TENAPANOR FOR THE CONTROL OF SERUM PHOSPHORUS (s-P) IN ADULTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS

SPONSOR BRIEFING DOCUMENT

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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ABBREVIATION	DEFINITION
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the concentration-time curve
BID	twice daily
BSFS	Bristol stool form scale
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
C_{max}	maximum plasma concentration
CRL	Complete Response Letter
CYP450	cytochrome P450
DDI	drug-drug interaction
EAIR	exposure-adjusted incidence rate
EAS	Efficacy Analysis Set
ESKD	end-stage kidney disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDRR	Formal Dispute Resolution Request
HD	hemodialysis
HIV	Human Immunodeficiency Virus
HP	hyperphosphatemia
GI	gastrointestinal
IBD	inflammatory bowel disease
IBS-C	irritable bowel syndrome with constipation
iFGF23	intact fibroblast growth factor 23
IND	Investigational New Drug (application)
IRT	Interactive Response Technology
ITT	Intention-to-Treat
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LOV	last observed value
LS	least squares
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model for repeated measures
NDA	New Drug Application

ABBREVIATION	DEFINITION
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
OND	Office of New Drugs
PB	phosphate binder
PD	pharmacodynamic(s)
PepT1	peptide transporter 1
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic(s)
PP	Per Protocol
PTH	parathyroid hormone
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RT	randomized treatment
RTP	randomized treatment period
RW	randomized withdrawal
RWP	randomized withdrawal period
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SD	standard deviation
s-P	serum phosphorus
$t_{½}$	elimination half-life
TID	3 times daily
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

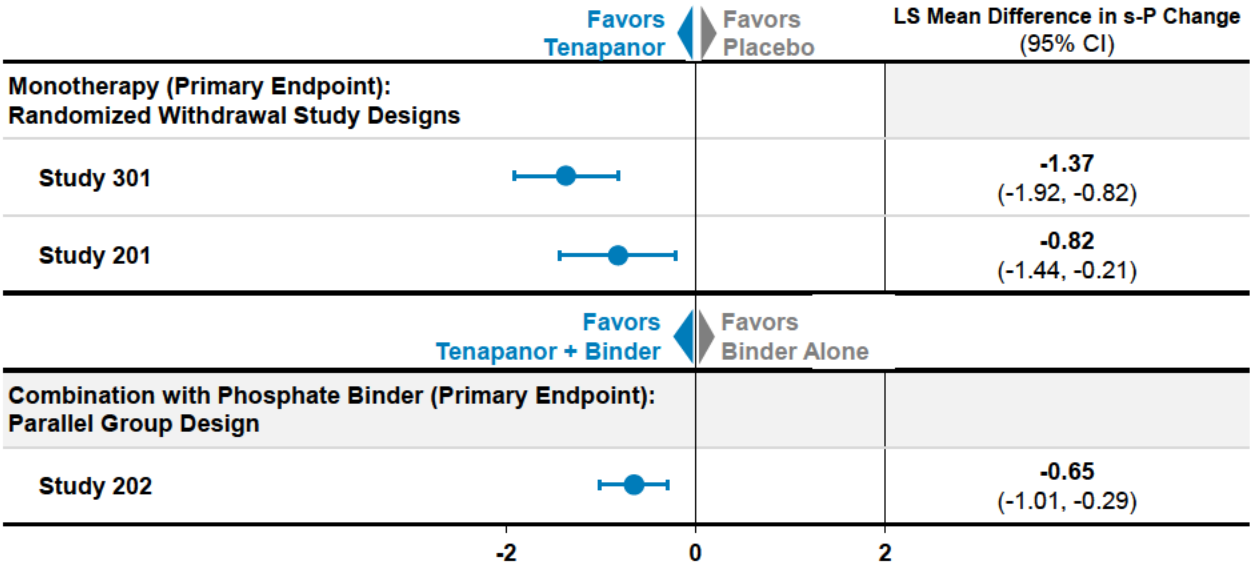
1.1 Introduction

Hyperphosphatemia (HP) is a near-universal complication that occurs in approximately 80% of patients with end-stage kidney disease (ESKD) on maintenance dialysis. Serum phosphorus (s-P) has been an accepted surrogate for HP treatment guidelines, clinical practice, and Food and Drug Administration (FDA) approval of all s-P lowering drugs. There is a strong link between HP and bone disease, coronary calcification, and several other coronary complications; observational studies have shown a strong association between elevated s-P and all-cause mortality in patients receiving maintenance dialysis (Block et al 2004; Kalantar-Zadeh et al 2006; Liu et al 2017; Tentori et al 2008). Phosphate binders (PBs) are the only approved class of drugs for the management of HP. Despite their significant use, approximately 45% of patients on PBs are above s--P target levels (> 5.5 mg/dL) at any given time, and 77% are not consistently within target levels over a 6-month period (Robinson et al 2020). Required dosing for PBs of several large pills 3 times per day with meals likely poses challenges to patients in achieving these target goals.

Ardelyx is seeking approval of tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis. Tenapanor is a first-in-class, minimally absorbed, phosphate absorption inhibitor with the potential to address an unmet medical need in the management of HP. Despite the widespread use of the current standard of care, PBs, the majority of patients are unable to control s-P (DOPPS 2019). If approved, tenapanor would provide a unique approach for the treatment of HP with a novel mechanism of action and simplified dosing regimen (30 mg twice daily [BID]).

Tenapanor has been studied in more than 900 patients receiving maintenance dialysis in Phase 2 and Phase 3 studies. The primary basis for tenapanor's efficacy comes from 3 adequate and well-controlled trials. A long-term monotherapy Phase 3 study (Study 301) provides the principal evidence of efficacy, with supportive evidence from a short--term monotherapy Phase 3 study (Study 201) and a Phase 3 study of tenapanor in combination with PBs in patients with inadequately controlled s-P on PB treatment (i.e., ≥ 5.5 mg/dL; Study 202). All 3 studies met their pre-specified primary efficacy endpoints, demonstrating the efficacy of tenapanor in reducing s-P (Figure 1). Across the clinical development program, tenapanor alone and in combination with PBs produced significant reductions in s-P and demonstrated an acceptable safety and tolerability profile with a different mechanism of action from current treatment options.

Figure 1: Treatment Comparisons of Change in Serum Phosphorus at Primary Study Endpoint From Three Phase 3 Tenapanor Trials



CI=confidence interval; LS=least squares; s-P=serum phosphorus.

Ardelyx submitted a New Drug Application (NDA) for tenapanor in June 2020. During the review, FDA requested that Ardelyx submit additional analyses to support a predictable responder population, extending the original Prescription Drug User Fee Act date by 3 months. In July 2021, Ardelyx received a Complete Response Letter (CRL) stating that while the FDA agreed that "...tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis, the magnitude of the treatment effect is small and of unclear clinical significance." Starting in December 2021, Ardelyx submitted 2 formal dispute resolution requests (FDRRs), the first to the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) and the second to the Office of New Drugs (OND), requesting resolution of the scientific and regulatory dispute pertaining to tenapanor and a finding that the treatment effect of tenapanor observed in the three Phase 3 trials was sufficient to permit approval of the NDA. In February 2022, OCHEN issued an Appeal Denied Letter in which, as noted in the original CRL, OCHEN agreed that the data submitted showed that tenapanor can reduce s-P in CKD patients on dialysis but were "unable to conclude tenapanor's overall clinical benefit is meaningful and outweighs the risk." Furthermore, OCHEN stated that "...it may still be reasonable to approve a drug if one can readily identify patients with meaningful response..." but did not believe the analyses in the NDA adequately demonstrated this fact. OCHEN agreed that FDA has accepted s-P as a surrogate endpoint and basis of approval for all s-P lowering drugs (i.e., PBs).

In February 2022, Ardelyx appealed to OND, which provided an Interim Appeal Response that stated that input from this panel would be valuable in considering what

level of s-P reduction is clinically meaningful and may be considered to support approval and whether tenapanor responders can be identified in practice.

In the CRL, FDA noted that the primary reason for non-approval of tenapanor was based on the magnitude of the treatment effect, which in their opinion was “small and of unclear clinical significance.” Of note, there are no disagreements between FDA and Ardelyx with respect to the use of observational data to support s-P as a surrogate for clinical outcomes, as these data form the basis for treatment guidelines in clinical practice and have been the standard for FDA approval of all PBs. Also, there is no disagreement between the FDA and Ardelyx regarding clinical trial designs, study conduct, or results of the three Phase 3 trials. Key questions and concerns posed by FDA during the FDRR process are highlighted in Table 1, which the Sponsor seeks to address in this document.

Table 1: Summary of Key FDA Questions/Concerns and Ardelyx Position

FDA Key Questions/Concerns	Ardelyx Position
1. Is the s-P reduction achieved with tenapanor clinically meaningful?	• The mean treatment difference in s-P reduction between tenapanor and placebo across all 3 studies is clinically meaningful, as it moves s-P towards normal[a]. • For the pre-specified primary analysis set, the mean treatment differences during the RWP of the 2 monotherapy studies were -0.8 and -1.4 mg/dL, with the latter aligning with historical data for approved PBs. • Data from the RTP (enrichment phase) also provides additional evidence of tenapanor's clinically meaningful effect. Among tenapanor-treated patients, there was a mean s-P reduction of 1.4 mg/dL, with a significant number of patients achieving clinically meaningful s-P reductions and target treatment goals. • Finally, tenapanor's novel mechanism of action and simplified dosing regimen (2 pills per day) are also clinically meaningful, providing another option for s-P lowering, either as monotherapy or in combination with PBs for those who require additional s-P reduction.
2. Identifying a responder population to support the clinical utility of tenapanor	• Early response or non-response tends to predict continued response or non-response, respectively, allowing nephrologists to assess benefit and modify treatment appropriately.
3. Potential risks associated with diarrhea AE	• Diarrhea and softer stool consistency is an expected PD effect of tenapanor. • The majority of diarrhea AEs occurred early, were mild to moderate in severity, were not treatment-limiting, and resolved with tenapanor dose reduction or discontinuation. • There were no significant associations between diarrhea and electrolyte abnormalities or blood pressure changes, and diarrhea events were generally not associated with more worrisome downstream consequences (e.g., dehydration, syncope, falls, or hospitalizations). • Across the entire clinical development program, tenapanor demonstrated an acceptable safety and tolerability profile, comparable to or better than PBs.

AE(s)=adverse event(s); BID=twice daily; PBs=phosphate binders; PD=pharmacodynamic; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.
[a] KDIGO normal range is 2.5–4.5 mg/dL and KDOQI recommends s-P maintained between 3.5–5.5 mg/dL

Ardelyx acknowledges that there is a range of s-P reductions seen in tenapanor clinical trials and maintains that when evaluating the totality of data, tenapanor's treatment effect is clinically meaningful.

1. FDA Key Issue: Clinical meaningfulness of s-P reduction with tenapanor

First, it is important to acknowledge that the results from all three Phase 3 studies were positive, having met the pre-specified efficacy analysis, and all three Phase 3 studies demonstrated an acceptable safety and tolerability profile.

The mean treatment differences seen during the randomized withdrawal period (RWP) in the monotherapy trials (Study 201 and Study 301) in both the primary analysis set (-0.8 and -1.4 mg/dL, respectively) and the non-primary analysis set (-0.7 and -0.7 mg/dL, respectively) are clinically meaningful, as they move s-P toward normal per international treatment guidelines (Fouque et al 2018; KDIGO 2017; National Kidney Foundation 2022).

While the Intention-to-Treat (ITT) population (i.e., the non-primary analysis set) is typically analyzed to assess treatment effects in a conventional parallel-group study, it is not the appropriate population for a RW design (Nair 2019). The RW design was used in the 2 tenapanor monotherapy Phase 3 studies where the primary endpoint was the difference in effect when drug is withdrawn vs continued, measuring the rise in the placebo group after the drug is withdrawn. The intent is to confirm that the effect seen during the enrichment phase is due to drug as it abates when drug is withdrawn.

Both tenapanor monotherapy trials were randomized withdrawal (RW) designs. The pre-specified primary analysis sets in these trials were the patients who achieved s-P reduction ≥ 1.2 mg/dL during an enrichment phase (i.e., Efficacy Analysis Set [EAS]). It is typical for RW studies to use this population as the primary analysis set because this population, per FDA Guidance on Enrichment Strategies (Food and Drug Administration 2019), provides the best population to evaluate for a treatment effect, as loss or maintenance of drug effect cannot be measured in patients who never had a drug effect (i.e., did not achieve the level of s-P reduction that met the response definition). However, unlike the approach taken in the tenapanor studies, most RW studies do not randomize patients who fail to meet the pre-specified responder definition.

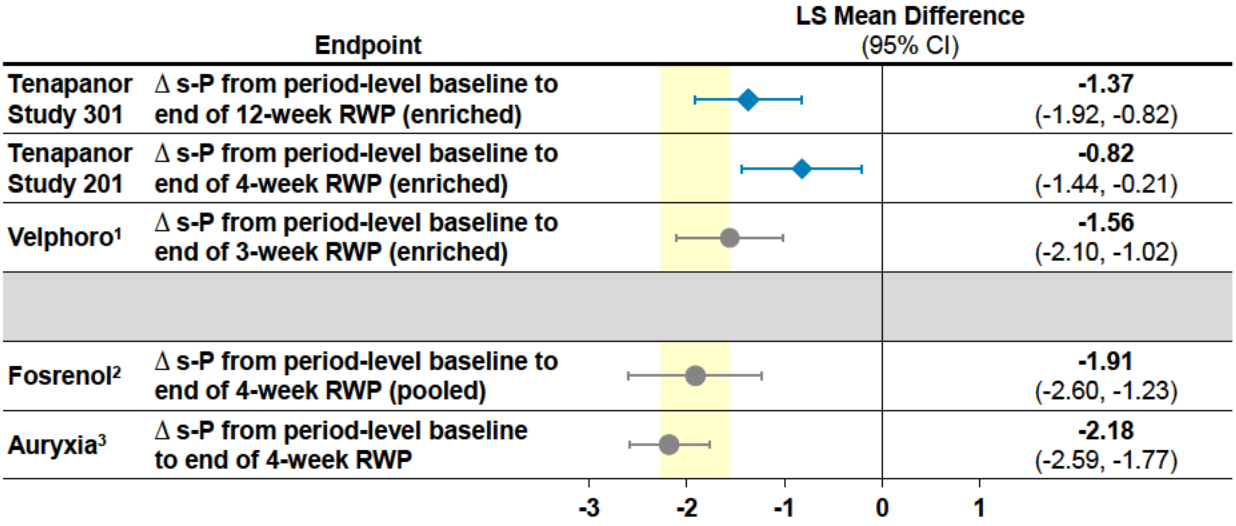
The mean treatment differences between tenapanor and placebo were -0.8 and -1.4 mg/dL in 2 monotherapy studies (Study 201 and 301) and -0.7 mg/dL in the combination therapy study (Study 202). Additionally, a Phase 2 monotherapy trial (D5613C00001), which was a typical randomized, placebo-controlled, parallel-group study (i.e., not a RW study) showed a mean treatment difference of -1.4 mg/dL between tenapanor 30 mg BID and placebo. These reductions in s-P are clinically meaningful.

The mean treatment difference of -1.4 mg/dL during the RWP observed in the primary analysis set (i.e., the EAS) of the more robust Study 301 is similar to the effect seen during the enrichment phase of the same study (i.e., the 26-week randomized treatment period [RTP] ITT), and likely provides a better estimate of tenapanor's s-P lowering effect. At the end of RTP, 53% of tenapanor-treated patients achieved a ≥ 1.2 mg/dL reduction in s-P, 46% achieved a ≥ 1.5 mg/dL reduction, and 36% reached the target range of ≤ 5.5 mg/dL. These results were achieved with 2 tenapanor pills per day.

These findings further support the clinically meaningful effect of tenapanor in lowering s-P.

Finally, the totality of the s-P lowering seen with tenapanor align with the approximately 1.5–2.2 mg/dL range historically referenced for PBs in studies that used RW design (Figure 2). Additional details on the RW study designs for Velphoro, Fosrenol, and Auryxia are provided in Section 1.5.1.

Figure 2: Mean Treatment Differences in Studies that Used Randomized Withdrawal Design



1. Velphoro USPI and FDA review report; 2. Fosrenol USPI and FDA review report; 3. Auryxia USPI and FDA review report
Yellow highlight represents the 1.5–2.2 mg/dL reduction in s-P as the mean treatment effect acknowledged by the FDA.
CI=confidence interval; LS=least squares; RWP=Randomized Withdrawal Period; s-P=serum phosphorus; USPI=United States prescribing information.

In the combination therapy Study 202, in which patients had inadequately controlled s-P while on PBs 3 times daily, 37% of patients treated with tenapanor + PBs were able to achieve s-P < 5.5 mg/dL vs 22% for placebo + PBs. In Study 401 (extension from Study 301), 171 patients with ESKD on maintenance dialysis continued treatment of tenapanor alone or in combination with sevelamer, an FDA-approved PB, for an additional 18 months (up to total treatment of 2.5 years). Approximately 47% achieved a s-P of ≤ 4.5 mg/dL after 6 months of treatment, as submitted in the NDA.

Moreover, the clinical meaningfulness of tenapanor is not limited to reduction in s-P but also includes additional clinical benefits of fewer pills, less frequent dosing, and a novel mechanism of action that allows it to be used either alone or in combination with PBs. Additionally, for patients who cannot tolerate PBs, tenapanor provides another treatment option.

2. FDA Concern: Identifying a responder population to support the clinical utility of tenapanor

The FDA also expressed interest in identifying a population where the effect of tenapanor would be quickly identifiable and suggested analyses that might help discern if an early response was predictive of a future response to tenapanor. As is true for PBs, there were no baseline demographics or patient characteristics that helped predict treatment response *a priori*. However, post hoc analyses from Study 301 suggest that an early response or non-response to tenapanor tends to predict continued response or non-response, respectively, and the same analysis conducted on the sevelamer group showed an equivalent percentage of patients who responded to treatment continued to respond (details in Section 1.5.6 and Appendix 9.2). This information allows nephrologists to assess and optimize patient benefit, as is currently done for PB therapy. The FDA Guidance on Enrichment Strategies states that "Labeling will reflect limitations and concerns, but it seems clear that a drug shown to be effective and safe in an enriched study should be available even if the responder population is not identified as precisely as would be desirable." As with other medications, tenapanor should be discontinued in patients who have not experienced a clinically meaningful reduction in s-P. The standard clinical practice of measuring s-P at least monthly allows effective management of patients, such that prolonged use of tenapanor in a setting of minimal benefit can be avoided.

3. FDA Concern: Potential risks associated with diarrhea adverse events

Lastly, while safety of tenapanor was not raised as a concern by the FDA in the CRL, during the Formal Dispute Resolution communications, the FDA cited the potential risks associated with diarrhea in the context of the clinical benefit. The Sponsor agrees with the FDA that a drug's benefit should be considered in the context of its risks.

Tenapanor is an NHE3 inhibitor that blocks dietary sodium absorption and results in retention of intestinal sodium and water, such that diarrhea and softer stool consistency are expected pharmacodynamic (PD) effects that have been observed in all tenapanor clinical studies. And notably, with its minimal systemic absorption, the only adverse event (AE) that meets product labeling standards for reporting of the patient population (≥ 5%) is diarrhea. It is important to note that most diarrhea AEs occurred early, were mild to moderate in severity, and typically resolved within 2 weeks.

There were 2 patients with severe diarrhea that led to hospitalization, one of which experienced a temporally associated AE of special interest (AESI) of dehydration. There were no significant changes in serum electrolytes, other laboratory findings, or blood pressure (details in Sections 6.8 and 6.9). Although the rate of diarrhea was highest (53%) during the 26-week RTP of the long-term monotherapy Study 301, 16% of patients discontinued due to diarrhea, indicating that diarrhea was not treatment-limiting in most cases. In addition, the other Phase 3 studies (Study 201 and 202), showed similar AE profiles. In summary, the data suggest that more worrisome potential downstream consequences of diarrhea are relatively infrequent.

1.2 Background on Hyperphosphatemia in Patients Receiving Maintenance Dialysis

CKD affects an estimated 37 million people in the United States (US) (CDC 2021). Despite the high prevalence of kidney disease, most people (as many as 9 in 10) who have CKD are unaware that they have the disease. In addition, approximately 786,000 individuals have ESKD and are being treated with renal replacement therapy (maintenance dialysis [71%] or kidney transplant [29%]), with Black and non-white Hispanic individuals being disproportionately affected compared to non-Hispanic white individuals (3:1 and 3:2, respectively) (USRDS 2020).

1.2.1 *Mechanism of Disease*

HP – elevated levels of phosphorus in the blood outside of the normal range of 2.5–4.5 mg/dL – is an integral part of the CKD mineral and bone disorder and results, in part, from the inability of failing kidneys to excrete the daily phosphorus load. HP is a nearly universal complication among patients receiving maintenance dialysis (Block and Port 2000). HP results in excessive serum and tissue concentrations of phosphorus and changes in circulating levels of hormones including fibroblast growth factor-23 (FGF-23), vitamin D, and parathyroid hormone (PTH). Excess s-P promotes vascular calcification, induces endothelial dysfunction, and may contribute to other emerging CKD-specific mechanisms of cardiovascular toxicity (Waheed et al 2013). Elevations in s-P > 5 mg/dL have been associated with significant increases in mortality risk of up to 102% (Block et al 2004; Kalantar-Zadeh et al 2006). Left untreated, HP is correlated with vascular and tissue calcifications, bone pain, fractures, and worsening secondary hyperparathyroidism (Sprague et al 2021). It is now understood that the paracellular pathway is the primary mechanism by which dietary phosphate is absorbed (King et al 2018; Saurette and Alexander 2019).

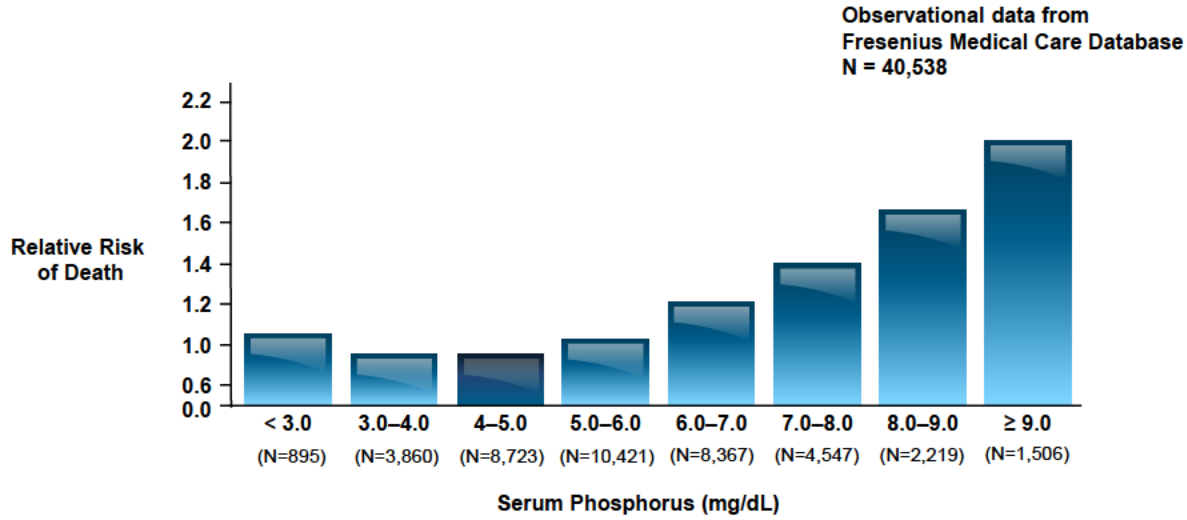
1.2.2 s-P as a Biomarker

s-P is an accepted surrogate endpoint in patients with HP receiving maintenance dialysis and has been the basis for FDA approval of PBs. As stated in FDA correspondence, “FDA has accepted serum phosphate reduction as a validated surrogate endpoint to support an indication for the control of serum phosphate levels in patients with CKD on dialysis” and that “[e]ven though there is an absence of interventional studies establishing the benefit of phosphate reduction in improving clinical outcomes in patients with CKD on dialysis, accepting this endpoint as a validated surrogate was and is reasonable.”

