at Post-Baseline Visits Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm), TEN-02-301

	Active Control (N=113)	**Tenapanor (N=248)**
Change from baseline to the end of the 26-week period [1]		
LS Mean (SE)	-1.80 (0.13)	-1.37 (0.09)
LS Mean difference (SE) (versus placebo)		0.43 (0.16)
95% CI LS mean difference (versus placebo)		(0.12, 0.74)
p-value		0.0064

The LS means, SEs, 95% CIs, and p-value were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.

1. For the 26-Week Treatment Period, Period-Level Baseline is defined as the last measurement collected prior to the first dose of study medication during the 26-Week Treatment Period.

Source: Table 14.2.3.1, Clinical Information Amendment, Module 1.11.3, TEN-02-301

Figure 9 displays a plot of LS mean change in serum phosphorus for the tenapanor arm and sevelamer carbonate arm in the 26-week RT period. The baseline is defined as the last measurement collected prior to the first dose of study medication.

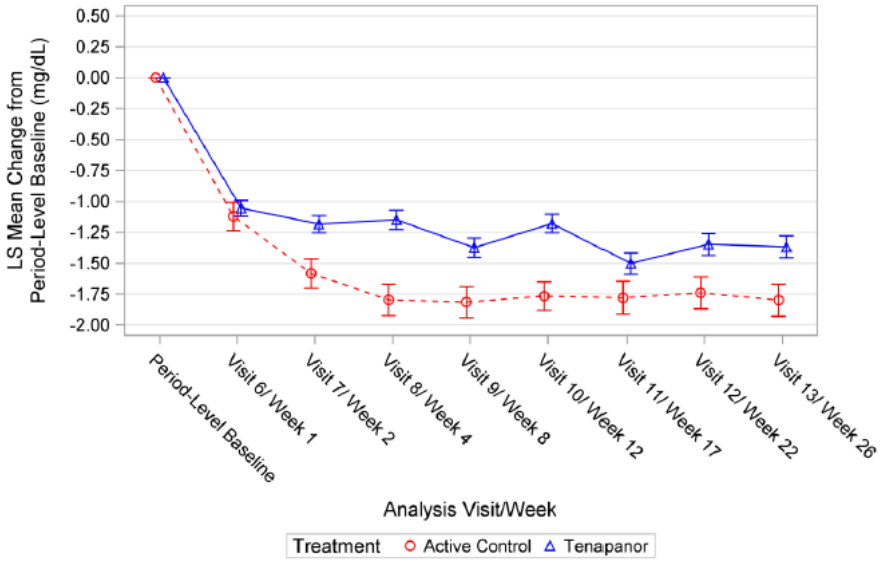


Figure 9. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA, 26-Week Treatment Period, Intent-to Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm), TEN-02-301

Source: Figure 14.2.3.3, Clinical Information Amendment, Module 1.11.3, TEN-02-301

Conclusion: Study TEN-02-301 was not optimally designed to assess comparative efficacy. Nevertheless, analyses of the data from the 26-week active-controlled treatment period of the study suggest that tenapanor's mean treatment effect on serum phosphorus is smaller than the mean treatment effect of the active comparator.

6.4.3. Magnitude of treatment effect when used with phosphate binders

Issue: The magnitude of the treatment effect when used as monotherapy was small. Data on the magnitude of the treatment effect when used in combination with phosphate binders were also reviewed.

Assessment: In Study TEN-02-202, 235 patients with CKD on dialysis and stable phosphate binder therapy were randomized 1:1 to receive tenapanor (n=116) or placebo BID (n=119) while continuing their established phosphate binder regimen. A total of 229 patients finished the four-week study, 112 in the tenapanor arm and 117 in the placebo arm.

The primary efficacy endpoint was the change from Baseline in serum phosphorus level at Week 4. Table 14 shows a summary of serum phosphorus levels and the primary analysis results using MMRM. The LS mean reduction in serum phosphorus level from Baseline to Week 4 was -0.84 mg/dL in the tenapanor group and -0.19 mg/dL in the placebo group, resulting in a statistically significant but small treatment effect of 0.65 mg/dL (p=0.0004).

Table 14. Summary of Serum Phosphorus (mg/dL) and Primary Analysis of Change from Baseline in Serum Phosphorus (mg/dL) at Week 4, Full Analysis Set, TEN-02-202

Visit Statistics	Placebo (N=119)		Tenapanor (N=116)	
Baseline [1]				
n	119		116	
Mean (SD)	6.93 (1.373)		6.73 (1.324)	
Week 4 [2]				
n	117		112	
Mean (SD)	6.67 (1.551)		5.92 (1.513)	
Change from Baseline to Week 4 [2]				
Mean (SD)	-0.29 (1.636)		-0.85 (1.375)	
LS mean (SE)	-0.19 (0.130)		-0.84 (0.131)	
95% CI LS mean	(-0.45, 0.07)		(-1.10, -0.58)	
	Difference (Treatment – Placebo)			
Treatment comparison	LS mean (SE)	95% CI LS Mean Difference	99% CI LS Mean Difference	p-value
Tenapanor vs placebo	-0.65 (0.182)	(-1.01, -0.29)	(-1.13, -0.18)	0.0004

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.

Source: Table 6 of the Clinical Study Report for TEN-02-202

Figure 10 presents the LS mean change in serum phosphorus from Baseline over the course of the study for the FAS. As shown in the figure, the addition of tenapanor to existing phosphate binder treatment reduced serum phosphorus levels compared with binder treatment alone. The onset of effect started from the first post-Baseline visit after 1 week of treatment and was maintained until the end of the 4-week Treatment Period.

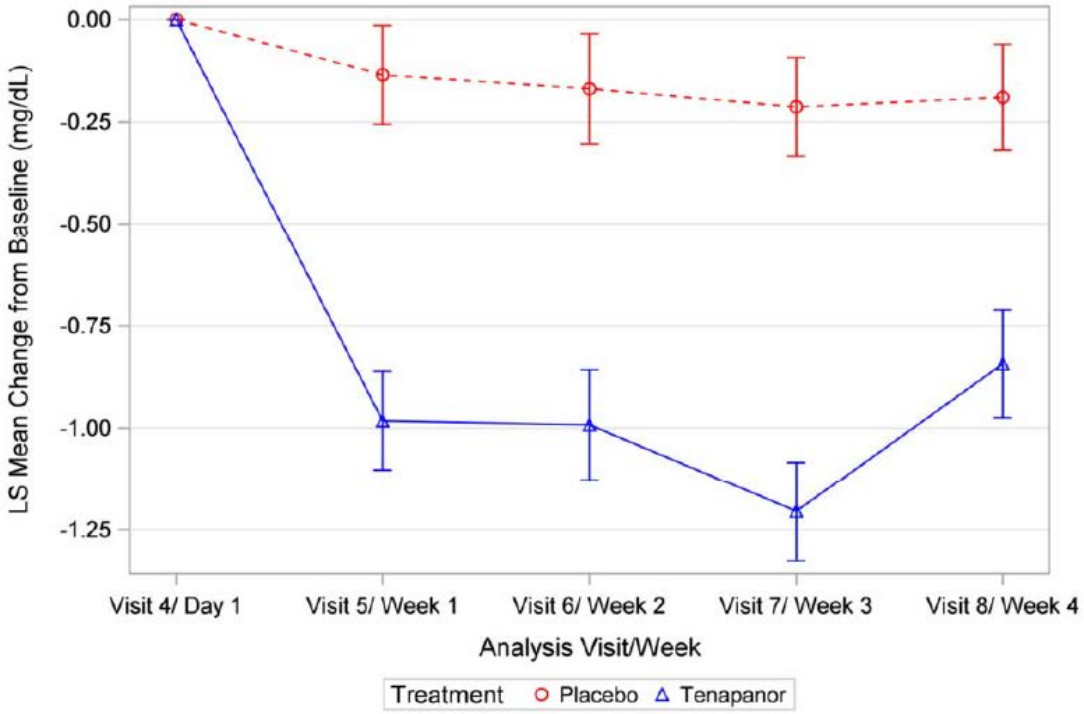


Figure 10. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline over Time, Full Analysis Set, TEN-02-202

Source: Figure 2 of the Clinical Study Report for TEN-02-202

Conclusion: When used in combination with phosphate binders, the size of the treatment effect was small and similar to that seen when used as monotherapy.

6.4.4. Addendum to Review Issue List

Concerns about the size of the mean effect and its clinical relevance were conveyed to the Applicant during the preNDA meeting. 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 by the Applicant and FDA to characterize the treatment effect. These analyses explored whether there might be a sizeable population of patients with a larger and clinically relevant response to treatment. FDA also performed additional analyses to explore 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)[10].

Analyses submitted by Applicant on April 29, 2021

During a call with the Applicant on April 27, 2021, the Agency voiced concern about the size of the mean effect on serum phosphorus but also acknowledged that it was possible that some

[10] For additional information on exploratory analyses that were conducted to determine whether it might be possible to individualize treatment based on a patient's early response to treatment, see the appendix.

patients could have a larger and clinically relevant response to treatment and that if such a population existed, it might be possible to individualize therapy based on a patient's response. The Agency recommended that the Applicant provide additional analyses of the trial data. Specifically, the Agency was interested in understanding the proportion of patients that both tolerated therapy (i.e., remained on treatment) and also had a clinically relevant treatment effect, as determined by achieving a serum phosphorus level below some threshold or by achieving a reduction in serum phosphorus concentration greater than some amount.

To address the Agency's request, the Applicant provided additional analyses of the data from the three study periods of Study TEN-02-301, a 52-week study with a 26-week treatment period, a 12-week randomized withdrawal period and a 14-week safety extension period.[11] The Applicant's analysis of the data from the 26-week treatment period of Study TEN-02-301 is discussed below. As previously noted, the 26-week treatment period of Study-02-301 included an active control, although a fair comparison is difficult to make between the two treatment arms because of differences in analysis sets.

The figure below shows the Applicant's analysis of the percentages of patients who achieved a serum phosphorus concentration below a certain threshold among the patients who completed the 26-week study period. Of those patients who completed the study period, 54% of patients treated with tenapanor had a serum phosphorus < 6.0 mg/dL and 40% had a serum phosphorus < 5.5. mg/dL. The percentages of patients who achieved these thresholds was numerically greater in the sevelamer arm. Because the trial lacked a placebo arm, we do not know what the percentages would have been in patients treated with placebo; it is also important to note that this analysis is based on a single measurement (i.e., the value at week 26) falling below the threshold.

[11] The Agency considered the new information to constitute a major amendment to the application, and as such, the goal date was extended to provide time for a full review of the submission.

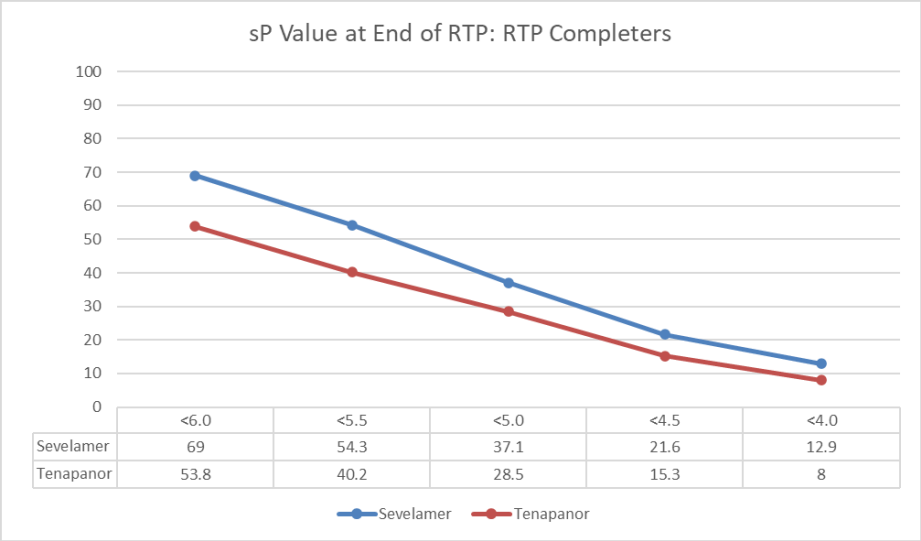


Figure 11. Percentage of Patients that Achieved a Serum Phosphorus (mg/dL) Concentration Below a Threshold Level: 26-Week Completers

Source: Figure 4 of the Sponsor's Clinical Information Amendment; Tenapanor, n=249; Sevelamer, n=116

The figure below shows the Applicant's analysis of the percentage of patients who had a reduction in serum phosphorus greater than some amount at the end of the treatment period in 26-week completers. Of patients who completed the study period, 42% of patients treated with tenapanor had a serum phosphorus reduction >= 1.7 mg/dL and 34% had a serum phosphorus reduction >= 2.0 mg/dL. As was observed in the prior analysis, the percentage of patients who achieved these reductions in 26-week completers was numerically greater in the sevelamer arm. As previously noted, the analysis is based on a single measurement at week 26 (as opposed to repeated measurements) and because the trial lacked a placebo arm, we do not know what the percentages would have been in patients treated with placebo.

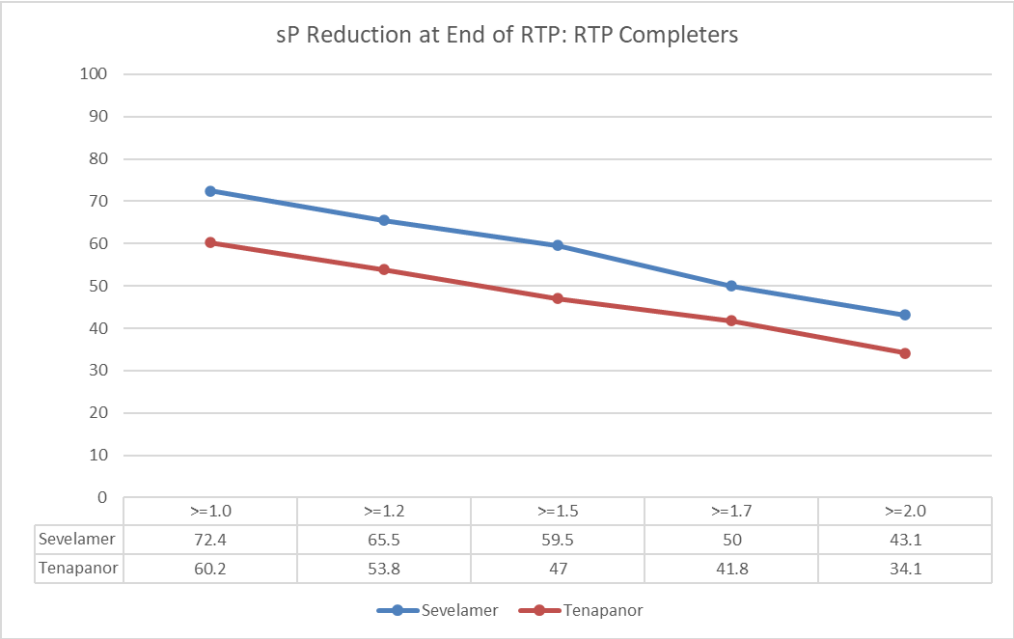


Figure 12. Percentage of Patients that Achieved Serum Phosphorus (mg/dL) Reductions from >=1.0 mg/dL to >=2.0 mg/dL: 26-Week Completers

Source: Figure 5 of the Sponsor's Clinical Information Amendment; Tenapanor, n=249; Sevelamer, n=116

Analyses conducted by FDA

As previously noted, a significant proportion of patients in the tenapanor arm did not complete the 26-week study period. As such, FDA analyzed the data to determine the percentage of patients who both completed the study period and (1) had a serum phosphorus concentration below a threshold level at the end of the period or (2) had a reduction in serum phosphorus greater than some value at the end of the period.

As depicted in the figure below, 34% of patients treated with tenapanor had a serum phosphorus < 6.0 mg/dL and 26% had a serum phosphorus < 5.5 mg/dL at the end of the study period. The percentages who had these values were numerically greater in the sevelamer arm.

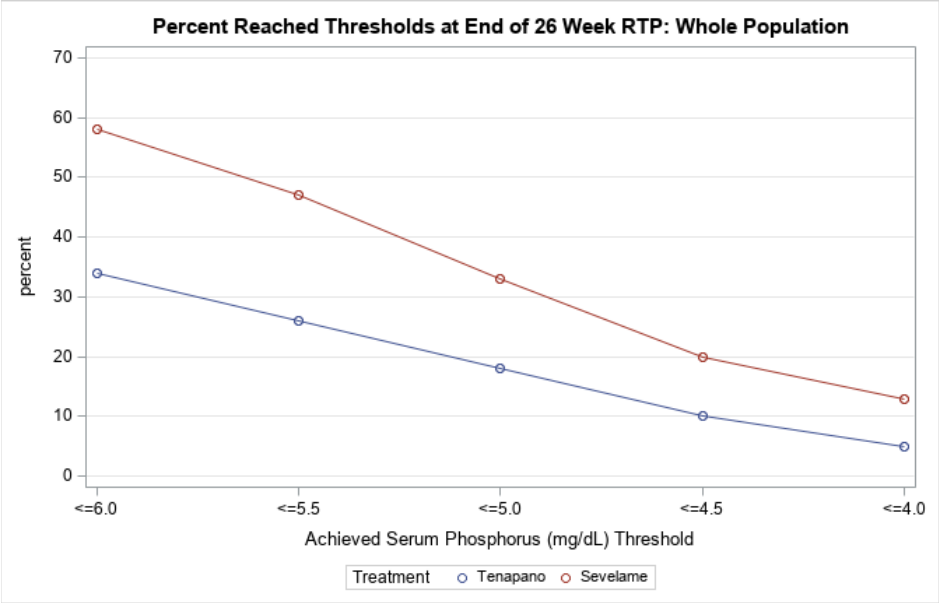


Figure 13. Percentage of Patients that Achieved a Serum Phosphorus (mg/dL) Concentration Below a Threshold Level in the 26-Week Randomization Treatment Period

Source: Statistical Reviewer; Tenapanor, n=407; Sevelamer, n=137

As shown in the figure below, 14% of patients treated with tenapanor had a serum phosphorus reduction ≥1.7 mg/dL and 11% had a serum phosphorus reduction ≥ 2.0 mg/dL at the end of the study period. The percentages of patients who had such reductions was numerically greater in the sevelamer arm.

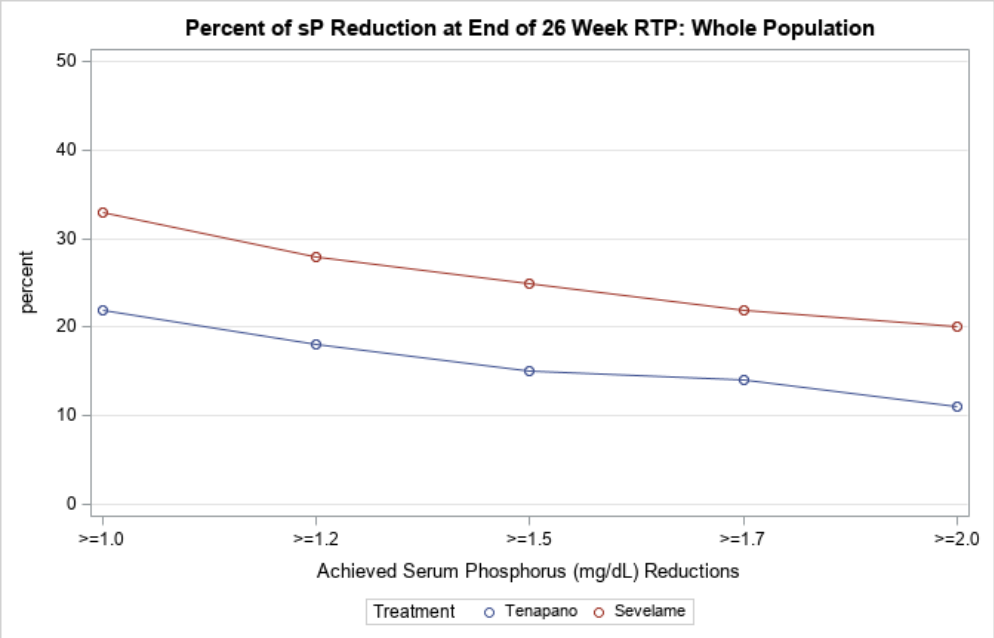


Figure 14. Percentage of Patients that Achieved Serum Phosphorus (mg/dL) Reductions from >=1.0 mg/dL to >=2.0 mg/dL in the 26-Week Randomization Treatment Period

Source: Statistical Reviewer; Tenapanor, n=407; Sevelamer, n=137

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The pivotal studies for tenapanor and the major metabolite (M1, AZ13792925) were reviewed during the IND stage and have been documented in DARRTS as well as in the Unireview for NDA 211801 (entered into DARRTS on September 5, 2019). In brief, toxicology studies showed adverse gastrointestinal effects, reflecting the expected pharmacological effects of tenapanor. Other findings of interest are summarized below. There are no outstanding nonclinical issues.

Safety pharmacology studies

Safety pharmacology studies indicate that the drug is a weak hERG inhibitor (10µM causing approximately 18% inhibition). A cardiovascular safety study in conscious, instrumented dogs showed a dose-related decrease in mean systolic arterial pressure following single oral doses of 100, 300, or 1000 mg/kg. A decrease in blood pressure secondary to volume reduction may reflect extended pharmacology.

The electrophysiological activity of the major metabolite (MI, AZ13792925) was evaluated in a panel of recombinant human cardiac ion channels. The Applicant found significant activity against 3 voltage-gated cardiac ion channels as shown below:

Table 15. Significant Activity of AZ13792925 in *in vitro* Electrophysiological Assays

AZ13792925 had significant activity (a defined IC_{50} value) at three of the four human recombinant voltage-gated cardiac ion channels as shown in Table 1.

Table 1 Significant activity of AZ13792925 in *in vitro* electrophysiological assays

Channel	IC_{50} (µM)	Maximum test concentration (µM)
$hK_v11.1$ (hERG)	16.5	33.3
$hK_v4.3$/hKChIP2.2 (hI_{to})	27.3	33.3
$hK_v7.1$ / hKCNE1 (hIK_s)	14.8	33.3

Source: Table 1, Study Report # 3625SV

The lowest IC_{50} among them is 14.8 µmole/L(14.8 nmol/ml), which is 5287 ng/ml, with a molecular weight of the major metabolite at 357.25 g/mole. The greatest clinical Cmax reported for the major metabolite was 17.3 ng/ml for a dose of 45 mg tenapanor, given BID. This dose is greater than the maximum recommended human dose for this NDA (i.e., 30 mg BID). Therefore, there is at least a 300X concentration difference between the IC_{50} values and the clinical Cmax for the major metabolite, a reasonable large safety margin.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The Warnings and Precautions section of the FDA approved labeling for tenapanor for IBS-C include the risk of serious dehydration in pediatric patients and diarrhea. Other adverse reactions included severe diarrhea in patients with renal impairment (defined as eGFR less than 90 mL/min/1.73m^2) and hyperkalemia in patients with CKD (defined as eGFR from 25-70 mL/min/1.73m^2). Adverse events of special interest (AESI) explored by the Applicant in the safety population for this application included AEs suggestive of diarrhea, dehydration, and hyponatremia.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

There are no safety concerns identified through postmarketing experience; tenapanor approved for IBS-C is not currently marketed in the US, and it is not approved in any other country.

7.4. FDA Approach to the Safety Review

The safety analysis included a review of data quality, adverse events, laboratory data, baseline characteristics, concomitant medications, and vital sign datasets. Adverse events were analyzed by MedDRA [version 21.0] preferred term and by pooling similar adverse events (referred to as the MedDRA SMQ or FMQ). The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported were reviewed and found to be acceptable.

During review of the application, the review team identified potential incompleteness in reporting or coding of AE terms. These included events that occurred preceding hospitalization,

same day of admission, or during hospitalization for another adverse event. The review team determined the omissions raised concerns about performing an evaluation of the gastrointestinal safety profile, including potential clinical consequences of severe diarrhea. Therefore, the Agency requested that the Applicant review their data to ensure completeness of reporting AEs and propose analyses to provide additional information on the clinical consequences for patients with severe diarrhea.

The Applicant performed an evaluation of the safety data and identified an additional 151 AE terms that were not included in the original datasets. The Applicant subsequently submitted the requested analyses, updated safety data tables, and updated analysis datasets, for individual trials TEN-02-201, -202, -301, and the Integrated Safety Summary (ISS). The review team did not identify any further major data quality or integrity issues that precluded performing a safety review. No further major issues were identified with respect to recording, coding, and categorizing AEs.

A limitation for the safety analysis is that there were no double-blind, placebo-controlled initial treatment periods with tenapanor monotherapy. The safety review of tenapanor focuses primarily on the phase 3 trial, Study TEN-02-301. This trial has the longest exposure of tenapanor monotherapy (52 weeks), employed the dosing regimen proposed in labeling and includes the longest period of controlled safety data (a 26-week open-label treatment period with an active comparator). As discussed elsewhere in this review, the trial included different periods with different designs and, for the purpose of safety analyses, these different periods of the trial were analyzed separately. For 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. Data from an ongoing open-label extension study TEN-02-401 (monotherapy and combination therapy extension study for patients from TEN-02-301) were used to evaluate the safety of longer-term exposure.

In addition to the aforementioned analyses, analyses of safety findings from the Applicant's pooled ISS CKD on Dialysis Safety (CKDDS) Analysis dataset were also conducted. It is acknowledged, however, that the results of analyses based on pooled data from studies that differ in key aspects of study design can be challenging to interpret. Nevertheless, because of the larger number of subjects included, this dataset can be used to detect rarer AEs that would require a larger population. This dataset included safety data collected up to the first 12 weeks of treatment; all 4 weeks of treatment for D5611C00001, D5613C00001, and TEN-02-202; and all 12 weeks of treatment for TEN-02-201 (excluding safety data collected during the randomized withdrawal period from patients who received placebo) and TEN-02-301 (the first 12 weeks of treatment during the randomized open-label treatment period). Data in the ongoing open-label extension study TEN-02-401 are not included in the pooled ISS CKD on Dialysis Safety Analysis dataset.

7.5. Adequacy of the Clinical Safety Database

Overall total patient exposures were sufficient to assess for common AEs and events with short latency for the proposed indication, dosage regimen, and patient population. A total of 934 subjects with CKD on dialysis received daily tenapanor, with 637 of these subjects from the two pivotal monotherapy trials. In Study TEN-02-301, 419 subjects received at least one dose of tenapanor for 239.9 patient-years, with a mean duration of 209 days (~30 weeks). One hundred

five (105) subjects received at least one dose of tenapanor for a mean duration of 359 days (~51 weeks), 76 subjects for at least 12 months. A summary of exposure for Study TEN-02-301 is shown in Table 16.

In addition to the safety data for subjects with CKD on dialysis, the Applicant provided safety data for 1073 tenapanor-treated subjects with IBS-C, exposed during clinical development for the approved tenapanor product, of which 130 were treated with tenapanor for 12 months.

Table 16. Duration of Exposure, Safety Population, TEN-02-301[1]

Parameter	Tenapanor N=419	Phosphate Binder N=137	Placebo N=126
Duration of treatment (days)			
Mean (SD)	209.1 (129.1)	321.2 (97.8)	74.8 (22.0)
Median (min, max)	271 (1, 400)	365 (1, 405)	84 (1, 104)
Patients treated, by duration, n (%)			
Any duration (at least 1 dose)	419 (100)	137 (100)	126 (100)
<1 month[2]	60 (14.3)	3 (2.2)	11 (8.7)
≥1 month	359 (85.7)	134 (97.8)	115 (91.2)
≥3 months	306 (73.0)	129 (94.2)	19 (15.0)
≥6 months	250 (59.7)	120 (87.6)	0 (0.0)
≥12 months	76 (18.1)	69 (50.4)	0 (0.0)
Patient-Years	239.9	120.5	25.8

Source: Reviewer's Analysis; adsl.xpt; JMP
[1] All Treatment Periods Combined
[2] 1 month = 30 days; 12 months = 365 days
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation.

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Overall Adverse Event Summary

In the 26-week OL treatment period in Study TEN-02-301, AEs were reported in a greater proportion of subjects in the tenapanor group (80%) as compared to the phosphate binder group (64%); while SAEs were reported in a greater proportion of subjects in the phosphate binder group (23%) as compared to the tenapanor group (17%). Adverse events leading to discontinuation and dose reduction occurred in a greater proportion of subjects in the tenapanor group (24% and 34%, respectively) as compared to the phosphate binder group (1.5% and 4%, respectively). See Table 17 for an overview of AEs in the TEN-02-301 safety population.

Table 17. Overview of Adverse Events[1], Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period[2]		
Event	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Relative Risk (95% CI)	Tenapanor N=125 n (%)	Placebo[3] N=126 n (%)	Relative Risk (95% CI)
Any AE	337 (80.4)	88 (64.2)	1.3 (1.1, 1.4)	58 (46.4)	70 (55.6)	0.2 (0.2, 0.3)
Moderate or severe AEs (Grade 3-5)[4]	258 (56.8)	58 (42.3)	1.3 (1.1, 1.6)	38 (30.4)	48 (38.1)	0.2 (0.2, 0.3)
SAE	73 (17.4)	32 (23.4)	0.7 (0.5, 1.1)	14 (11.2)	13 (10.3)	0.3 (0.2, 0.7)
SAEs with fatal outcome	1 (0.2)	0 (0.0)	1.0 (0.0, 24.1)	0	0	0.3 (0, 15.2)
AE leading to discontinuation	102 (24.3)	2 (1.5)	16.7 (4.2, 66.7)	11 (8.8)	17 (13.5)	0.2 (0.1, 0.4)
AE leading to dose reduction	142 (33.9)	5 (3.6)	9.3 (3.9, 22.2)	1 (0.8)	0	0.9 (0, 22.1)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio
[1] 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
[2] Subjects in the 26-week treatment period who continued on the phosphate binder in the 12-week RWP were not included
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; Severe: events interrupt the patient'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
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event; OL, open-label; RW, randomized withdrawal

7.6.2. Deaths

Few deaths were reported during the 26-week OL treatment period in Study TEN-02-301 and the proportion was similar in the two arms (1.7% tenapanor arm and 2.2% phosphate binder arm). 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 ongoing TEN-02-401 OLE trial, two in the tenapanor group (1.8%) and 3 in the phosphate binder group (4.8%).

Table 18 shows the causes of deaths reported for the safety population in Study TEN-02-301. Death narratives, as well AEs, vital signs, electrocardiograms (ECGs), and laboratory data were reviewed. Most subjects had multiple cardiovascular risk factors and died due to cardiovascular disease or sepsis, which are common causes of death in patients with CKD on dialysis. There were no reports of severe diarrhea or diarrhea-related AEs in the tenapanor-treated subjects who died. Table 43 in the Appendix, Section 17, provides additional information on deaths during the 26-week OL treatment period.

Table 18. Deaths in Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Risk Difference (95% CI)	Tenapanor N=125 n (%)	Placebo[2] N=126 n (%)	Risk Difference (95% CI)
Total deaths[1]	**7 (1.7)**	**3 (2.2)**	**-0.5 (-1.8, 4.6)**	**1 (0.8)**	**1 (0.8)**	**0.0 (-3.3, 1.5)**
Reported Cause						
Cardiac arrest	2 (0.5)	0 (0.0)	0.5 (-2.2, 1.8)	1 (0.8)	0 (0.0)	0.8 (-2.0, 2.2)
Cardiac arrest, Septic shock	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Cardiogenic shock, Septic shock	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Chronic kidney disease/End Stage	0 (0.0)	1 (0.7)	-0.7 (-0.4, 4.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Myocardial infarction	0 (0.0)	1 (0.7)	-0.7 (-0.4, 4.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Respiratory Failure	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Sepsis	2 (0.5)	0 (0.0)	0.5 (-2.2, 1.8)	0 (0.0)	1 (0.8)	-0.8 (-2.0, 2.2)
Sudden Cardiac Death	0 (0.0)	1 (0.7)	-0.7 (-0.4, 4.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; JMP
[1] Includes treatment-emergent defined as any death that occurred after the first dose of drug up to end of the 12-week RW treatment period
[2] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

7.6.3. Serious Adverse Events

SAEs were reported in a higher proportion of phosphate binder-treated subjects as compared to tenapanor-treated subjects in the 26-week OL treatment period of Study TEN-02-301. SAEs occurring in ≥ 3 subjects and at a 0.5% higher risk difference in the tenapanor than the comparator group are shown in the table below. These SAEs included chest pain, acute respiratory failure, gastrointestinal hemorrhage, diarrhea, and hypertensive emergency. Narratives and vital signs and laboratory data were reviewed to evaluate the chest pain, hypertensive emergency, and respiratory AEs. Most narratives for subjects reporting AEs of chest pain, hypertensive emergency, and respiratory AEs described noncompliance with hemodialysis management or preexisting comorbidities of congestive heart failure or chronic obstructive pulmonary disorder, which are common in this patient population. Additional analyses for diarrhea and gastrointestinal hemorrhage are presented in Section 7.6.6.

The ISS CKDDS Analysis Set was also assessed to determine if any particular SOC was over-represented. Results of these analyses were as a whole, consistent with the analyses of Study TEN-02-301. Table 42 is provided in the Appendix, Section 17.

Table 19. Serious Adverse Events Occurring in ≥ 3 Subjects and 0.5% Higher Risk Difference in Tenapanor Than Comparator, By Descending Order, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Serious Adverse Event[1,2]	**Tenapanor N=419 n (%)**	**Phosphate Binder N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
Subjects with at least one SAE	73 (17.4)	32 (23.4)	-0.7 (0.5, 1.1)	14 (11.2)	13 (10.3)	0.9 (-7.0, 8.8)
Chest Pain[4]	2 (0.5)	5 (3.6)	-3.1 (0.7,7.7)	5 (4.0)	2 (1.6)	2.4 (-2.2, 7.6)
Acute Respiratory Failure[5]	11 (2.6)	1 (0.7)	1.9 (-1.6, 4.0)	0 (0.0)	1 (0.8)	-0.8 (-0.8, -2.34)
Gastrointestinal hemorrhage[6]	3 (0.7)	0 (0.0)	0.7 (-0.2, 1.1)	1 (0.8)	1 (0.8)	0.0 (0.0, 0.0)
Diarrhea[7]	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	1 (0.8)	0 (0.0)	0.8 (-0.8, 2.4)
Hypertensive emergency[8]	5 (1.2)	1 (0.7)	0.5 (-2.8, 2.2)	1 (0.8)	0 (0.0)	0.8 (-0.8, 2.4)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; MAED
[1] 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;
[2] Terms included are coded as MedDRA PT and those that occurred more often in the treatment than comparator group
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PTs non-cardiac chest pain, angina unstable, angina pectoris
[5] Includes PTs respiratory failure, respiratory distress
[6] Includes PTs rectal hemorrhage and upper gastrointestinal hemorrhage
[7] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[8] Includes hypertensive crisis
Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term.

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

As previously noted, the proportion of subjects who discontinued treatment due to an AE was substantially greater in the tenapanor as compared to the phosphate binder group in the 26-week OL treatment period of Study TEN-02-301 (24.3% and 1.5%, respectively). Table 20 provides an overview of the AEs leading to discontinuation. The most common reasons for discontinuation in the tenapanor-treated subjects were diarrhea (15.5%) and hyperphosphatemia (6%). The majority of discontinuations occurred in the first 30 days of tenapanor treatment; however, discontinuations were reported even beyond the initial 30 days (Figure 11). During the randomized withdrawal period, most discontinuations were for hyperphosphatemia events, which, as might be expected, occurred in greater proportion of subjects randomized to the placebo arm. Analyses of Studies TEN-02-202 and TEN-02-201, and the ISS CKDDS analysis dataset gave similar results.

Table 20. Adverse Events Leading to Discontinuation Occurring in ≥ 3 Subjects and 0.5% Higher Risk Difference in Tenapanor Than Comparator, by Descending Difference Order, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Adverse Event[1]	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Risk Difference (95% CI)	Tenapanor N=125 n (%)	Placebo[2] N=126 n (%)	Risk Difference (95% CI)
Subjects with at least 1 AE leading to discontinuation	102 (24.3)	2 (1.5)	22.8 (17.4, 27.3)	11 (8.8)	17 (13.5)	-4.7 (-3.3, 12.7)
Diarrhea[3]	65 (15.5)	1 (0.7)	14.8 (11.0, 18.5)	1 (0.8)	0 (0.0)	0.8 (-0.8, 2.4)
Hyperphosphatemia	25 (6.0)	0 (0.7)	5.2 (2.6, 7.9)	7 (5.6)	15 (11.9)	-6.3 (-0.8, 13.7)
Hypophosphatemia	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	1 (0.8)	-0.8 (-0.8, -2.34)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; MAED
[1] Coded as MedDRA PT
[2] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[3] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

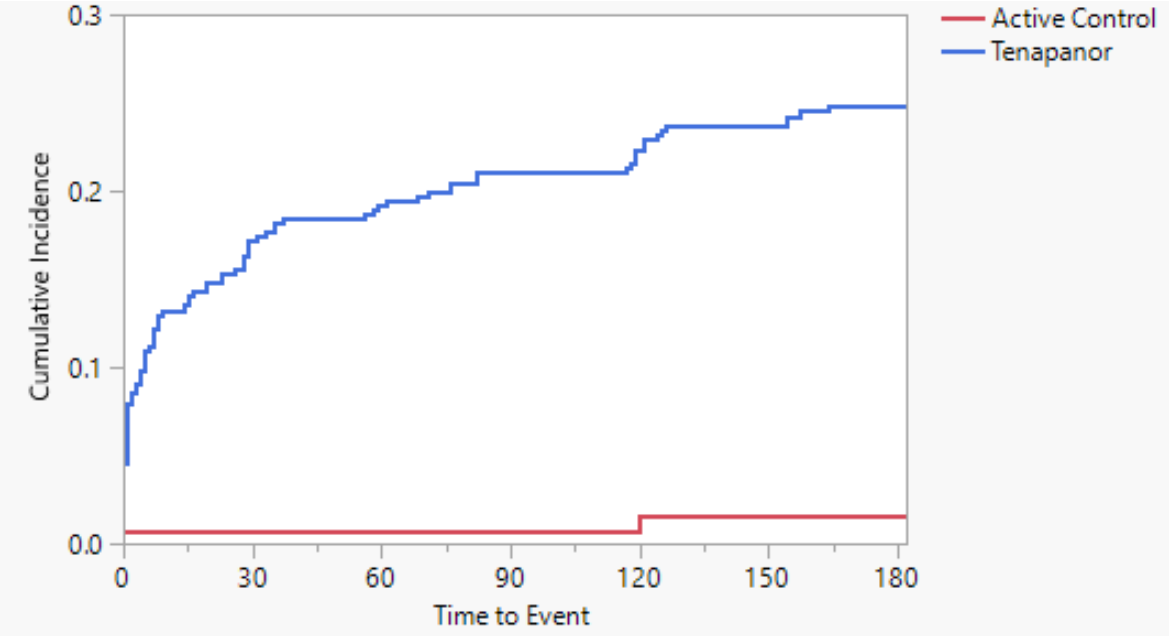


Figure 15. Kaplan-Meier Plot of Subjects with Permanent Discontinuation of Study Drug due to and Adverse Event, Safety Population, TEN-02-301, 26-Week Treatment Period

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

7.6.5. Treatment-Emergent Adverse Events

Common TEAEs that occurred in a greater proportion of subjects in the tenapanor group than in the phosphate binder in the 26-week OL treatment period of Study TEN-02-301 included diarrhea and hyperphosphatemia. AEs occurring in ≥ 3 subjects and at 0.5% higher incidence in tenapanor-treated subjects than in the comparator group in Study TEN-02-301 are shown in the table below. A number of the adverse event groupings in this table are FDA MedDRA queries

(FMQs). Additional analyses for diarrhea, hyponatremia, and AEs related to dehydration and gastrointestinal hemorrhage are presented in Section 7.6.6.

Analyses of Studies TEN-02-202, TEN-02-201, and the ISS CKDDS analysis dataset gave similar results.

Table 21. Adverse Events[1] Occurring in ≥ 3 Subjects and 0.5% Higher Risk Difference in Tenapanor Than Comparator, Safety Population, TEN 02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Adverse Event[2]	**Tenapanor N=419 n (%)**	**Phosphate Binder 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] Treatment-emergent adverse event defined as any event that occurred after the first dose of drug up to end of the 12-week RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[5] Includes PTs blood phosphorus increased
[6] Includes PTs respiratory failure and respiratory distress
[7] Includes PT hypoxia
[8] Includes PT hypertensive crisis
[9] Includes PT cardiac failure
[10] Includes PT hypovolemia
[11] Includes PTs rectal hemorrhage, hemorrhoidal hemorrhage, upper gastrointestinal hemorrhage
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.; COPD, Chronic obstructive pulmonary disorder

Table 22. FDA MedDRA Queries[1] Occurring in ≥ 3 Subjects and at 0.5% Higher Frequency in Treatment Arm Than Comparator Arm, Safety Population, TEN-02-301, First 26 Weeks

FDA MedDRA Query[2]	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Risk Difference (95% CI)
FMQ Narrow			
Diarrhea	222 (53)	10 (7.3)	45.7 (38.3, 51.5)
Dyspnea	9 (2.1)	1 (0.7)	1.4 (-2.0, 3.4)
Malignancy	5 (1.2)	0 (0.0)	1.2 (-1.6, 2.8)
Diabetic ketoacidosis	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)
Hemorrhage	19 (4.5)	5 (3.6)	0.9 (-4.0, 4.1)
Back pain	10 (2.4)	2 (1.5)	0.9 (-3.0, 3.1)
FMQ Broad			
Diarrhea	226 (53.9)	11 (8.0)	45.9 (38.4, 51.8)
Diabetic ketoacidosis	11 (2.6)	1 (0.7)	1.9 (-1.6, 4.0)
Dyspnea	9 (2.1)	1 (0.7)	1.4 (-2.0, 3.4)
Malignancy	5 (1.2)	0 (0.0)	1.2 (-1.6, 2.8)
Hepatic failure	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)
Urinary retention	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)
Confusional state	5 (1.2)	1 (0.7)	0.5 (-2.8, 2.2)
Hepatic injury	5 (1.2)	1 (0.7)	0.5 (-2.8, 2.2)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; 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 RW treatment period.
[2] Coded as MedDRA PT
Abbreviations: CI, confidence interval; FMQ, FDA MedDRA Query; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.

Table 23. FDA MedDRA Queries[1] Occurring in ≥ 3 Subjects and at 0.5% Higher Frequency in Tenapanor Arm than Comparator Arm, Safety Population, TEN-02-301, 12-Week Treatment Period

FDA MedDRA Query[2]	Tenapanor N=125 n (%)	Placebo[3] N=126 n (%)	Risk Difference (95% CI)
FMQ Narrow			
Diarrhea	5 (4.0)	2 (1.6)	2.4 (-2.2, 7.6)
Pruritis	3 (2.4)	2 (1.6)	0.8 (-3.5, 5.4)
Systemic Hypertension	3 (2.4)	2 (1.6)	0.8 (-3.5, 5.4)
FMQ Broad			
Diarrhea	6 (4.8)	3 (2.4)	2.4 (-2.7, 7.9)
Dyspepsia	4 (3.2)	2 (1.6)	1.6 (-2.9, 6.5)
Rash	3 (2.4)	1 (0.8)	1.6 (-2.3, 6.1)
Pruritis	3 (2.4)	2 (1.6)	0.8 (-3.5, 5.4)
Syncope	3 (2.4)	2 (1.6)	0.8 (-3.5, 5.4)
Systemic Hypertension	3 (2.4)	2 (1.6)	0.8 (-3.5, 5.4)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; 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 RW treatment period.
[2] Coded as MedDRA PT
Abbreviations: CI, confidence interval; FMQ, FDA MedDRA Query; N, number of subjects; n, number of subjects with adverse event

7.6.6. Adverse Events of Special Interest

Pre-defined AESIs for Study TEN-02-301 were based on the known mechanism of action of tenapanor and included diarrhea, dehydration, and hyponatremia. Overall, the incidence of these events was higher in the tenapanor group as compared to the phosphate binder group in the 26-week OL treatment period of Study TEN-02-301, with diarrhea having the greatest observed risk difference. Table 24 provides a summary of the pre-defined AESIs in both the 26-week OL treatment period of Study TEN-02-301 and the 12-week randomized withdrawal treatment period. These findings are discussed further below.

Table 24. Adverse Events of Special Interest[1,2], Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Experienced any AESI	**Tenapanor N=419 n (%)**	**Phosphate Binder N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
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)
Dehydration[5]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0
Hyponatremia	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio
[1] Treatment-emergent adverse event defined as any event that occurred after the first dose of drug up to end of the 12-week RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[5] Includes PT hypovolemia
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term.; COPD, Chronic obstructive pulmonary disorder

7.6.6.1. Diarrhea

Study TEN-02-301

In the 26-week OL treatment period of Study TEN-02-301, the incidence of diarrhea was 54% in the tenapanor group, corresponding to an event rate of 144 per 100 patient-years and 8% in the phosphate binder group, corresponding to an event rate of 12 per 100 patient-years (Table 25). The incidence of SAEs was much lower; three (0.5%) patients in the tenapanor group versus none in the phosphate binder group had SAEs related to diarrhea. 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; and Subject (b) (6) was hospitalized with dehydration on day 6 of the study due to severe diarrhea that started after the first dose. No patient reported a SAE of diarrhea during the 12-week randomized withdrawal period.