Observational studies have shown a strong association between elevated s-P and all-cause mortality in patients receiving maintenance dialysis (Block et al 2004; Kalantar-Zadeh et al 2006; Liu et al 2017; Tentori et al 2008). As stated above, experimental studies provide support for the epidemiologic findings: excess s-P promotes vascular calcification, induces endothelial dysfunction, and may contribute to other emerging CKD-specific mechanisms of cardiovascular toxicity (Waheed et al 2013). Hence,

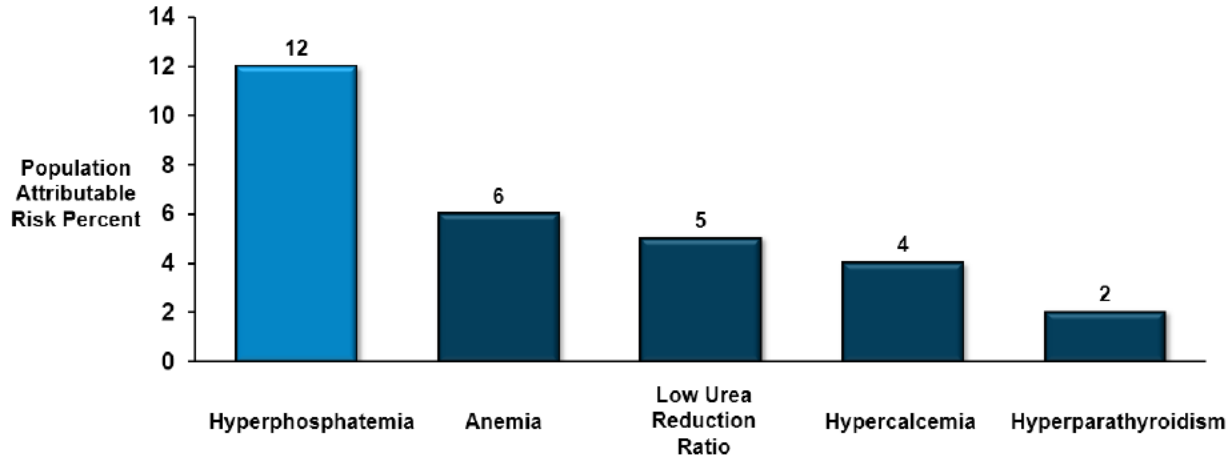
Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (2003) suggest maintaining s-P within 3.5–5.5 mg/dL, and the Kidney Disease Improving Global Outcomes (KDIGO) 2017 Guideline Update recommends lowering elevated s-P toward the normal range (i.e., 2.5–4.5 mg/dL) (Fouque et al 2018; KDIGO 2017; National Kidney Foundation 2022). Elevated s-P above the reference range of 4–5 mg/dL is associated with statistically significant and clinically meaningful increases in the risk of death (Figure 3). Even modest increases in s-P concentrations are associated with higher adjusted risk of death in this patient population. Moreover, the population risk associated with HP, for mortality, is higher than that associated with anemia, low urea reduction ratio (a metric of hemodialysis efficiency), hypercalcemia, and secondary hyperparathyroidism (Figure 4) (Moe and Chertow 2006). The high attributable risk is related to both a high relative risk and high prevalence. In addition, data from the Dialysis and Outcomes Practice Patterns Study (DOPPS 2019) also show a strong association between elevated s-P over time and mortality (Figure 5) (Lopes et al 2020).

Figure 3: s-P and Mortality in Patients Receiving Hemodialysis



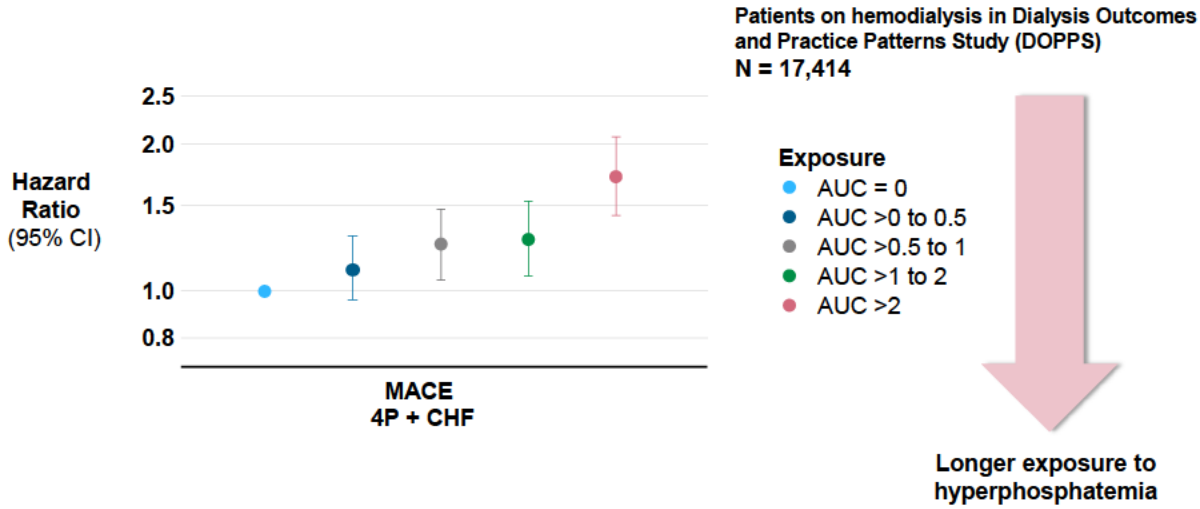
CI=confidence interval; s-P=serum phosphorus.
Note: Adjusted for case mix and other laboratory values.
Source: Block et al 2004

Figure 4: Population Attributable Risks on Mortality



Source: Moe et al 2006

Figure 5: Correlation Between Elevated s-P Over Time and MACE



AUC=area under the concentration-time curve; CI=confidence interval; CHF=congestive heart failure; CV=cardiovascular; MACE 4P=major adverse cardiovascular events (cardiovascular death + non-fatal myocardial infarction + non-fatal angina + non-fatal stroke); s-P=serum phosphorus.
Source: Lopes et al 2020

1.2.2.1 HiLo Trial

HiLo is an ongoing, multicenter, cluster-randomized, open-label, non-inferiority, outcomes trial sponsored by the National Institutes of Health. The HiLo trial was developed, in part, out of frustration by clinicians and patients around the inability to consistently achieve current s-P target goals with currently available therapies for most patients, as well as concern around the potential long-term effects of large doses of PBs used in clinical practice (Edmonston et al 2021). The main objective of the HiLo Trial is to evaluate whether treatment outcomes (hospitalizations and deaths) are impacted by

target levels for s-P; more specifically, to assess if the current more stringent targets of < 5.5 mg/dL are associated with better clinical outcomes than a less stringent target of < 6.5 mg/dL.

The study has a pragmatic design with no case report form, no data entry, and no onsite study coordinator. Facility level cluster randomization is being used to enroll approximately 4,400 participants, from 120–150 hemodialysis centers, with broad eligibility criteria including all adult patients on standard in-center dialysis. Enrollment delays have shifted the availability of data from the original date of April 2023 to mid-2025 (599 patients are currently enrolled) (HiLo Study). While this study represents a laudable effort that will hopefully add to the understanding of optimal s-P target levels for patients on maintenance dialysis, it will not negate the need to lower s-P in these patients or determine the degree of s-P reductions that can be linked to clinical outcomes. As such, these results should not be used to limit the number (type or class) of available s-P lowering agents, but rather, if a new target goal is substantiated based on robust data, that target goal should be applied to all s-P lowering agents, including tenapanor, if approved.

1.2.3 Current Treatment Options and Unmet Need

The goal of HP treatment to lower s-P toward the normal range is important, because the risks associated with elevated s-P are on a continuum rather than anchored to a specific threshold. Dietary modifications and increasing the frequency and duration of maintenance dialysis can help to control HP, but dietary modification is rarely sufficient, and more frequent and longer dialysis sessions increase the burden of care. Patients are placed on strict diets and counseled to restrict processed foods, since preservatives and additives typically include inorganic phosphates, which are more efficiently absorbed than organic phosphates, such as those in protein sources and dairy products. Restriction of processed food is particularly challenging for patients with limited resources, who are disproportionately represented among patients with ESKD in the US. Other dietary restrictions imposed by comorbidities, including diabetes, hypertension, and hyperlipidemia, can further complicate dietary phosphate restrictions. Conventional 3 times weekly maintenance dialysis does not remove adequate phosphate to treat HP. Increases in dialysis frequency (> 3 times per week) or extended duration (> 4 hours per session) adds to the immense dialysis burden already experienced by these patients (Rastogi et al 2021). Even with these initial interventions, approximately 80% of these patients are prescribed PBs, the current standard of care and only therapy available for the last 25 years.

Unfortunately, the large pill burden posed by PBs (pills are typically taken with every meal and snack) often proves challenging for these patients. Many patients use multiple PBs, although clinical trials have not shown an additive effect of PBs in lowering s-P. In a US survey, patients receiving maintenance dialysis who were prescribed PBs reported taking a median number of 19 pills per day with 25% of them taking more than 25 pills per day (Chiu et al 2009). Frequent dosing, number of pills, and large pill size are

primary drivers of the lack of consistent use of PBs in this patient population, which can then lead to ineffective s-P control (Fissell et al 2016; Ghimire et al 2015; Karamanidou et al 2008). The side effect profile including poor gastrointestinal (GI) tolerability and concerns for potential long-term negative effects add additional challenges for treatment (Palmer et al 2016).

Despite the widespread use of PBs, the majority of patients with HP who are receiving maintenance dialysis are unable to consistently achieve s-P targets, underscoring the significant unmet need (DOPPS 2019). New treatment options with different mechanisms of action are needed to help these patients and their treating nephrologists lower s-P towards the normal range.

1.3 Overview of Tenapanor

Tenapanor provides a new treatment option with a distinct mechanistic approach to managing s-P. Tenapanor is a small molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) and targets the primary pathway of phosphate absorption, paracellular absorption in the GI tract (Labonte et al 2015). Tenapanor works by inhibiting NHE3, which is expressed on the luminal surface throughout the small intestine and proximal colon and normally functions as a transporter to import luminal sodium (Zachos et al 2005). Direct inhibition of NHE3 by tenapanor reduces paracellular phosphate permeability and significantly lowers s-P in patients receiving maintenance dialysis (Block et al 2017). In addition, its mechanism of action makes tenapanor a potential treatment option as monotherapy or in combination with PBs.

Tenapanor is active at doses of tens of milligrams per day (e.g., 10 mg to 30 mg twice daily [BID]), compared with several grams per day required for PBs (Auryxia PI 2014; Block et al 2019; Fosrenol PI 2011; Phoslo PI 2011; Renvela PI 2014; Spencer et al 2014; Velphoro PI 2013), allowing for a smaller pill size. Tenapanor tablets (e.g., 30 mg oval tablet; 11.8 mm × 6.8 mm × 4.2 mm, 300 mg total weight per tablet) are much smaller than PB tablets (e.g., sevelamer carbonate 800 mg oval tablet 19.0 mm × 9.5 mm × 8 mm, 1.15 g total weight per tablet) (Generic Partners 2015) and are taken BID, while PBs are typically taken as several large pills with every meal and snack to bind ingested phosphate and prevent it from being absorbed.

Tenapanor was approved for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults in the US on 12 September 2019, with a recommended dose of 50 mg BID.

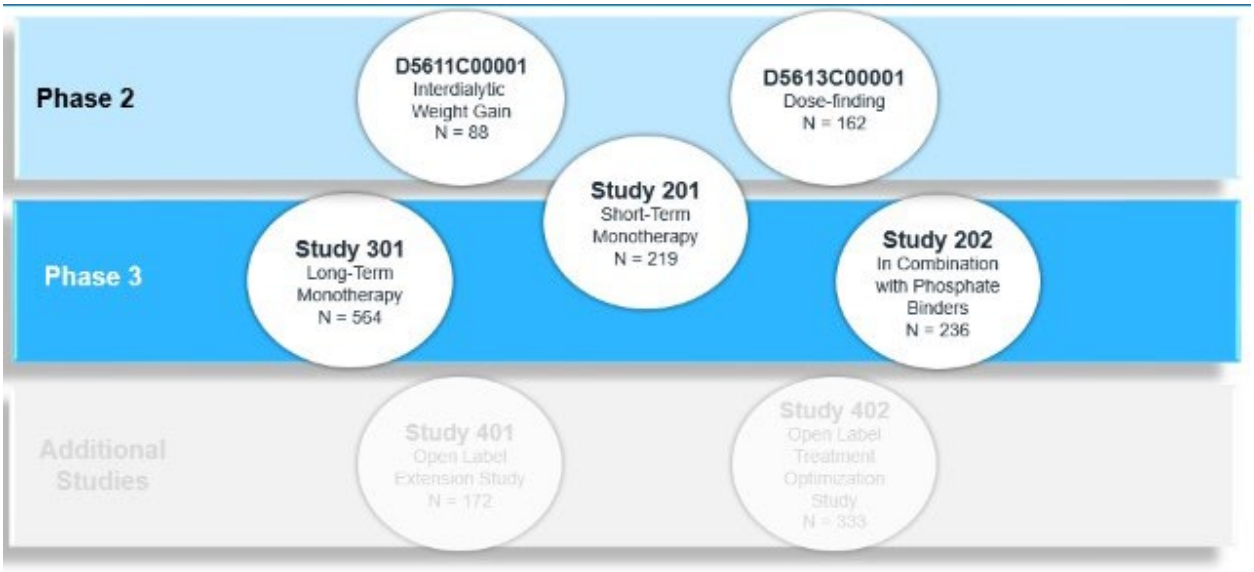
1.4 Clinical Development Program

The tenapanor clinical development program for the treatment of HP in patients receiving maintenance dialysis has been ongoing since 2012. Tenapanor has been studied in approximately 1,600 patients receiving maintenance dialysis in mid- to late -stage clinical trials (Figure 6). Phase 3 studies included 2 monotherapy trials and 1 trial with tenapanor in combination with PBs in a more difficult-to-treat population of

patients whose s-P remained elevated (≥ 5.5 mg/dL) despite ongoing treatment on a stable dose of PB therapy.

The 2 monotherapy studies, Study 201 and 301, employed a RW design, and the combination therapy study, Study 202, used a conventional parallel-group design. All 3 studies met their pre-specified primary and key secondary efficacy endpoints and demonstrated an acceptable safety/tolerability profile. Study 301 included an active safety comparator to sevelamer. Additionally, 2 supportive Phase 2 studies and 2 open -label studies have been conducted (details are provided in Section 4.2 and 5.4-5.5, respectively).

Figure 6: Tenapanor Clinical Development Program



1.5 Efficacy Findings

1.5.1 Discussion of Study Designs

A RW study offers a straightforward enrichment strategy often used when a treatment response can be identified early. Both Study 201 and 301 used an RW design approach. In a typical RW design, after an initial treatment period or enrichment phase, where all participants receive active treatment, non-responders exit the trial and only the responders continue. Responders are then randomized to receive either active treatment or placebo. The primary endpoint is evaluated and other key analyses are conducted using only data from the responder population in the RWP with the goal to ascertain loss of effect in the placebo group and maintenance of effect in the active treatment group for the purpose of confirming that the effect seen during the enrichment phase is drug induced. For the tenapanor clinical program, patients were randomized into the double-blind RWP to placebo or tenapanor and non-responder patients were not exited.

Study 201 was originally designed as an 8-week double-blind Phase 2b study followed by a 4-week double-blind, placebo-controlled RWP to evaluate the efficacy, safety, and tolerability of tenapanor (3 mg BID, 10 mg BID, or 30 mg BID [down-titrated in a stepwise fashion as needed]) to treat HP in patients receiving maintenance dialysis. Upon completion of the 8-week RTP, patients were re-randomized to either remain on their current dose of tenapanor without dose titration or receive a matching placebo during the 4-week RWP.

Under the original design, the primary efficacy endpoint was change in s-P from baseline to the endpoint of the 8-week RTP, and all analyses of s-P change from the 8--week RTP to the end of 4-week RWP were specified as secondary. After discussion with the FDA, the study was converted to a Phase 3 study, and the s-P change from the end of the 8-week RTP to the endpoint of the 4-week RWP was converted from a secondary efficacy endpoint to the primary efficacy endpoint. In addition, an agreement was reached with the FDA to define patients who had a reduction of ≥ 1.2 mg/dL at the end of the RTP as responders. The responders comprised the EAS, which was pre-specified as the analysis set for all efficacy analyses. The planned sample size for the RTP was also increased from 150 to 200 to ensure that 78 responders to the 8-week tenapanor treatment would comprise the EAS for the primary efficacy analysis. Based on results from the 3 tenapanor dose groups included in the RTP of Study 201, the 30 mg dose-titration regimen was selected for the second pivotal Phase 3 monotherapy study, Study 301, as the only tenapanor dose group in the RTP.

Study 301 evaluated the efficacy, safety, and tolerability of tenapanor in patients receiving maintenance dialysis. The study consisted of a 26-week open-label RTP in which patients were randomized (3:1) to receive tenapanor (30 mg BID with dose titration permitted) or sevelamer (active safety comparator), an up to 12-week double -blind placebo-controlled RWP in which patients randomized to tenapanor upon completion of the 26-week RTP were re-randomized (1:1) to either remain on tenapanor at their current dose or switch to placebo, and a 14-week open-label tenapanor safety extension period for a total treatment period of up to 52 weeks. Dose titration of tenapanor was only permitted during the 26-week RTP and the 14-week safety extension period. The EAS comprised patients who entered the RWP with s-P reduction of ≥ 1.2 mg/dL from baseline to the end of the 26-week RTP. Patients in the open-label sevelamer group received sevelamer per standard of care instructions in the package insert for the entire 52-week study. The sevelamer group was intended as a safety comparator only, with no pre-specified efficacy analyses and no specified directions for the Investigator with regard to dose changes. Of note, approximately 65% of the patients who received sevelamer in Study 301 had been previously treated with sevelamer alone or in combination with non-sevelamer binder(s) prior to the start of study treatment.

Both Studies 201 and 301 randomized all patients completing the RTP and defined responders at the end of RTP as patients achieving ≥ 1.2 mg/dL reduction from baseline in s-P to standardize the trials. All patients (both responders and non-responders) were

kept in the trials for the RWP because the studies were double-blind, and the s-P change was not known for each patient at the time of re-randomization into the RWP. Although it is not typical for a RW design to randomize all completers of the previous treatment period, the inclusion of non-responders to tenapanor in the RWP provided additional information on safety and level of continued response in a double-blind manner. However, these non-responders were included in a pre-specified key secondary analysis of the RWP (the ITT analysis set) in Study 301 and in a post hoc ITT analysis set in Study 201. Not surprisingly, this analysis was not requested by FDA because loss or maintenance of efficacy cannot be measured in a population of non--responders where pre-specified efficacy threshold was never achieved. Therefore, the best population to analyze in the RW design is the responders (i.e., the EAS), which was the pre-specified analysis set for the primary efficacy endpoint in both studies.

The Phase 3 combination therapy study, Study 202, evaluated the s-P lowering effect of tenapanor administered orally BID for 4 weeks in patients receiving maintenance dialysis with inadequately controlled HP (≥ 5.5 mg/dL) despite receiving ongoing treatment with a stable regimen of PB therapy (detailed further in Section 5.3).

1.5.2 Study 201: Short-Term Monotherapy

A total of 219 patients receiving maintenance dialysis were randomized (1:1:1) to receive tenapanor 3 mg BID (N=74), 10 mg BID (N=73), or 30 mg BID allowing for dose down titration (N=72) during the 8-week RTP of Study 201. Only patients randomized to the dose-titration group who started at tenapanor 30 mg BID could be down-titrated at the end of Weeks 1, 2, 3, and 4 of the RTP in a stepwise fashion to 20, 15, 10, and 3 mg BID based on GI tolerability; once down-titrated, the dose could not be increased. The RTP was followed by a 4-week placebo-controlled RWP during which patients were re-randomized (1:1) to tenapanor (current dose) or placebo.

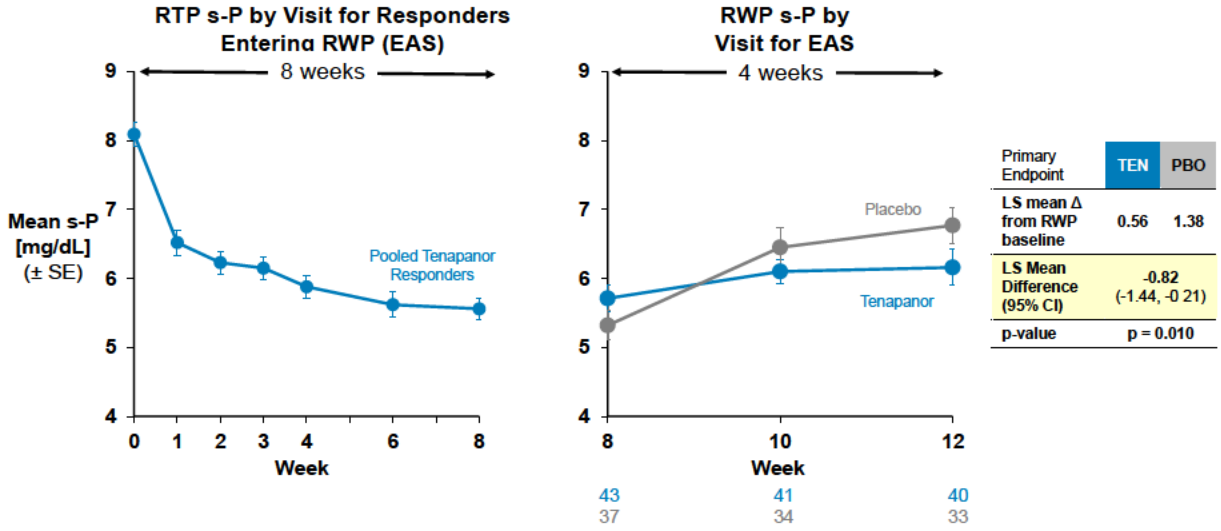
Overall, 77.0% of patients in the tenapanor 3 mg BID, 74.0% of patients in the tenapanor 10 mg BID, and 73.6% of patients in the tenapanor dose-titration group completed the RTP. In total, 55 patients (25.1%) withdrew from the study before completing the 8-week RTP. The most common primary reasons for early withdrawal from the RTP were AE, HP, withdrawal by participant, and intolerable GI side effects. In total, 164 patients entered the 4-week RWP, of which 80 were responders from the RTP (i.e., entered the RWP with s-P reduction of at least 1.2 mg/dL from study baseline to the end of RTP). The most common primary reasons for early withdrawal from the RWP were HP and AE. During the study, 18 patients withdrew due to diarrhea and all such diarrhea events occurred during the RTP.