Diarrhea severity was classified by the investigator as mild, moderate, or severe.[12] Approximately 15%, 33%, and 6% of subjects in the tenapanor group experienced at least one

[12] Severity definitions: Mild - The patient experiences awareness of symptoms but these are easily tolerated or managed without specific treatment. Moderate - The patient experiences discomfort enough to cause interference

episode of mild, moderate, or severe diarrhea, respectively, versus 5%, 3%, and 0 subjects in the phosphate binder group in the 26-week OL treatment period. Baseline patient characteristics that were evaluated, such as age, weight, and serum phosphorus concentration, did not predict severity. Concomitant antidiarrheals during treatment were reported in a higher proportion of tenapanor-treated subjects (34%) versus subjects in the phosphate binder group (19%). Approximately 32% of tenapanor- treated subjects required a dose reduction and 16% required discontinuation because of diarrhea during the initial 26-week period. In comparison, one subject in the active control arm had their treatment discontinued for diarrhea and no subject had a dose reduction or interruption. Among the tenapanor-treated subjects who entered the RW period,[13] few subjects in either arm reported moderate diarrhea events (3% tenapanor versus 2% placebo) or severe events (0 events in the tenapanor group versus one in the placebo group).

The majority of diarrhea events in the tenapanor group occurred in the first 7 days (Figure 12). Diarrhea lasted for a mean duration of 41 days (median 13 days) and was recurrent (≥ 2 episodes reported) in 14% of the tenapanor-treated subjects versus 2% of phosphate binder-treated subjects. In subgroup analyses, males and subjects over 65 years old appeared to have the greatest risk difference (Figure 13).

Study TEN-02-201
Diarrhea was reported in 40% of tenapanor-treated subjects in the initial 8-week parallel group treatment period of Study TEN-02-201 (n=218; no comparator). Approximately 18%, 20%, and 2% of subjects experienced at least one episode of mild, moderate or severe diarrhea, respectively. Study medication discontinuation due to diarrhea was reported in 8% of patients, and dose reduction was reported in 10% (Table 44, provided in the Appendix).

Study TEN-02-202
In the 4-week placebo-controlled treatment period of Study TEN-02-202, 50 subjects (43%) treated with tenapanor (plus a phosphate binder) versus 8 subjects (7%) treated with placebo (plus a phosphate binder) reported diarrhea. Approximately 19%, 21%, and 3% of tenapanor-treated experienced at least one episode of mild, moderate or severe diarrhea respectively, versus 5%, 2%, and 0 in the placebo arm. In contrast to the other trials, discontinuations due to diarrhea were uncommon and were reported in a similar proportion of subjects in the tenapanor arm (3%) and placebo arm (2%). However, dose reductions were reported in 27% of subjects in the tenapanor arm as compared to 4% of placebo arm (Table 45, provided in the Appendix).

ISS
A list of diarrhea AEs leading to discontinuation by treatment group and dosage for the ISS CKD on Dialysis Safety Analysis Set is provided in the Appendix.

Other findings

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.
[13] Only 255 of the 419 tenapanor-treated subjects (61%) completed the 26-week treatment period and were re-randomized 1:1 to receive tenapanor (n=128) or placebo (n=127) during the 12-week RW period; included in the Safety Analysis Data Set were 125 subjects randomized into the tenapanor arm and 126 randomized in the placebo arm.

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 and hyponatremia are discussed in subsequent sections.

In the 26-week OL treatment period of Study TEN-02-301, two of the six cases of GI-related hemorrhage in the tenapanor arm were temporally-associated with diarrhea; one patient reported rectal hemorrhage and one patient (subject (b) (6)) reported hemorrhoidal bleed on study day 3 for which the drug was permanently withdrawn (Table 26). In the randomized withdrawal period, one patient 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 trial TEN-02-401, two other tenapanor-treated subjects have 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.

There were two tenapanor-treated subjects that reported colitis in the 26-week treatment period as compared to none in the phosphate binder group. No such cases were reported during the randomized withdrawal period. One of these subjects (b) (6) reported colitis (non-serious) 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 non-serious) on days 153-176 of the study which resulted in a dose reduction; the subject discontinued the study on day 175. There were no other reports of colitis in the phase 2 or 3 trials included in the ISS CKD on Dialysis Safety Analysis Set.

Table 25. Diarrhea, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Preferred Term[1,2]	**Tenapanor N=419 n (%)**	**Phosphate Binder N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
Diarrhea[4]	226 (53.9)	11 (8.0)	45.9 (38.4, 51.8)	6 (4.8)	2 (1.6)	3.2 (-1.6, 8.6)
AE Severity[5]						
Mild	61 (14.6)	7 (5.1)	9.5 (3.6, 14.0)	2 (1.6)	0 (0.0)	1.6 (-1.6, 5.6)
Moderate	140 (33.4)	4 (2.9)	30.5 (24.4, 35.5)	4 (3.2)	1 (0.8)	2.4 (-1.7, 7.2)
Severe	25 (6.0)	0	6.0 (2.7, 8.7)	0 (0.0)	1 (0.8)	-0.8 (-2.3, 4.4)
Moderate or Severe AE	165 (39.3)	4 (2.9)	36.4 (30.1, 41.4)	4 (3.2)	2 (1.6)	1.6 (-2.9, 6.5)
SAE	3 (0.7)	0 (0.0)	0.7 (-0.1, 1.5)	1 (0.8)	0 (0.0)	0.8 (-2.2, 4.4)
Action Taken with Drug						
Discontinuation	65 (15.5)	1 (0.7)	14.8 (10.3, 18.6)	1 (0.8)	0 (0.0)	0.8 (-2.2, 4.4)
Interruption	6 (1.4)	0	1.4 (-1.4, 3.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Dose Reduction	135 (32.2)	0	32.2 (27.1, 36.8)	1 (0.8)	0 (0.0)	0.8 (-2.2, 4.4)

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 RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] At least one episode; Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[5] Includes first episode only; Severity definitions were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

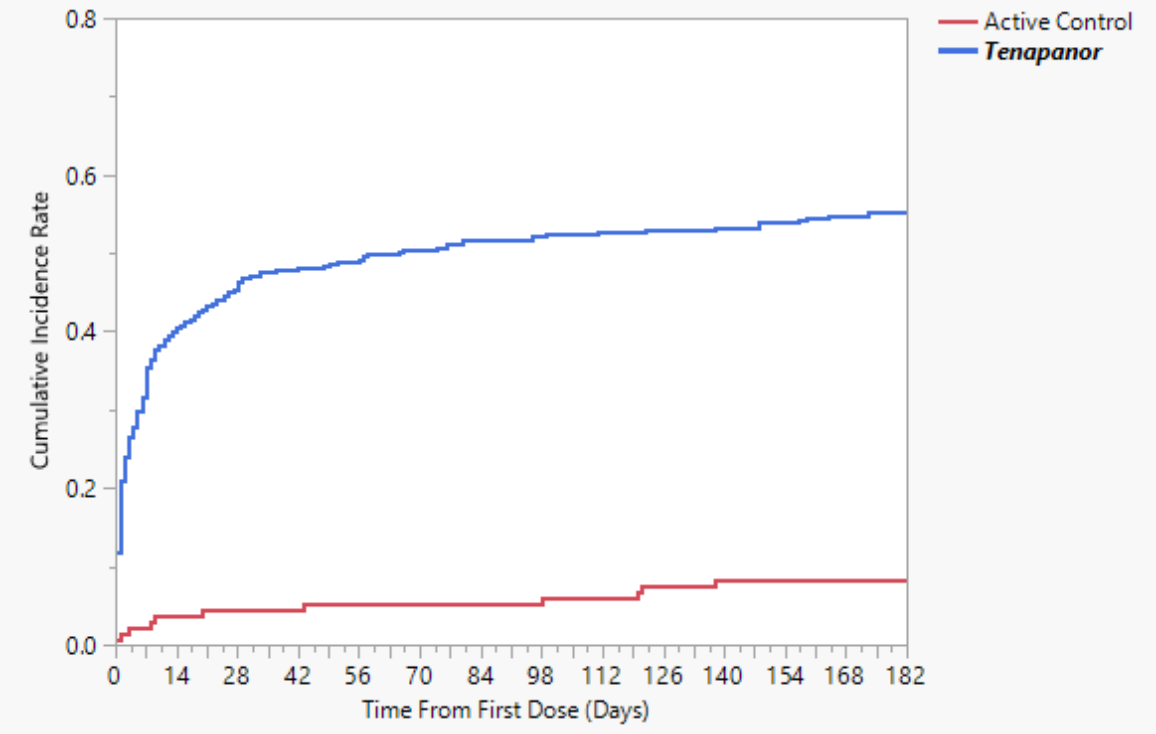


Figure 16. Kaplan Meier Plot of Subjects Reporting First Occurrence of Diarrhea, Safety Population, TEN-02-301, 26-Week Treatment Period

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

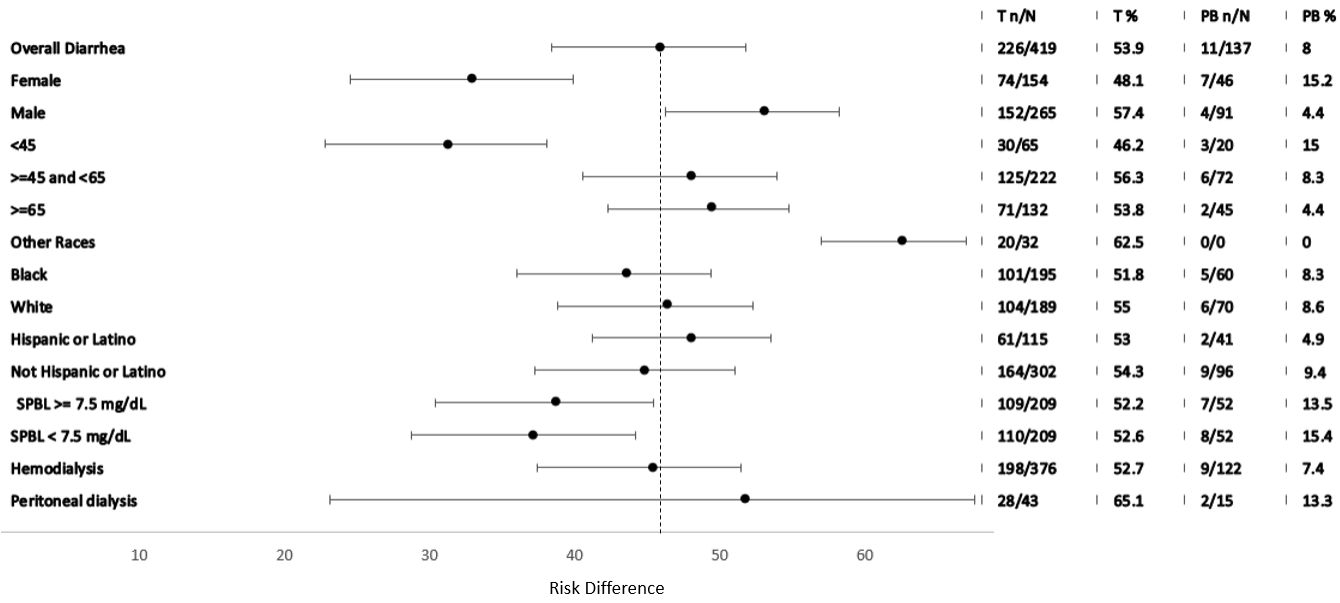


Figure 17. Diarrhea by Subgroup, Safety Population, TEN-02-301, 26-Week Treatment Period

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

Table 26. Gastrointestinal Hemorrhage, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
	Tenapanor N=419 n (%)	Phosphate Binder N=137 n (%)	Risk Difference (95% CI)	Tenapanor N=125 n (%)	Placebo[1] N=126 n (%)	Risk Difference (95% CI)
GI-related Hemorrhage	6 (1.4)	0 (0.0)	1.4 (-1.4, 3.0)	1 (0.8)	2 (1.6)	-0.8 (-3.0, 4.8)
SAE	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	1 (0.8)	1 (0.8)	0
Preferred Term[2,3]						
GI Hemorrhage	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	1 (0.8)	1 (0.8)	0
Hemorrhoidal hemorrhage	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Rectal hemorrhage	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	0 (0.0)	0 (0.0)	0
Upper GI Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	-0.8 (-2.3, 4.4)
Action Taken with Drug						
Discontinuation	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	1 (0.8)	1 (0.8)	0
Interruption	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	1 (0.8)	1 (0.8)	0
Dose not changed	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	0 (0.0)	0 (0.0)	0
Temporally related to diarrhea	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	0 (0.0)	0 (0.0)	0
Sex						
Female	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	1 (0.8)	1 (0.8)	0
Male	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)	0 (0.0)	1 (0.8)	-0.8 (-2.3, 4.4)
Age (years)						
<45	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	0 (0.0)	0 (0.0)	0
>=45 to 65	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	1 (0.8)	0 (0.0)	0.8 (-2.2, 4.4)
>65	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	0	2 (1.6)	-1.6 (-2.3, 4.4)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio, JMP
[1] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[2] Treatment-emergent adverse event defined as any event that occurred after the first dose of drug up to end of the 12-week RW treatment period.
[3] Coded as MedDRA preferred terms
Abbreviations: CI, confidence interval; GI, gastrointestinal; N, number of subjects; n, number of subjects with adverse event

7.6.6.2. Dehydration

In Study TEN-02-301, there were five reports of dehydration in the tenapanor group, event rate of 3.2 per 100 patient-years, and all were reported in the first 60 days of the 26-week OL treatment period (Figure 14). In contrast, no events were reported in the phosphate binder group (Table 27). Two reports of dehydration were temporally related to diarrhea, (discussed in Section 7.6.6.1); in both cases, the subjects were hospitalized and withdrew from the study. Subject (b) (6) was hospitalized with dehydration on study day 6 due to an episode of severe diarrhea. Subject (b) (6) was hospitalized on study day 36 with dehydration after a several weeks of moderate diarrhea. One report of dehydration was temporally related to the subject's second bout of worsening colitis on study day 37. The remaining two subjects reported mild and severe diarrhea, but not temporal to the dehydration event; these subjects completed the study with the dose unchanged or reduced.

There were no other reports of dehydration in the phase 2 or 3 trials included in the ISS CKD on Dialysis Safety Analysis Set.

Table 27. Dehydration, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Preferred Term[1,2]	**Tenapanor N=419 n (%)**	**Phosphate Binder N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
Dehydration[4]	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0
SAE	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Action Taken with Drug						
Discontinuation	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	0 (0.0)	0 (0.0)	0
Interruption	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Dose Reduction	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Temporally related to diarrhea	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	0 (0.0)	0 (0.0)	0
Sex						
Female	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Male	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)	0 (0.0)	0 (0.0)	0
Age						
>=45 to 65	2 (0.5)	0 (0.0)	0.5 (-2.3, 1.8)	0 (0.0)	0 (0.0)	0
>65	3 (0.7)	0 (0.0)	0.7 (-2.1, 2.1)	0 (0.0)	0 (0.0)	0

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 RW treatment period.
[2] Coded as MedDRA preferred terms
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PT hypovolemia
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

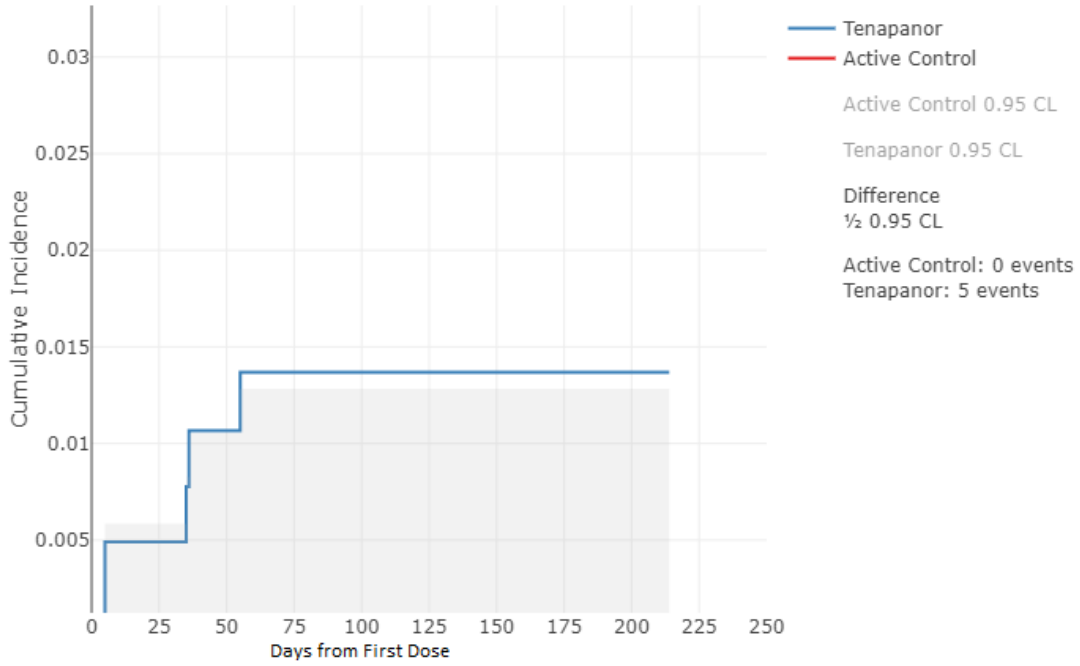


Figure 18. Kaplan Meier Plot of Subjects Reporting First Occurrence of Dehydration, Safety Population, TEN-02-301, 26-Week Treatment Period

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Temporal Tool

7.6.6.3. Hyponatremia

In Study TEN-02-301, there were five reports of hyponatremia in the tenapanor group, event rate of 3.2 per 100 patient-years; all reported in the initial 26-week OL treatment period (Figure 15). None were reported in the phosphate binder group (Table 28). There was one serious report of hyponatremia temporally related to diarrhea; the subject ([redacted] (b) (6), discussed above) was hospitalized and withdrew from the study. Three of the remaining 4 subjects reported moderate diarrhea during the study, but not temporal to the hyponatremia event. Two of the five subjects completed the study. Although hyponatremia was not reported as an AE in the randomized withdrawal period, abnormalities for 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 (Table 29).

There were no other reports in the phase 2 or 3 trials included in the ISS CKD on Dialysis Safety Analysis Set.

Table 28. Hyponatremia, Safety Population, TEN-02-301

	26-Week OL Treatment Period			12-Week RW Treatment Period		
Preferred Term[1,2]	**Tenapanor N=419 n (%)**	**Phosphate Binder N=137 n (%)**	**Risk Difference (95% CI)**	**Tenapanor N=125 n (%)**	**Placebo[3] N=126 n (%)**	**Risk Difference (95% CI)**
Hyponatremia	5 (1.2)	0 (0.0)	1.2 (0.2, 2.2)	0 (0.0)	0 (0.0)	0
SAE	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Action Taken with Drug						
Discontinuation	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Interruption	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Dose Reduction	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Temporally related to diarrhea	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Sex						
Female	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0
Male	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)	0 (0.0)	0 (0.0)	0
Age						
>=45 to 65	4 (1.0)	0 (0.0)	1.0 (-1.8, 2.5)	0 (0.0)	0 (0.0)	0
>65	1 (0.2)	0 (0.0)	0.2 (-2.5, 1.3)	0 (0.0)	0 (0.0)	0

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 RW treatment period.
[2] Coded as MedDRA preferred terms
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

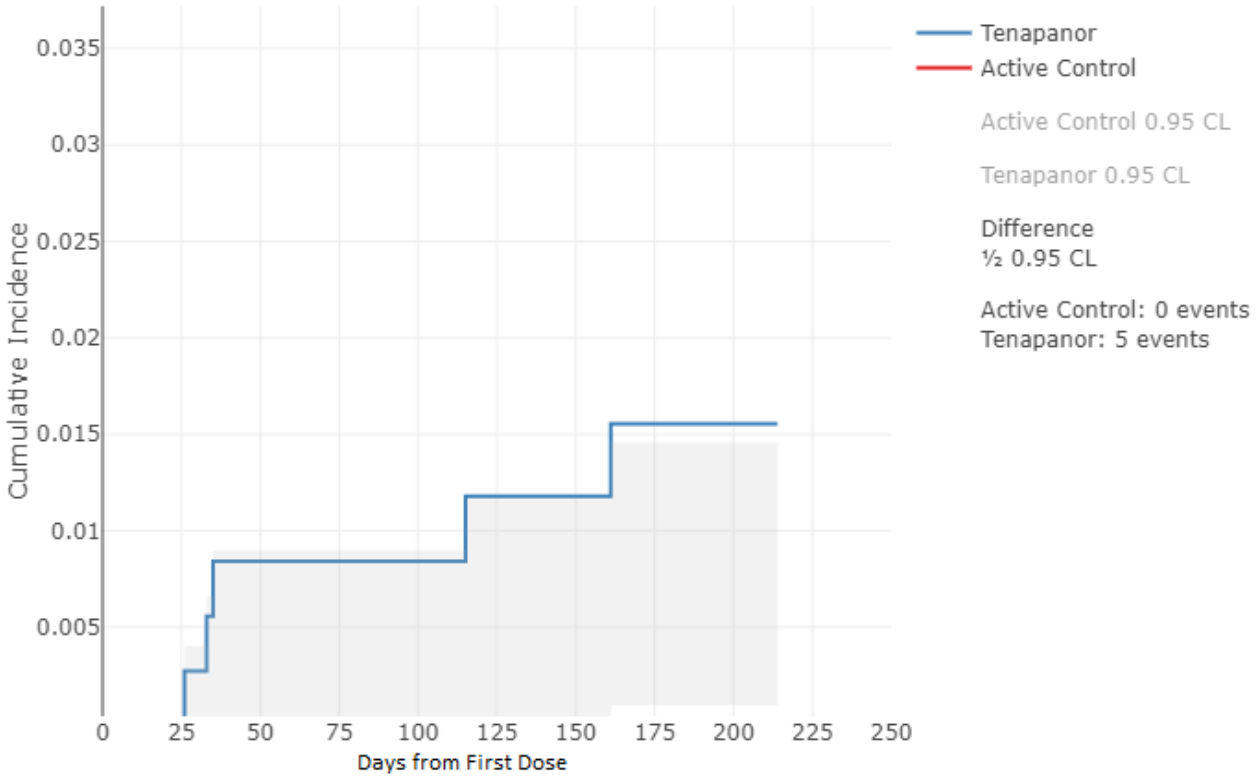


Figure 19. Kaplan Meier Plot of Subjects Reporting First Occurrence of Hyponatremia, Safety Population, TEN-02-301, 26-Week Treatment Period

Source: Reviewer's analysis; adae.xpt, adsl.xpt; OCS Temporal Tool

7.6.7. Laboratory Findings

Analyses were conducted for the following laboratory values: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin (BILI), bicarbonate, blood urea nitrogen (BUN), chloride, hemoglobin, leukocytes, neutrophils, platelet count, potassium, and sodium. Mean laboratory values at each visit and mean change from baseline values were compared between treatment groups for trial TEN-02-301 by treatment period. Shifts from normal at baseline to above the upper limit of normal (ULN) or below the lower limit of normal (LLN) at the end of the treatment periods were also compared between treatment groups.

Significant differences detected between treatment groups for the laboratory tests in TEN-02-301 included sodium, potassium, bicarbonate, creatine kinase, calcium, and alkaline phosphatase (Table 29).

Sodium

A shift in sodium from normal at baseline to below normal at the end of the randomized withdrawal period occurred in a greater proportion of subjects in the tenapanor arm (15%) versus placebo (5%). The decrease in sodium is likely due to the mechanism of action for tenapanor

Potassium

A shift in potassium from normal at baseline to above normal at the end of the randomized withdrawal period occurred in a greater proportion of subjects in the tenapanor arm (17%) versus placebo (7%). This increase in potassium is likely due to an intracellular mechanism to compensate for excess export of sodium.

Bicarbonate

A shift in bicarbonate from normal at baseline to below normal was observed at the end of the 26-week and randomized withdrawal treatment periods in a greater proportion of the tenapanor-treated (8% and 9%, respectively) versus comparators, phosphate binder (4%) and placebo (4%). This decrease in bicarbonate could potentially be related to the diarrhea.

Creatine Kinase

A shift in creatine kinase from normal at baseline to above normal was observed at the end of the 26-week and randomized withdrawal treatment periods in a greater proportion of the tenapanor-treated (6% and 8% respectively) versus comparators, phosphate binder (3%) and placebo (5%). This increase in creatine kinase could potentially be related to the diarrhea.

Calcium

A shift in calcium and corrected calcium from normal at baseline to below normal was observed at the end of the 26-week treatment period in a greater proportion of the tenapanor-treated (14% and 13%, respectively) versus the phosphate binder treated (11% and 11%, respectively).

Alkaline Phosphatase

A shift in alkaline phosphatase from normal at baseline to above normal at the end of the randomized withdrawal period occurred in a greater proportion of subjects in the tenapanor arm (13%) versus placebo (4%). These findings were not observed in the other hepatic enzymes.

Results were similar for the CKD on Dialysis Integrated Safety Analysis Set.

Hepatic Enzyme Changes Meeting Hy's Law Criteria

There were no subjects reporting hepatic enzyme changes that met Hy's Law criteria at any time during TEN-02-301 or in the CKD on Dialysis Integrated Safety Analysis Set. There was one subject (b) (6) who died from sepsis with biliary source on day 48 of Study TEN-02-301; the narrative described an AST level of 40 times ULN and ALT level three times ULN at hospital admission on day 45 of the study; bilirubin and alkaline phosphatase were not reported. The AST and ALT levels continued to increase during hospitalization (3 days after tenapanor was interrupted). Results from a hepatobiliary scan reported markedly abnormal and suggestive of severe hepatocellular dysfunction. The subject was unable to undergo cholecystostomy drain placement due to hemodynamic instability. The subject had no history of hepatic illness and the baseline hepatic enzymes were reported as normal. Concomitant medications included amiodarone which is known to cause liver toxicity.

There was one other subject (b) (6) with acute cholecystitis with gallbladder stones and transaminitis that occurred on day 20 of Study TEN-02-301; the patient underwent cholecystectomy and later withdrew from the study.

Table 29. Subjects Meeting Laboratory Abnormality Criteria, From Baseline Through Week 38, Safety Population, TEN-02-301

	26-Week OL Treatment Period		12-Week RW Treatment Period	
Laboratory Analysis	**Tenapanor**	**Phosphate Binder**	**Tenapanor**	**Placebo**
Sodium				
Measured[1]	N=249	N=114	N=104	N=114
Normal Baseline to <LLN (n; %)	23 (9.2)	13 (11.4)	16 (15.4)	6 (5.3)
Mean Value[2] (mEq/L)	131.6	131.8	130.9	131.8
Mean Change from Baseline[2]	-4.7	-4.8	-5.7	-3.3
Potassium				
Measured[1]	N=240	N=107	N=103	N=111
Normal Baseline to >ULN (n; %)	32 (13.3)	17 (15.9)	17 (16.5)	8 (7.2)
Mean Value[2] (mmol/L)	5.8	5.6	5.9	5.3
Mean Change from Baseline[2]	0.7	0.5	1.1	0.7
Bicarbonate				
Measured[1]	N=250	N=114	N=104	N=114
Normal Baseline to <LLN (n; %)	21 (8.4)	5 (4.4)	9 (8.7)	5 (4.4)
Mean Value[2] (mEq/L)	18.6	19.3	19.3	18.8
Mean Change from Baseline[2]	-3.8	-2.4	-4.0	-5.2
Creatine Kinase				
Measured[1]	N=250	N=114	N=104	N=113
Normal Baseline to >ULN (n; %)	14 (5.6)	3 (2.6)	8 (7.7)	6 (5.3)
Mean Value[2] (U/L)	293.9	224.8	365.9	354.7
Mean Change from Baseline[2]	152.2	107.8	245.5	234.7
Calcium				
Measured[1]	N=249	N=113	N=104	N=113
Normal Baseline to <LLN (n; %)	35 (14.1)	12 (10.6)	13 (12.5)	27 (23.9)
Mean Value[2] (mmol/L)	8.2	8.2	8.0	8.0
Mean Change from Baseline[2]	-0.8	-0.7	-1.0	-0.9
Corrected Calcium				
Measured[1]	N=249	N=113	N=104	N=113
Normal Baseline to <LLN (n; %)	32 (12.9)	12 (10.6)	14 (13.5)	25 (22.1)
Mean Value[2] (mmol/L)	8.1	8.3	8.0	8.0
Mean Change from Baseline[2]	-0.7	-0.8	-0.8	-0.9
Alkaline Phosphatase				
Measured[1]	N=250	N=114	N=104	N=114
Normal Baseline to >ULN (n; %)	32 (12.8)	14 (12.2)	14 (13.4)	5 (4.4)
ALP >3X ULN (n; %)	0	0	0	0

Source: Reviewer's analysis: adlb.xpt, JMP
[1] Collected at the end of the treatment period
[2] Subjects reporting shift only
Abbreviations: LLN, lower limit of normal; N, number of subjects; n, number of subjects with abnormality; ULN, upper limit of normal.

7.7. Review Issues Relevant to the Evaluation of Risk

7.7.1. Diarrhea

Issue: Diarrhea was the most common adverse reaction in clinical trials of tenapanor in patients with CKD on dialysis and resulted in dose reductions and treatment discontinuations in a significant proportion of tenapanor-treated patients. In addition to raising concerns about tolerability, diarrhea can also lead to complications, such as dehydration and clinically significant electrolyte losses. Because of age and underlying comorbidities, the target population may be particularly susceptible to such complications.

Assessment: Tenapanor acts locally in the GI tract by inhibiting the sodium/hydrogen exchanger isoform 3 in the intestine. In Study TEN-02-301, over half of tenapanor-treated patients (226/419; 54%) reported diarrhea in the initial 26-week treatment period and of those patients reporting diarrhea, 73% (165/226) had at least one adverse event of moderate to severe diarrhea. Among tenapanor-treated patients, approximately 32% required a dose reduction and 16% required discontinuation of tenapanor because of diarrhea during the initial 26-week period. In comparison, one patient in the active control arm had their treatment discontinued for diarrhea and no subject had a dose reduction or interruption for diarrhea. In contrast to the monotherapy trials, in Study TEN-02-202, which assessed use in combination with existing phosphate binder treatment, discontinuations due to diarrhea were uncommon (3% in tenapanor arm, vs 2% placebo). Although rare, there were serious AEs of rectal bleeding, dehydration, and hyponatremia temporally associated with diarrhea, resulting in hospitalization and treatment withdrawal.

Conclusion: Diarrhea, sometimes severe, was the most common adverse reaction in tenapanor-treated patients with CKD on dialysis. Although this risk can be addressed via labeling, in clinical trials, a significant proportion of tenapanor-treated patients discontinued treatment because of adverse events of diarrhea, suggesting that poor tolerability may limit chronic use. Available data suggest that diarrhea may be improved when tenapanor is used in combination with phosphate binder treatment.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment
In an open-label, single-dose study (TEN-01-107) investigating the PK, safety, and tolerability of tenapanor in subjects with moderate hepatic impairment compared with subjects who had normal hepatic function, tenapanor exhibited minimal systemic bioavailability following a single oral dose of 100 mg in both sets of subjects. While the geometric mean C_{max} was approximately 53% higher in subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function, values were very low for both groups (1.27 ng/mL versus 0.830 ng/mL, respectively). Formal statistical assessment could not be performed due to insufficient quantitative plasma concentration data (i.e., most samples < 0.5 ng/mL), which is commonly noted for tenapanor due to its limited absorption. Systemic exposure, as assessed by C_{max} and AUC, to tenapanor's major

metabolite, M1, was approximately 27.0% to 35.4% lower following administration of tenapanor to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function.

Dose adjustment in hepatic impairment is not needed due to the overall low exposures of tenapanor and M1 in both groups and the lack of pharmacological activity of M1.

Renal Impairment
PK data in patients with renal impairment is provided by Study D5611C00001, in which subjects with an eGFR <15 mL/min/1.73m^2 on dialysis received tenapanor HCl 45 mg or 60 mg capsules (42 mg or 56 mg in tenapanor). The mean plasma concentration of M1 in subjects with an eGFR <15 mL/min/1.73m^2 on dialysis was 2.55 ng/mL (n=5), in comparison to 7.99 ng/mL (n=12) in healthy subjects following similar doses. The absolute exposure of M1 is generally very low in healthy subjects and in subjects with renal impairment.

The doses for the proposed indication are based on the efficacy and safety results from Studies TEN-02-201, TEN-02-301, and TEN-02-202, which were conducted in patients with CKD on dialysis.

8.2. Drug Interactions

In Study TEN-02-108, a drug interaction was observed between tenapanor and enalapril/ enalaprilat (active metabolite of enalapril). Tenapanor inhibited the rate and extent of absorption of enalapril and enalaprilat [C_{max}: ~↓70%, AUC: ↓60-65% (enalapril), ↓50-55% (enalaprilat)]. The mechanism of this interaction was not known during the conduct of the study or immediately following review of the results. However, later, the Applicant conducted in vitro studies as recommended by the review team which showed that tenapanor is a potent inhibitor of OATP2B1 but not PepT1, while enalapril is a substrate of OATP2B1. The decreased exposure of enalapril and enalaprilat may be due to the inhibition of OATP2B1-mediated absorption of enalapril by tenapanor.

It is known that enalapril and enalaprilat's exposure is higher in patients with eGFR <30 mL/min including subjects on dialysis. As per the product insert of enalapril, a lower starting dose of 2.5 mg is recommended for patients with eGFR <30 mL/min or on dialysis. In the scenario when enalapril and tenapanor are co-administered, the increase in enalaprilat (active moiety) systemic exposure observed in patients with CKD on dialysis administered enalapril alone may be offset by the decrease in systemic exposure observed in the presence of tenapanor. Therefore, a lower starting dose of enalapril is not required when enalapril is co-administered with tenapanor in patients with CKD on dialysis.

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

The Applicant submitted an Agreed Initial Pediatric Study Plan (iPSP) with the application. The Agreed iPSP contained a plan (b) (4)

(b) (4)

Based on the available data, the Division and PeRC recommend a full waiver of pediatric studies because the product would be ineffective and/or unsafe in pediatric patients with CKD on dialysis. The product can cause severe diarrhea and dehydration, a risk that is not seen with other approved agents for the control of serum phosphorus and is considered to have an unfavorable risk/benefit profile in pediatric patients. If/when approved, labeling should include a contraindication in pediatric patients <(b) (4) years of age due to the risk of diarrhea and serious dehydration. In nonclinical studies, deaths occurred in young juvenile rats (<1 week-old rats; approximate human age-equivalent of <2 years of age) following oral administration of tenapanor. There are no data available in older juvenile rats (human age-equivalent 2 years to <12 years).

8.4. Pregnancy and Lactation

Data related to use in the setting of Pregnancy and Lactation were reviewed by the Division of Pediatric and Maternal Health (DPMH) as part of FDA's review of NDA 211801 for IBSRELA. In her review dated May 24, 2019, Dr. Mastroyannis noted that there have been very few pregnancies on tenapanor treatment and that complete records of those pregnancies are not available. DPMH concluded that based on what information is available, case reports on tenapanor exposure in pregnant women have not identified any drug associated risk. In the current application, the Applicant states that no pregnancies were reported in the trials conducted in patients with CKD on dialysis. With regard to lactation, previous reviews note and the current application asserts that no data are available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. As previously noted, to date, IBSRELA has not been marketed.

Finalization of labeling has been deferred until the application can otherwise be approved. Absent new information suggesting otherwise, the Division plans to adopt the IBSREBLA Pregnancy labeling language and terser Lactation labeling language, noting that tenapanor is essentially not systemically absorbed and that administration will not result in clinically relevant exposure to breastfed infants.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 213931 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

10. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators and Trials TEN-02-201 and TEN-02-301 appear to have been conducted in compliance with US regulations pertaining to Good Clinical Practice. No clinical sites were inspected because efficacy findings were not driven by a single site and review of financial disclosure information did not raise significant concerns.

11. Advisory Committee Summary

No Advisory Committee Meeting was held. There are multiple products approved for the proposed indication and the issues raised by the application were not felt to warrant discussion at an Advisory Committee Meeting.

III. Appendices

12. Summary of Regulatory History

IND 120566 to develop AZD1722 for the treatment of hyperphosphatemia in patients with end-stage renal disease on dialysis was submitted in December 2013 by Astra Zeneca LP in December 2013. In 2015, sponsorship of the IND was reassigned to Ardelyx, Inc. and the product was renamed tenapanor. There were a number of interactions with Ardelyx ("the Sponsor") over the course of development. Key topics of discussion included the efficacy and safety data needed to support approval, the drug's safety and tolerability profile, the dosing regimen, the systemic absorption of the product and the M1 metabolite, and statistical considerations. With regard to important milestones and advice:

- An **End-of-Phase 2** meeting was held in May 2016. At that meeting, the Sponsor and Agency discussed the data package needed to establish safety and effectiveness. Based on feedback received at that meeting, the Sponsor altered the design of Study TEN-02-201, which was ongoing at the time, and also revised the design of Study TEN-02-301.

- In June 2016, the Agency issued an Advice Letter to the Sponsor pertaining to the statistical analysis plan for **Study TEN-02-201** and use of the study "as one of two well-controlled clinical trials" supporting the registration of tenapanor for the control of serum phosphorus levels in patient with chronic kidney disease on dialysis. In the letter, the Agency provided the following feedback:

  > *"…Without knowing exactly what information is currently available from this trial and absent review of the final trial data, it is difficult to provide a definitive answer as to whether Study TEN-02-201 will be considered an "adequate and well-controlled trial." We note, however, that your proposed phase 3 trial, Study TEN-02-301, will have a 52-week active-controlled randomized treatment period followed by a 4-week placebo-controlled, randomized withdrawal period. Assuming statistically significant effects on serum phosphorus levels are observed in both the randomized withdrawal phases of Study TEN-02-301 and Study TEN-02-201. In addition, the consistent and supportive findings in the 8-week treatment phases of Study TEN-02-201 and Study TEN-02-301 as a whole, will provide the data needed to establish effectiveness for your development program."*

- In November 2017, the Agency issued an Advice Letter in response to a request for feedback on the protocol and statistical analysis plan for **Study TEN-02-301**, which was designed as a 26-Week, phase 3, open label study with a 12-week, placebo-controlled, randomized withdrawal period followed by an open label long term safety extension study. In response to the sponsor's proposal (b) (4) the Agency responded as follows:

"No, we do not agree (b) (4) (b) (4)

...We do not agree that the proposed design will provide the data needed to characterize the safety of your product in the proposed population. The safety data from your trial will not be interpretable without a control arm in the initial treatment period. The proposed trial will also not provide safety data beyond 6 months of treatments. We recommend that you revert to the previously proposed design[14]. If you do not believe that a full year of controlled safety data in this population is needed to characterize safety, then you should address why a shorter period of controlled data should be considered sufficient."

The Agency also advised the Sponsor that:

(1) "...While it is acceptable to enroll subjects with serum phosphorus levels of 5.5 mg/dL, it is important that your development program obtain sufficient data to address efficacy in subjects with more marked elevations (e.g., serum phosphorus levels > 7.0 mg/dL)..."
(2)"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**, a randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenapanor as adjunctive therapy to phosphate binder therapy in end-stage renal disease patients with hyperphosphatemia, and a proposed drug-drug interaction study. In response to the Sponsor'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."*

- In March 2020, a meeting was held to discuss the **planned NDA submission** for tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis. The meeting discussion focused on the clinical relevance of the size of the treatment effect on serum phosphorus. 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

[14] At the End-of-Phase 2 meeting, the Sponsor had proposed a 52-week active control trial with a 4-week placebo-controlled randomized withdrawal period to evaluate the efficacy, safety and tolerability of tenapanor to treat hyperphosphatemia.

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 size is not considered sufficient to support approval.

The Agency indicated that the Sponsor should address the clinical relevance of the size 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 size of the treatment effect is clinically relevant, as opposed to "expert opinion". The Agency also indicated that data indicating that the Sponsor's product has a marked treatment effect in patients with more marked elevations at baseline could be compelling."

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

The pivotal studies for tenapanor (also known as RDX5791, AZ13667691, and AZD1722) and the major metabolite (M1, AZ13792925) were reviewed during the IND stage and have been documented in DARRTS as well as in the Unireview for NDA 211801 (entered into DARRTS on September 5, 2019). An inventory of the reviews for this product are included as an appendix to that NDA review. There are no nonclinical issues that stand in the way of approval.

Overview of Studies:
The Applicant has conducted nonclinical studies in vitro and in vivo to characterize the pharmacological properties of tenapanor and the M1 metabolite (AZD13792925). Potential off-target pharmacology of tenapanor was assessed in receptor binding and enzyme interaction studies. In vitro and in vivo safety pharmacology studies of tenapanor were conducted according to ICHS7A and S7B guidelines. Nonclinical studies of the absorption, distribution, metabolism, and excretion were evaluated in addition to the nonclinical toxicology studies recommended under the ICH guidelines to support chronic use of tenapanor in humans. This includes chronic toxicology, reproductive and developmental toxicology, juvenile toxicology, genetic toxicology and carcinogenicity studies. The pivotal studies were conducted according to good laboratory practice (GLP) guidelines.

The M1 metabolite, AZD13792925, is present in human plasma at greater than 10% of the total tenapanor-related exposure, a higher level than reported for the nonclinical species. M1 is both a major metabolite and also disproportionate in humans. The M1 metabolite has been evaluated for pharmacology, secondary pharmacology, genetic toxicology, developmental toxicity(zebrafish), embryo-fetal development (rats), and carcinogenicity in a 26-week CbyB6F1/TgRasH2 mouse study. Cardiovascular effects of M1 were also assessed in vitro in cardiac ion channel assays and in vivo in the 3-month and 9-month dog studies. The pivotal studies for M1 were GLP compliant. The 9-month repeat dose dog toxicity study had a NOAEL of 1000mg/kg/day of

tenapanor, the highest dose evaluated. There are no safety concerns arising from the M1 metabolite.

13.2. Individual Reviews of Studies Submitted to the NDA

No new nonclinical studies were submitted to this NDA.

14. Clinical Pharmacology Assessment: Additional Information

14.1. In Vitro Studies

1. **Study RDX5791-PK-22 In Vitro Evaluation of Tenapanor as an Inhibitor of Human PEPT1 and OATP2B1, and Enalapril as a Substrate of Human OATP2B1**

This was a non-GLP in vitro study to determine whether tenapanor is an inhibitor of OATP2B1 and PEPT1 using human embryonic kidney (HEK293) cells and Chinese hamster ovary (CHO) cells expressing OATP2B1 and PEPT1, respectively. Another non-GLP in vitro study was conducted to determine whether enalapril is a substrate of OATP2B1 using HEK293 cells expressing OATP2B1. The study design and results are shown in Table 30 and 31, respectively.

Table 30. Test Articles (Tenapanor and Enalapril) and Transporter Assays, Study RDX5791-PK-22

Test article	Transporter	Assay	Applied nominal concentrations (µM)
Tenapanor	OATP2B1	Uptake inhibition	0.003, 0.01, 0.031, 0.092, 0.278, 0.833, and 2.5
	PepT1		0.007, 0.021, 0.062, 0.185, 0.555, 1.67, and 5
Enalapril	OATP2B1	Uptake substrate	0.1, 1, 10, and 100

Source: RDX5791-PK-22 (Table 1, page 4)

Table 31. Summary of Results, Study RDX5791-PK-22

Inhibition assessment of SLC transport by Tenapanor		
Transporter	**Maximum % inhibition**	**IC_{50} (Mm)**
OATP2B1	94	0.01
PepT1	No	NA
Substrate assessment of Enalapril for SLC transporters		
Transporter	**Maximum transporter-specific fold accumulation**	**Substrate**
OATP2B1	3.22	Yes

Source: RDX5791-PK-22 (Table 2, page 9)

Based on the *in vitro* assessment results, tenapanor is an inhibitor of human OATP2B1 with an IC_{50} value of 0.01 µM. Tenapanor did not inhibit human PepT1 up to 5 µM. Enalapril was found to be a substrate of human OATP2B1.

14.2. In Vivo Studies

1. **Study TEN-01-107: Effect of hepatic impairment on the pharmacokinetics of tenapanor**

This was a Phase 1, open-label, single-dose study to investigate the PK, safety, and tolerability of a single dose of tenapanor administered orally in male and female subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Child-Pugh (CP) scoring was used to determine hepatic impairment and subjects were assigned to one of the following two groups:

- Moderate hepatic impairment, CP Class B (7 to 9 points)
- Normal hepatic function

All subjects received 100 mg tenapanor, given orally as 2 × 50 mg tablets on Day 1 after an overnight fast (at least 10 hours). Blood samples for tenapanor and M1 PK analyses were obtained pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after the single dose of tenapanor.