Study 201 met its pre-specified primary endpoint, with a statistically significant (p=0.010) difference between tenapanor and placebo in s-P change from the end of the 8-week RTP (i.e., period-level baseline for RWP) to the end of the 4-week RWP in the EAS, an enriched population comprising patients who were responders in the RTP (right panel, Figure 7). The least squares (LS) mean s-P change in the RWP was 1.38 mg/dL for placebo and 0.56 mg/dL for tenapanor, with an LS mean difference of 0.82 mg/dL.

Results of the pre-specified sensitivity analysis on the RWP completers in the EAS were consistent with the result of the primary efficacy analysis.

In the EAS, the onset of s-P lowering effect of tenapanor was observed as early as 1 week on treatment during the RTP and was sustained with a mean reduction of 2.50 mg/dL at Week 8 (left panel, Figure 7).

Figure 7: Study 201: Primary Efficacy Analysis for Primary Endpoint – Change in s-P from Period-Level Baseline to End of 4-Week RWP (EAS)



Note: The primary endpoint was an LOV-type endpoint; each patient in the EAS contributed their last observed s-P change during the RWP to the primary efficacy analysis shown in the table. The LS means, CI, and p-value came from an ANCOVA model. The line plots show the raw mean s-P by visit for the EAS based on observed data.
ANCOVA=analysis of covariance; CI=confidence interval; EAS=Efficacy Analysis Set; LOV=last observed data; LS=least squares; PBO=placebo; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

1.5.3 Study 301: Pivotal Longer-Term Study of Tenapanor as Monotherapy

A total of 564 patients receiving maintenance dialysis were randomized (3:1) to receive tenapanor (N=423) or sevelamer (N=141) during the 26-week RTP of Study 301. The dose of tenapanor could be titrated during the RTP based on s-P and/or GI tolerability in 10 mg increments to a minimum of 10 mg BID or a maximum of 30 mg BID, and the dose of sevelamer was permitted to be adjusted based on standard of care per label.

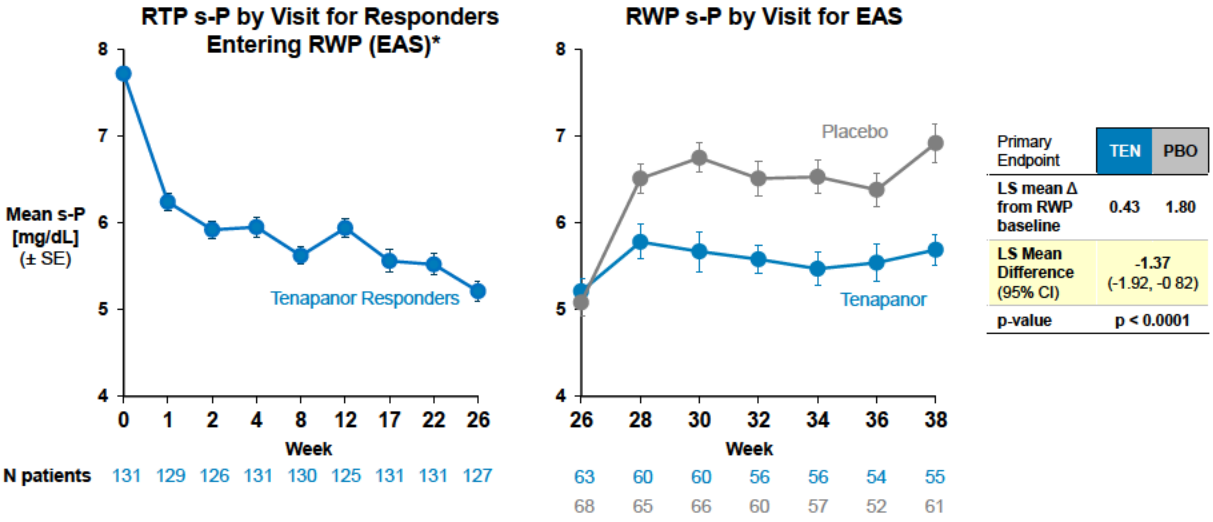
Overall, 60.5% of patients in the tenapanor group and 83.0% in the sevelamer group completed the RTP. The most common primary reason for early withdrawal from the RTP was AE, which included 77 patients (18.2%) in the tenapanor group and 2 (1.4%) in the sevelamer group. Specifically, 67 patients experienced diarrhea during the RTP that led to study drug discontinuation, and the majority (65 patients) were from the tenapanor group. As noted above, approximately 65% of patients in the sevelamer group had previously been treated with sevelamer, such that safety and tolerability

differences between treatment groups were anticipated, with AE rates different from those seen in sevelamer-naïve patients noted in its USPI.

Of the 556 patients in the Safety Analysis Set, the mean age at screening was approximately 58 years. The majority of patients (89.6%) were receiving maintenance hemodialysis, and the remainder (10.4%) were receiving peritoneal dialysis. At baseline, the mean duration since ESKD diagnosis was 4.9 years and the mean duration since first recorded dialysis was 4.6 years. The mean baseline s-P was 7.38 mg/dL.

Study 301 met its primary efficacy endpoint, change in s-P from the period-level baseline (i.e., the end of the 26-week RTP) to the end of RWP. Similar to Study 201, approximately 50% of patients met the responder definition and were included in the EAS; in these patients, the mean s-P reduction from baseline was 2.52 mg/dL at Week 26 (Figure 8, left panel). In the pre-specified primary efficacy analysis on the EAS, the LS mean difference between tenapanor and placebo in s-P change from period-level baseline to the end of the 12-week RWP was -1.37 mg/dL and was statistically significant ($p < 0.0001$) in favor of tenapanor (Figure 8, right panel).

Figure 8: Study 301: Primary Efficacy Analysis for Primary Endpoint – Change in s-P from Period-Level Baseline to End of 12-Week RWP (EAS)

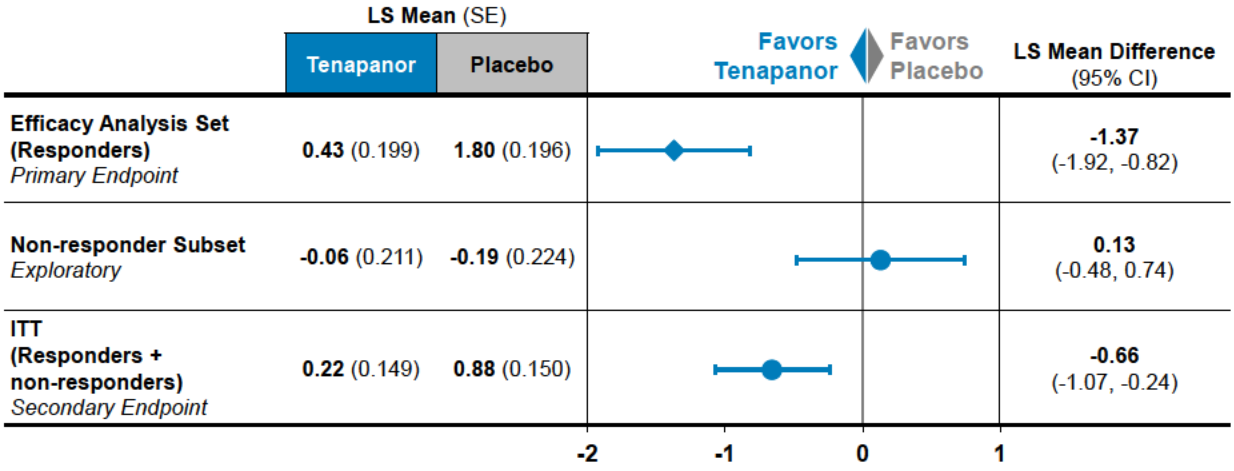


*Pre-specified exploratory endpoint.
Note: The primary endpoint was an LOV-type endpoint; each patient in the EAS contributed their last observed s-P change during the RWP to the primary efficacy analysis shown in the table. The LS means, CI, and p-value came from an ANCOVA model. The line plots show the raw mean s-P by visit for the EAS based on observed data.
ANCOVA=analysis of covariance; CI=confidence interval; EAS=Efficacy Analysis Set; LOV=last observed data; LS=least squares; PBO=placebo; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

A post hoc analysis of the primary efficacy endpoint was performed on the non-responder subset (i.e., a subset of the ITT patients entering the RWP with s-P reduction < 1.2 mg/dL at the end of the RTP), and as expected, the LS mean difference was not

statistically significant (Figure 9). As the unenriched population (i.e., ITT Analysis Set for the RWP) comprised both apparent responders (i.e., the EAS) and non-responders, the size of treatment difference between tenapanor and placebo observed in pre-specified secondary efficacy analysis on the ITT Analysis Set for the RWP (LS mean difference -0.66 mg/dL) was smaller than that observed in the primary efficacy analysis on the EAS (LS mean difference -1.37 mg/dL).

Figure 9: Study 301: Analysis for Primary Endpoint by Response Status at End of RTP – Change in s-P from Period-Level Baseline to End of 12-Week RWP (RWP ITT)



Note: The primary endpoint was an LOV-type endpoint; each patient in the analysis set contributed their last observed s-P change during the RWP to the analysis. The LS means, SEs, and CIs came from an ANCOVA model.
ANCOVA=analysis of covariance; CI=confidence interval; ITT=Intention-to-Treat; LOV=last observed value; LS=least squares; RWP=Randomized Withdrawal Period; SE=standard error; s-P=serum phosphorus.

1.5.4 Supportive Evidence from Study 202: Pivotal Study of Tenapanor in Combination with Phosphate Binders

Study 202 evaluated the s-P lowering effect of tenapanor when administered to patients receiving maintenance dialysis on stable PB therapy with HP (≥ 5.5 mg/dL) inadequately controlled on PBs. The study consisted of a 2- to 4-week run-in period in which all patients were on a stable dose of PB(s). Patients were required to have s-P ≥ 5.5 and ≤ 10.0 mg/dL at Screening and the end of the run-in period while receiving ≥ 1 PB, representing a more difficult-to-treat patient population. Eligible patients were then randomized (1:1) to placebo (N=119) or tenapanor (N=117) starting at a dose of 30 mg BID. Within the first 2 weeks of treatment, the dose of tenapanor could be down-titrated based on s-P concentration and/or GI tolerability in 10 mg increments to a minimum of 10 mg BID and up-titrated back to a maximum of 30 mg BID as needed.

Treatment with tenapanor in combination with PBs (i.e., tenapanor + binder) resulted in a statistically significant s-P reduction from baseline to Week 4 compared with binder alone (i.e., placebo + binder) for the Full Analysis Set (FAS), achieving the primary

efficacy endpoint (-0.84 vs -0.19 mg/dL). The LS mean (95% CI) difference between groups was -0.65 (-1.01, -0.29) (p=0.0004). Approximately twice as many patients achieved the established s-P treatment goal of < 5.5 mg/dL in the tenapanor + binder group compared with placebo + binder at each week (e.g., 37–49% vs 18–24%).

1.5.5 Clinical Meaningfulness of Efficacy Results and Additional Benefits

Despite the availability of PBs, patients with HP continue to struggle with s-P control and the associated complications including cardiovascular disease, vascular and tissue calcifications, bone pain, fractures, worsening secondary hyperparathyroidism, and premature death. No large, long-term prospective outcome studies have been completed to date to establish the impact of reductions of s-P on long-term outcomes. However, preclinical research and observational studies have led to the understanding that the risks associated with HP are decreased with s-P reductions toward the normal range in patients receiving maintenance dialysis. In a clinical setting, nephrologists strive to lower s-P towards normal, and treatment decisions are based on numerous clinical factors including monthly s-P measures, a patient's individual tolerance to PBs, dietary restrictions, and frequency of dialysis.

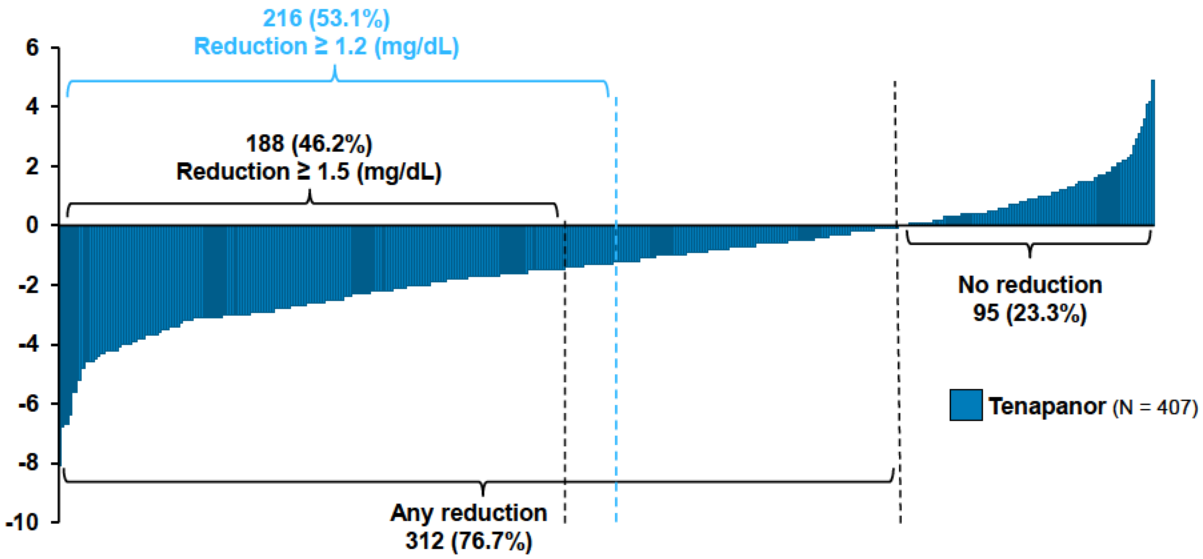
The clinical relevance of tenapanor's s-P lowering effect can be shown by the assessments shown in Table 2 in addition to the mean changes in s-P at the end of the RWP in the 2 monotherapy studies.

Table 2: Summary of Assessments to Establish Clinical Meaningfulness of Tenapanor Effect

Assessment	Finding
Individual s-P reduction from baseline during the 26-week RTP for patients treated with tenapanor in Study 301	53% of tenapanor-treated patients achieved a reduction of ≥ 1.2 mg/dL, and 46% achieved a reduction of ≥ 1.5 mg/dL
Individual s-P change from baseline during the RTP for patients treated with tenapanor in Studies 201 and 202	Consistent trends in individual patients' s-P change across the duration of the studies
Reduction from baseline in s-P for tenapanor vs sevelamer during 26-week RTP	Both groups showed decrease in s-P from baseline, but tenapanor group did not show as large of a reduction compared to the sevelamer
Responders' reduction from baseline in s-P during the 26-week RTP	Similar magnitude of s-P reduction in tenapanor and sevelamer responders
Reduction in s-P among 26-week completers and 52-week completers	Similar magnitude of s-P reduction in tenapanor and sevelamer completers
Percent of patients achieving s-P < 5.5 mg/dL	Nearly twice as many patients achieved the target goal of < 5.5 mg/dL in the tenapanor + PB group compared with the placebo + PB group
Percent of patients achieving s-P reduction ≥ 1.2 mg/dL at Weeks 1, 2, and 4 who met this target during Weeks 17, 22, and 26	79% of patients with an early response to tenapanor also had a late response, and 66% of patients who did not respond early also did not respond later in the treatment period

Figure 10 shows a waterfall plot of the s-P change from baseline to the end of the 26--week RTP, derived as the last observed s-P minus baseline s-P, for all eligible patients who received at least 1 dose of tenapanor and had at least 1 post-baseline s-P during the RTP (i.e., ITT population for the RTP). While the response to tenapanor varies by patient, regardless of the completion status, 77% of patients had some s-P reduction at the end of RTP, and 53% had a reduction of ≥ 1.2 mg/dL, a threshold that was also used to define the apparent responders (i.e., the EAS for the primary efficacy analysis).

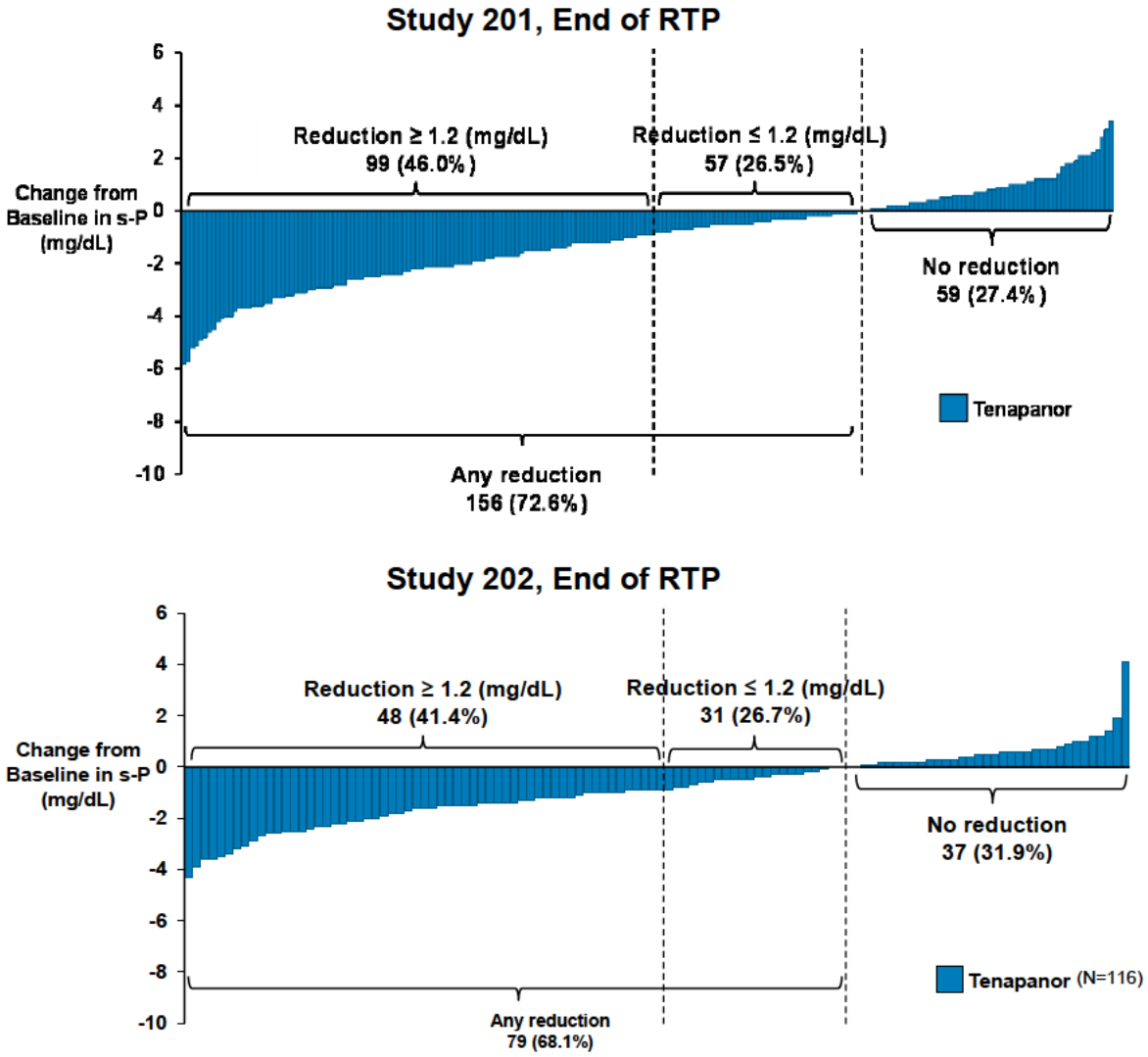
Figure 10: Study 301: Waterfall Plot of Change in s-P from Baseline to End of RTP (RTP ITT)



Note: LOV data shown
ITT=Intention-to-Treat; LOV=last observed value; RTP=Randomized Treatment Period; s-P=serum phosphorus.

A similar trend was seen in individual patients' s-P change from baseline across studies (Figure 11). Although the time periods are different for each study, the range in response is consistent. As mentioned above, 53% of patients in Study 301 achieved a reduction of ≥ 1.2 mg/dL, and 46% of patients in Study 201 and 41% of patients in Study 202 met this threshold.

Figure 11: Studies 201 and 202: Waterfall Plots of Change in s-P from Baseline to End of RTP (RTP ITT with Post-Baseline s-P for Study 201; FAS for Study 202)



Note: LOV data shown
FAS=Full Analysis Set; LOV=last observed value; RTP=Randomized Treatment Period; s-P=serum phosphorus.

A post hoc subgroup analysis was performed to compare the response to tenapanor and placebo at the end of RWP by study baseline s-P. In general, in the EAS, patients randomized to tenapanor had greater s-P reductions from study baseline at the end of RWP than patients randomized to placebo.

The clinical relevance of tenapanor in controlling s-P in patients receiving maintenance dialysis was also supported by the level of response to tenapanor in patients with baseline s-P ≥ 7.5 mg/dL (Table 3), a pre-specified subpopulation of patients with increased relative risk of mortality (Block et al 2004; Liu et al 2017; Tentori et al 2008).