Tenapanor exhibited minimal systemic bioavailability following a single oral dose of 100 mg administered in both groups. Geometric mean Cmax of tenapanor was approximately 53% higher following administration of tenapanor to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function, which suggests that moderate hepatic impairment inhibited the metabolism of tenapanor (reduced first pass effect). Systemic exposure, as assessed by Cmax and AUCs, to M1 was approximately 27.0% to 35.4% lower following administration to subjects with moderate hepatic impairment versus healthy subjects with normal hepatic function (Table 32), which further supports that moderate hepatic impairment inhibited the metabolism of tenapanor. The ratio of geometric least squares means (90% Cis) for AUC0-∞, AUC0-t, and Cmax of M1 were 73.0% (45.3, 117), 64.6% (38.0, 110), and 67.2% (43.7, 103), respectively (Table 33). The effect of moderate hepatic impairment on the PK of tenapanor and M1 is not likely clinically relevant for two reasons: 1) the safety and tolerability of tenapanor were similar between the moderate hepatic impairment group and normal hepatic function group, and 2) the exposure of M1 was lower in subjects with moderate hepatic impairment which has no clinical significance in terms of efficacy and safety since M1 is not pharmacologically active.

Table 32. Summary of Pharmacokinetic Parameters for M1, TEN-01-107

Parameter	Normal Hepatic Function (N = 10)	Moderate Hepatic Impairment (N = 10)
AUC_{0-t} (h×ng/Ml)	475[a] (41.8)	332 (73.2)
$AUC_{0-\infty}$ (h×ng/Ml)	513 (37.8)	374 (69.5)
C_{max} (ng/Ml)	14.3 (44.2)	9.60 (56.5)
t_{max} (h)	4.00 (4.00, 24.00)	8.00 (4.00, 16.00)
t_{last} (h)	96.00[a] (72.00, 96.33)	96.00 (48.00, 96.00)
$t_{1/2}$ (h)	25.4 (9.52)	23.8 (8.91)
MR_{AUC0-t}	NC	413[c] (205)
MR_{Cmax}	80.5[c] (43.5)	21.8[b] (73.0)

Source: Clinical Study Report: TEN-01-107 (Table 9, page 34)
a: n = 9.
b: n = 6.
c: n= 3.
Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{0-t} = AUC from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time zero to infinity; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects; NC = not calculated; MR_{AUC0-t} = metabolic ratio based on AUC0-t; MR_{Cmax} = metabolic ratio based on C_{max}; $t_{1/2}$ = apparent terminal elimination half-life; t_{last} = time of last quantifiable plasma concentration; t_{max} = time of maximum observed plasma concentration.
Note: Geometric mean (geometric CV%) results are presented unless otherwise indicated. Median (minimum, maximum) results are presented for tmax and tlast. Arithmetic mean (SD) results are presented for $t_{1/2}$.

Table 33. Statistical Analysis of the Pharmacokinetic Parameters of M1, TEN-01-107

Parameter	Hepatic Function Groups[1]	n	Geometric Least Squares Means	Ratio (%) of Geometric Least Squares Means	90% CI for the Ratio[2]	
					Lower	Upper
AUC_{0-t} (h×ng/Ml)	Moderate	10	374			
	Normal	10	513	73.0	45.3	117
$AUC_{0-\infty}$ (h×ng/Ml)	Moderate	9	307			
	Normal	9	475	64.6	38.0	110
C_{max} (ng/Ml)	Moderate	10	9.60			
	Normal	10	14.3	67.2	43.7	103

Source: Clinical Study Report: TEN-01-107 (Table 10, page 35)
[1] Each subject in the moderate hepatic impairment group is matched to one subject in the normal hepatic function group.
[2] The ratio and corresponding confidence limits (expressed as percentages) are back-transformed from the difference and confidence limits calculated on the log scale
Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{0-t} = AUC from time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$ = AUC from time zero to infinity; C_{max} = maximum observed plasma concentration; n = number of observations; CI = confidence interval.

2. Study TEN-01-108: Drug-drug interaction study with enalapril, digoxin and warfarin in CKD patients on dialysis

This study was designed to determine the potential for drug interaction between tenapanor and three drugs – enalapril, digoxin, and warfarin. There were two cohorts based on the treatment:

- Cohort 1 (enalapril and digoxin):
  - Days 1 and 22: a single oral dose of enalapril 20 mg
  - Days 5 and 26: a single oral dose of digoxin 0.25 mg
  - Days 18-28: oral doses of 30 mg tenapanor BID

- Cohort 2 (warfarin):
  - Days 1 and 22: a single oral dose of warfarin 10 mg
  - Days 18-28: oral doses of 30 mg tenapanor BID

Concentrations for tenapanor were not quantifiable (i.e., < 0.5 ng/Ml) in all plasma samples. As a result, assessments of tenapanor plasma concentration time profiles and PK parameters were not performed. In Cohort 1 and Cohort 2, M1 geometric mean C_{trough} ranged from 11.5-14.4 ng/Ml and 7.86-11.1 ng/Ml, respectively, indicating steady state was achieved. As shown in Tables 3 and 4, tenapanor reduced enalapril and enalaprilat peak exposure to the same extent (69% and 68%, respectively, Tables 34-35). The total systemic exposure was 60-65% lower for enalapril and 50-55% lower for enalaprilat. The mechanism of this interaction was not known during the conduct of the study or immediately following review of the results. Later through in vitro

studies recommended by the review team, it became apparent that the interaction between enalapril and tenapanor is mediated by intestinal uptake transporter, OATP2B1.

The 90% Cis of the geometric least squares mean ratios of C_{max} and AUC_{0-72h} were within 80-125% for digoxin, R-warfarin and S-warfarin, therefore, no clinically significant drug interaction was noted between tenapanor and digoxin/R-warfarin/S-warfarin based on systemic exposure.

Table 34. Statistical Analysis of Enalapril Pharmacokinetics, With and Without Concomitant Tenapanor, TEN-02-108

Parameter	Treatment	N	Geometric LS means	Ratio (%)	90% Confidence Interval	
					Lower Limit	Upper Limit
C_{max} (ng/Ml)	Enalapril	25	129.46			
	Enalapril + Tenapanor	25	40.06	30.95	27.13	35.30
AUC_{0-t} (h×ng/Ml)	Enalapril	25	190.33			
	Enalapril + Tenapanor	25	68.81	36.15	32.41	40.33
$AUC_{0-\infty}$ (h×ng/Ml)	Enalapril	17	193.77			
	Enalapril + Tenapanor	17	75.41	38.92	34.06	44.47

Source: Clinical Study Report: TEN-02-108 (Table 14.2.1.1.3.1, page 120)

Table 35. Statistical Analysis of Enalaprilat Pharmacokinetics, With and Without Concomitant Tenapanor, TEN-02-108

Parameter	Treatment	N	Geometric LS means	Ratio (%)	90% Confidence Interval	
					Lower Limit	Upper Limit
C_{max} (ng/Ml)	Enalapril	25	87.52			
	Enalapril + Tenapanor	25	28.10	32.11	27.64	37.30
AUC_{0-t} (h×ng/Ml)	Enalapril	25	789.87			
	Enalapril + Tenapanor	25	378.38	47.90	44.20	51.92
$AUC_{0-\infty}$ (h×ng/Ml)	Enalapril	25	829.04			
	Enalapril + Tenapanor	25	411.63	49.65	46.04	53.55

Source: Clinical Study Report: TEN-02-108 (Table 14.2.1.1.3.2, page 121)

3. Study TEN-02-106: Bioequivalence assessment of two formulations of tenapanor in healthy volunteers

The purpose of this study was to establish a bridge between the drug product formulations used in Study TEN-02-201, and the to-be-marketed (TBM) commercial drug product used in two Phase 3 studies, TEN-02-301 and TEN-02-202. In this study, subjects received two different 10 mg tablet formulations (Cohort 1) or two different 30 mg tablet formulations (Cohort 2) of tenapanor. Each subject was randomized to one of the following cohorts:

- Treatment A (Reference): Tenapanor 10 mg tablet (formulation 1) used in Study TEN-02-201 twice daily prior to meals for 4 days.
- Treatment B: Tenapanor 10 mg tablet (formulation 2) used in Study TEN-02-301/TBM twice daily prior to meals for 4 days.
- Treatment C (Reference): Tenapanor 30 mg tablet (formulation 1) used in Study TEN-02-201 twice daily prior to meals for 4 days
- Treatment D: Tenapanor 30 mg (formulation 2) TBM twice daily prior to meals for 4 days

As shown in Tables 36, the primary endpoint (urinary sodium) demonstrated the bioequivalence between the two formulations of tenapanor at both the 10 and 30 mg dose

levels; the other PD endpoints, urinary phosphorus and creatinine also showed no differences. Pharmacokinetic parameters were determined for the major metabolite of tenapanor, M1, but not for tenapanor since it was not quantifiable in plasma. AUC_{0-12} and C_{max} of M1 were slightly decreased for the test (TBM) formulation compared to the reference (TEN-02-201) formulation at the 10 mg dose level, however this is not clinically relevant because M1 is not a pharmacologically active metabolite (Table 37). No statistical difference was detected between the formulations at the 30 mg BID dose level.

Table 36. Summary of the Post-hoc Statistical Analysis[1] of Urine PD Endpoints, TEN-02-106

Analyte (Units)	Treatment	n	Geometric Least Squares Means	Ratio (%) of Geometric Least Squares Means (Test : Reference)	90% CI for the ratio[2] (Test : Reference)	
					Lower	Upper
Sodium (mmol/day)	Treatment A (Reference)	24	133	103.8	96.1	112.1
	Treatment B (Test)	24	128			
	Treatment C (Reference)	24	136	98.5	92.1	105.4
	Treatment D (Test)	24	138			
Phosphorus (mg/day)	Treatment A (Reference)	24	590	104.7	98.1	111.8
	Treatment B (Test)	24	563			
	Treatment C (Reference)	24	542	100.8	94.7	107.2
	Treatment D (Test)	24	537			
Creatinine (mg/day)	Treatment A (Reference)	24	1350	98.5	94.9	102.3
	Treatment B (Test)	24	1370			
	Treatment C (Reference)	24	1310	100.7	95.9	105.8
	Treatment D (Test)	24	1300			

Source: Post-hoc Analysis of Log-transformed Data: TEN-02-106 (Table 11, page 33)
[1] The mean (Overall [0 to 96 h]) excretion of the pharmacodynamic analyte is assessed using a mixed effect analysis of covariance model with sequence, period, and treatment as fixed effects, corresponding PD endpoint values at baseline as a continuous covariate, and subject nested within sequence as a random effect.
[2] The ratio and corresponding confidence limits (expressed as percentages) are back-transformed from the difference and confidence limits calculated on the log scale.
Abbreviations: Treatment A = tenapanor 10 mg tablet BID with formulation used in TEN-02-201; Treatment B = tenapanor 10 mg tablet BID with TBM formulation; Treatment C = tenapanor 30 mg tablet BID with formulation used in TEN-02-201; Treatment D = tenapanor 30 mg tablet BID with TBM formulation; n = number of observations; CI = confidence interval; BID = twice daily; TBM = to-be-marketed; ph = post-hoc

Table 37. Summary of the Pharmacokinetic Parameters for M1, TEN-02-106

Parameter	Treatment A	Treatment B	Treatment C	Treatment D
AUC_{0-12} (h×ng/Ml)	50.9 (41.3)	43.9 (58.6)	151 (37.3)	146 (43.0)
C_{max} (ng/Ml)	4.97 (41.3)	4.28 (55.5)	14.8 (36.1)	14.3 (42.2)
t_{max} (h)	4.00 (1.00, 11.92)	4.00 (1.00, 8.00)	4.00 (2.00, 8.00)	4.00 (1.00, 6.00)

Source: Clinical Study Report: TEN-02-106 (Table 12, page 41)
Abbreviations: AUC_{0-12} = area under the concentration versus time curve in plasma from time zero to 12 hours postdose; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects;

NC = not calculated; t_{max} = time of maximum observed plasma concentration;Treatment A = tenapanor 10 mg tablet BID with formulation used in TEN-02-201;Treatment B = tenapanor 10 mg tablet BID with TBM formulation; Treatment C = tenapanor 30 mg tablet BID with formulation used in TEN-02-201; Treatment D = tenapanor 30 mg tablet BID with TBM formulation.
Note: Geometric mean (geometric CV%) results are presented unless otherwise indicated. Median (minimum, maximum) is presented for tmax. N=24 in each treatment group.

4. Study D5613C00001 (phase 2): Tenapanor in patients with end-stage renal disease patients on hemodialysis

In this Phase 2, randomized, double-blind, placebo-controlled study, 162 patients were randomized 23 to tenapanor 1 mg BID, 21 to tenapanor 3 mg BID, 23 to tenapanor 10 mg BID, 26 to tenapanor 30 mg BID, 22 to tenapanor 3 mg QD, 21 to tenapanor 30 mg QD, and 26 to placebo. A total of 160 subjects completed the study according to the protocol: placebo (n=26), tenapanor 1 mg BID (n=23), tenapanor 3 mg BID (n=21), tenapanor 10 mg BID (n=23), tenapanor 30 mg BID (n=24), tenapanor 3 mg QD (n=22), and tenapanor 30 mg BID (n=21). The primary endpoint i.e., change from baseline in serum phosphorus level at end of treatment /early termination was achieved in this study (Table 38). The tenapanor treatment reduced serum phosphorus levels in a dose-dependent manner. Phosphorus-lowering activity was observed as early as 1 week after the start of treatment (first post-baseline visit) with tenapanor 3 mg BID, 10 mg BID, 30 mg BID, and 30 mg QD.

Table 38. Change from Baseline in Serum Phosphorus at the End of Treatment/Early Termination (mg/dL), Study D5613C00001

Group	n	Mean	SD	Min	Max	LS Mean	95% CI
Tenapanor 1 mg BID (N = 23)	23	–0.43	1.553	–3.2	3.4	–0.47	–1.18, 0.24
Tenapanor 3 mg BID (N = 21)	21	–1.09	1.391	–2.8	3.2	–1.18	–1.93, –0.44
Tenapanor 10 mg BID (N = 23)	23	–1.76	2.018	–5.3	2.1	–1.70	–2.41, –0.99
Tenapanor 30 mg BID (N = 26)	24	–2.00	2.007	–7.3	1.6	–1.98	–2.67, –1.28
Tenapanor 3 mg QD (N = 22)	22	–0.57	1.763	–2.8	5.3	–0.56	–1.28, 0.17
Tenapanor 30 mg QD (N = 21)	21	–1.09	1.469	–3.4	2.2	–1.11	–1.85, –0.37
Placebo (N = 26)	26	–0.58	1.802	–6.5	2.3	–0.54	–1.21, 0.13

Source: Clinical Study Report: D5613C00001 (Table 7, page 34)

14.3. Summary of Bioanalytical Method Validation and Performance

Tenapanor, M1 (a major human metabolite of tenapanor), digoxin, enalapril, enalaprilat, and warfarin (R- and S-Warfarin) concentrations in human plasma were measured by validated LC-MS/MS methods. The bioanalytical methods used were adequately validated. The methods for quantification of tenapanor, M1, and digoxin in human plasma were developed and validated at

Contract Research Organization (b) (4), while the methods for quantification of enalapril, enalaprilat, and warfarin in human plasma were developed and validated at Contract Research Organization (b) (4).

The methods consist of a liquid-liquid extraction (digoxin and warfarin) or protein precipitation (tenapanor, M1, enalapril, and enalaprilat) after addition of stable isotope labelled internal standards. The resulting extracts were evaporated to dryness, reconstituted and then injected on a reversed phase HPLC column using a gradient method. Detection was done by tandem mass spectrometry in the multiple reaction monitoring mode with in the positive (tenapanor, M1, enalapril, and enalaprilat) or negative (warfarin) ion mode. The summary of bioanalytical method and validation metrics are presented in Tables 39 and 40.

Table 39. Summary Review of Bioanalytical Methods Measuring Tenapanor, M1, and Digoxin

	Tenapanor/M1	Digoxin
Bioanalytical method validation report	(b) (4) Study Number 8396237	(b) (4) Study Number 8274044
Validation assay range (ng/Ml)	0.5-100/0.5-500	0.05-10
QCs (ng/Ml)	0.5, 1.5, 8, 50, 80, and 1600/0.5, 1.5, 24, 250, 400, and 8000	0.05, 0.15, 0.5, 3, and 7.5
Recovery (%)	91.6-121.1/100.3	54.5
Inter-day precision (% CV)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)
Inter-day accuracy (% Bias)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)
Intra-day precision (% CV)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)
Intra-day accuracy (% Bias)	≤15.0% (≤20.0% at the LLOQ)	≤15.0% (≤20.0% at the LLOQ)
Reference standard	Lot No.: 15600T0003/ ET9585-55-P1	Lot No.: P0I054
Specificity	No significant interference observed in the blank matrix	No significant interference observed in the blank matrix
Freeze/thaw stability	5 freeze (-60 to -80°C)-thaw cycles	3 freeze (-60 to -80°C)-thaw cycles
Stock stability	89 days at 100 µg/Ml in ®:DMSO (50:50): at 2-8°C/35 days at 500 MG/mL ®ACN:DMSO (50:50): at 2-8°C	70 days at -10 to -30°C
Bench-top stability	24 hours at 2 to 8°C	6 hours at room temperature
Processed stability	212/140 hours at 2 to 8°C	98 hours at 2 to 8°C
Long-term storage stability	168 days at -60 to -80°C	251 days at -60 to -80°C

Table 40. Summary Review of Bioanalytical Methods Measuring Enalapril, Enalaprilat, R- and S-Warfarin

	Enalapril/ Enalaprilat	R-Warfarin/ S-Warfarin
Bioanalytical method validation report	EAI-V4-676(R1)	WRI-V2-453(R1)
Validation assay rangE (ng/mL)	0.25-300 ng	5-1000
QCS (ng/mL)	0.25, 0.75, 30, 150, and 225	5, 15, 200, and 750
Recovery (%)	97.6-105.8/92-101.4	72.5-82.5/73.4-83.2
Inter-day precision (% CV)	3.8-7.0/3.3-8.2	4.0-5.1/3.5-6.0
Inter-day accuracy (%)	98.2-109/94.4-104.4	97.5-101.4/99.5-102.4
Intra-day precision (% CV)	1.5-7.3/1.2-9.1	1.2-5.8/1.5-5.8
Intra-day accuracy (%)	95.5-115.6/94.1-110.7	93.8-104.1/94.9-106.1
Reference standard	Lot No.: RS-0065-F/ RS-0067-F	Lot No.: RS-1233-A(R)/ RS-1234-A(R)
Specificity	No significant interference observed	No significant interference observed
Freeze/thaw stability	3 freeze (-20°C)-thaw (4°C) cycles	4 freeze (-20°C)-thaw (22°C) cycles
Stock stability	194 days at approximately 100 µg/mL in MeOH: H2O 50:50% v/v at 4°C	85 days in MeOH at 200 µg/mL at 4°C
Bench-top stability	24.6 hours at 4°C in human plasma; 2 hours at 0°C in human whole blood	24.3 hours at 22°C in human plasma; 2 hours at 0°C in human whole blood
Processed stability	70.8 hours at 4°C	92.6 hours at 4°C
Long-term storage stability	60 days at -20°C in human plasma	63 days at -20°C in human plasma

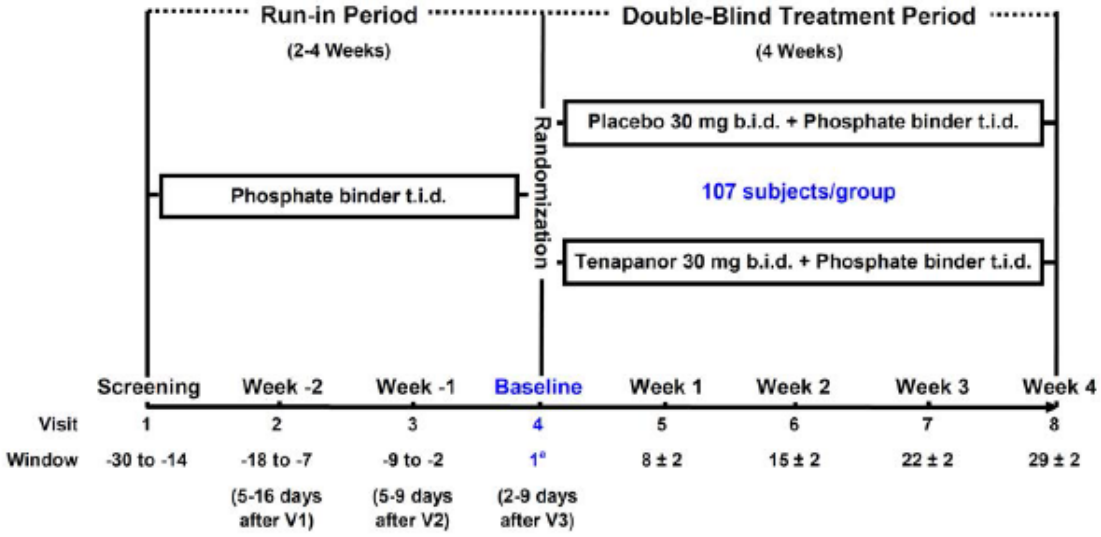
15. Trial Design: Additional Information and Assessment

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

The study consisted of a Screening visit; a Run-in Period of at least 2 weeks and up to 4 weeks, where existing phosphate binder treatment was maintained; and a 4-week Double-Blind Treatment Period, during which subjects were randomized in a 1:1 ratio to receive tenapanor or placebo at a dose of 30 mg twice daily (bid; three 10 mg tablets each time) 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).

Approximately 214 subjects were to be randomized at 40 to 50 sites. The primary efficacy endpoint was the change from baseline in serum phosphorus level at Week 4. The primary analysis was to be a treatment comparison of the mean change using a MMRM on observed cases of the full analysis set (all ITT subjects who have at least one post-baseline serum phosphorus measurement during the study). The MMRM was to include type of phosphate binder (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), treatment-by-visit interaction as fixed effects; baseline (Visit 4) serum phosphorus level and baseline-by-visit as covariates; and subject as a random effect. An unstructured (UN) covariance matrix was to be used to model the within-subject errors.

An overview of the Study Design is shown below.



[a] Day 1 is the randomization day and serves as the reference day for all visits.

Figure 20. Diagram of Study Design, TEN-02-202

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

16. Efficacy Assessment Additional Information and Assessment

16.1.1. Efficacy Results for the 26-Week RT Period in Study TEN-02-301

The Agency sent an Information Request to the Applicant on January 8, 2021 requesting addition data for the 26-week RT period in Study TEN-02-301. Specifically, the Agency requested:

1. A dataset that contains the serum phosphorus (s-P) value at every visit from baseline to the end of the treatment period (Visit 13) for both treatment arms. The dataset should also include the covariates that were used in the primary efficacy analysis of the data from the randomized withdrawal period.
2. The least squares estimate of the treatment effect on s-P for both the tenapanor and active control sevelamer arms at each post baseline visit up to week 26 using the same statistical method as was used for the primary efficacy analysis of the data from the randomized withdrawal period, along with the accompanying figures.
3. Analyses that explore whether/how the baseline s-P level affects the size of the treatment effect in each treatment arm during the 26-week treatment period, e.g., the least squares mean change in s-P in each treatment arm over time in the subgroup with a baseline s-P above and below 7.5 mg/dL.

In response to the request, the Applicant provided a dataset including the actual s-P values and change-from-baseline values at all scheduled visits of the 26-week randomized treatment period up to Visit 13. This included the ITT analysis set for tenapanor-treated subjects and the safety analysis set for sevelamer-treated subjects. Note that the sevelamer carbonate group did not need to satisfy the inclusion-exclusion criteria so the populations in the two treatment groups can be

different. As indicated earlier, the Safety analysis set consisted of all subjects who received at least 1 dose of study drug while the ITT analysis set only consisted of subjects who met the study entry inclusion/exclusion criteria, received at least 1 dose of tenapanor, and had at least 1 post-treatment s-P measurement during this study period. The Applicant performed analysis using ANCOVA on the observed s-P changes from baseline at each post-baseline visit up to Visit 13 (Week 26) in the RT period. Similar analyses were also performed on two subgroups (baseline s-P < 7.5 mg/dL and ≥ 7.5 mg/dL).

Of the 564 subjects who were randomized 1:3 into the 26-week RT period (141 in the sevelamer carbonate group, and 423 in the tenapanor group), 373 (66%) subjects completed the 26-week treatment period. 24 (17%) subjects in the sevelamer carbonate group and 167 (40%) subjects in the tenapanor group withdrew early from the 26-week RT period. Subject withdrawal was highly unbalanced between two treatment groups with significantly more subjects withdrawing from the tenapanor group. Two subjects in the sevelamer carbonate group and 77 subjects in the tenapanor group withdrew due to adverse events. Specifically, 69 subjects withdrew due to diarrhea, and the majority (67) were from the tenapanor group. Twenty-two subjects in the tenapanor group withdrew due to hyperphosphatemia. It is challenging to provide a reliable estimate of the treatment effect, as the results are largely influenced by the approach taken to impute missing data and MAR assumption is unlikely to hold. The Applicant provided comparisons between two treatment arms at every visit based on an observed case analysis during the 26-week RT period.

Table 41 presents the efficacy results. Of the 564 subjects who were randomized into the 26-week RT period, 248 subjects were in the ITT analysis set of the tenapanor group and 113 subjects in the safety analysis set of the active group at Week 26, the LS mean change in s-P from period-level baseline to the end of the 26-week RT period was -1.37 mg/dL for the tenapanor group and -1.80 mg/dL for the active control group. The LS mean difference was 0.43 mg/dL (p=0.0064) favoring sevelamer carbonate group.

Table 41. Analysis of Change from Baseline in Serum Phosphorus (mg/dL) at Post-Baseline Visits Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

	Tenapanor vs. Placebo	
	Active Control (N=113)	**Tenapanor (N=248)**
Change from baseline to the end of the 26-week period[1,2]		
LS Mean (SE)	-1.80 (0.13)	-1.37 (0.09)
LS Mean difference (SE) (versus placebo)		0.43 (0.16)
95% CI LS mean difference (versus placebo)		(0.12, 0.74)
p-value		0.0064

Source: Table 14.2.3.1, Clinical Information Amendment, Module 1.11.3
[1] The LS means, SEs, 95% CIs, and p-value were from an ANCOVA model with treatment and pooled site as factors and period-level baseline value as a covariate.
[2] For the 26-Week Treatment Period, Period-Level Baseline is defined as the last measurement collected prior to the first dose of study medication during the 26-Week Treatment Period.

Figure 17 displays a plot of LS mean change in s-P from period-level baseline to the end of the 26-week RT period for the tenapanor arm and the sevelamer carbonate arm. The baseline is defined as the last measurement collected prior to the first dose of study medication. The LS means of s-P values were comparable at baseline between the two treatment groups. The s-P values started to decrease in both groups after the treatment began. The mean differences in s-P values between two groups ranged between 0.28 and 0.64.

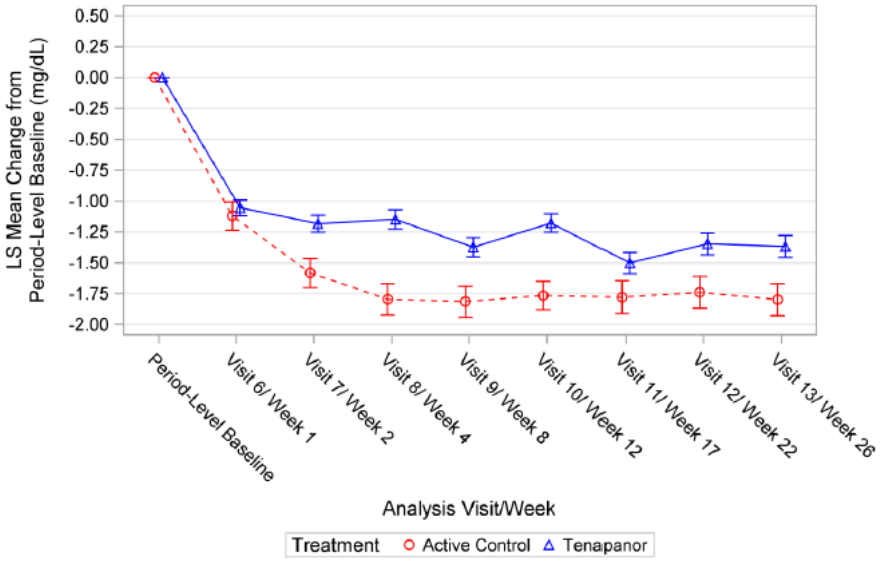


Figure 21. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

Source: Figure 14.2.3.3, Clinical Information Amendment, Module 1.11.3.

In addition, Figures 18 and 19 depict the histograms of the two treatment groups at Weeks 2 and 4. These histograms indicate that the inter-subject variations are large, and the distributions overlap for the most part.

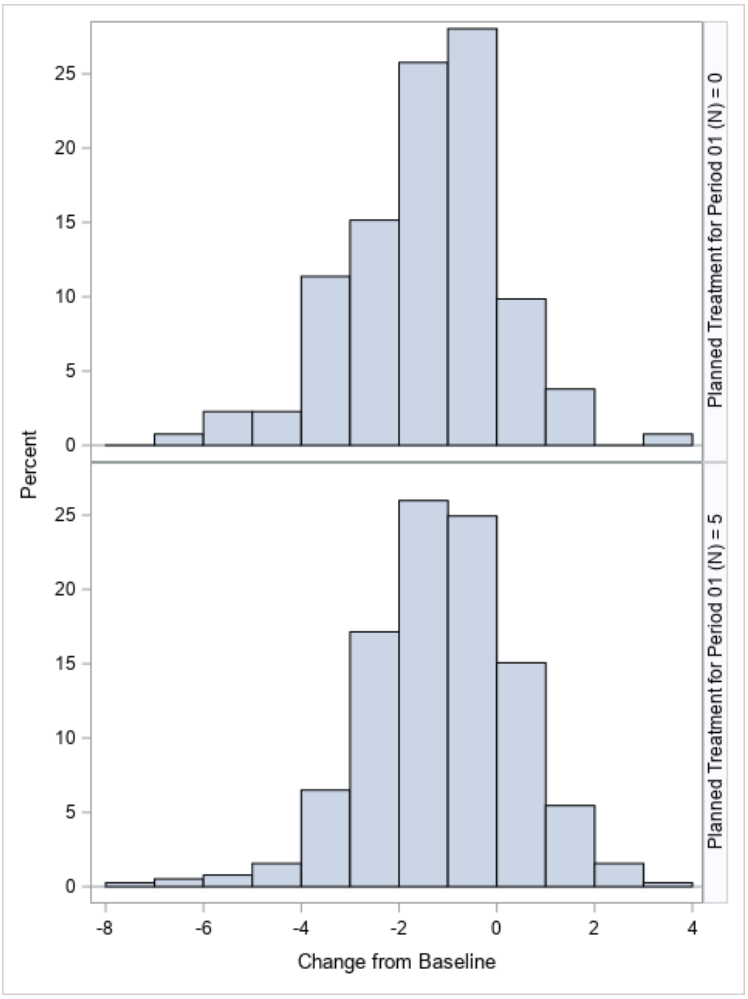


Figure 22. Histograms of the Change from Baseline in Serum Phosphorus (mg/dL) at Visit 7/Week 2, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

Top panel=tenapanor; bottom panel=active control
Source: Statistical Reviewer

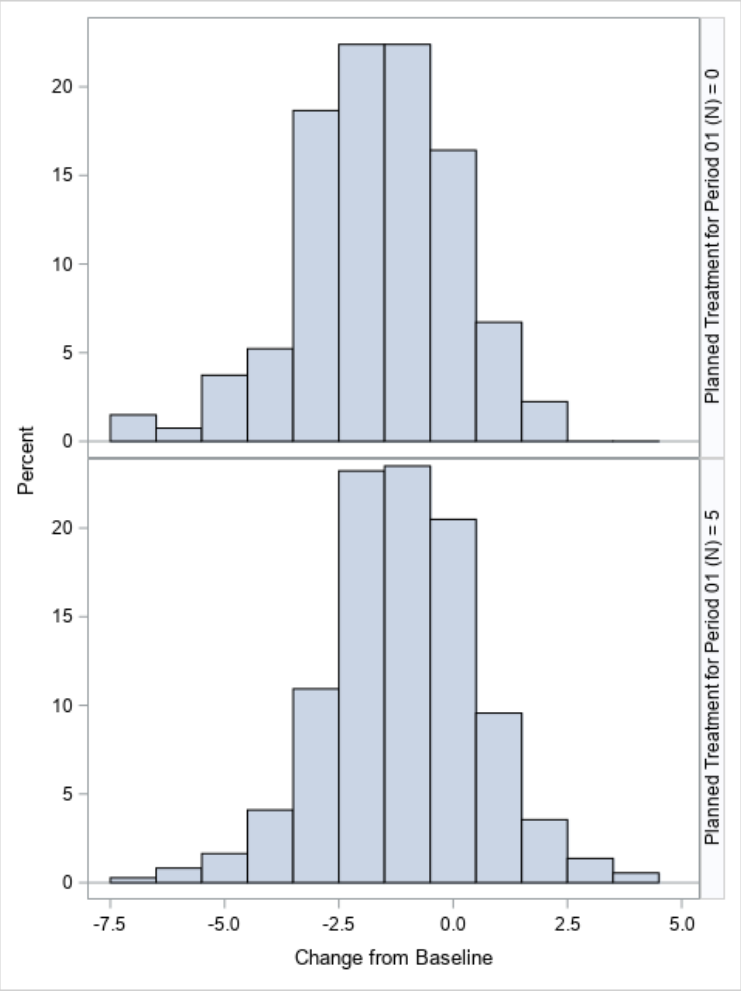


Figure 23. Histograms of the Change from Baseline in Serum Phosphorus (mg/dL) at Visit 8/Week 4, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

Top panel=tenapanor; bottom panel=active control
Source: Statistical Reviewer

The Applicant conducted the similar subgroup analyses on the s-P change in populations with baseline s-P value above or below 7.5 mg/dL. Figures 20 and 21 display the plots of LS mean changes in s-P for the tenapanor arm and the active control arm for both sub-populations. The analyses were based on observed data only.

The mean change in s-P from period-level baseline to the end of the 26-week RT period showed similar pattern. The mean differences varied between 0.10 and 0.55 in the sub-population with baseline s-P value < 7.5 mg/dL. The mean differences varied between 0.29 and 0.93 in the sub-population with baseline s-P value ≥ 7.5 mg/dL. Both subgroups showed better results for the sevelamer carbonate arm.

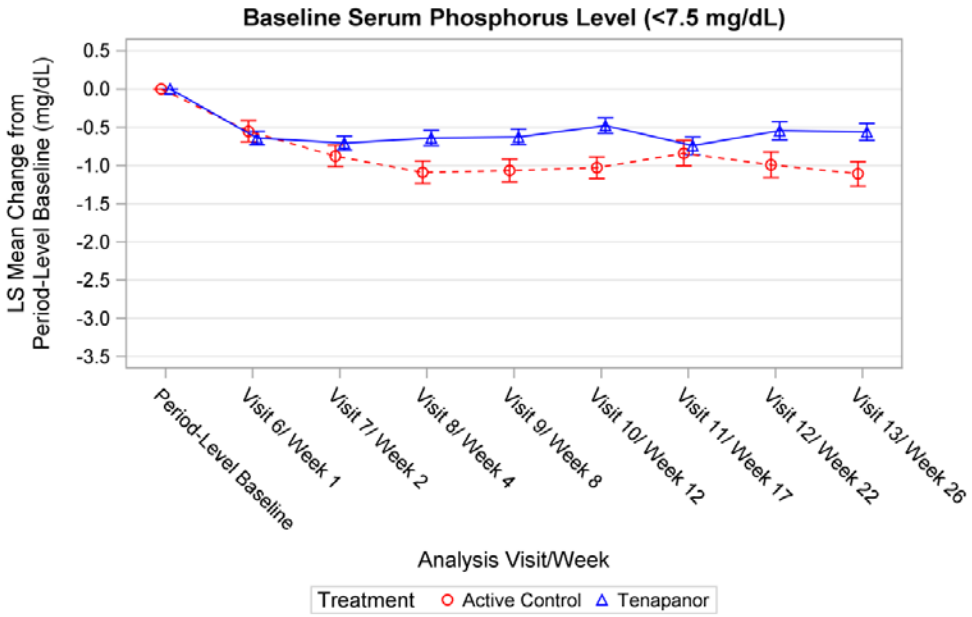


Figure 24. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA, 26-Week Treatment Period, Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

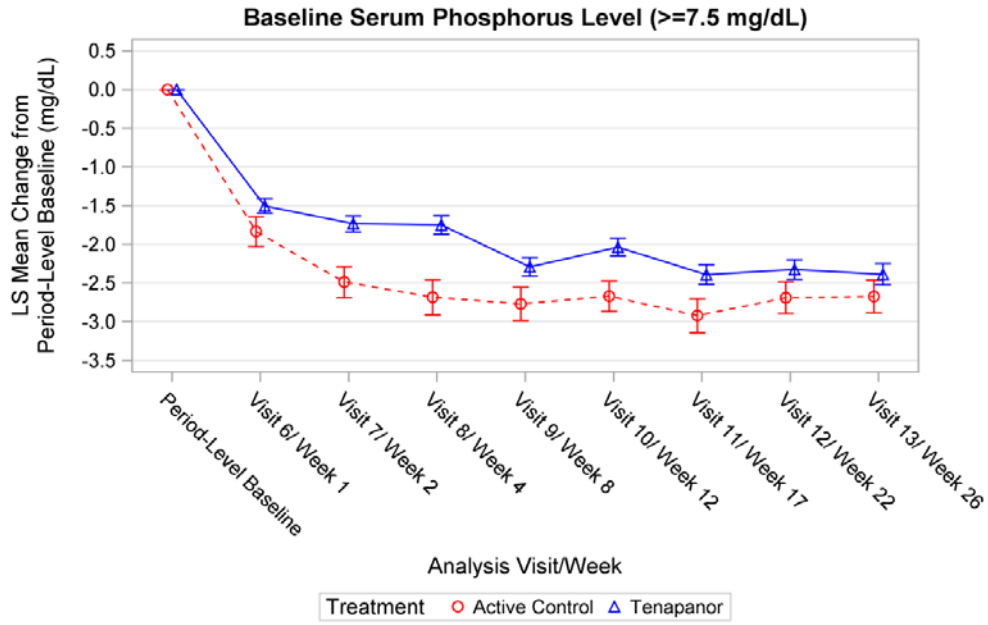


Figure 25. Least Squares Mean Change +/- Standard Error in Serum Phosphorus (mg/dL) from Baseline Over Time Using ANCOVA 26-Week Treatment Period Intent-to-Treat Analysis Set (Tenapanor Arm) and Safety Analysis Set (Active Control Arm)

In summary, in the 26-week RT period, subject withdrawal was highly imbalanced between the two treatment arms. The tenapanor arm had a much higher rate of withdrawal and the

missingness were unlikely due to missing at random. It is therefore difficult to use an appropriate statistical model to provide a reliable estimate of the treatment effect. Due to the original study design, the two treatments arms were compared over different analysis data sets. Tenapanor-treated subjects were from the ITT analysis set and sevelamer-treated subjects were from the safety analysis set. Subjects in the safety analysis set did not need to meet the inclusion/exclusion criteria which were required for those in the ITT analysis set. There was not a specific dosage regimen in the sevelamer group as in the tenapanor group. Given the difference between the two analysis sets, it is difficult to know how different these populations were and therefore what the true treatment effect was.

Nevertheless, a comparison between the two treatment arms may bring some insight to the treatment effect of tenapanor relative to the active control, as used in the trial. The Applicant compared two treatment arms at all visits using ANCOVA based on the observed data only in the 26-week RT period. The sevelamer carbonate arm had a larger treatment effect compared to the tenapanor arm. The results were consistent over visits, and in both baseline s-P categories of below or above 7.5 mg/dL. The distributions of mean change in s-P in two treatment groups overlap substantially suggesting a small treatment difference compared to a large inter-subject variability. Such a treatment difference may not be clinically relevant.

Other Exploratory Analyses

Given the small size of the treatment effect, a question that was raised during internal discussions was whether it might to 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).

FDA conducted exploratory analyses of the data from the 26-week treatment period of Study TEN-02-301 to assess whether the available data indicate that such a strategy might be viable. In the analysis discussed below, FDA defined a patient as being a "responder" if the patient either reached a certain serum phosphorus threshold or achieved a certain reduction in serum phosphorus at a specified time point following initiation of treatment. FDA then assessed whether the proportion of patients who had a reduction in serum phosphorus greater than some amount at the end of the treatment period was greater in patients who met the "responder" definition as compared to the trial population as a whole.

The table below shows the percentages of patients who had a reduction in serum phosphorus at Week 26 greater than some amount (e.g., a reduction ≥ 1 mg/dL, ≥ 1.5 mg mg/dL) in the following analysis populations: (1) patients who met the "responder" definition at Week 1 or 2; (2) patients who met the "responder" definition at Week 2 or 4; and (3) the trial population as a whole. The results suggest that a single measurement of serum phosphorus obtained within the first few weeks of starting treatment may not provide meaningful insight into a patient's response to treatment (also assessed via a single measurement) at a later time point.

Table 42. Percentage of Patients with Serum Phosphorus (mg/dL) Reduction of at least the Specified Amount in the 26-Week Randomization Treatment Period: Patients with a Serum Phosphorus Reduction of at least 2.0 mg/dL at Week 1 or 2, at Week 2 or 4, and in the Trial Population as a Whole

Analysis Population	Reduction in Serum Phosphorus (from baseline) at Week 26 (mg/dL)				
	≥1.0	≥1.2	≥1.5	≥1.7	≥2.0
Responder* at Week 1 or 2					
Tenapanor (177)	35 (20%)	29 (16%)	23 (13%)	23 (13%)	20 (11%)
Active Control (60)	21 (35%)	19 (32%)	15 (25%)	13 (22%)	12 (20%)
Responder* at Week 2 or 4					
Tenapanor (203)	41 (20%)	33 (16%)	27 (13%)	27 (13%)	23 (11%)
Active Control (67)	25 (37%)	20 (30%)	16 (24%)	14 (21%)	13 (19%)
Trial population					
Tenapanor (407)	90 (22%)	74(18%)	61 (15%)	55 (14%)	44 (11%)
Active Control (137)	45 (33%)	39(28%)	34 (25%)	30 (22%)	28 (20%)

*Responder=To be considered a "responder," a patient had to have a serum phosphorus reduction from baseline of at least 2 mg/dL at the specified time point
Source: Statistical Reviewer

The following table shows the percentages of patients who had a serum phosphorus at Week 26 below some threshold in the following analysis populations: (1) patients who had a serum phosphorus concentration ≤ 5.0 mg/dL at Week 1 or 2; (2) patients who had a serum phosphorus concentration ≤ 5.0 mg/dL at Week 2 or 4; and (3) the trial population as a whole. As compared to the population as a whole, the proportion of patients who had a serum phosphorus below the threshold value at Week 26 was numerically higher in the subset of patients who achieved a serum phosphorus of 5 mg/dL at Week 1 or Week 2, and, to a lesser extent, in the subset who achieved a serum phosphorus of 5 mg/dL at Week 2 or Week 4.

Table 43. Percentage of Patients with a Serum Phosphorus (mg/dL) Concentration Not More Than the Specified Value in the 26-Week Randomization Treatment Period: Patients with a Serum Phosphorus ≤ 5.0 mg/dL at Week 1 or 2, at Week 2 or 4, and in the Trial Population as a Whole

Analysis Population	Serum Phosphorus Concentration (mg/dL) at Week 26		
	≤ 6.0	≤ 5.5	≤ 5.0
Serum Phosphorus ≤ 5.0 at Week 1 or 2			
Tenapanor (150)	67 (45%)	58 (39%)	42 (28%)
Active Control (58)	41 (71%)	36 (62%)	28 (48%)
Serum Phosphorus ≤ 5.0 at Week 2 or 4			
Tenapanor (173)	66 (38%)	57 (33%)	39 (23%)
Active Control (70)	46 (66%)	41 (59%)	32 (46%)
Trial population			
Tenapanor (407)	139 (34%)	107(26%)	75 (18%)
Act Control (137)	79 (58%)	64(47%)	45 (33%)

Source: Statistical Reviewer

Conclusion: 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 discontinue treatment in patients who do not appear to have an adequate 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.