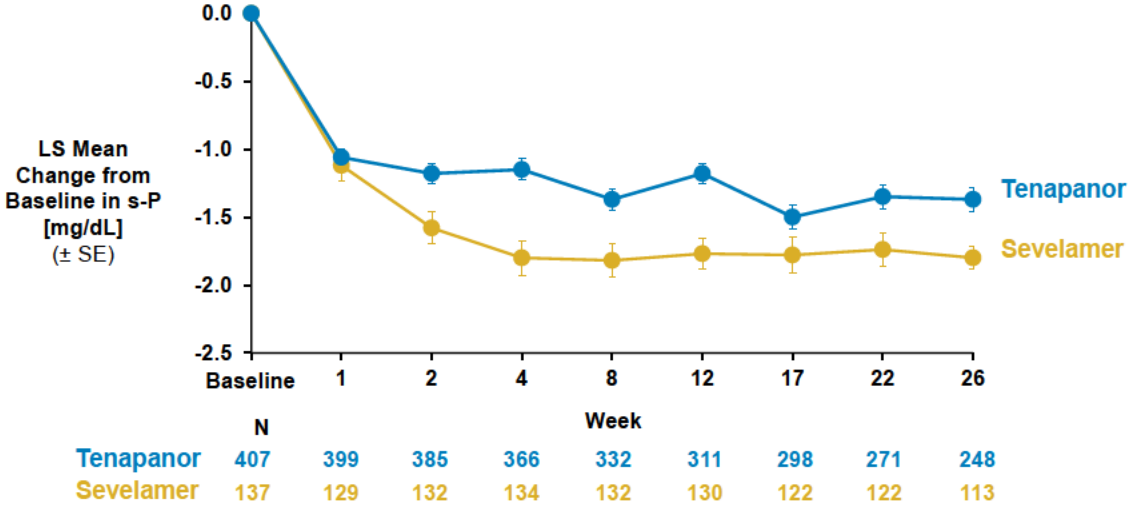
Table 3: Studies 201 and 301: Mean s-P Reduction in Tenapanor 30 mg BID Dose-Titration Group (RTP ITT Patients with Baseline s-P ≥ 7.5 mg/dL)

Analysis	Study	Mean s-P Reduction (mg/dL)	
		Week 8	Week 26
Endpoint Analysis[1]	201 (8-Week RTP)	n=37 1.91	--
	301 (26-Week RTP)	n=204 2.03	n=204 1.94
	Combined	n=241 2.01	--
Observed Case[2]	201 (8-Week RTP)	n=29 1.94	--
	301 (26-Week RTP)	n=158 2.26	n=113 2.30
	Combined	n=187 2.21	--

1. Based on the last observed s-P changes by Week 8 (or Week 26) for ITT patients.
2. Based on the observed s-P changes at Week 8 (or Week 26), including s-P collected at unscheduled or early termination visits that were mapped to Week 8 (or Week 26).
ITT=Intention-to-Treat; RTP=Randomized Treatment Period; s-P=serum phosphorus.

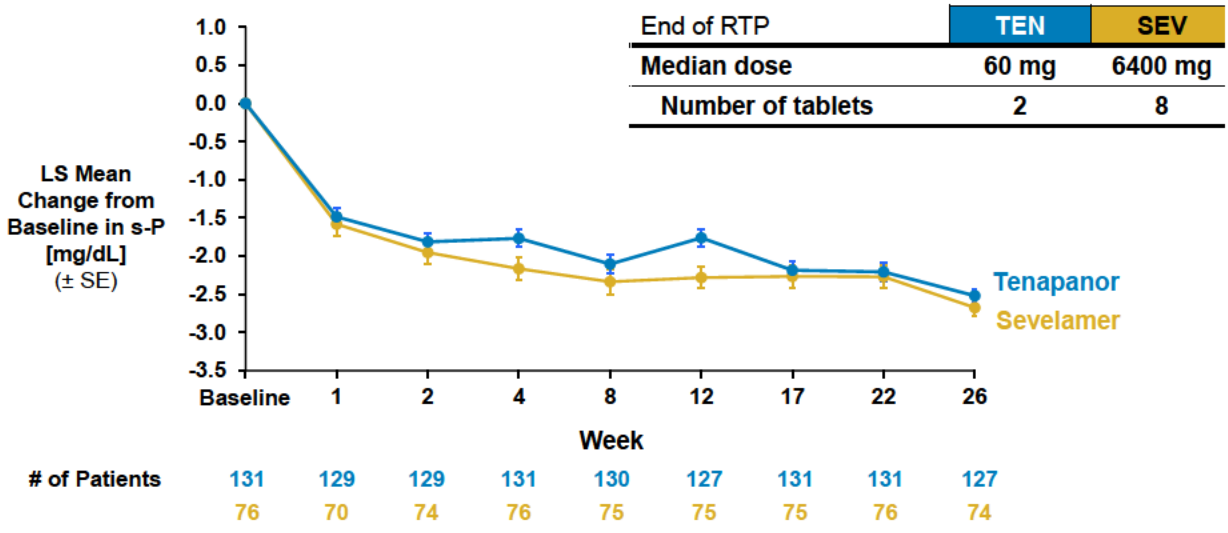
Although sevelamer (a PB approved by the FDA in 2007) was included in Study 301 as a safety comparator, during the review, FDA inquired about the s-P changes in the treatment enrichment phase, noting that the range of s-P lowering provided by approved PBs should be considered a reasonable benchmark to evaluate new drugs for HP. As shown in Figure 12, at Week 26, tenapanor-treated patients achieved an LS mean s-P reduction of 1.4 mg/dL compared to 1.8 mg/dL for sevelamer-treated patients. It is important to note that while a greater proportion of patients in the trial remained on sevelamer than tenapanor, the population was enriched for tolerability by prior treatment with sevelamer (63.5% of patients received sevelamer prior to the start of study treatment). Additional analyses of patients who achieved s-P reduction of ≥ 1.2 mg/dL at the end of RTP and entered the RWP (i.e., the EAS and corresponding sevelamer treated- patients in the Safety Analysis Set) showed similar magnitudes of s--P lowering between tenapanor (2.5 mg/dL) and sevelamer (2.7 mg/dL) at Week 26 in such responders (Figure 13). Importantly, this reduction was achieved with 2 tablets for tenapanor vs a median of 8 large tablets with sevelamer.

Figure 12: Study 301: Least Squares Mean Change from Baseline in s-P by Visit During RTP (RTP ITT and Sevelamer-Treated Patients in Safety Analysis Set)



The LS mean and SE at each post-baseline visit were from an ANCOVA model with treatment and pooled site as factors and baseline s-P as a covariate. Only observed data were included in the analysis.
ANCOVA=analysis of covariance; LS=least squares; RTP=Randomized Treatment Period; SE=standard error; s-P=serum phosphorus.

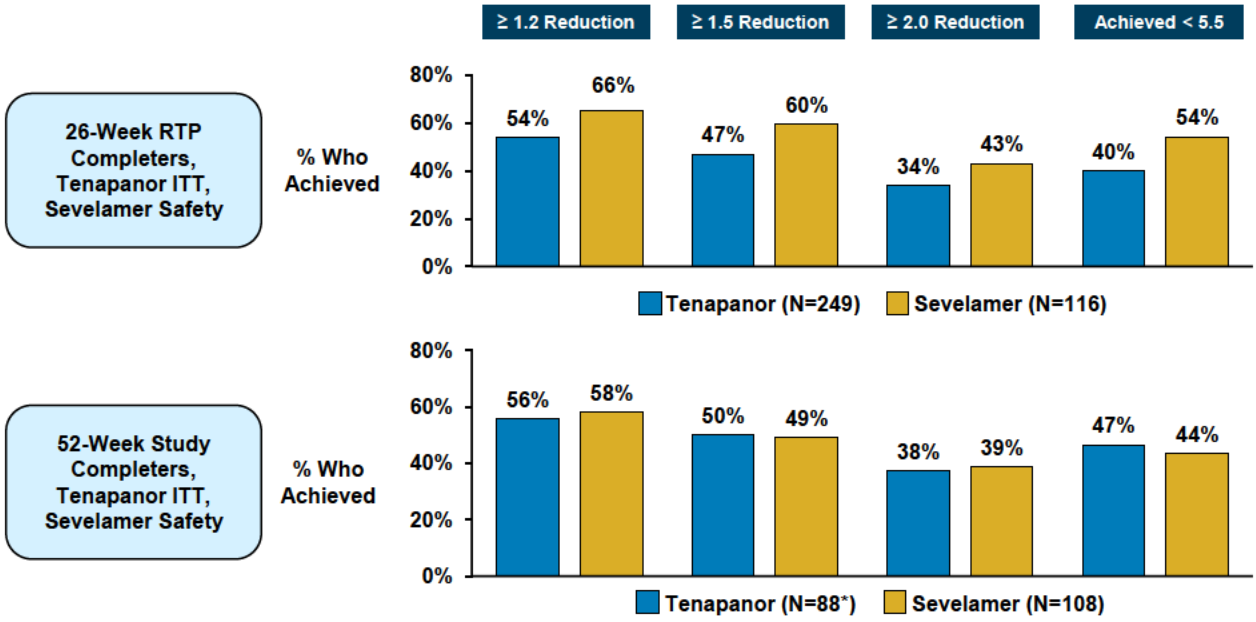
Figure 13: Study 301: Least Squares Mean Change from Baseline in s-P by Visit During RTP (EAS and Sevelamer-Treated Patients in Safety Analysis Set Who Achieved s-P Reduction of ≥ 1.2 mg/dL at End of RTP and Entered RWP)



The LS mean and SE at each post-baseline visit were from an ANCOVA model with treatment and pooled site as factors and baseline s-P as a covariate. Only observed data were included in the analysis.
ANCOVA=analysis of covariance; EAS=Efficacy Analysis Set; LS=least squares; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; SE=standard error; SEV=sevelamer; s-P=serum phosphorus; TEN=tenapanor.

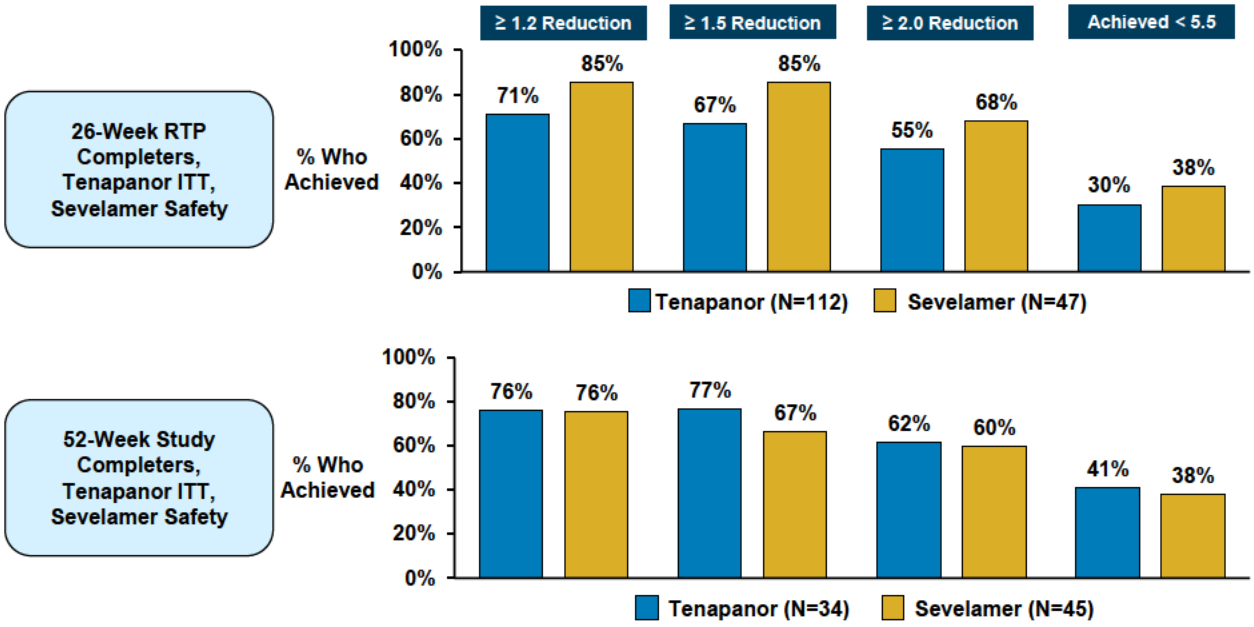
An additional post hoc analysis of the proportion of patients achieving s-P response at various thresholds in Study 301 demonstrated that a substantial number of tenapanor-treated patients who completed the 26-week RTP had significant levels of s-P reduction and/or achieved target goals (Figure 14, top panel). Moreover, patients remaining on tenapanor treatment for the full 52-week study duration maintained this effect (Figure 14, bottom panel). Similar responses were also demonstrated in patients with baseline s-P ≥ 7.5 mg/dL for 26- and 52-week completers (Figure 15, top panel), and especially in responses at end of the 52-week study (Figure 15, bottom panel).

Figure 14: Study 301: Proportion of Patients Achieving s-P Response with Tenapanor or Sevelamer Treatment at End of RTP or End of Study (RTP or Study Completers)



*52-week study completers who were re-randomized to receive placebo during the 12-week RWP were excluded.
ITT=Intention-to-Treat; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

Figure 15: Study 301: Proportion of Patients Achieving s-P Response with Tenapanor or Sevelamer Treatment at End of RTP or End of Study (RTP or Study Completers with Baseline s-P ≥ 7.5 mg/dL)



*52-week study completers who were re-randomized to receive placebo during the 12-week RWP were excluded.
ITT=Intention-to-Treat; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

Additional Benefits: Decreased Pill Burden and Patient Satisfaction

Tenapanor offers additional benefits to patients receiving maintenance dialysis. Tenapanor pills are much smaller than PB tablets and are taken BID, while PBs must be taken as several pills with every meal.

Patient satisfaction was evaluated in the Phase 4 Study, OPTIMIZE, and the questionnaire results in the 2 cohorts of patients being treated with PBs at randomization were published (details in Appendix 9.1) (Edelstein et al 2022a). On Study Day 1, patients on PBs with s-P > 5.5 mg/dL were randomized to Cohort 1 (N=151) discontinued PBs and were immediately started on tenapanor 30 mg BID and could add back some or all of their binder treatment as necessary. Patients in Cohort 2 (N=152) had their PB dose decreased by at least 50% and started on tenapanor 30 mg BID. Both cohorts allowed for adjustment to tenapanor and PB doses based on s-P concentrations.

- 84.4% (n=205) of patients in Cohort 1 and Cohort 2 combined reported an improved perception of their phosphate management routine. Among those patients,
    - 64.4% (n=132) stated a reduction in medication burden as the top reason for the improved perception.

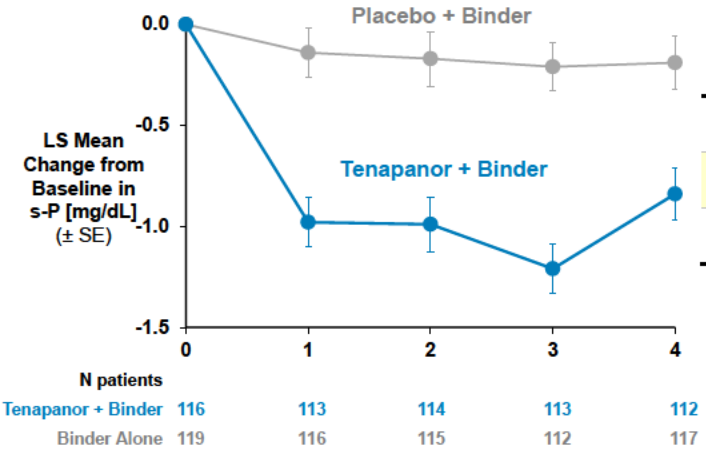
- 31.2% (n=64) reported an improved perception of the form or frequency of bowel movements as the top reason.

- 69.1% (n=168) of Cohort 1 and Cohort 2 patients found it easier to control their s-P during the study compared with their prior regimen.

Benefit of Combination Therapy

Tenapanor has been shown to lower s-P in patients with inadequately controlled s-P despite being on a stable dose of PB(s). In Study 202, tenapanor in combination with PBs met the primary endpoint demonstrating a statistically significant reduction of s-P compared to placebo plus PBs. The early onset of s-P lowering effect of tenapanor was observed as early as 1 week on treatment (Figure 16), which is particularly relevant as the majority of patients who are prescribed PB(s) are unable to consistently maintain target goals for s-P (DOPPS 2019).

Figure 16: Study 202: Primary Efficacy Analysis for Primary Endpoint – Change from Baseline in s-P at Week 4 (FAS)



Primary Endpoint	TEN + Binder	PBO + Binder
LS mean Δ from baseline to Week 4	-0.84	-0.19
LS Mean Difference (95% CI)	-0.65 (-1.01, -0.29)	
p-value	p = 0.0004	

The LS means, SEs, CI, and p-value came from an MMRM model on observed cases.
CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed-effects model for repeated measures; PBO=placebo; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

1.5.6 Identifying a Responder Population to Support the Clinical Utility of Tenapanor

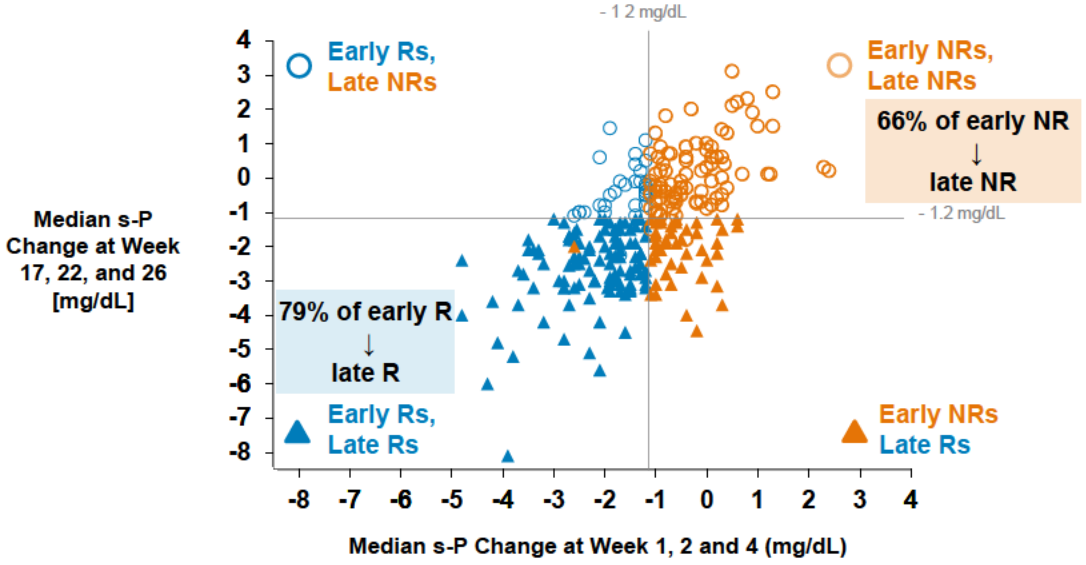
An additional post hoc analysis was conducted to assess if early response could predict later response based on s-P measures during the RTP of Study 301 in an effort to ultimately prevent the long-term use of a therapy in the setting where patients are receiving minimal benefits. Of important note, s-P measurements vary over time to a greater extent in patients requiring dialysis than the general population. This variability is influenced by a number of factors including time of day, food intake, adherence to and timing of drug intake, dialysis itself, and drugs and factors affecting bone regulation. However, adequately controlled studies can nonetheless demonstrate a statistically

significant drug effect that is discernible on an individual patient basis by serial measurements of s-P over time.

In this post hoc analysis of Study 301, 189 (46.4%) of the 407 tenapanor-treated patients in the ITT Analysis Set were considered to have an early response (i.e., s-P reduction ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4) and 139 patients continued the tenapanor treatment with at least 2 s-P measures collected at Weeks 17, 22, and 26. Among these 139 early responders, 79.1% continued to have a response later in the RTP (i.e., s-P reduction ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26) (Figure 17). Conversely, and equally as importantly, patients who did not meet the early response criteria also continued to not meet the response criteria later in the RTP based on observed cases (65.9%). This would allow clinicians to effectively ascertain treatment response at the individual patient level after the first 3 s-P measurements, which in normal practice translates to a 2–3-month treatment period. While the duration of Study 201 was too short for such an analysis, the results were consistent.

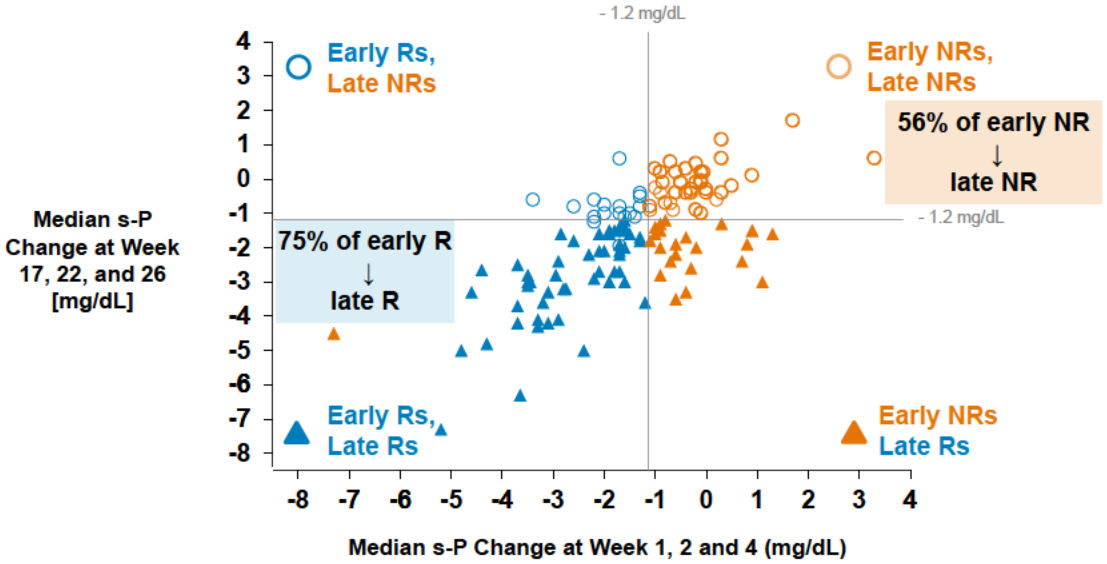
This analysis was repeated at cutoffs of 1.7 mg/dL, 1.5 mg/dL, and 1.0 mg/dL and the results were consistent with the 1.2 mg/dL cutoff (Appendix 9.2). Additionally, the analysis was repeated on sevelamer-treated patients and also showed that early response was generally predictive of late response (Figure 18).

Figure 17: Study 301: Early Response to Tenapanor Predicts Late Response (RTP ITT Patients with Observed Late Response Status)



Early responders (Early Rs): patients who had s-P reduction of ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4 within the first month of the RTP.
Late responders (Late Rs): patients who had s-P reduction of ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26 within the second half of the RTP.
ITT=Intention-to-Treat; NR=non-responder; R=responder; s-P=serum phosphorus.

Figure 18: Study 301: Early Response to Sevelamer Predicts Late Response using Cutoff of 1.2 mg/dL (Sevelamer-Treated Patients in the Safety Analysis Set with Observed Late Response Status)



Early responders (Early Rs): patients who had s-P reduction of ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4 within the first month of the RTP.
Late responders (Late Rs): patients who had s-P reduction of ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26 within the second half of the RTP.
ITT=Intention-to-Treat; NR=non-responder; R=responder; s-P=serum phosphorus.

Within the first month of the RTP, a meaningful proportion of patients treated with tenapanor (46.4%) achieved a response with at least 2 of 3 s-P reductions ≥ 1.2 mg/dL. This finding aligns with the early onset of s-P lowering effect as assessed by mean s-P reductions from baseline by visit, which was typically observed within the first week of treatment. Among the early responders identified within the first month of the RTP with observed late response status, 79.1% continued to achieve a response during the second half of the RTP, indicating that patients who will benefit from tenapanor over an extended period of time can be identified early, allowing nephrologists to make informed treatment decisions for individual patients based on tolerability and early response status.

1.6 Safety Findings

The integrated safety assessment for tenapanor includes 1,259 patients from the CKD on Maintenance Dialysis Safety Analysis Set (including 5 studies D5611C00001, D5613C00001, 201, 301, and 202). Of these 1,259 patients, 934 were treated with tenapanor, 69 received placebo, and 256 received PB(s). Based on the integrated data from the analysis period of up to 12 weeks, the mean duration of exposure to tenapanor ranged from 4–10 weeks across multiple tenapanor dose groups. Taking into consideration the exposure to tenapanor during the extension study of Study 301 (i.e.,

Study 401), 20% (183/934) of patients were treated with tenapanor for 26 – < 52 weeks, and 8% (75/934) remained on tenapanor for ≥ 52 weeks.

During the 26-week RTP, 419 patients received tenapanor and 137 received sevelamer. The majority of patients in both groups experienced AEs, with 80% in the tenapanor group and 64% in the sevelamer group. In the tenapanor group, as expected, diarrhea was the most commonly reported AE (53%); HP was reported in 6% of patients, and all other AEs were reported in < 5% of patients. In the sevelamer group, the most commonly reported AEs were diarrhea (7%), cough (7%), fall (7%), hypertension, fluid overload, arteriovenous fistula, and pneumonia (5%, each).

A higher proportion of patients in the tenapanor group than the sevelamer group experienced AEs that led to study drug discontinuation (24% and 1%, respectively) However, approximately 65% of patients were treated with sevelamer prior to the start of study treatment and would be expected to have a higher tolerability to potential side effects. In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, overall adverse reactions among patients treated with sevelamer hydrochloride occurring in > 5% of patients included vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%) (Renvela PI 2014). Other approved PBs including Velphoro, Fosrenol, and Auryxia cause GI adverse reactions (Appendix 9.3) (Auryxia PI 2014; Fosrenol PI 2011; Velphoro PI 2013).

The overall incidence of serious adverse events (SAEs) during the 26-week RTP was higher in the sevelamer group (23%) than the tenapanor group (17%), and the most common SAE in the tenapanor group was acute respiratory failure (2% vs 1% in the sevelamer group).

Longer-term safety was assessed for up to 52 weeks in Study 301, including data from the 26-week RTP, the 12-week RWP, and the 14-week safety extension period. Compared to the first 26 weeks of treatment, the overall incidence rates of AEs were lower in all treatment groups during the 12-week RWP and the 14-week safety extension period. Importantly, the incidence of diarrhea decreased during the 12-week RWP (4% in the tenapanor group, 4% in the sevelamer group, and 2% in the placebo group) and during the 14-week safety extension period (7% in the tenapanor group and no patients in the sevelamer group).

Study 202 provides safety data for tenapanor in combination with PB(s) compared to PB(s) alone. As expected, the overall incidence of AEs was higher in the “tenapanor + binder” group (51.3%) than the “placebo + binder” group (27.7%). As in Study 301, the most commonly reported AE in Study 202 was diarrhea, which again was not treatment-limiting (42.7% experienced AEs of diarrhea and 2.6% discontinued due to diarrhea).

Based on the integrated safety assessment for tenapanor, 20 deaths occurred across the tenapanor clinical program: 15 occurred in tenapanor-treated patients (total N=934) and 5 occurred in PB-treated patients (total N=256). The incidence of death was similar across treatment groups (1.6% in tenapanor vs 1.9% in PB). Causes of death were

primarily due to cardiovascular and infectious etiology, which are common in patients receiving maintenance dialysis. Of the 15 deaths on tenapanor, 1 occurred in the Phase 2b study, 1 occurred in Study 201, and the remaining 13 deaths occurred in Study 301, which would be expected as this 52-week study was the longest in the tenapanor program. The remaining 5 deaths occurred in the sevelamer treatment group in Study 301. No deaths were considered to be related to study drug by the Investigator.

Based on tenapanor's mechanism of action, diarrhea was expected to be the most common AE. By extension, other events that could be temporally associated with diarrhea, such as presyncope, syncope, hypotension, orthostatic hypotension, falls, dizziness, hypovolemia, and dehydration were also AEs of special interest (AESIs). An AE was considered temporally associated if it started at or after the diarrhea start date and within 3 days of the diarrhea end date, if the diarrhea ended by the End of Study, or the AE started at or after the diarrhea start date if the diarrhea was ongoing at the End of Study. While all hospitalizations were captured as SAEs, those specifically related to diarrhea and dehydration were of interest.

For reference, MedDRA classifies any report of "bothersome" loose stool(s), loose bowels, and/or mushy stool(s) as "diarrhea" events, with or without increased "stool frequency." As previously stated, this PD effect was anticipated given the mechanism of action of tenapanor. Most cases (nearly 90%) were reported as mild to moderate in severity and were not treatment-limiting. As requested by the FDA on 04 December 2020 during the NDA review, a post hoc analysis of the temporal association between severe diarrhea and any AESIs leading to hospitalization was conducted, and this analysis identified one event of dehydration leading to hospitalization that was temporally associated with a severe diarrhea event in the tenapanor group of Study 301 and one event of diarrhea that led to hospitalization in the placebo group in the Phase 2b study. Other AESIs occurred infrequently (details provided in Section 6.7) and did not suggest a temporal relationship to diarrhea events. Although the eDiary data collected from tenapanor-treated patients in Study 201 showed a slightly higher mean average weekly stool frequency and consistency during each treatment week of the 8-week RTP relative to the baseline week, all the post-baseline mean averages remained in the normal range. Additionally, there were no significant changes in serum electrolytes, other laboratory findings, or blood pressure measurements in the overall safety population and among those with events of severe diarrhea (Table 40; Table 41).

In summary, data from the clinical development program demonstrated that tenapanor has an acceptable safety and tolerability profile. Diarrhea was the most commonly reported AE; the majority of diarrhea events occurred early, were mild to moderate in intensity, and were not treatment-limiting. In Study 301, a long-term study with an active safety control, there was no significant difference in SAEs between tenapanor- and sevelamer-treated patients. Rates of death were low and also balanced between treatment groups, and no deaths were deemed related to study treatment by study Investigators.

1.7 Post-Marketing Data

Tenapanor's efficacy and safety profile have been established in adults with IBS-C. Tenapanor was approved for the treatment of IBS-C in the US on 12 September 2019, with a recommended dose of 50 mg BID. However, as it was only recently launched, under the trade name Ibsrela® in April 2022, there are limited post-marketing surveillance data available. In this limited time, there have been no new safety signals identified, and diarrhea has been the major AE reported consistent with Ibsrela's label. Tenapanor was also approved in Canada for the treatment of IBS-C in adults and is being evaluated in clinical trials in both Japan and China for the treatment of HP in adults on maintenance dialysis.

1.8 Benefit-Risk Summary

Hyperphosphatemia in patients receiving maintenance dialysis is an extremely common issue and is correlated with progressive morbidity and mortality, including cardiovascular disease. The only current class of pharmacological intervention for HP in patients receiving maintenance dialysis is PBs, which require large doses several times per day, leading to high pill burden and patient dissatisfaction. Even with widespread use of PBs in patients receiving maintenance dialysis, the majority of patients do not reach and maintain target s-P treatment goals, leading to persistent risk of vascular and tissue calcifications, bone pain, fractures, and worsening secondary hyperparathyroidism, leading to cumulative morbidity and mortality (Block et al 2004; Kalantar-Zadeh et al 2006). Data from the tenapanor clinical trials have shown that this novel mechanism of action therapy provides clinically relevant s-P lowering as monotherapy and in combination with PBs. For a significant number of patients, tenapanor as monotherapy could simplify the dosing regimen, with smaller pills and less frequent dosing, an attribute that should prove both beneficial and meaningful for patients receiving maintenance dialysis.

The pivotal Phase 3 monotherapy studies, Studies 301 and 201, demonstrated statistically significant and clinically meaningful efficacy and an acceptable safety/tolerability profile for tenapanor in patients receiving maintenance dialysis. During the RTP, s-P reductions were observed as early as the first week of tenapanor treatment, and early response identified based on the first 3 s-P assessments tended to predict continued response during the RTP. A significant number of patients (~40%) reached s-P target goals, and mean s-P was significantly reduced from study baseline.

Likewise, Study 202, in a more difficult-to-treat patient population, met its pre-specified primary efficacy endpoint and confirmed the safety/tolerability profile for tenapanor in combination with PBs compared to PBs alone. This result is particularly relevant in this population of patients receiving maintenance dialysis with inadequately controlled s-P (i.e., s-P > 5.5 mg/dL) despite treatment with PBs. In addition, Study 202 provides the first positive results for a combination therapy approach in patients with HP in a placebo-controlled clinical trial.

Tenapanor has demonstrated an acceptable safety and tolerability profile. Diarrhea was the most common AE in patients randomized to tenapanor, and the majority of diarrhea events were of mild to moderate intensity, tended to occur early during treatment, and were not treatment-limiting. Potentially more worrisome consequences that might have been temporally associated with diarrhea were infrequent and rarely led to hospitalizations; SAEs were more commonly seen in the active safety comparator group and deaths were similar across treatment groups, with none thought to be related to study drug by the Investigators.

In conclusion, the overall benefit-risk profile for tenapanor is favorable. HP in patients receiving maintenance dialysis is correlated with progressive morbidity and mortality, including cardiovascular disease. There is only one currently approved FDA class of therapy for the treatment of HP, which requires frequent, large doses several times per day and likely impacts the ability to achieve target s-P goals for many patients receiving maintenance dialysis. More than 930 patients were exposed to tenapanor in the clinical development program, and tenapanor met its pre-specified primary efficacy endpoint in 3 controlled clinical trials, where it also demonstrated an acceptable safety and tolerability profile.

Overall, the benefits of an additional treatment option, for both clinicians and patients, to lower s-P towards normal, outweigh the potential safety risk of diarrhea. The addition of this first-in-class phosphate absorption inhibitor to the treatment armamentarium could help to address an unmet medical need in this patient population that deserves innovative treatment options. The totality of data highlights the clinical relevance of tenapanor’s treatment effect, both as monotherapy and in combination with PBs in a condition where a significant proportion of patients are currently unable to achieve guideline-recommended target values. In conclusion, the benefit-risk assessment for tenapanor is favorable.

2 TENAPANOR PRODUCT DESCRIPTION

Summary

- Tenapanor is a first-in-class, minimally absorbed, small molecule NHE3 inhibitor, with a novel mechanism of action.
  - The unique mechanism of action of tenapanor allows the drug to be active at doses of tens of milligrams per day (e.g., 10 mg to 30 mg BID), compared with several grams per day required for PBs.
- Tenapanor inhibits NHE3, which is expressed on the luminal surface throughout the small intestine and proximal colon, blocking absorption of dietary sodium.
- Direct inhibition of NHE3 by tenapanor reduces paracellular phosphate absorption and significantly lowers s-P in patients receiving maintenance dialysis.

2.1 Proposed Indication and Dosing

Tenapanor is a NHE3 inhibitor indicated for the control of s-P in adult patients with CKD on dialysis. The recommended dosage is 30 mg orally BID; immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

2.2 Product Overview

Tenapanor is a first-in-class, minimally absorbed, small molecule NHE3 inhibitor with a novel mechanism of action (detailed in Section 2.3). The unique mechanism of action of tenapanor allows the drug to be active at doses of tens of milligrams per day (e.g., 10 mg to 30 mg BID), compared with multiple grams per day required for PBs (Auryxia PI 2014; Block et al 2019; Fosrenol PI 2011; Phoslo PI 2011; Renvela PI 2014; Spencer et al 2014; Velphoro PI 2013). Tenapanor tablets (e.g., 30 mg oval tablet; 11.8 mm × 6.8 mm × 4.2 mm; 300 mg total weight per tablet) are also much smaller than PB tablets (e.g., sevelamer carbonate 800 mg oval tablet 19.0 mm × 9.5 mm × 8 mm; 1.15 g total weight per tablet) (Generic Partners 2015) and can be taken BID, while PBs must be taken with every meal and snack to bind ingested phosphate in the lumen of the GI tract and prevent it from being absorbed into the rest of the body.

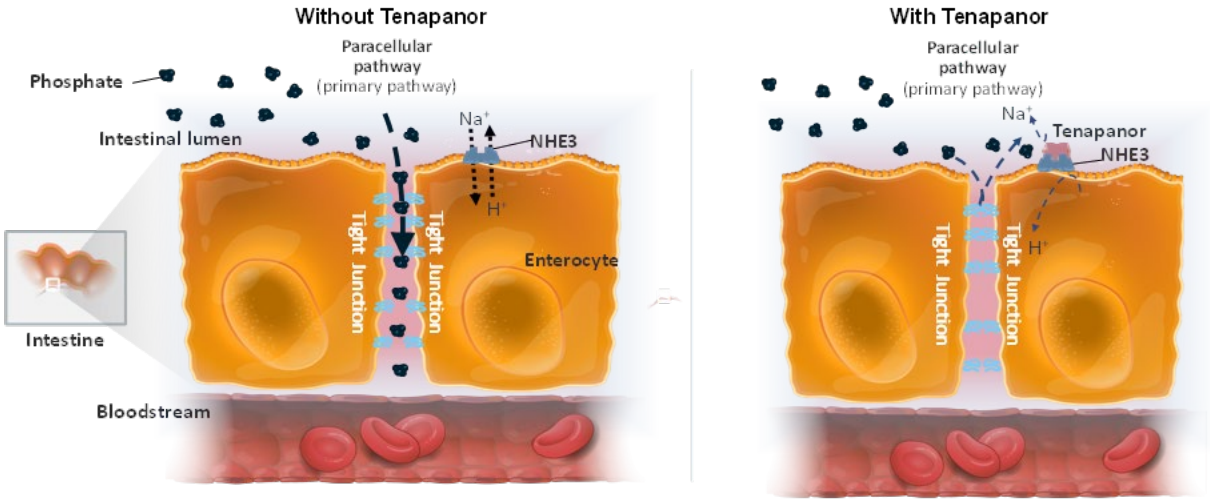
2.3 Mechanism of Action

Dietary phosphate absorption occurs in the GI tract via 2 distinct pathways: transcellular absorption (which is active movement via carrier or transporter proteins through epithelial cells) and paracellular absorption (which occurs passively along concentration gradients through tight junction complexes between intestinal epithelial cells) (Saurette and Alexander 2019). Accumulating evidence demonstrates that the paracellular

pathway is the primary mechanism of phosphate absorption in the GI tract because phosphate is highly permeable through the tight junctions in the small intestine and there are high amounts of inorganic phosphates in the Western diet, which drive the electrochemical gradients in the intestine towards paracellular absorption (Saurette and Alexander 2019).

In contrast to PBs, which bind dietary phosphate in the intestine via a physiochemical interaction, to decrease its absorption, tenapanor targets the primary pathway of phosphate absorption, paracellular absorption in the GI tract (Labonte et al 2015). Tenapanor works by inhibiting NHE3, which is expressed on the luminal surface throughout the small intestine and proximal colon and normally functions as a transporter to import luminal sodium in exchange for a cellular proton (Zachos et al 2005) (Figure 19). Direct inhibition of NHE3 by tenapanor reduces paracellular phosphate permeability and significantly lowers s-P in patients receiving maintenance dialysis (Block et al 2017), a result of decreased intracellular pH that modulates the tight junction to increase transepithelial electrical resistance (King et al 2018). Inhibition of NHE3 by tenapanor causes increased fecal excretion of phosphate resulting in the lowering of s-P. Inhibition of NHE3 by tenapanor also results in reduced dietary sodium absorption, increased fecal sodium excretion, and softer stool form (Spencer et al 2014). Tenapanor inhibited the absorption of 20 to 50 mmol of sodium per day (equivalent to up to ~3 g of dietary salt) in healthy volunteers. Besides phosphate and sodium, no other ions have been shown to be significantly affected by this mechanism based on clinical data.

Figure 19: Tenapanor Mechanism of Action



3 REGULATORY AND DEVELOPMENT HISTORY

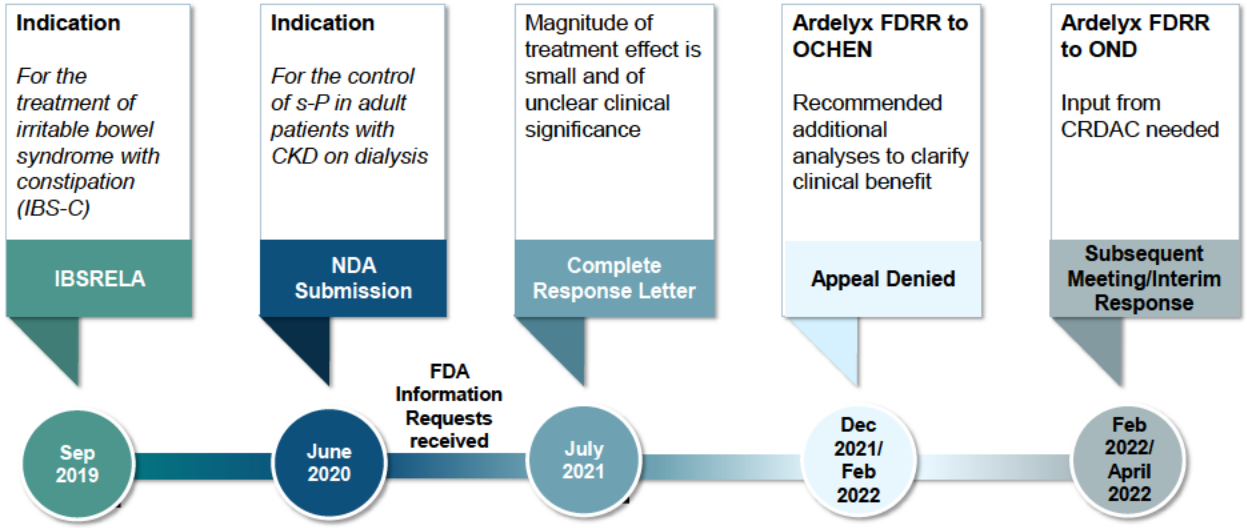
Summary

- Tenapanor is approved for the treatment of IBS-C in adults at a recommended dose of 50 mg BID.
- The Sponsor received a CRL for the tenapanor NDA for HP due to questions regarding the clinical relevance of the treatment effect of tenapanor on s-P lowering in the ITT population. There were no concerns raised in the CRL regarding the safety of tenapanor.
- The primary evidence supporting approval of tenapanor in patients receiving maintenance dialysis comes from one Phase 2 trial (D5613C00001) and three Phase 3 studies (2 monotherapy studies – Studies 201 and 301 – and 1 study of tenapanor in combination with PB, Study 202).
- All 3 Phase 3 registration studies met their pre-specified primary and key secondary efficacy endpoints and demonstrated an acceptable safety/tolerability profile.

3.1 Regulatory Milestones

Tenapanor was approved for the treatment of IBS-C in adults in September 2019 under the tradename Ibsrela. Ardelyx submitted the NDA for the control of s-P in adult patients receiving maintenance dialysis under the 505(b)(1) pathway with a different proprietary name and label, as previously agreed by the FDA, given disparate indications. The NDA for the HP indication was submitted in June 2020 and filed by the FDA in September 2020. After several information requests followed by initial label negotiations in April 2020, the FDA requested additional analyses that led to a major amendment and a new Prescription Drug User Fee Act date. Subsequently, the Sponsor received a CRL, in which the Division acknowledged that "submitted data provided substantial evidence that tenapanor is effective in reducing s-P in patients receiving maintenance dialysis, the magnitude of the treatment effect (of tenapanor) is small and of unclear clinical relevance," despite the Sponsor's attempt to address the clinical relevance of tenapanor's effect size in the original NDA and in subsequent amendments. In December 2021, the Sponsor moved forward with an FDRR. Figure 20 shows a timeline of the regulatory history of tenapanor for HP, and Table 4 highlights key regulatory interactions during tenapanor development.

Figure 20: Regulatory History of Tenapanor for Hyperphosphatemia



CKD=chronic kidney disease; CRDAC=Cardiovascular and Renal Drug Advisory Committee; FDA=Food and Drug Administration; FDRR=Formal Dispute Resolution Request; OCHEN=Office of Cardiology, Hematology, Endocrinology, and Nephrology; OND=Office of New Drugs.

Table 4: Key Regulatory Interactions in Tenapanor Development

Date	Meeting	Content
25 October 2013	Pre-IND Meeting	Discussion of the Phase 2b clinical study, need for QT/QTc (QT interval corrected for heart rate)-specific study, characterization of the major metabolite of tenapanor, the importance of the magnitude of effect of s-P lowering, and patients with inadequately controlled HP.
09 May 2016	End-of-Phase 2 Meeting	Discussion of comparability of Phase 2b formulation with Phase 3/ to-be-marketed formulation, adequacy of nonclinical data for registration, need for QT/QTc-specific study, primary endpoint of Phase 2b study, and Phase 3 clinical plan. The Agency recommended the Phase 2b trial be a RW design.
12 September 2019	Tenapanor approved for IBS-C	Approval of 50 mg BID oral tenapanor for the treatment of IBS-C in adults based on 2 randomized, double-blind, placebo-controlled trials.
02 April 2020	Pre-NDA Meeting	Advice on adequacy of the NDA safety database, inclusion of clinical relevance of the size of the treatment effect observed, inclusion of data from TEN-02-401 in the prescribing information, and inclusion of TEN-02-108 in the initial NDA. FDA noted: "you should address in your submission why you believe that the observed magnitude of the treatment effect on serum phosphorus is clinically relevant."