17. Clinical Safety Assessment Additional Information and Assessment

Table 44. Serious Adverse Events by MedDRA System Organ Class, Safety Population, Integrated CKD on Dialysis Safety Analysis Set, First 12 Weeks

	All Tenapanor (N=934)	Phosphate Binder (N=256)	Placebo (N=69)
System Organ Class			
Infections and infestations	27 (2.9)	7 (2.7)	1 (1.4)
Metabolism and nutrition disorders	13 (1.4)	6 (2.3)	0
Respiratory, thoracic and mediastinal disorders	14 (1.5)	6 (2.3)	1 (1.4)
Vascular disorders	13 (1.4)	2 (0.8)	0
Cardiac disorders	11 (1.2)	3 (1.2)	1 (1.4)
Nervous system disorders	11 (1.2)	1 (0.4)	1 (1.4)
Gastrointestinal disorders	11 (1.2)	1 (0.4)	1 (1.4)
Injury, poisoning and procedural complications	10 (1.1)	4 (1.6)	0
Blood and lymphatic system disorders	3 (0.3)	0	2 (2.9)
General disorders and administration site conditions	4 (0.4)	3 (1.2)	0
Musculoskeletal and connective tissue disorders	2 (0.2)	2 (0.8)	0
Hepatobiliary disorders	1 (0.1)	1 (0.4)	0
Investigations	2 (0.2)	0	0
Psychiatric disorders	1 (0.1)	0	0
Renal and urinary disorders	2 (0.2)	1 (0.4)	0
Skin and subcutaneous tissue disorders	1 (0.1)	0	0
Reproductive system and breast disorders	1 (0.1)	0	0

Source: Reviewer's Table; adae.xpt, adsl.xpt; OCS Analysis Studio

Table 45. Deaths, Initial Treatment Period, 26-Weeks, Safety Population, TEN-02-301

Study/ SUBJID	Age/Sex	Co-morbid conditions	Cause of Death/ Narrative Reason for Death	Days from starting study drug to death/ Last day of study drug	AEs reported within 14 days of Event/ additional events in narrative
Tenapanor					
TEN-02-301 (b) (6)	36M	hyperlipidemia, hypertension, DM Type 2, diabetic retinopathy, IBS, history of drug abuse (cocaine)	Cardiac arrest	16/14	Hyperglycemia/ acute pulmonary edema; hyperkalemia, acute respiratory failure with hypoxia; diabetic ketoacidosis, anoxic encephalopathy, and aspiration pneumonia
TEN-02-301 (b) (6)	75M	CHF, DM Type 2, cardiomyopathy, COPD, A Fib, hypertension, history of syncope, GI bleed and large intestine removal	Cardiac arrest	30/22	Syncope/ hypotension, ventricular tachycardia, fall, fracture, A fib and rapid ventricular rate during dialysis
TEN-02-301 (b) (6)	66M	HIV/AIDS, hyperlipidemia, hypertension, DM Type 2, malnutrition	Respiratory failure	30/8	Mental status changes, pleural effusion, pneumothorax, respiratory failure/ Malnutrition
TEN-02-301 (b) (6)	85F	A Fib, hypertri-glyceridemia, Parkinson's disease	Cardiac arrest, Septic shock	49/45	None/ Hyperkalemia, Hepatic failure
TEN-02-301 (b) (6)	67M	DM Type 2, hypertension, hyperlipidemia, atherosclerosis	Sepsis	54/25	Deafness in left ear/ Gangrene
TEN-02-301 (b) (6)	49M	CHF, CAD, DM Type 2, hypertension, history of finger & toe amputations	Cardiogenic shock, Septic shock	76/65	Acute myocardial infarction, back pain, hypotension, vision blurred, acute left ventricular failure, right ventricular failure/ MRSA sepsis
TEN-02-301 (b) (6)	69F	Asthma, COPD, hypercholesterolemia, hypertension, rheumatoid arthritis, UTI, history of thyroidectomy and cholecystectomy	Sepsis	94/83	Pathogen resistance/ UTI

Study/ SUBJID	Age/Sex	Co-morbid conditions	Cause of Death/ Narrative Reason for Death	Days from starting study drug to death/ Last day of study drug	AEs reported within 14 days of Event/ additional events in narrative
TEN-02-301 (b) (6)	51M	Hypertension, hyperlipidemia, DM Type 2, CHF, cardiomyopathy, CAD, history of MI and left below knee amputation	Cardiac Arrest	258/257	None/ Collapsed 1 hour into dialysis
Phosphate Binder					
TEN-02-301 (b) (6)	50M	hyperlipidemia, HIV, hypertension, hypocalcemia, gastroparesis, myocardial ischemia, cardiac ablation, DM Type 2, acidosis	Myocardial infarction	96	Nasopharyngitis/ Pneumonia, cardiac failure
TEN-02-301 (b) (6)	54M	angina, coagulopathy, hypertension, hyperlipidemia, DM Type 2, malnutrition, hyperkalemia	Sudden cardiac death	108	None/ None
TEN-02-301 (b) (6)	61M	A fib, CHF, hepatic cirrhosis, DM Type 2, hyperlipidemia, hypertension, history of gastric and colon cancer	End stage renal disease	188	Pulmonary edema, bilateral pleural effusions, worsening of end stage renal disease/ None
Placebo					
TEN-02-301 (b) (6)	75F	Hypertension, coagulation defect, hyperlipidemia, history of lung and kidney cancer	Sepsis	240	None/ Hypotension during dialysis, hypertensive urgency, aortic aneurysm, hypokalemia, vasovagal syncope, pericardial effusion

Source: Reviewer's analysis; adsl.xpt, adae.xpt; JMP; TEN-02-301 Study Report

Abbreviations: A fib, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; F, female; DM, diabetes mellitus; IBS, irritable bowel syndrome; M, male; UTI, urinary tract infection

Table 46. Diarrhea, Safety Population, TEN-02-201

	8-Week PG Treatment Period	4-Week RW Treatment Period	
Preferred Term[1,2]	**Tenapanor N=218 n (%)**	**Tenapanor N=82 n (%)**	**Placebo[3] N=82 n (%)**
Diarrhea[4]	86 (39.4)	1 (2.9)	3 (3.7)
Diarrhea FMQ Broad	87 (39.9)	1 (2.9)	3 (3.7)
Severity[5]			
Mild	40 (18.3)	1 (1.2)	1 (1.2)
Moderate	43 (19.7)	0	2 (2.4)
Severe	4 (1.8)	0	0
Moderate or Severe	47 (21.5)	0	2 (2.4)
SAE	1 (0.5)	0	0
Action Taken with Drug			
Discontinuation	18 (8.3)	0	0
Interruption	2 (0.9)	0	0
Dose Reduction	21 (9.6)	0	0

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 4-week RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PTs gastroenteritis, colitis, defecation urgency, frequent bowels movements, gastroenteritis viral, gastrointestinal hypermotility
[5] Severity categories were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

Table 47. Diarrhea, Safety Population, TEN 02-202

	4-Week Treatment Period		
Preferred Term[1,2]	**Tenapanor + PB N=117 n (%)**	**Placebo + PB N=119 n (%)**	**Risk Difference % (95% CI)**
Diarrhea[4]	50 (42.7)	8 (6.7)	36.0 (25.5, 45.6)
Diarrhea FMQ Broad	50 (42.7)	8 (6.7)	36.0 (25.5, 45.6)
Severity[5]			
Mild	22 (18.8)	6 (5.0)	13.8 (5.6, 22.3)
Moderate	24 (20.5)	2 (1.7)	18.8 (11.2, 27.1)
Severe	4 (3.4)	0	3.4 (-0.4, 8.4)
Moderate or Severe	28 (23.9)	2 (1.7)	22.2 (14.2, 30.8)
SAE	0	0	0
Action Taken with Drug			
Discontinuation	4 (3.4)	2 (1.7)	1.7 (-3.0, 6.9)
Interruption	2 (1.7)	0	1.7 (-1.7, 6.0)
Dose Reduction	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 defined as any event that occurred after the first dose of drug up to end of the 12-week RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
[4] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[5] Severity categories were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

Table 48. Phosphate Binder Used and Subjects Reporting Diarrhea, Safety Population, TEN-02-202

	4-Week Treatment Period			
Phosphate Binder Type	**Tenapanor + PB N=117 n (%)**	**Placebo + PB N=119 n (%)**	**Diarrhea Reported, Tenapanor + PB N=117 n (%)**	**Diarrhea Reported, Placebo + PB N=119 n (%)**
Calcium Acetate	25 (21.4)	23 (19.3)	17 (14.5)	1 (0.8)
Calcium Carbonate	2 (1.7)	2 (1.7)	2 (1.7)	0
Ferric Citrate	9 (7.7)	13 (10.9)	1 (0.9)	2 (1.7)
Lanthanum Carbonate	3 (2.6)	1 (0.8)	0	1 (0.8)
Multiple	12 (10.3)	6 (5)	4 (3.4)	0
Sevelamer + Non-sevelamer	15 (12.8)	12 (10.1)	10 (8.5)	0
Sevelamer Carbonate	42 (35.9)	42 (35.3)	13 (11.1)	2 (1.7)
Sevelamer Hydrochloride	4 (3.4)	3 (2.5)	1 (0.9)	0
Sucroferric Oxyhydroxide	5 (4.3)	17 (14.3)	2 (1.7)	2 (1.7)

Source: Reviewer's analysis; adsl.xpt, adae.xpt; OCS Analysis Studio, JMP
Abbreviations: N, number of subjects; n, number of subjects; PB, Phosphate Binder

Table 49. Diarrhea, Safety Population, Integrated CKD on Dialysis Safety Analysis Set, 12 Weeks

Preferred Term[1,2]	TEN 2-30 mg (N=257) n (%)	TEN 60 mg (N=515) n (%)	TEN 60mg + PB (N=117) n (%)	All TEN (N=889) n (%)	PB (N=256) n (%)	Risk Difference % (95%CI)
Diarrhea	90 (35.0)	262 (50.9)	50 (42.7)	402 (45.2)	15 (5.9)	39.3 (34.5, 43.3)
Diarrhea FMQ Broad[3]	95 (37.0)	265 (51.5)	50 (42.7)	410 (46.1)	15 (5.9)	40.2 (35.4, 44.2)
>= 2 Episodes	21 (8.2)	57 (11.1)	9 (7.7)	87 (9.8)	3 (1.2)	8.6 (5.7, 10.9)
Moderate or Severe AE[4]	58 (22.6)	193 (37.5)	30 (25.6)	281 (31.6)	5 (2.0)	29.6 (25.7, 32.9)
SAE	1 (0.4)	3 (0.6)	0	4 (0.4)	0	0.4 (-1.1, 1.1)
Action Taken with Drug	27 (10.5)	74 (14.4)	4 (3.4)	105 (11.2)	2 (0.8)	10.4 (7.6, 12.7)
Discontinuation	13 (5.1)	137 (26.6)	37 (31.6)	187 (20.0)	5 (2.0)	18.0 (14.4, 21.0)
Dose Reduction	90 (35.0)	262 (50.9)	50 (42.7)	402 (45.2)	15 (5.9)	39.3 (34.5, 43.3)

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 RW treatment period.
[2] Coded as MedDRA PT
[3] Includes PTs gastroenteritis, colitis, defecation urgency, gastroenteritis viral
[4] Severity categories were pre-defined by the Applicant and classified by the investigator as mild, moderate, or severe
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

Table 50. Diarrhea AEs Leading to Discontinuation by Treatment Group and Dosage, Integrated CKD on Dialysis Safety Analysis Set, 12 Weeks

Treatment Group	N	Subjects Reporting Diarrhea AE[1,2] n (%)	Diarrhea AE Led to Discontinuation n (%)
Placebo[3]	69	7 (10.1)	0 (0)
Phosphate Binder	256	15 (5.9)	2 (0.8)
Tenapanor			
2-30 mg	257	90 (35.0)	15 (5.8)
60mg	515	265 (51.5)	60 (11.7)
60mg + PB	117	50 (42.7)	4 (3.4)
90-120mg	45	26 (57.8)	1 (2.2)
All Doses	934	431 (46.1)	79 (8.5)

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 RW treatment period.
[2] Coded as MedDRA PT
[3] Placebo arm includes patients rerandomized to placebo from tenapanor; all patients previously received tenapanor
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects; n, number of subjects with adverse event; PT, preferred term

18. Mechanism of Action / Drug Resistance Additional Information and Assessment

None.

19. Other Drug Development Considerations Additional Information

None.

20. Data Integrity-Related Consults (OSI, Other Inspections)

None.

21. Labeling Summary of Considerations and Key Additional Information

Finalization of labeling has been deferred until the application can otherwise be approved. The Division has provided initial comments on the prescribing information and the Applicant has responded, but no further negotiations has occurred.

The following are notable areas where substantive revisions have been discussed with the Applicant;

Under Dosage and Administration;

Revisions are in progress to clarify instructions for administration of tenapanor as relates to meals and hemodialysis days.

Under Contraindications;

(b) (4)

Under Warnings and Precautions;

A warning as relates (b) (4) has been removed. The underlying risk is covered in a revised warning for diarrhea and (b) (4) is addressed in the revised contraindication.

Under Adverse Reactions;

The Division advised the applicant that it believes the most clinically relevant and readily interpretable data on adverse reactions are provided by the randomized, active-controlled portion of TEN-02-301. The Applicant revised this section accordingly, but the Division has not reviewed these revisions in this cycle.

Under Drug Interactions;

(b) (4) A revised subsection addressing OATP2B1 substrates has been drafted in collaboration with the Applicant.

Under Use in Specific Populations;

Labeling proposals with respect to Pregnancy and Lactation are discussed in 8.4 of this review. The proposed subsection (b) (4) has been removed. (b) (4)

(b) (4)

Under Clinical Pharmacology;

Under mechanism of action, the Division revised to only include mechanisms we are reasonably confident in.

Section 12 has also been revised in parallel with various topics discussed throughout labeling, e.g., administration with respect to meals, hepatic impairment, and drug interactions.

Under Clinical Studies;

The Division has provided no comments to the applicant this cycle as relates to the clinical studies section of labeling.

22. Postmarketing Requirements and Commitments

None.

23. Financial Disclosure

Table 51. Covered Clinical Studies: [Studies TEN-02-201, TEN-02-202 and TEN-02-301]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 195		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: the investigator owns the company's stocks Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

24. References

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.

25. Review Team Acknowledgements

Table 52. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Sabry Soukehal
Nonclinical Reviewer	Elizabeth Hausner
Nonclinical Team Leader	Xuan Chi
Office of Clinical Pharmacology Reviewer	Li Wang
Office of Clinical Pharmacology Team Leader	Sudharshan Hariharan
Clinical Reviewers	Shen Xiao (Efficacy; left FDA before review completed/finalized); Selena DeConti (Safety); Kirtida Mistry (Pediatrics/PREA)
Statistical Reviewer	Fanhui Kong
Statistical Team Leader	Jialu Zhang
Division Director (OB)	Mark Rothman
Division Deputy Director for Safety	Mary Ross Southworth
Clinical Team Leader, Cross-Disciplinary Team Leader, and Division Signatory	Aliza Thompson

Table 53. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Mohan Sapru (Application Technical Lead), Joseph Leginus (Drug Substance), Dan Berger (Drug Product), Feiyan Jin (Process and Facility), Min Sung Suh (Biopharmaceutics)
OPDP	Carrie Newcomer
OSE/DPV	Ali Naik (Medical Officer), Christian Cao (Team Leader)
OSE/DEPI	Marie Bradley (Safety Evaluator), Efe Eworuke (Team Leader)
OSE/DMEPA	Mariette Aidoo (Safety Evaluator), Hina Mehta (Team Leader)
OSE/DRM	Courtney Cunningham (Safety Evaluator), Laura Zendel (Team Leader)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Elizabeth Hausner	OND/DPT-CHEN	Section 7.1 ☒ Authored ☐ Approved
Reviewer	**Signature:** Elizabeth A. Hausner -S Digitally signed by Elizabeth A. Hausner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300147069, cn=Elizabeth A. Hausner -S Date: 2021.07.23 10:03:37 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Pharmacology/Toxicology	Xuan Chi	OND/DPT-CHEN	Section 7.1 ☐ Authored ☒ Approved
Team Leader	**Signature:** Xuan Chi -S Digitally signed by Xuan Chi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xuan Chi -S, 0.9.2342.19200300.100.1.1=2001466742 Date: 2021.07.23 10:22:03 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical Pharmacology	Li Wang	OTS/OCP/DCEP	Section 5 (Table 5), 6.1, 8.1, 8.2, 14 ☒ Authored ☐ Approved
Reviewer	**Signature:** Li Wang -S (Affiliate) Digitally signed by Li Wang -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002641068, cn=Li Wang -S (Affiliate) Date: 2021.07.23 10:48:41 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical Pharmacology	Sudharshan Hariharan	OTS/OCP/DCEP	Section 5 (Table 5), 6.1, 8.1, 8.2, 14 ☒ Authored ☒ Approved
Team Leader	**Signature:** Sudharshan Hariharan -S Digitally signed by Sudharshan Hariharan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000394743, cn=Sudharshan Hariharan -S Date: 2021.07.23 11:01:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Fanhui Kong	OB/DB II	Sections 6.2.3, 6.3, 6.4, Appendices 15, 16 ☒ Authored ☐ Approved
Reviewer	**Signature:** Fanhui Kong -S Digitally signed by Fanhui Kong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fanhui Kong -S, 0.9.2342.19200300.100.1.1=1300172988 Date: 2021.07.22 17:52:25 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Statistical	Jialu Zhang	OB/DB II	Sections 6.2.3, 6.3, 6.4, Appendices 15, 16 ☐ Authored ☒ Approved
Team Leader	**Signature:** Jialu Zhang -S Digitally signed by Jialu Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jialu Zhang -S, 0.9.2342.19200300.100.1.1=1300369843 Date: 2021.07.22 17:56:51 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical	Kirtida Mistry	OND/OCHEN-DCN	Section 8.3. ☒ Authored ☐ Approved
Reviewer	**Signature:** Kirtida Mistry -S Digitally signed by Kirtida Mistry -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kirtida Mistry -S, 0.9.2342.19200300.100.1.1=2002814821 Date: 2021.07.22 18:55:36 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Clinical	Selena DeConti	OND/OCHEN-DCN	Section 7 and 17 ☒ Authored ☐ Approved
Reviewer	**Signature:** Selena S. Deconti -S Digitally signed by Selena S. Deconti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000695680, cn=Selena S. Deconti -S Date: 2021.07.23 06:38:37 -04'00'		
Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
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OTS=Office of Translational Sciences
OCP=Office of Clinical Pharmacology
OB= Office of Biostatistics
OND= Office of New Drugs
OCHEN= Office of Cardiology, Hematology, Endocrinology, and Nephrology
DPT-CHEN= Division of Pharmacology and Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology

DB II= Division of Biostatistics II
DCEP= Division of Cardiometabolic and Endocrine Pharmacology
DPV= Division of Cardiology and Nephrology
[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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07/28/2021 03:49:37 PM

ALIZA M THOMPSON
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA213931
Supporting document/s:	0001
Applicant's letter date:	June 29, 2020
CDER stamp date:	June 29, 2020
Product:	Tenapanor ([redacted (b) (4)])
Indication:	Control of serum phosphorous in adults with chronic kidney disease on dialysis
Applicant:	Ardelyx
Review Division:	Pharmacology/Toxicology for the Office of Cardiology, Hematology, Endocrinology, and Nephrology
Reviewer:	Elizabeth Hausner
Supervisor/Team Leader:	Xuan Chi
Division Director:	Todd Bourcier
Project Manager:	Sabry Soukehal

Template Version: September 1, 2010 (Modified by DCRP: June 10, 2013)

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of [NDA number] are owned by [name of applicant] or are data for which [name of applicant] has obtained a written right of reference.
Any information or data necessary for approval of [NDA number] that [name of applicant] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of [NDA number].

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Appears this way on original

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Tenapanor is an inhibitor of the sodium/hydrogen exchanger isoform 3(NHE3). By inhibiting NHE3 on the apical surface of enterocytes, tenapanor reduces the uptake of sodium from the lumen of the gastrointestinal tract, resulting in increased luminal fluid. Tenapanor has also been demonstrated to decrease urinary phosphorous excretion while increasing fecal phosphate excretion. As the parent drug is minimally absorbed, this drug has been presented as a locally acting inhibitor of phosphate absorption, differentiating this from a phosphate binder.

1.2 Brief Discussion of Nonclinical Findings

The pivotal studies for tenapanor (also known as RDX5791, AZ13667691, and AZD1722) and the major metabolite (M1, AZ13792925) were reviewed during the IND stage and have been recorded in DARRTS as well as in the Unireview for NDA211801 (entered into DARRTS September 5, 2019). An inventory of the reviews for this product are included as an appendix. Because tenapanor has been extensively evaluated in NDA211801 with an equivalent toxicology portfolio, this review will only consider material unique to the pharmacology supporting this application. Tenapanor was approved in September 2019, for irritable bowel syndrome with constipation, under the trade name Ibsrela®. There are no nonclinical issues that stand in the way of approval.

The sponsor has conducted nonclinical studies in vitro and in vivo to characterize the pharmacological properties of tenapanor and the M1 metabolite (AZD13792925). Potential off-target pharmacology of tenapanor was assessed in receptor binding and enzyme interaction studies. In vitro and in vivo safety pharmacology studies of tenapanor were conducted according to ICHS7A and S7B guidelines. Nonclinical studies of the absorption, distribution, metabolism, and excretion were evaluated in addition to the nonclinical toxicology studies recommended under the ICH guidelines to support chronic use of tenapanor in humans. This includes chronic toxicology, reproductive and developmental toxicology, juvenile toxicology, genetic toxicology and carcinogenicity studies. The pivotal studies were conducted according to GLP guidelines.

The M1 metabolite, AZD13792925, is present in human plasma at greater than 10% of the total tenapanor-related exposure, a higher level than reported for the nonclinical species. M1 is both a major metabolite and also disproportionate in humans. The M1 metabolite has been evaluated for pharmacology, secondary pharmacology, genetic toxicology, developmental toxicity(zebrafish), embryo-fetal development (rats), and carcinogenicity in a 26-week CByB6F1/TgRasH2 mouse study. Cardiovascular effects of M1 were also assessed in vitro in cardiac ion channel assays and in vivo in the 3-month and 9-month dog studies. The pivotal studies for M1 were GLP compliant. The 9-month repeat dose dog toxicity study had a NOAEL of 1000mg/kg/day of tenapanor, the highest dose evaluated.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, tenapanor is approvable.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The label has been modified from Ibsrela® (up to 50 mg BID) for the indication of (b) (4) with the lower dose regimen (up to 30 mg BID). This includes modifications of the margins of exposure. The only recommendations will be consistency with any changes in format.

2 Drug Information

2.1 Drug

CAS Registry Number:

1234365-97-9
1234423-95-0 (free base)

Generic Name:
Tenapanor hydrochloride

Code Name:

AZD1722 dihydrochloride, AZD1722, NTX791, RDX5791
ADX-1-0, 17LV04SD, AZ13667691

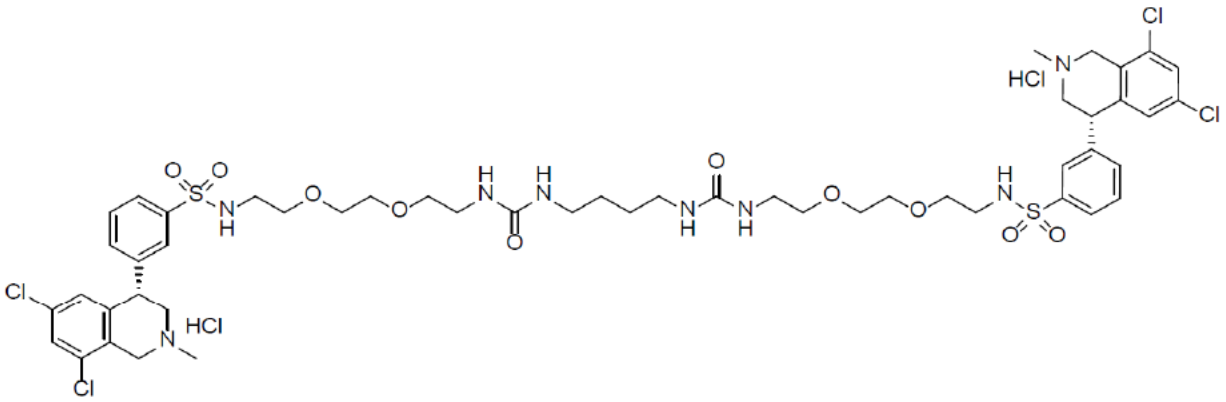
Chemical Name:

Systematic Chemical Name (IUPAC):	1-[2-[2-[2-[[3-[(4S)-6,8-dichloro-2-methyl-3,4-dihydro-1H-isoquinolin-4-yl]phenyl]sulphonylamino]ethoxy]ethoxy]ethyl]-3-[4-[2-[2-[2-[[3-[(4S)-6,8-dichloro-2-methyl-3,4-dihydro-1H-isoquinolin-4-yl]phenyl]sulphonylamino]ethoxy]ethoxy]ethylcarbamoylamino]butyl]urea dihydrochloride

Molecular Formula/Molecular Weight

$C_{50}H_{68}Cl_6N_8O_{10}S_2$ / 1217.97 Daltons

Structure or Biochemical Description



Tenapanor hydrochloride contains 2 stereocenters, both of which are in the *S* configuration.