June 2020	Ardelyx submits NDA	
September 2020	FDA files NDA	
28 July 2021	FDA issues CRL	The CRL noted that the submitted data provide substantial evidence that tenapanor is effective in reducing s-P but that stated that the magnitude of the treatment effect is small and of unclear clinical significance. The CRL stated that the applicant will need to conduct another trial demonstrating clinically relevant treatment effect on s-P or an effect on clinical outcome thought to be caused by hyperphosphatemia for the application to be approved. The Division noted that, in principle, it may be possible to individualize treatment based on a patient's early response to a drug that lowers s-P (i.e., assess for a response at some early time point and only continue treatment in patients who have a clinically relevant response); however, such a strategy would need to be prospectively tested and would also likely need to be based on multiple measurements of s-P over time to distinguish the treatment effect from intrasubject variability No safety issues identified.
Formal Dispute Resolution Request Timeline		
03 December 2021	Ardelyx submits Formal Dispute Resolution Request to OCHEN	Ardelyx asserted that: • Tenapanor safety and effectively controls HP in a large proportion of patients with robust s-P reductions in these responders. • There is no evidence-based support for a threshold of s-P efficacy of 1.5 mg/dL. • The CRL's comparative effectiveness standard is inappropriate and cross-study comparisons are inherently confounded. • There is a place for tenapanor in the armamentarium for the treatment of HP.
04 February 2022	OCHEN issues Appeal Denied Letter	OCHEN stated that it was unable to conclude that tenapanor's overall clinical benefit is meaningful. While OCHEN acknowledged tenapanor is minimally absorbed, it stated that it is not without risks (e.g., diarrhea and potential other AEs associated with diarrhea) which have to be considered in context of the clinical benefit. In addition, OCHEN acknowledged that it may be reasonable to approve a drug with a smaller mean treatment effect, if one can identify patients who respond to the drug in a meaningful manner. OCHEN

		recommended resubmission of the NDA with multiple additional analyses that potentially may address their concerns.
18 February 2022	Ardelyx submits Formal Dispute Resolution Request to OND	The FDRR sought review from the Office of New Drugs and stated that: • Additional analyses were not necessary to find substantial evidence of the effectiveness of tenapanor. • Appeal Denial Letter mischaracterized the efficacy and misunderstood the realities of clinical decision making in dialysis units, utilized an arbitrary standard for meaningfulness, and failed to consider relevant analyses of tenapanor-related AEs.
15 April 2022	OND issues INTERIM APPEAL RESPONSE INPUT NEEDED FROM ADVISORY COMMITTEE	OND stated that while it felt the Division's expectation of phosphate lowering of a drug was reasonable, additional input from CRDAC would be valuable before OND makes a decision on the appeal.
November 2022	Cardiovascular and Renal Drugs Advisory Committee	

AEs=adverse events; BID=twice daily; CRDAC=Cardiovascular and Renal Drug Advisory Committee; CRL=Complete Response Letter; FDA=Food and Drug Administration; FDRR=Formal Dispute Resolution Request; IBS-C=irritable bowel syndrome with constipation; IND=Investigational New Drug; NDA=New Drug Application; OCHEN=Office of Cardiology, Hematology, Endocrinology, and Nephrology; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

3.2 Clinical Development Program

The efficacy and/or safety of tenapanor for the treatment of HP in patients receiving maintenance dialysis have been evaluated in the following studies summarized in Table 5:

- Phase 2 studies (D5611C00001 and D5613C00001)
- Phase 3 studies of tenapanor as monotherapy (Studies 201 and 301)
- Phase 3 study of tenapanor in combination with PB(s) (Study 202)
- Long-term open-label efficacy and safety study of tenapanor as monotherapy or in combination with PBs (Study 401)
- Open-label study to evaluate different methods of initiating tenapanor therapy as monotherapy or in combination with PB(s) (Study 402)

While Study 201 adds to the body of evidence from well-controlled studies that demonstrate the requisite safety and efficacy of tenapanor, Study 301 is a more robust study employing the same enrichment design. Study 301 has the largest sample size in the HP program, a longer treatment duration to identify responders with a single recommended tenapanor dosing regimen (30 mg BID with dose titration) and longer RW

duration to allow for s-P rise in the placebo group, and an active safety comparator. Therefore, Study 301 provides the most accurate representation of tenapanor's treatment effect.

The Phase 2 study, D5611C00001, was a study evaluating the effect of tenapanor on inter-dialytic weight gain. Therefore, efficacy data for this study are not provided in this briefing document, but safety data are included in the CKD on Dialysis Safety Analysis Set for the integrated summary of safety. Phase 2 study D5613C00001 was a dose-finding study and is detailed in Section 4.2.

In the Phase 3 monotherapy studies, 218 patients in Study 201 and 419 patients in Study 301 received treatment with tenapanor during the RTP (8 weeks and 26 weeks, respectively), which was followed by a double-blind RWP (4 weeks and 12 weeks, respectively). Studies 201 and 301 randomized patients to receive tenapanor in the RTP at a starting dose of 30 mg BID (titrated in a stepwise fashion as needed). Study 201 also randomized patients to receive tenapanor at fixed doses of 3 mg and 10 mg, and responders to the 8-week tenapanor treatment from the 3 tenapanor dose groups were pooled as the EAS for the primary efficacy analysis. Details on the efficacy findings from Studies 201 and 301 are provided in Section 5.

Study 202 evaluated the s-P lowering effect of tenapanor when tenapanor was administered orally BID for 4 weeks to a more difficult-to-treat population of patients receiving maintenance dialysis with HP (≥ 5.5 mg/dL) despite being on stable PB therapy (detailed further in Section 5.3).

The open-label studies, 401 and 402, provide additional efficacy data, which are discussed in Sections 5.4 and 5.5, respectively. The safety profiles from these studies were consistent with the Phase 3 studies, and there were no new safety findings.

Table 5: Overview of Tenapanor Clinical Development Program for Hyperphosphatemia

Study Identifier/Phase	Study Title
D5611C00001/ Phase 2a	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 HD
D5613C00001/ Phase 2b	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
TEN-02-201/ Phase 3	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 (BLOCK)
TEN-02-202/ Phase 3	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 (AMPLIFY)
TEN-02-301/ Phase 3	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 (PHREEDOM)
TEN-02-401 Phase 3	A Long-Term, Open-Label Study to Evaluate the Ability of Tenapanor Alone or in Combination with Sevelamer to Treat to Goal s-P in Patients with End-Stage Renal Disease on Dialysis (NORMALIZE) – an extension of PHREEDOM Study (Study 301)
TEN-02-402 Phase 4	Randomized Open-Label Study to Evaluate Tenapanor as the Core Therapy in the Treatment of Hyperphosphatemia in Patients with Chronic Kidney Disease Who Are Phosphate Binder Naive or on Phosphate Binders to Optimize s-P Management (OPTIMIZE)

Note: AZD1722 and RDX5791 are tenapanor.
HD=hemodialysis.

4 CLINICAL PHARMACOLOGY

Summary

- Tenapanor is minimally absorbed and excreted in the feces, mostly as the parent drug. More than 95% of the plasma samples collected from healthy participants and patients receiving maintenance dialysis administered tenapanor had parent drug concentrations below the quantitative limit (i.e., < 0.5 ng/mL).
- The major metabolite of tenapanor, AZ13792925 (also known as M1), is not pharmacologically active and is generated by CYP3A4/5-mediated metabolism. AZ13792925 systemic exposure is low at steady state (~14 ng/mL C_{max} in plasma following 30 mg BID tenapanor in patients receiving maintenance dialysis) and is excreted in the urine.
- Tenapanor and AZ13792925 are highly bound to human plasma proteins.
- Tenapanor reduced s-P in a dose-dependent manner, with the most pronounced effect in the 30 mg BID group.
- There were no clinically significant differences in the PK of tenapanor and AZ13792925 in patients with hepatic/renal impairment compared to healthy participants.
- Co-administration of tenapanor with a strong CYP3A4/5 inhibitor did not cause clinically relevant effects on the PK of tenapanor and AZ13792925.
- Tenapanor is an inhibitor of the intestinal transporter, organic anion transporting polypeptide 2B1 (OATP2B1). Tenapanor 30 mg BID reduced the exposure of enalapril (OATP2B1 substrate) and its active metabolite, enalaprilat. There was no clinically relevant effect on CYP2C9- and CYP3A4 mediated metabolism and H+-coupled peptide transporter-1 (PepT1)- and P glycoprotein (P-gp)-mediated intestinal transport.

4.1 Pharmacokinetics

4.1.1 Absorption, Distribution, Metabolism, Excretion

Absorption

Tenapanor has negligible systemic availability following repeated, BID oral administration. All tenapanor plasma concentrations were below the lower limit of quantification (LLOQ) (< 0.5 ng/mL) in healthy volunteers following multiple doses of tenapanor 10 mg or 30 mg BID and in healthy Japanese and Caucasian participants administered 90 mg BID tenapanor for 7 days. In patients receiving maintenance dialysis from the Phase 2a study, D5611C00001, only 3 of 758 plasma samples contained quantifiable concentrations of tenapanor (0.538–0.964 ng/mL) which confirmed the minimal systemic exposure of tenapanor in this patient population.

Distribution

In vitro protein binding studies show tenapanor and its major metabolite which is inactive, AZ13792925 (also known as M1), are highly bound (approximately 99% and 97%, respectively) to human plasma proteins.

Metabolism

Tenapanor is metabolized primarily by CYP3A4/5, and low levels of its major metabolite, AZ13792925, are detected in plasma. In vitro studies indicate that AZ13792925 is not active against human NHE3, which is inhibited by tenapanor. Systemic exposures of AZ13792925 were similarly low at steady state in healthy participants and patients receiving maintenance dialysis (approximately 14 ng/mL mean C_{max} at steady state following 30 mg BID tenapanor).

Excretion

Following administration of a single 15 mg radiolabeled ^{14}C-tenapanor dose to healthy participants, approximately 70% of the radioactivity was excreted in feces through 120 hours post-dose (79% through 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. AZ13792925 is excreted in urine unchanged accounting for 1.5% of dose within 144 hours post-dose.

4.1.2 Effect of Intrinsic Factors

Several studies have been conducted to examine the effect of intrinsic factors, including race, hepatic impairment, and renal impairment, on the PK and PD of tenapanor.

Race

A double-blind, randomized, placebo-controlled, multiple-dose study of 83 healthy adult Japanese and Caucasian participants receiving either a single dose of tenapanor (180 mg) or BID ascending doses of tenapanor (15–90 mg) was conducted. At a dose of 90 mg BID for 7 days, there was no evidence of a difference in the PK of tenapanor and AZ13792925 between Japanese and Caucasian participants.

Hepatic Impairment

Tenapanor exhibited minimal systemic exposure following a single oral dose of 100 mg in participants with moderate hepatic impairment and normal hepatic function. While the geometric mean C_{max} was approximately 53% higher in participants with moderate hepatic impairment vs normal hepatic function, values were very low for both hepatic function groups (1.27 ng/mL vs 0.830 ng/mL, respectively). Median t_{max} of AZ13792925 was 4.0 hours later when tenapanor was administered to participants with moderate hepatic impairment compared with normal hepatic function. Arithmetic mean plasma elimination half-life ($t_{1/2}$) of AZ13792925 was similar between the moderate hepatic impairment and normal hepatic function groups (23.8 and 25.4 hours, respectively). These changes are not likely to be clinically relevant due to the overall low exposures of

tenapanor and AZ13792925 in both hepatic function groups and the lack of pharmacological activity of AZ13792925.

Renal Impairment

In patients receiving maintenance dialysis from the Phase 2a study, D5611C00001, systemic exposure of tenapanor was below the limit of quantification (i.e., < 0.5 ng/mL) in the majority of samples. Only 3 of 758 plasma samples contained quantifiable levels of tenapanor (0.538–0.964 ng/mL), which confirmed the minimal systemic exposure of tenapanor in patients.

The effect of renal impairment on AZ13792925 PK was assessed in Study 301. The geometric mean plasma concentrations of AZ13792925 at steady state on Day 85 and Day 183 of the 26-week RTP following 30 mg BID tenapanor administration were 10.4 ng/mL and 8.97 ng/mL, respectively. The systemic exposure of AZ13792925 was consistent with the results from healthy participants administered 30 mg BID tenapanor using the same tenapanor tablet formulation.

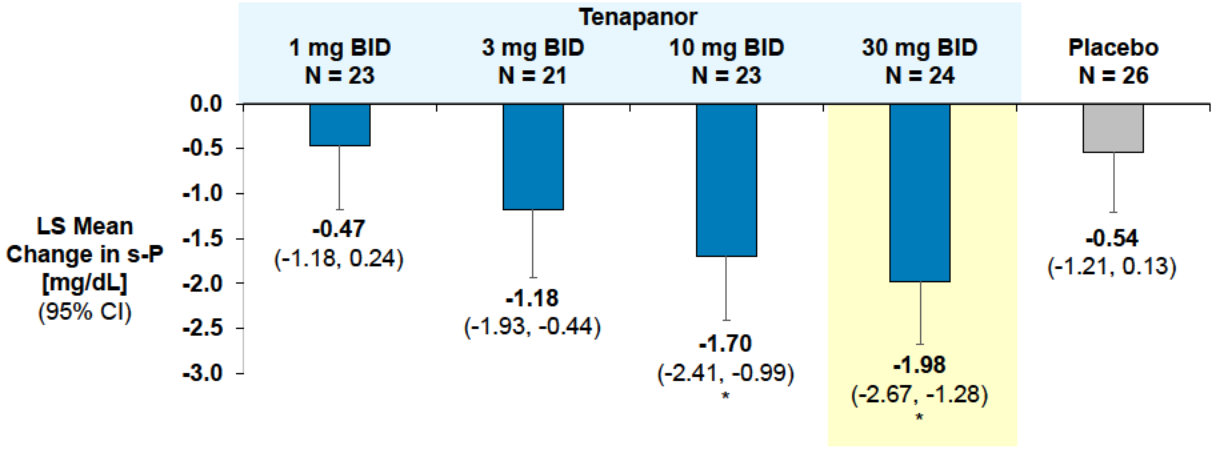
4.2 Dose Selection

Results from single ascending dose (SAD) and multiple ascending dose (MAD) studies suggest that tenapanor is generally safe and well tolerated when administered as a single dose ranging from 10 mg to 900 mg (9 mg to 840 mg free base), and as multiple doses up to 90 mg BID (180 mg/day) for 7 days in healthy participants.

In a double-blind, randomized, placebo-controlled, multiple-dose study (RDX5791-102), 105 healthy participants received a variety of multiple dose regimens of tenapanor or placebo capsules for 7 days. Each participant was randomized to 1 of 9 cohorts, and total daily doses ranged from 30 mg to 120 mg (28 mg to 112 mg free base) administered in a once daily or twice daily regimen. The PD data demonstrated that tenapanor decreases the urinary excretion of sodium, while increasing the fecal excretion of sodium in a roughly dose-proportional manner. These data also suggested that more frequent dosing (BID and 3 times per day [TID]) might be more effective than once daily (QD) dosing, and that the differences between BID and TID regimens were minimal.

Additionally, in a Phase 2, fixed-dose, dose-finding study in patients receiving maintenance dialysis (D5613C00001), tenapanor reduced s-P in a dose-dependent manner, with a statistically significant difference among treatment groups, with the most pronounced placebo-adjusted effect (1.44 mg/dL) in the 30 mg BID group (Figure 21). Overall, tenapanor BID dosing (1–30 mg BID) showed higher efficacy than QD dosing (3 and 30 mg QD) in reducing s-P.

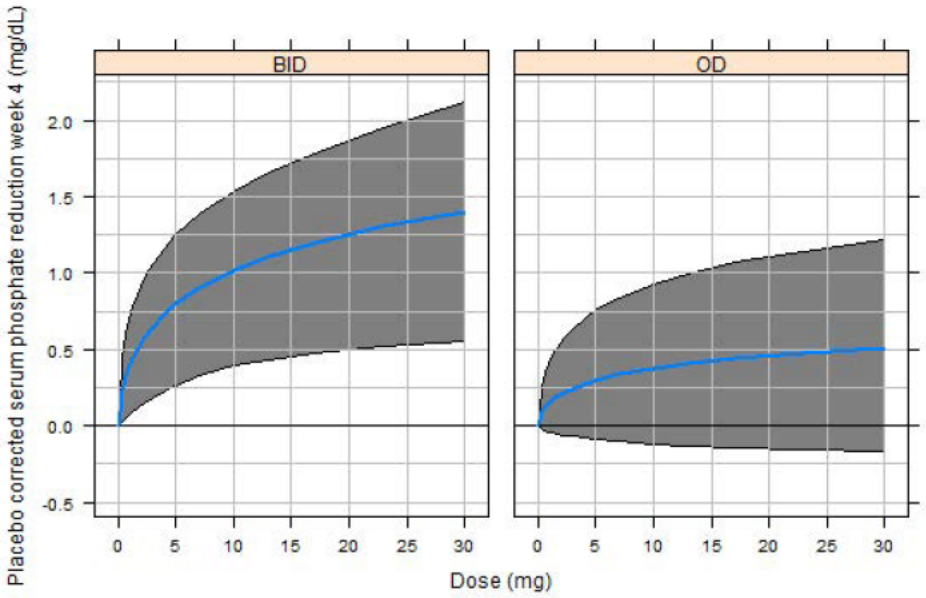
Figure 21: Study D5613C00001: Primary Efficacy Analysis for Primary Endpoint – Change in s-P from Baseline at End of Treatment/Early Termination (FAS)



*p < 0.05 vs placebo.
The primary endpoint was an LOV-type endpoint. The LS means, CIs, and p-value came from an ANCOVA model.
ANCOVA=analysis of covariance; BID=twice daily; CI=confidence interval; FAS=Full Analysis Set; LOV=last observed value; LS=least squares; QD=once daily; s-P=serum phosphorus.

A dose-response modeling analysis with 161 patients and nearly 1,000 observations showed that there was adequate agreement between the model and the observed data, supporting the predictability of s-P reduction by dose (Figure 22). Overall, these findings supported the proposed dosage regimen of tenapanor 30 mg BID in patients receiving maintenance dialysis.

Figure 22: Study D5613C0001: Model Predicted Placebo-Adjusted Dose-Response for Tenapanor



Note: shading shows 95% CI.
BID=twice daily; CI=confidence interval; QD=once daily.

4.3 Drug-Drug Interactions

In vitro drug-drug interaction (DDI) studies were conducted with tenapanor and AZ13792925 in accordance with FDA guidelines. Overall, the risk of in vivo cytochrome P450 (CYP450) and transporter-mediated drug interactions is low based on the low systemic exposures of tenapanor and AZ13792925. Data derived from clinical studies indicate that tenapanor at 50 mg BID or below has no clinically relevant effect on CYP2C9- and CYP3A4 mediated metabolism and PepT1- and P-gp-mediated intestinal transport. Co-administration of tenapanor with a strong CYP3A4/5 inhibitor did not cause clinically relevant effects on the PK of tenapanor and AZ13792925. Concomitant administration of sevelamer (Renvela™) did not affect the PD of tenapanor.

Tenapanor is an inhibitor of OATP2B1. Following administration of a single 20 mg dose of enalapril (OATP2B1 substrate) with tenapanor (30 mg BID) at steady state, the mean area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of enalapril was decreased by 64% and 69%, respectively, in healthy participants. The mean AUC and C_{max} of enalaprilat (active metabolite of enalapril) was decreased by 52% and 68%, respectively, in healthy participants (TEN-02-108). However, the decrease in enalaprilat exposure with tenapanor may be offset by the inherently higher exposures observed in patients receiving maintenance dialysis due to its reduced renal clearance. In April 2021, this finding was commented on by FDA and they suggested label language to Prescribing Information (PI) be included in the Drug Interaction section that read, "However, the decrease in enalaprilat’s exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with tenapanor.”

5 CLINICAL EFFICACY

Summary

- Study 201 and 301 were designed in accordance with the FDA Guidance on *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* for implementing RW studies.
- Results from pivotal Study 201 demonstrate that tenapanor lowers s-P concentrations in patients receiving maintenance dialysis.
    - The pre-specified primary endpoint was met, with a statistically significant (p=0.010) difference between the pooled tenapanor group (5 different fixed doses) and the placebo group in s-P change from the end of the 8-Week RTP to the end of the 4-Week RWP in the EAS.
- Results from pivotal Study 301 also demonstrate that tenapanor lowers s-P in patients receiving maintenance dialysis.
    - Study 301 has the largest sample size in the HP program, a longer treatment duration to identify responders with a single recommended tenapanor dosing regimen (30 mg BID with dose titration) and longer RW duration compared with Study 201 to allow for s-P rise in the placebo group, and an active safety comparator, providing the most reliable estimation of tenapanor's s-P lowering effect as monotherapy in patients receiving maintenance dialysis.
    - Study 301 met its primary efficacy endpoint; treatment with tenapanor significantly ($p < 0.0001$) improved s-P from period-level baseline to the end of the 12-week RWP relative to placebo in the EAS.
- The clinically relevant s-P lowering effect of tenapanor was also supported by the following findings from Study 301:
    - Approximately 55% of Week 26 completers with observed s-P in the tenapanor group achieved a reduction of ≥ 1.2 mg/dL from baseline, and 43% of these patients achieved s-P of < 5.5 mg/dL at Week 26.
    - s-P improvements were maintained in tenapanor-treated patients but decreased in patients switched to placebo, which was consistent across the EAS and the ITT population for the RWP as well as their subgroups.
- Interim analysis of Study 401 demonstrated that tenapanor alone or in combination with sevelamer carbonate produced a substantial s-P lowering effect, with a mean reduction of 2.33 mg/dL after up to 21 months of exposure to phosphorus lowering treatment.
- Study 402 demonstrated that tenapanor alone or in combination with PBs lowered s-P with reduced pill burden and increased patient satisfaction.

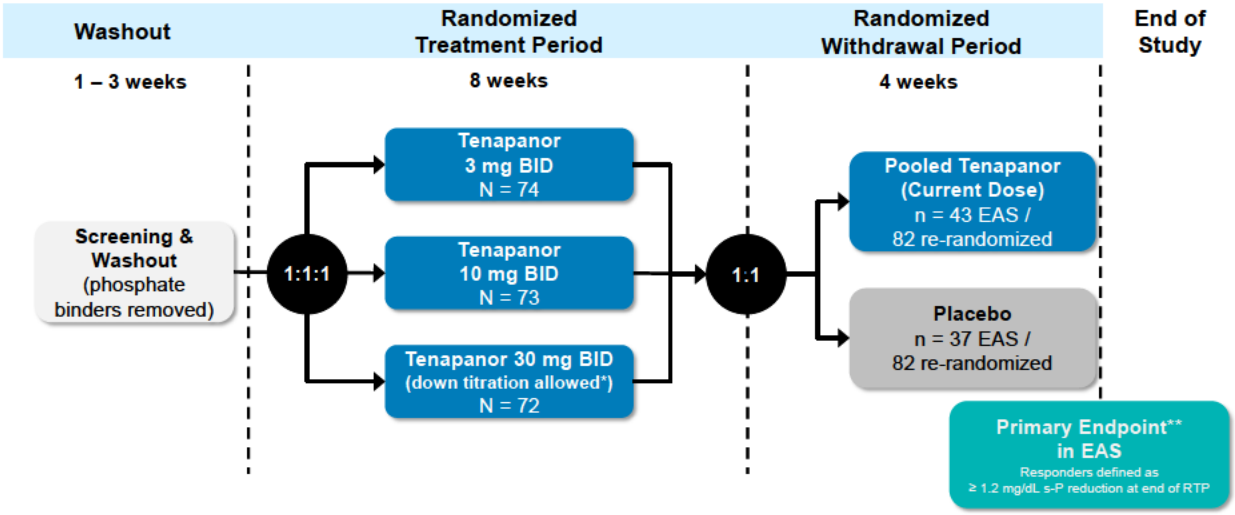
5.1 Phase 3 Short-Term Monotherapy Study TEN-02-201

5.1.1 Study Design

Study 201 was a Phase 3, multicenter, randomized, double-blind, parallel-group study with a placebo-controlled RWP to evaluate the efficacy, safety, and tolerability of tenapanor to treat HP in patients receiving maintenance dialysis. The primary efficacy objective of Study 201 was to evaluate the effect of tenapanor by comparing the difference in the change in s-P from the end of the 8-week RTP to the end of the 4-week RWP between the pooled tenapanor treatments and placebo. s-P was consistently measured pre-dialysis over the short interval.

The study comprised a screening visit, a wash-out period of up to 3 weeks, an 8-week RTP in which all patients received tenapanor blinded to dose (3 mg BID, 10 mg BID, or 30 mg BID [down-titrated in a stepwise fashion as needed]; 1:1:1), and a 4-week placebo--controlled RWP during which patients were re-randomized (1:1) to tenapanor or placebo (Figure 23). Patients re-randomized to tenapanor remained on the ending dose of the RTP throughout the RWP.

Figure 23: Study 201: Study Design



*Down titration was only allowed during the RTP, starting from a dose of 30 mg to a minimum dose of 3 mg in a stepwise fashion.
**Difference in s-P change from RWP baseline to end of RWP between pooled tenapanor and placebo in the EAS (i.e., ITT patients entering the RWP with an s-P reduction ≥ 1.2 mg/dL at the end of 8-week RTP)
BID=twice daily; EAS=Efficacy Analysis Set; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period.

5.1.1.1 Key Enrollment Criteria

Participants in the study were enrolled in 41 study centers in the US. Key enrollment criteria for Study 201 included:

- ≥ 18 and ≤ 80 years of age
- Chronic maintenance hemodialysis 3 times per week for ≥ 3 months

- Prescribed and took ≥ 3 doses of PB per day
- s-P ≥ 4.0 and ≤ 7.0 mg/dL at screening
- s-P ≥ 9.0 mg/dL and ≤ 10.0 mg/dL with an increase ≥ 1.5 mg/dL vs pre-wash-out value after 1 week or s-P ≥ 6.0 mg/dL and ≤ 10.0 mg/dL with an increase ≥ 1.5 mg/dL vs pre-wash-out after weeks 2 or 3 of PB wash-out

Patients were ineligible if they had s-P > 10.0 mg/dL, serum/plasma PTH > 1,200 pg/mL, persistent metabolic acidosis, defined as serum carbon dioxide < 18 mmol/L from 2 consecutive measurements during screening and wash-out periods, history of inflammatory bowel disease or diarrhea predominant IBS, 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, and positive serology of hepatitis B/C infection, or human immunodeficiency virus (HIV) with evidence of significant hepatic impairment or white blood cell elevation determined by the Sponsor.

A full list of eligibility criteria is provided in Appendix 9.4.1.

5.1.1.2 Endpoint Definitions and Study Populations

The primary efficacy endpoint was the change in s-P from the end of the 8-week RTP to the end of RWP (i.e., Week 4 or the endpoint visit of the RWP).

Secondary efficacy endpoints included:

- Change in s-P from baseline to Week 8 or the endpoint visit of the RTP, and
- Proportion of patients reaching s-P goal levels, defined as < 5.5 mg/dL, during the 8-week RTP.

Exploratory endpoints included actual values and change from baseline values for parathyroid (PTH) and intact Fibroblast Growth Factor (iFGF23) at each assessment time during the 8-week RTP and 4-week RWP. Changes in PTH and FGF23 are a clinically meaningful effect of s-P, as changes in hormone levels indicate a biological effect of lowering s-P.

The EAS was the analysis set for the primary efficacy analysis and was used for the analysis of all other efficacy variables in the 4-week RWP. The EAS included all eligible patients who completed the 8-week RTP and achieved ≥ 1.2 mg/dL reduction in s-P from baseline to the end of the 8-week RTP. The EAS was a subset of the ITT Analysis Set, which included eligible patients who received ≥ 1 dose of study drug and had ≥ 1 s-P assessment during the 8-week RTP.

Although the statistical analysis plan (SAP) specified that all efficacy analyses for the 4-week RW period would be carried out using the EAS while all efficacy analyses for the 8-week treatment period would be carried out using the ITT Analysis Set, the ITT Analysis Set was used for not only the analysis of all efficacy variables in the 8-week RTP but also the analysis of the primary efficacy endpoint and other efficacy variables in the 4-week RWP (in a post hoc manner).

5.1.1.3 Statistical Analyses

5.1.1.3.1 Determination of Sample Size

A sample size of 39 patients in each of the pooled tenapanor treatments and placebo group was expected to provide 90% power to detect a difference in the change in s-P from the end of the 8-week RTP to the end of the 4-week RWP 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 standard deviation (SD) for this difference of no greater than 2.0 mg/dL. A total sample size of 200 allowed for a 20% dropout rate and assumed that ≥ 50% of participants would be considered responders in the 8-week RTP.

5.1.1.3.2 Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy analysis evaluated the change in s-P from the end of the 8-week RTP to the end of the 4-week RWP or the endpoint visit for this period and was based on the difference between the pooled tenapanor treatments and placebo in the EAS (i.e., ITT patients entering the RWP with an s-P reduction ≥ 1.2 mg/dL at the end of 8-week RTP). Baseline for this analysis was defined as s-P at the end of the 8-week RTP. Endpoint for this analysis was defined as the last s-P laboratory value assessment during and up to the end of the 4-week RWP. The statistical analysis was carried out using an analysis of covariance (ANCOVA) model with baseline as a covariate and 2 fixed factors: pooled site and treatment group. A 2-sided significance level of 0.050 corresponding to 95% CIs was presented. All other p-values and/or CIs were considered descriptive.

Sensitivity Analyses of the Primary Endpoint Results

Sensitivity analyses were carried out for the primary efficacy analysis to assess the influence of (1) early termination during the 4-week RWP and (2) the impact of patients already randomized into the RWP after the primary efficacy endpoint was changed. Sensitivity analyses were performed by including only patients who completed the 4-week RWP as well as excluding patients who were randomized into the 4-week RWP prior to the protocol/ SAP amendment.

Secondary Efficacy Analyses

The change from baseline or change from the end of the 8-week RTP to the end of the 4-week RWP was presented accordingly, including differences between the pooled tenapanor treatments and placebo. The proportion of patients reaching s-P goal levels of < 5.5 mg/dL at each visit during the 8-week RTP was estimated and presented with exact 95% CI. All secondary p-values were considered descriptive.

Exploratory Analyses

The exploratory analysis of iFGF23 used an ANCOVA approach analogous to the method outlined for the primary efficacy analysis.

5.1.2 Patient Disposition and Baseline Characteristics

5.1.2.1 Disposition

A total of 219 patients were randomized into Study 201, and 164 (74.8%) patients completed the 8-week RTP of the study (Figure 24). In total, 55 (25.1%) patients withdrew from the study before completing the 8-week RTP. The most common primary reasons for early withdrawal were AEs, HP, withdrawal by participant, and intolerable GI side effects. Among these patients, 18 withdrew due to diarrhea.

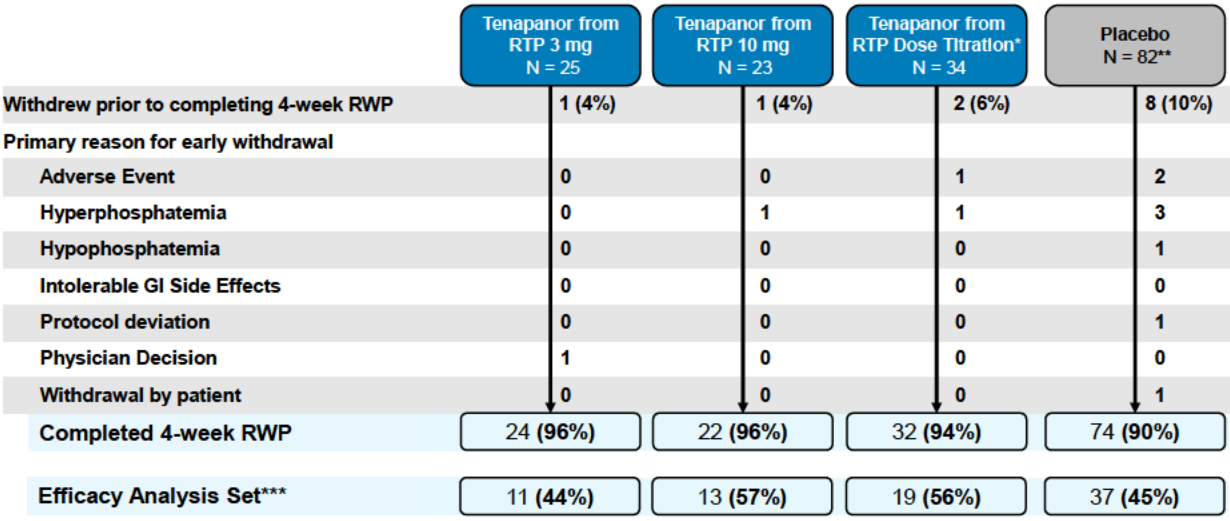
Figure 24: Study 201: Patient Disposition – 8-Week RTP (All Randomized Patients)

	Tenapanor 3 mg BID N = 74	Tenapanor 10 mg BID N = 73	Dose Titration* N = 72
Withdrew prior to completing 8-week RTP	17 (23%)	19 (26%)	19 (26%)
Primary reason for early withdrawal			
Adverse Event	6	5	6
Hyperphosphatemia	2	5	3
Hypophosphatemia	0	1	1
Intolerable GI Side Effects	1	4	2
Protocol deviation	1	1	1
Physician Decision	1	0	2
Withdrawal by patient	3	3	3
Lost to Follow-up	1	0	0
Other	2	0	1
Completed 4-week RTP	57 (77%)	54 (74%)	53 (74%)
Continued on tenapanor in 4-week RWP**	N = 25	N = 23	N = 34

*Down titration was only allowed during the RTP, starting from a dose of 30 mg to a minimum dose of 3 mg in a stepwise fashion.
**All patients who completed 8-week RTP entered 4-week RWP. Half of the RTP completers remained on tenapanor in RWP at a fixed dose and the other half switched to placebo.
GI=gastrointestinal; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

In total, 164 patients entered the 4-week RWP, and 152 patients completed the 4-week RWP of the study (Figure 25). The most common primary reasons for the early withdrawal from the 4-week RWP were HP (5 patients) and AE (3 patients).

Figure 25: Study 201: Patient Disposition – 4-Week RWP (All Re-Randomized Patients)



*Down titration was only allowed during the RTP, starting from a dose of 30 mg to a minimum dose of 3 mg in a stepwise fashion.
**Placebo group had 32, 31, and 19 patients from the 3 RTP tenapanor groups (3 mg, 10 mg, and dose titration), respectively.
***Comprised ITT patients who entered RWP with an s-P reduction of ≥ 1.2 mg/dL reduction at end of 8-week RTP
GI=gastrointestinal; ITT=intention-to-treat; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

5.1.2.2 Baseline Demographics

Baseline demographics were similar across tenapanor treatment groups in the Safety Analysis Set (Table 6). The majority of patients were male, Black/African American or White, and not Hispanic or Latino. The mean age of patients at informed consent was approximately 56 years old.

Table 6: Study 201: Baseline Demographics (Safety Analysis Set)

Characteristic	Tenapanor 3 mg BID (N=74)	Tenapanor 10 mg BID (N=73)	Tenapanor Dose-Titration (N=71)
Age (years), mean (SD)	55.7 (11.5)	57.4 (10.8)	54.2 (10.9)
Male, n (%)	46 (62.2)	34 (46.6)	48 (67.6)
Race, n (%)			
African American/Black	40 (54.1)	45 (61.6)	40 (56.3)
White	30 (40.5)	25 (34.2)	30 (42.3)
Asian	2 (2.7)	0	0
American Indian or Alaskan Native	1 (1.4)	2 (2.7)	1 (1.4)
Other	1 (1.4)	1 (1.4)	0
Not Hispanic or Latino, n (%)	61 (82.4)	65 (89.0)	53 (74.6)
Baseline BMI (kg/m^2), mean (SD)	32.5 (8.5)	33.6 (8.5)	33.4 (8.1)

BID=twice daily; BMI=body mass index; ITT=Intention-to-Treat; SD=standard deviation.

5.1.2.3 Baseline Disease Characteristics

The distribution of baseline disease characteristics was similar across all tenapanor treatment groups in the Safety Analysis Set (Table 7). Overall, patients had a history of ESKD for an average of 5.4 years at baseline.

Table 7: Study 201: Baseline Disease Characteristics (Safety Analysis Set)

Characteristic, mean (SD)	Tenapanor 3 mg BID (N=74)	Tenapanor 10 mg BID (N=73)	Tenapanor Dose-Titration (N=71)
Duration since ESKD diagnosis before randomization (years)	4.9 (5.17)	5.9 (5.21)	5.4 (5.46)
Baseline iFGF23 level (pg/mL)	n=59 8,136.9 (13,178.33)	n=57 10,466.7 (22,681.52)	n=54 10,993.9 (11,497.83)
Baseline intact PTH level (pg/mL)	470.7 (267.91)	393.4 (237.21)	433.2 (212.68)
Duration since first dialysis before randomization (months)	58.1 (63.06)	62.0 (53.14)	57.1 (57.08)

BID=twice daily; ESKD=end-stage kidney disease; iFGF23=intact fibroblast growth factor 23; ITT=Intention-to-Treat; PTH=parathyroid hormone; SD=standard deviation.

5.1.3 Results of Primary Endpoint – Change in s-P from Period-Level Baseline to End of 4-Week RWP

Tenapanor met the pre-specified primary endpoint, with a statistically significant difference compared to placebo (p=0.010) in s-P change from the period-level baseline to the end of the 4-Week RWP in the EAS (p=0.010). The LS mean change in s-P was 0.82 mg/dL lower for the pooled tenapanor group compared to the placebo group (right panel, Figure 7).

In the EAS, the early onset of s-P lowering effect of tenapanor in the RTP was observed as early as the first week on treatment and was sustained with a mean reduction of 2.50 mg/dL at Week 8 (left panel, Figure 7).

5.1.3.1 Sensitivity Analysis

For sensitivity analysis of the primary endpoint, inclusion of only patients who completed the 4-week RWP resulted in a statistically significant difference between tenapanor and placebo (p=0.014), demonstrating that early termination from the 4-week RWP did not significantly impact the primary efficacy results. Moreover, the treatment comparison of the primary endpoint excluding patients re-randomized into the RWP prior to the protocol/SAP amendment, also demonstrated a statistically significant difference between tenapanor and placebo (p=0.028), further supporting the primary efficacy results.

5.1.4 Secondary Endpoint Results

5.1.4.1 Proportion of Patients with s-P Response (< 5.5 mg/dL) at End of RTP (RTP ITT)

At the end of the 8-week RTP, the proportion of patients reaching the s-P goal level of < 5.5 mg/dL was similar in the 3 mg BID tenapanor, 10 mg BID tenapanor, and tenapanor dose-titration groups (Table 8). The mean ending tenapanor dose of the RTP was 24.4 mg BID in the dose-titration group.

Table 8: Study 201: Analysis of Secondary Endpoint – Proportion of Patients with s-P Response (< 5.5 mg/dL) at End of RTP (RTP ITT)

	Tenapanor 3 mg BID (N=74)	Tenapanor 10 mg BID (N=73)	Tenapanor Dose-Titration (N=71)
End of RTP[a]			
n/N' (%)	24/74 (32.4)	23/72 (31.9)	20/69 (29.0)
95% CI	(22.0, 44.3)	(21.4, 44.0)	(18.7, 41.2)

a. The end of the 8-week RTP was defined as the last assessment during the 8-week RTP.
BID=twice daily; CI=confidence interval; ITT=Intention-to-Treat; N'=number of patients with valid serum phosphorus assessment at specified timepoint; RTP=Randomized Treatment Period; s-P=serum phosphorus.

5.1.5 Exploratory Endpoint Results

5.1.5.1 Change in iFGF23 at End of RTP

The LS mean change in iFGF23 from study baseline to the end of RTP was -1202.91 pg/mL for the 3 mg BID tenapanor group, -771.06 pg/mL for the 10 mg BID tenapanor group, and -2167.99 pg/mL for the tenapanor dose-titration group. The iFGF23 mean change was statistically significant for the dose-titration group (p-value=0.020), while not statistically significant for the 3 mg BID tenapanor and 10 mg BID tenapanor groups.

5.2 Phase 3 Long-Term Monotherapy Study TEN-02-301

5.2.1 Study Design

Study 301 was a Phase 3 study with a placebo-controlled RWP followed by an open -label long-term safety extension to evaluate the safety and efficacy of tenapanor to treat hyperphosphatemia in patients receiving maintenance dialysis. The study comprised a screening visit, a wash-out period of up to-4 weeks, a 26-week RTP, an up -to-12-week placebo-controlled RW period, and an open-label safety extension period for a total treatment period of up to 52 weeks (Figure 26).

Patients were randomized (3:1) to receive either tenapanor 30 mg BID or sevelamer carbonate (standard of care) after 1, 2, or 3 weeks of wash-out if they had s-P ≥ 6.0 mg/dL and ≤ 10.0 mg/dL and had an increase in s-P of ≥ 1.5 mg/dL vs pre-wash-out.

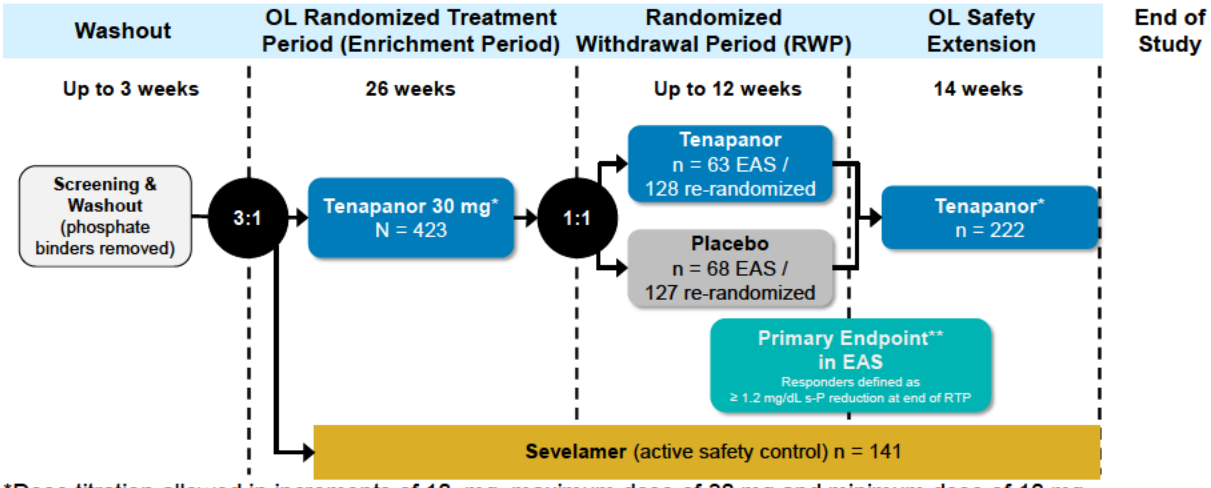
It is important to note that sevelamer was included as an active control for safety comparisons to tenapanor. This active safety comparator in a controlled trial also established assay sensitivity to detect an effect of tenapanor during the 26-week RTP. However, the study was not designed nor planned to compare s-P lowering effect between tenapanor and sevelamer in any study period, and as such, there were no pre-specified comparative efficacy analyses. s-P measurements for sevelamer-treated patients were collected weekly or monthly to monitor s-P throughout the study, and treatment comparisons of s-P change in the RTP between tenapanor and sevelamer were requested by the FDA and are provided in Section 1.5.5. Efficacy results of s-P response rates for tenapanor and sevelamer are also provided in Section 1.5.5.

During the 26-week RTP and the Safety Extension period, patients on tenapanor with s-P ≥ 10 mg/dL at any time after Week 2 of treatment or patients with s-P ≥ 9 mg/dL for 2 consecutive visits after Week 2 were discontinued and all procedures scheduled for Visit 23 were completed at the Early Termination visit, if possible. Patients on sevelamer did not have specific discontinuation criteria.

Upon completion of the 26-week RTP, patients in the tenapanor group were re-randomized 1:1 either to remain on their tenapanor dose at the end of RTP or to receive placebo for up to an additional 12 weeks (RWP). During the RWP, patients with s-P ≥ 9 mg/dL were discontinued from the RWP and were eligible to enter the Safety Extension period; those who did not enter the Safety Extension period completed all procedures scheduled for Visit 23 at the Early Termination visit, if possible.

It is also important to note that Study 301, which utilizes an RWP, was designed in accordance with the FDA Guidance on *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products*. According to this FDA guidance, the RW design randomizes only patients meeting a pre-specified threshold into the placebo-controlled portion of the trial. Those who do not respond are typically excluded from re-randomization into RWP, as loss of treatment effect is less likely to be measured in a population where treatment effect was not initially present. As such, inclusion of both patients with and without a response in a formal ITT analysis for the RWP is atypical. While the Sponsor's decision to continue to follow patients without a response to obtain safety insights in a double-blind, controlled setting and continue to evaluate their response over time during the RWP provided valuable information, inclusion of this subset in a formal ITT secondary efficacy analysis was not requested by FDA nor consistent with the RW study design. It was not FDA-mandated and provided no additional scientific insight for evaluation of tenapanor's treatment effect and should not have been done. Therefore, the best estimate of the increase in s-P when tenapanor is withdrawn during the RWP comes from the patients who responded to treatment (i.e., the EAS), which was the pre-specified analysis set for the primary analysis of the primary efficacy endpoint.

Figure 26: Study 301: Study Design



*Dose titration allowed in increments of 10 mg, maximum dose of 30 mg and minimum dose of 10 mg.
**Difference in s-P change from RWP baseline to end of RWP between tenapanor and placebo in the EAS (i.e., ITT patients entering the RWP with an s-P reduction ≥ 1.2 mg/dL at the end of 26-week RTP).
EAS=Efficacy Analysis Set; ITT=Intention-to-Treat; OL=open-label; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period.

5.2.1.1 Key Enrollment Criteria

The 301 study included patients ≥ 18 years of age who were receiving chronic maintenance hemodialysis 3 times per week for ≥ 3 months or chronic maintenance peritoneal dialysis for ≥ 6 months. Eligible patients were prescribed and taking ≥ 3 doses of PB therapy per day and had s-P ≥ 4.0 and ≤ 8.0 mg/dL at screening or re-screening. Patients may have been re-screened after a minimum of 1 week if s-P at Visit 1 was outside of the inclusion range, and the patient had historical s-P > 4.5 mg/dL and < 7.5 mg/dL during the 2 months immediately prior to the screening date. Patients must have had s-P ≥ 6.0 mg/dL and ≤ 10.0 mg/dL and must have had an increase ≥ 1.5 mg/dL vs pre-wash-out value after 1-, 2-, or 3-week wash-out of PBs.

Patients were excluded from the study for severe HP, defined as having s-P > 10.0 mg/dL on PBs at any time point during clinical monitoring for the 3 months preceding the screening visit, a serum/plasma PTH level > 1,200 pg/mL, any clinical signs of hypovolemia at enrollment as judged by the Sponsor, or a history of inflammatory bowel disease or diarrhea predominant IBS.

A full list of inclusion and exclusion criteria is provided in Appendix 9.4.2.

5.2.1.2 Endpoint Definitions and Study Populations

The primary efficacy endpoint was the change in s-P from the end of the 26-week RTP (i.e., the RWP baseline) to the end of RWP (i.e., endpoint visit of the RWP, defined as the last visit with s-P assessment during the RWP).

Secondary efficacy endpoints included:

- Change in s-P from the RWP baseline at each post-baseline visit during the RWP
- Change in s-P from study baseline at each post-baseline visit during the 26-week RTP
- Proportion of patients achieving s-P < 5.5 mg/dL at each post-baseline visit during the 26-week RTP
- Relative change in iFGF23 from study baseline at each post-baseline visit during the RTP, derived as “iFGF23 at the post-baseline visit during the RTP/iFGF23 at study baseline – 1”

The EAS was used for the primary efficacy analysis and applicable key secondary efficacy analyses. The EAS represented the responder subset of the ITT analysis set for the RWP. It included all ITT patients who received ≥ 1 dose of tenapanor during the 26-week RTP, completed the 26-week RTP, and achieved a reduction of ≥ 1.2 mg/dL in s-P from study baseline to the end of the 26-week RTP.