Pharmacologic Class
Sodium/hydrogen exchanger 3 (NHE3) inhibitor

There are no new excipients and all are compendial.

Table 1-2 Composition of Tenapanor Tablets, (10, 20, and 30 mg)

Component	Quality Standard	Function	% w/w	Unit Formula 10 mg mg/tablet	20 mg mg/tablet	30 mg mg/tablet
Core Tablet						
Tenapanor Hydrochloride	In-house	Drug Substance	(b) (4)			
Microcrystalline Cellulose[c]	USP-NF		(b) (4)			
Low-substituted Hydroxypropyl Cellulose	USP-NF					
Colloidal Silicon Dioxide	USP-NF					
Tartaric Acid[d]	USP-NF					
Propyl Gallate	USP-NF					
Stearic Acid[e]	USP-NF					
Core Weight	N/A					

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND108732 (DG) constipation-related disorders

(b) (4)

IND120566 (DCN) hyperphosphatemia in patients with end stage renal disease

(b) (4)

NDA 211801(DG) IBSRELA® (tenapanor, 50 mg tablet) approved September 12, 2019 for treatment of irritable bowel syndrome with constipation (IBS-C)

2.7 Regulatory Background

Tenapanor has also been known as RDX5791, AZ13667691, and AZD1722. The major metabolite (M1) is AZ13792925, representing >10% of the total tenapanor-related drug exposure in humans based on AUC.
During the clinical development with tenapanor for IBS, the observation was made that tenapanor decreased urine phosphorous excretion and increased stool phosphorous excretion. The sponsor decided to explore the therapeutic potential of this effect.

3 Studies Not Reviewed

The majority of nonclinical studies were reviewed during the IND stage. An inventory of the studies provided and reviewed are attached to this review as an appendix. Only those studies pertaining to the pharmacology for the present indication have been reviewed. The reader is referred to the Unireview available in DARRTS for NDA 211801 for a detailed evaluation of the nonclinical studies.

4 Pharmacology

4.1 Primary Pharmacology

Tenapanor is proposed as an inhibitor of the sodium/hydrogen exchanger isoform 3(NHE3). By inhibiting NHE3 on the apical surface of enterocytes, tenapanor reduces the uptake of sodium from the lumen of the gastrointestinal tract, resulting in increased luminal fluid. Tenapanor has also been demonstrated to decrease urinary phosphorous excretion while increasing fecal phosphate excretion. Recently provided mechanistic studies (review entered into DARRTS February 2, 2020 for IND120566) suggest that passive paracellular absorption is reduced and that there is a modulation to the intercellular tight junctions manifested experimentally as increased transepithelial electrical resistance (TEER),thereby reducing paracellular phosphate Permeability.

There have been species differences in tolerability of tenapanor, mainly due to susceptibility to intestinal fluid retention and diarrhea, which the sponsor summarized as follows:

- Rat NOAEL <30 mg/kg/day in a 28-day repeat doses study

- Dog NOAEL =1000 mg/kg/day in 28-day and 9-month studies
- In IBS-C patients, 50 mg BID (100 mg per day; 1.7mg/kg/day for a 60 kg person) is generally well tolerated.

The sponsor examined baseline expression levels of NHE3 (*SLC9A3*) and ENaC (*SCNN1A, SCNN1B, SCNN1G*) in the intestines of rat, dog, and human to see if differences in gene expression could explain different sensitivities. Of note, ENaC is expressed in the distal colon on the apical epithelium and selectively transports sodium down an electrochemical gradient.

The brief description of sample collection does not discuss any standardization of methods for collection. Nor is there any discussion of different life stages for the different species and the possibility of differences in expression level associated with maturity. The sponsor reports that expression was similar between the species within each segment of intestine but with higher expression in rat small intestine and proximal colon compared to the expression in the dog. It is not clear how much weight to give to these results given the apparent limitations of the methods.

The effect of AZD1722 in renal insufficiency and high salt feeding was investigated in 5/6th nephrectomized Sprague-Dawley rats (see Figure 1 for the study design). Three doses of AZD1722 hydrochloride (water vehicle, 0.3, 1, or 3 mg/kg/day) were evaluated in this rat model. A high salt feeding (4% of diet) was started one week after the surgical procedure. Administration of the drug or vehicle was started at the same time as the addition of dietary salt. Systolic and diastolic blood pressure were measured via tail cuff.

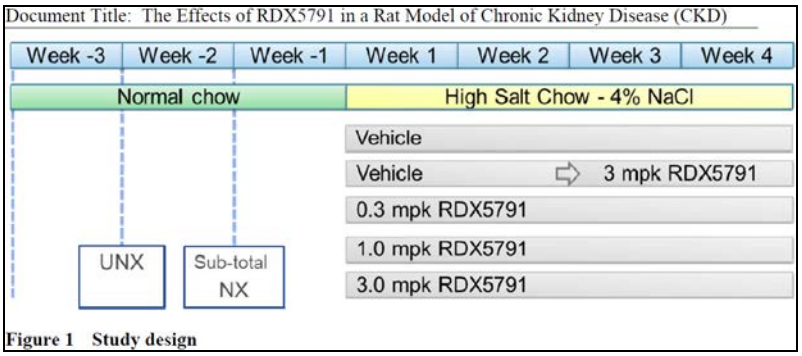


Figure 1. Study design of AZD1722 (RDX5791) in a rat model of chronic kidney disease (CKD).

Blood and urine samples were collected at 7, 14, 21, and 28 days after starting the increased salt diet and drug administration.

The study is exploratory in nature and non-GLP compliant. The methods section is minimal, there is no analysis of dosing solutions and no comparator compounds, making it difficult to assess the informative value of the work. The data is presented as graphs of mean values with no individual animal data.

The data as presented is not entirely clear. BUN, serum creatinine, diastolic and systolic blood pressure are presented as basal values without specifying what point in the study was considered basal. The next set of graphs appears to show no difference from vehicle to the high dose of 3 mg/kg at 14 days, the point at which the treatment groups were divided into groups based upon evaluations to be made.

Extracellular fluid volume as a percent of body weight decreases with AZD1722 treatment, in a seemingly dose-dependent manner. Intracellular fluid volume as a function of body weight is shown to be inversely related to the amount of drug administered. A piece of information not included in the report is the effect of procedures and drug administration on the consistency and volume of feces. It is not unexpected that the extracellular fluid is decreased given the pharmacology of the test article. Both systolic and diastolic blood pressure show concurrent decreases.

Urinary protein is also shown to decrease in a dose-dependent manner with AZD1722 treatment (Figure 2). But there is no information on the serum protein concentration or protein excreted in the feces in each group.

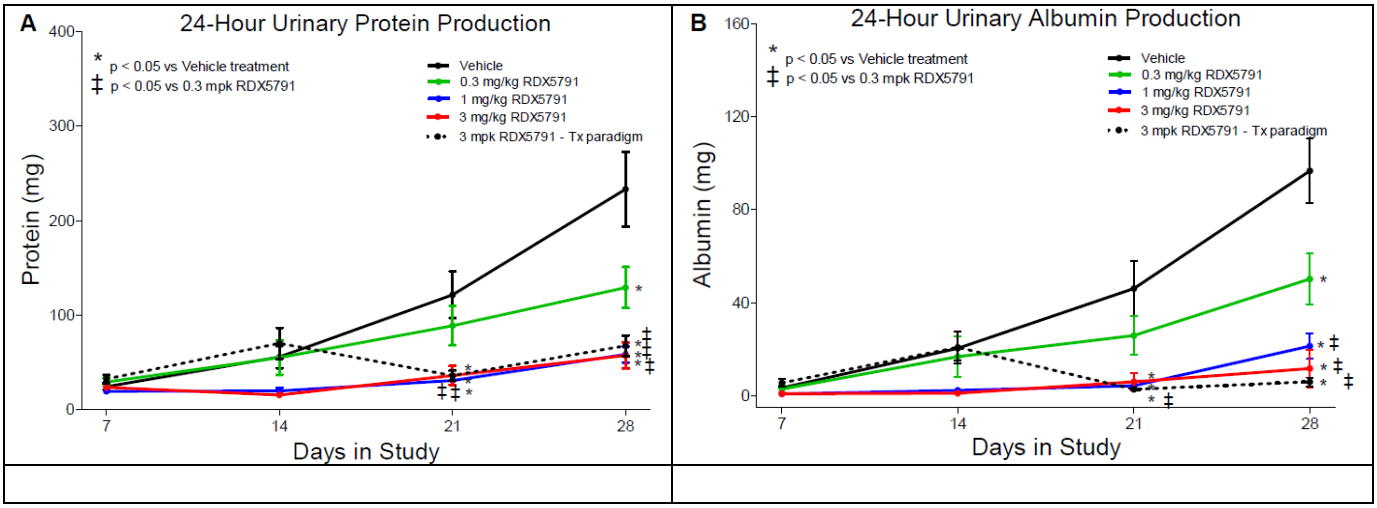


Figure 2. Reduction of proteinuria and albuminuria by AZD1722 in the rat model of CKD.

Creatinine clearance, determined by unspecified methods, shows no difference between the vehicle and the animals treated with the 0.3 and 1 mg/kg/day doses of AZD1722 (Figure 3). The highest dose of 3 mg/kg/day seems to decrease creatinine clearance.

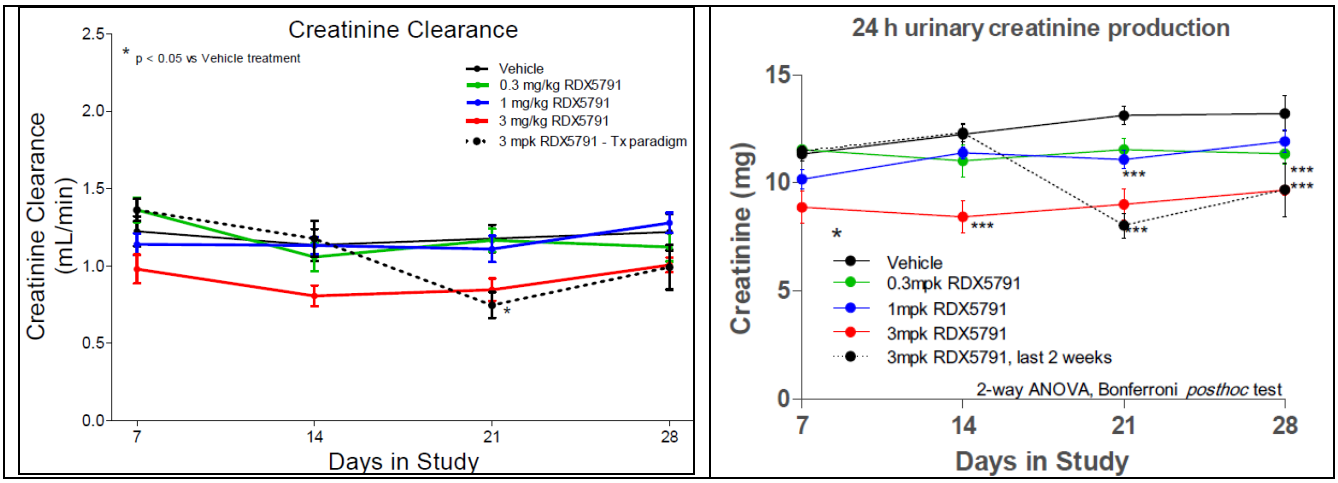


Figure 3. Creatinine clearance.

Urinary excretion of sodium, chloride, potassium, phosphorous and calcium are shown graphically. Serum calcium was presented but not the other electrolytes. Serum creatinine was also not presented. There is also no histopathology of the kidney. The graph of creatinine clearance versus days in study shows a perceptible decrease in the 3 mg/kg/dayRDX5791-Tx paradigm group. The 24-hour urinary creatinine suggests an upward trend for all groups except the "3mpk RDX5791,
last 2 weeks group". The overall conclusion that can be drawn about pharmacodynamics is that use of the test article decreased the extracellular fluid volume.

The major metabolite AZ13792925 was tested for pharmacologic activity against the NHE3 receptor and for secondary activities. While no activity was detected in the radioligand binding assays, cell-based functional assays did show activity. The sponsor's summary tables are shown below.

Table 1 Effect of AZ13792925 in *in vitro* radioligand binding, enzyme and functional assays

Target[a]	Binding K_i or Enzyme IC_{50} (μM)	Functional IC_{50} or EC_{50} (μM)	Pharmacological mode of action
Dopamine D_3 Receptor	0.13	12	Antagonist
5-HT_7 Receptor	0.24	>100[d]	nd
5-HT_{2B} Receptor	0.37	81	Antagonist
Carbonic Anhydrase II	0.43	nt	Inhibitor
5-HT_{1A} Receptor	1.2	>30[d]	nd
α_{2C} Adrenoceptor	1.4	>100[d]	nd
5-HT_{1D} Receptor (rat binding	2.3	1.2	Agonist
Opioid μ Receptor	2.5	22	Agonist
α_{1A} Adrenoceptor	2.7	7.2[f]	Antagonist
α_{1B} Adrenoceptor	3.2	51	Antagonist
Melatonin MT_2 Receptor	3.2	1.1	Agonist
Dopamine D_{2S} Receptor	7.8	13	Antagonist
GABAA Receptor, BNZ (rat)	8.0	nt	nd
Glucocorticoid Receptor NR3C1	11	nt	nd
Opioid δ Receptor (human binding, rat function)	11	>30[e]	nd
5-HT_{1B} Receptor (rat binding, hamster function)	14	>9[e]	nd
L-type Calcium Channel (Diltiazem) (rat)	15	nt	nd
L-type Calcium Channel (Verapamil) (rat)	15	nt	nd
Sigma σ_1 Receptor	15	nt	nd

Table 1 Effect of AZ13792925 in *in vitro* radioligand binding, enzyme and functional assays

Target[a]	Binding K_i or Enzyme IC_{50} (μM)	Functional IC_{50} or EC_{50} (μM)	Pharmacologic mode of action
Peroxisome Proliferator-Activated Receptor γ	18	nt	nd
α_{2A} Adrenoceptor	18	>30[d]	nd
Adenosine Transporter (guinea pig)	19	nt	nd
Dopamine Transporter	19	nt	nd
5-HT_{2C} Receptor	22	>100[e]	nd
Tachykinin NK_1 Receptor	24	27[f]	Antagonist
GABAA Receptor, TBPS	27	nt	nd
Serotonin Transporter	29	nt	nd
Prostaglandin-endoperoxide synthase 1 (COX1)	30	nt	nd
Dopamine D_1 Receptor	37	>100[d]	nd
5-HT_3 Receptor	37	nt	nd
Opioid κ Receptor (rat)	42	68	Agonist
Noradrenaline Transporter	44	nt	nd
Phosphodiesterase $PDE4D_2$	46	nt	Inhibitor
Thromboxane A_2 Synthase	57	nt	Inhibitor
Histamine H_1 Receptor	61	>100[d]	nd
Somatostatin sst_4 Receptor	68	>100[d]	nd
Muscarinic M_1 Receptor	86	16[f]	Antagonist
Cannabinoid CB_1 receptor	>100	8.7	Agonist
AT1	>100	19[f]	Antagonist
Ghrelin	>100	9.0[f]	Antagonist
Adenosine A1 receptor	>100	3.2	Agonist

[a] all human except where noted.
[b] nt - not tested (no assay available)
[c] nd - not determined: tested but inactive or data inconclusive
[d] No activity above assay baseline up to maximum test concentration tested
[e] Activity detected above assay baseline but no defined curve fit
[f] Effect detected in both the agonist and antagonist functional assays. Antagonist IC_{50} presented based on dose response effect (see below)

The sponsor also evaluated the main metabolite for electrophysiological activity in a panel of recombinant human cardiac ion channels. The sponsor found significant activity against 3 voltage-gated cardiac ion channels as shown below:

AZ13792925 had significant activity (a defined IC_{50} value) at three of the four human recombinant voltage-gated cardiac ion channels as shown in Table 1.

Table 1 Significant activity of AZ13792925 in *in vitro* electrophysiological assays

Channel	IC_{50} (µM)	Maximum test concentration (µM)
$hK_v11.1$ (hERG)	16.5	33.3
$hK_v4.3$/hKChIP2.2 (hI_{to})	27.3	33.3
$hK_v7.1$ / hKCNE1 (hIK_s)	14.8	33.3

The clinical pharmacology reviewer was asked for information about clinical steady state plasma levels for the M1 metabolite. At a dose of 30 mg BID, the steady state in dialysis patients was reached in 4-5 days, consistent with the 24-hour terminal elimination half-life of AZ13792925. Dr Wang provided the following table:

Table 2 Comparison of AZ13792925 Plasma Concentration (ng/mL) at Steady State in Humans Following Oral Administration of Tenapanor

Study	Subjects	N	Tenapanor Dose (mg)	Days	$C_{max,ss}$ (ng/mL)	$C_{ave,ss}$ (ng/mL)
TEN-02-106	Healthy	24	10, BID (TBM)	4	4.28	3.66
TEN-02-106	Healthy	24	30, BID (TBM)	4	14.3	12.2
D5613C00003	Healthy	26	15, BID	14	7.82	6.13
D5611C00005	Healthy	12	30, BID	7	13.5	NC
TEN-01-103	Healthy	28	50, BID	13	14.3	12.2
D5611C00001	CKD-5D	26	45, BID	28	17.3	12.8[b]
TEN-02-301	CKD-5D	110	30, BID (TBM)	85	14[a]	10.4[b]

The lowest concentration for an IC_{50} reported above is 14.8µM. Using the greatest plasma concentration reported above, 17.3 ng/ml (for a dose greater than the MRHD), the IC_{50} and the Cmax concentration are roughly equivalent. The molecular weight of M1 is 357.25 g/mole. 14.8µmole/L = 14.8nmol/ml

14.8nmol/ml x 357.25ng/nmol =5287 ng/ml which means there is approximately 300X concentration difference between the IC_{50} values and the clinical Cmax, a reasonable safety margin.

13 Appendix

Summary of nonclinical reviews for tenapanor (related IND108732, IND (b) (4), 120566, NDA 211801 approved Sept.12, 2019)((b) (4)

Application Number	Reviewer	Date Filed	Comments
108732	Gautam	1/3/2013	Genetic toxicology, safety pharmacology, 14-day repeat dose toxicology, impurities
108732	Seifried	12/19/2013	Minutes of Executive CAC discussion of CA protocols
108732	Chakraborti	7/30/2014	Sdn 038 Sponsor notifying agency that rat CA protocol has been revised as advised by ECAC. Seeking concurrence regarding continuation of rat CA study as amended
108732	Chakraborti	2/2/2015	042 Modifications to CA protocols
108732	Chakraborti	6/22/2015	SDN053 Sponsor seeking agency input regarding early termination of groups in CA study
108732	Gautam	11/17/2016	SDN075 Single Dose Pharmacokinetic Study of AZ13792925 (a major metabolite of tenapanor). Tenapanor: Estimation of Plasma Exposures to Metabolites of Tenapanor in M Dog, Mouse and Rat. Determination of the Pharmacokinetics of Tenapanor Hydrochloride and M1 (metabolite of tenapanor) after a Single Oral Dose to Dogs. Single Dose Toxicity Study of AZ13792925. A 4-Day Repeat Dose Toxicity Study of AZ13792925. A 14-Day Repeat Dose Toxicity Study of AZ13792925. A 28-Day Oral Gavage Dose Range-Finding Toxicity and Toxicokinetic Study of AZ13792925 in Hemizygous RasH2 [CbyB6F 1-Tg(HRAS)2Jic]. AZD1722: Oral Maximum Tolerated Dose and Dose Range-Finding Toxicity Study in CByB6FI Hybrid Mice. AZD1722: 1-Month Oral Range-Finding Toxicity Study in CByB6FI Hybrid Mice. Protocol for a 26-week repeated oral dose carcinogenicity study in Tg.rasH2 mice.
108732	Chakder	3/14/2017	SDN 0080 Request to lower doses in ongoing mouse CA study
108732	Gautam	2/13/2019	SDN 104,107 final report of 104 week CA in rats, 26-week CA of tenapanor and AZD13792925 (M1) in CByB6F1/TgRasH2 mice
108732	Gautam	1/10/2019	SD95, SD110 Juvenile animal dose range-finding, JAS
NDA211801	Gautam	9/5/2019	NDA review
108732	Gautam	3/12/2020	SDN120 Comments on draft juvenile rat protocol for post-weaning rat pups

Inventory of reviews continued

Application Number	Reviewer	Date Filed	Comments
(b) (4)	Hausner	3/8/2013	(b) (4)
120566	Hausner	1/21/2014	Primary pharmacology GI transit time in rats In vitro protein binding in mouse, rat, rabbit, dog, human GI PK in rats ADME in rats PK of coadministered enalapril MTD iv dose in rat Rat micronucleus Embryo-fetal development studies in rats
120566	Hausner	6/5/2015	SDN013. AZD1722 and fosrenol, AZD and renvela, off-target pharmacology, Mouse fertility and early embryonic development
120566	Hausner	7/5/2016	SDN0031, 0032. M1 pharmacology, secondary pharmacology PK of M1 and AZD1722 canine plasma

			6 month rat and male fertility, 9 month dog study M1 genetic toxicology Rabbit SegII dose-range finding
120566	Hausner	3/22/2017	Memo.protocol3.10.17 Comments on proposed JAS protocol
120566	Hausner	1/12/2018	Sdn 053 cross species comparison of plasma metabolites. JAS pilot
120566		2/12/2020	Sdn103. Pharmacology of phosphate effects.
120566		12/10/2019	Sdn104 memo to file
(b) (4)	Hausner	3/1/2019	(b) (4)

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