The ITT analysis set for a study period included all eligible patients who received ≥ 1 dose of study drug and had ≥ 1 post-treatment s-P measurement for the study period. Patients randomized to the active safety control group were not included in the ITT analysis set for any study period.

The Per Protocol (PP) analysis set was a subset of the ITT analysis set for the 12-week RWP. It included all ITT patients who completed the 12-week RWP as planned with no major protocol deviations that could impact the primary efficacy endpoint.

5.2.1.3 Statistical Analyses

5.2.1.3.1 Determination of Sample Size

As this is an RW study design, the enriched population (i.e., the EAS) was pre-specified as the primary analysis set and therefore, the sample size of Study 301 was planned based on the power calculation for the EAS.

A sample size of 146 patients (73 patients/group) was expected to provide 96% power to detect a treatment difference of -1.0 mg/dL in the primary efficacy endpoint between the tenapanor and placebo groups assuming a common SD of 1.6 mg/dL. This calculation was based on a 2-sided t-test with a significance level of 0.05.

Assuming a 30% dropout rate and a response rate of 50% in the tenapanor group at the end of the 26-week RTP, 417 patients needed to be randomized to the tenapanor group at Day 1 to achieve the planned sample size of 146 patients for the RWP. Approximately 420 randomized patients in the tenapanor group corresponded to an overall sample size of approximately 560 for randomization at Day 1 based on the 3:1 allocation ratio.

5.2.1.3.2 Primary and Key Secondary Analyses

The primary efficacy endpoint was the change in s-P from the end of the 26-week RTP to the end of RWP (i.e., the last visit with s-P assessment during the RWP). In the primary analysis, the treatment comparison of the mean change was performed on the EAS using an analysis of covariance (ANCOVA) model. The model included treatment and pooled site as fixed effects and baseline s-P of the RWP as a continuous covariate. Significance was tested with a 2-sided t-test with a significance level of 0.05.

The same statistical analysis method of the primary efficacy endpoint was applied to the key secondary analyses of the primary efficacy endpoint, i.e., treatment comparisons between tenapanor and placebo on the ITT analysis set of the RWP (i.e., RWP ITT), between individual tenapanor dose and placebo on the EAS, and between individual tenapanor dose and placebo on the RWP ITT.

A sequential testing procedure was followed to control the overall Type I error rate associated with the primary and the key secondary analyses at the 0.05 level (2-sided).

5.2.1.3.3 Sensitivity Analyses

To support the primary efficacy analysis, a sensitivity analysis was performed using a mixed-effects model for repeated measures (MMRM) approach. The dependent variable for the MMRM model was the change in s-P from the end of the 26-week RTP to each visit during the 12-week RWP. The MMRM included treatment, pooled site, visit, treatment-by-visit interaction, as fixed effects; and baseline s-P as a continuous covariate. The baseline was defined as s-P at the end of 26-week RTP. The covariance matrix for the repeated measures was assumed to be unstructured.

Within the framework of this model, the treatment group difference between tenapanor and placebo in the mean change from the end of the 26-week RTP to Week 12 of the 12-week RWP was estimated. The corresponding two-sided 95% CI and the p-value for the treatment difference was presented.

Additional sensitivity analysis included the primary efficacy analysis described in Section 5.2.3.1 repeated on the PP analysis set.

5.2.1.3.4 Subgroup Analyses

To assess the heterogeneity of treatment effects among subgroups, the primary efficacy endpoint was analyzed for the Efficacy and ITT analysis sets of the RWP by age group (< 45 years, ≥ 45 and < 65 years, or ≥ 65 years), sex (male or female), race (White, or Black or African American), pooled site (West, Central, or East), baseline s-P of the RWP (< 7.5 mg/dL or ≥ 7.5 mg/dL), and type of maintenance dialysis (hemodialysis or peritoneal dialysis).

5.2.1.3.5 Analyses of Secondary Endpoints

For the continuous secondary endpoint of s-P change from the RWP baseline at each post-baseline visit during the RWP, the mean values were estimated for each treatment

group and compared between tenapanor and placebo using an MMRM on observed cases in the Efficacy, ITT, and PP analysis sets, separately. Each MMRM included pooled site, treatment, visit, and treatment-by-visit interaction as fixed effects; baseline s-P of the RWP and baseline by visit as covariates; and patient as a random effect.

No inferential analyses will be performed for continuous secondary endpoints of the 26-week.

5.2.1.3.6 Handling of Missing Data

For the primary efficacy analysis, patients who completed the RWP, the endpoint visit was Visit 19 (Week 12 of the RWP) and for patients who prematurely discontinued the RWP, the endpoint visit was the last visit with s-P assessment during the RWP. As a results, no imputation of missing data was needed for any analysis of the primary endpoint.

For continuous secondary endpoints to be analyzed using the MMRM, no imputation of missing data was needed either as the MMRM analysis was performed on observed cases.

5.2.2 Patient Disposition and Baseline Characteristics

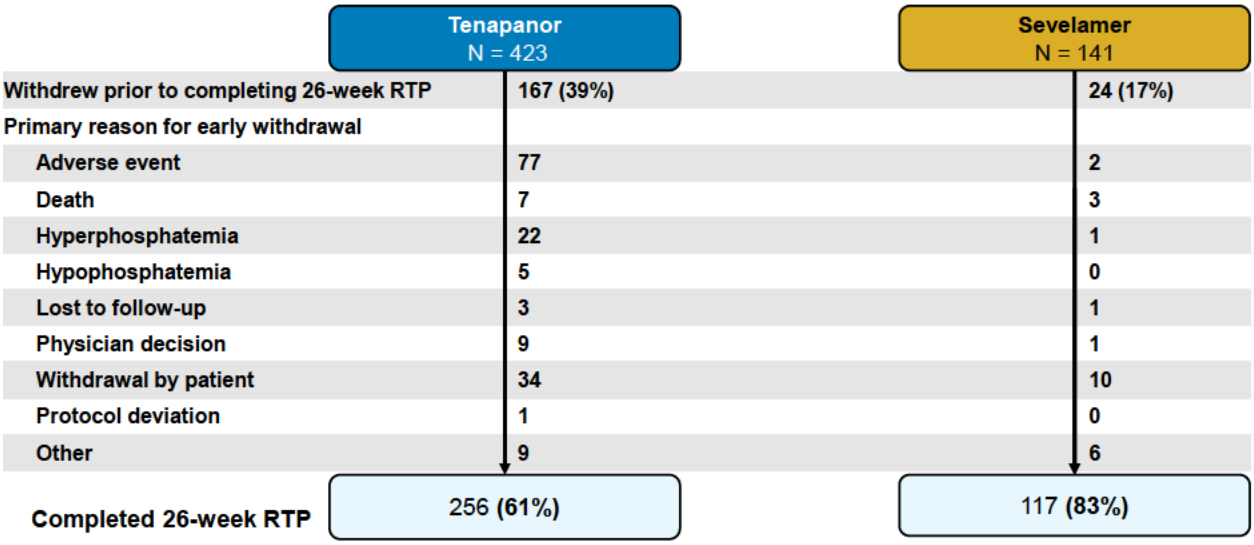
5.2.2.1 Disposition

A total of 564 patients were randomized (3:1) into the study: 423 were assigned to the tenapanor group and 141 to the sevelamer group. Of note, approximately 65% of patients had been treated with sevelamer prior to the start of study treatment, such that the majority of patients in the sevelamer arm demonstrated tolerability of the drug.

As shown in Figure 27, a total of 373 patients completed the 26-week RTP. In total, 167 (39.5%) patients in the tenapanor group and 24 (17.0%) patients in the sevelamer group withdrew early. The most common primary reason for early withdrawal was AE and included 77 (18.2%) patients in the tenapanor group and 2 (1.4%) in the sevelamer group. Other common primary reasons for early withdrawal from the 26-week RTP included withdrawal by patient (34 patients in the tenapanor group and 10 patients in the sevelamer group) and HP (22 patients in the tenapanor group and 1 patient in the sevelamer group). Ten patients were withdrawn early due to kidney transplant: 6 patients in the tenapanor group and 4 patients in the sevelamer group. Ten patients were withdrawn early due to death.

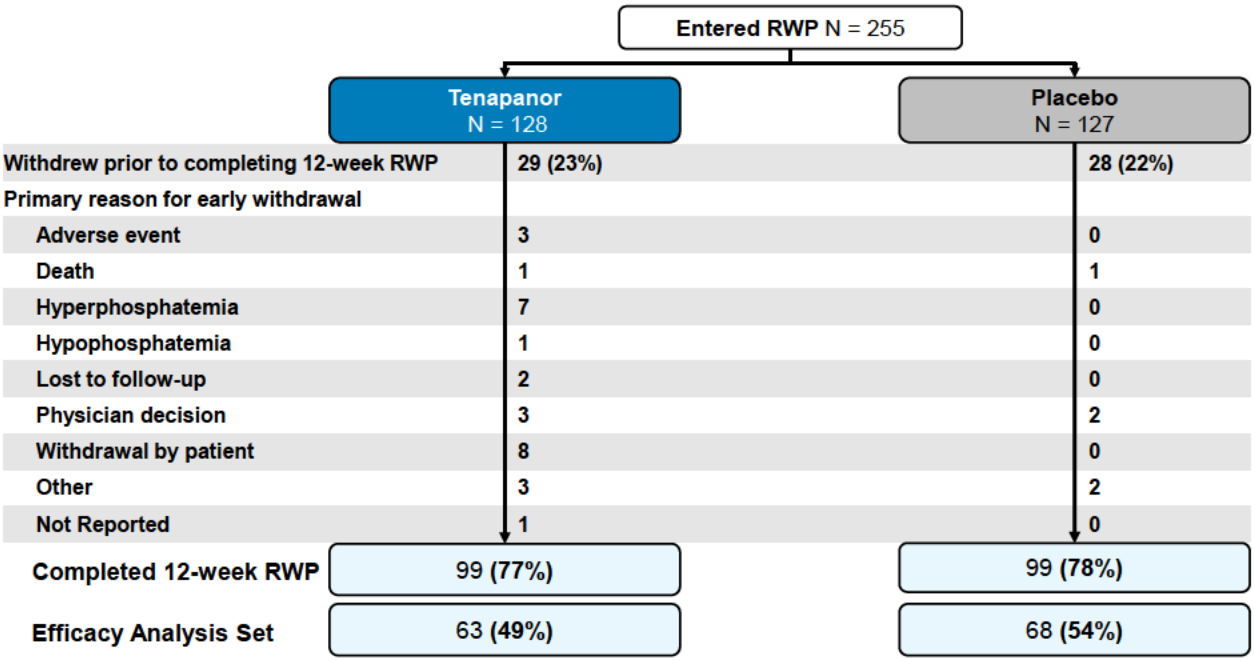
Of the patients entering the RWP, approximately 77% of the tenapanor group and 78% of the placebo group completed the 12 weeks (Figure 28). Of the completers, 49% of the tenapanor group and 54% of the placebo group were included in the EAS based on achieving s-P reduction of ≥ 1.2 mg/dL at the last visit of the RTP.

Figure 27: Study 301: Patient Disposition – 26-Week RTP (All Randomized Patients)



RTP=Randomized Treatment Period.

Figure 28: Study 301: Patient Disposition – 12-Week RWP (All Re-randomized Patients)



RWP=Randomized Withdrawal Period.

5.2.2.2 *Baseline Demographics*

Patient demographics were similar between tenapanor and sevelamer groups and representative of the patient population expected to use tenapanor (Table 9). The

majority of patients were male, white or Black/African American, and not Hispanic or Latino. The mean age of patients at screening was approximately 58 years old.

Table 9: Study 301: Baseline Demographics (Safety Analysis Set)

Characteristics	Tenapanor (N=419)	Sevelamer (N=137)
Age at screening, mean (SD)	57.7 (12.64)	59.0 (12.64)
Age group, n (%), years		
< 45	65 (15.5)	20 (14.6)
≥ 45 and < 65	222 (53.0)	72 (52.6)
≥ 65	132 (31.5)	45 (32.8)
Male, n (%)	265 (63.2)	91 (66.4)
Race, n (%)		
White	189 (45.1)	70 (51.1)
African American/Black	195 (46.5)	60 (43.8)
Asian	21 (5.0)	7 (5.1)
American Indian or Alaska Native	11 (2.6)	0
Native Hawaiian or Other Pacific Islander	2 (0.5)	0
Other	1 (0.2)	0
Ethnicity, n (%)		
Not Hispanic or Latino	302 (72.1)	96 (70.1)
Hispanic or Latino	115 (27.4)	41 (29.9)
Not reported	1 (0.2)	0
Unknown	1 (0.2)	0
Baseline BMI (kg/m^2), mean (SD)	31.3 (7.51)	31.4 (9.92)
Prior use of sevelamer, n (%)	224 (53.5)	87 (63.5)

BMI=body mass index; SD=standard deviation; s-P=serum phosphorus.

5.2.2.3 Baseline Disease Characteristics

In general, the distribution of baseline disease characteristics was similar between treatment groups and representative of the patient population expected to use tenapanor (Table 10). The majority of patients were receiving hemodialysis, and approximately 10% were receiving peritoneal dialysis. The mean duration since ESKD diagnosis at baseline was approximately 5 years, and the mean baseline s-P was approximately 7.4 mg/dL.

Table 10: Study 301: Baseline Disease Characteristics (Safety Analysis Set)

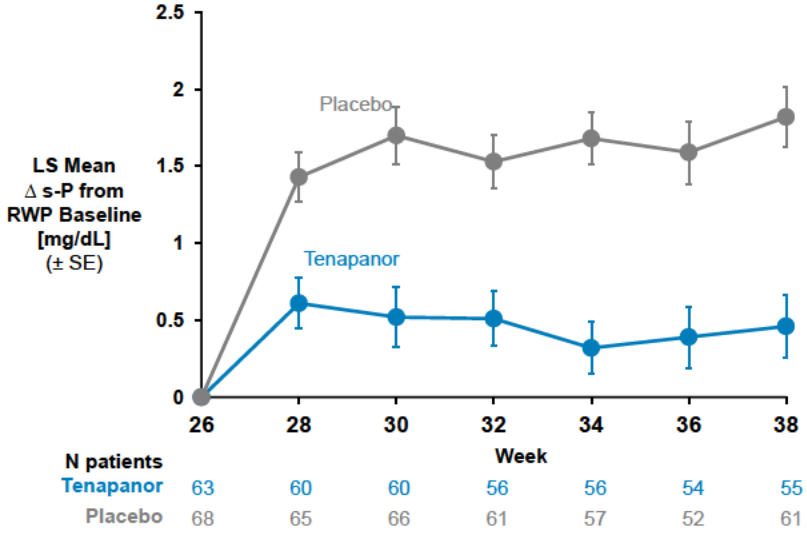
Characteristics	Tenapanor (N=419)	Sevelamer (N=137)
Duration since ESKD diagnosis at baseline, years, mean (SD)	4.8 (4.44)	5.1 (5.10)
Type of dialysis, n (%)		
Hemodialysis	376 (89.7)	122 (89.1)
Peritoneal dialysis	43 (10.3)	15 (10.9)
Baseline s-P, mean (SD)	7.4 (1.44)	7.2 (1.45)
Baseline s-P, n (%)		
< 7.5 mg/dL	210 (50.1)	85 (62.0)
≥ 7.5 mg/dL	209 (49.9)	52 (38.0)
Baseline iFGF23 level (pg/mL), mean (SD)	12,316.4 (14,772.88)	11,467.0 (14,054.69)
Baseline intact PTH level (pg/mL), mean (SD)	421.4 (252.19)	402.0 (254.95)

CKD=chronic kidney disease; ESKD=end-stage kidney disease; iFGF23=intact fibroblast growth factor 23; PTH=parathyroid hormone; SD=standard deviation; s-P=serum phosphorus.

5.2.3 Primary Efficacy Results – Change in s-P from Period-Level Baseline to End of 12-Week RWP (EAS)

Study 301 met its primary efficacy endpoint, change in s-P from the period-level baseline to the end of the RWP for the EAS comprised of 131 ITT patients entering RWP, with an s-P reduction of ≥ 1.2 mg/dL at the end of RTP (Figure 29). The placebo-adjusted LS mean s-P change from the RWP baseline to the end of RWP was -1.37 mg/dL for the tenapanor group and was statistically significant ($p < 0.0001$) in favor of tenapanor.

Figure 29: Study 301: Primary Endpoint – Change in s-P from Period-Level Baseline to End of 12-Week RWP (EAS)



Primary Endpoint	TEN	PBO
LS mean Δ from RWP baseline	0.43	1.80
LS Mean Difference (95% CI)	-1.37 (-1.92, -0.82)	
p-value	p < 0.0001	

EAS=Efficacy Analysis Set; PBO=placebo; LS=least squares; RWP=Randomized Withdrawal Period; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

5.2.3.1 Sensitivity Analysis

The result of the pre-specified sensitivity analysis on the PP patients from the EAS was consistent with the result of the primary efficacy analysis and showed that tenapanor statistically significantly reduced s-P compared to placebo (-1.24 mg/dL; p-value < 0.0001).

5.2.4 Key Secondary Analysis Results

The majority of the key secondary analyses of the primary endpoint achieved statistical significance following a pre-specified sequential testing procedure.

Using the ANCOVA model on the ITT analysis set of the RWP, the LS mean difference in s-P change from period-level baseline to the end of the 12-week RWP was -0.66 mg/dL for the tenapanor group relative to placebo, with a statistically significant difference in favor of tenapanor (p=0.0020) (Table 11).

Using the ANCOVA model on the EAS, the LS mean difference in s-P from period-level baseline to the end of the 12-week RWP was -1.69 mg/dL for the tenapanor 30 mg BID group, -0.96 mg/dL for the tenapanor 20 mg BID group, and -1.02 mg/dL for the tenapanor 10 mg BID group relative to placebo. The LS mean differences were statistically significant in favor of tenapanor 30 mg BID (p < 0.0001) and tenapanor 20 mg BID (p=0.0138) relative to placebo. The p-value for the LS mean difference between the tenapanor 10 mg BID group and the corresponding placebo group was not reported, as the sample size in the tenapanor 10 mg BID group (N=6) did not meet the pre-specified sample size requirement for testing (N ≥ 15).

Using the ANCOVA model on the ITT analysis set of the RWP, the LS mean change in s-P from period-level baseline to the end of the 12-week RWP was 0.10 mg/dL for the tenapanor 30 mg BID group, 0.35 mg/dL for the tenapanor 20 mg BID group, 0.56 mg/dL for the tenapanor 10 mg BID group, and 0.88 mg/dL for the placebo group. Relative to placebo, the LS mean difference was -0.78 mg/dL for the tenapanor 30 mg BID group, -0.53 mg/dL for the tenapanor 20 mg BID group, and -0.32 mg/dL for the tenapanor 10 mg BID group. The LS mean difference relative to placebo was statistically significant in favor of tenapanor 30 mg BID (p=0.0015). The LS mean difference between the tenapanor 20 mg BID group and the placebo group favors tenapanor, although it missed statistical significance (p=0.1047). Statistical significance was not determined for the tenapanor 10 mg BID group because statistical significance was not achieved for the 20 mg BID group and the sample size (N=14) did not meet the pre-specified sample size requirement for testing (N ≥ 15).

Table 11: Study 301: Primary and Key Secondary Analyses for Primary Endpoint – Change in s-P from Period-Level Baseline to End of 12-Week RWP

Population	Comparison	Tenapanor		Placebo		LS Mean Difference
		N	LS Mean Change	N	LS Mean Change	
EAS	TEN vs PBO	63	0.43	68	1.80	-1.37
Non-responder subset (post hoc)	TEN vs PBO	57	-0.06	55	-0.19	0.13
ITT Analysis Set (EAS + Non-responder subset)	TEN vs PBO	120	0.22	123	0.88	-0.66
EAS	TEN 30 mg BID vs PBO	35	0.11	68	1.81	-1.69
	TEN 20 mg BID vs PBO	22	0.85	68	1.81	-0.96
	TEN 10 mg BID vs PBO	6*	0.79	68	1.81	-1.02
ITT Analysis Set	TEN 30 mg BID vs PBO	74	0.10	123	0.88	-0.78
	TEN 20 mg BID vs PBO	32	0.35	123	0.88	-0.53
	TEN 10 mg BID vs PBO	14*	0.56	123	0.88	-0.32

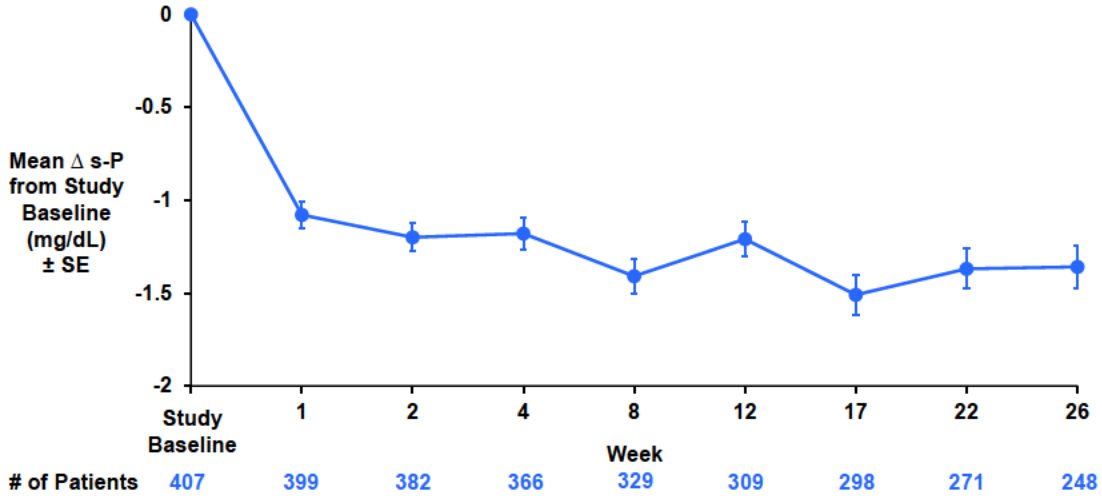
*Did not meet the pre-specified sample size requirement for testing (N ≥ 15)
Note: The primary endpoint was an LOV-type endpoint; each patient in the analysis population contributed their last observed s-P change during the RWP to the analysis. The LS means came from an ANCOVA model.
ANCOVA=analysis of covariance; BID=twice daily; EAS=Efficacy Analysis Set; ITT=Intention-to-Treat; LOV=last observed value; LS=least squares; PBO=placebo; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

5.2.5 Analysis Results of Secondary Endpoints

5.2.5.1 Change in s-P from Study Baseline to End of 26-Week RTP

By the end of the 26-week RTP, mean s-P decreased from 7.45 mg/dL at study baseline to 6.18 mg/dL, with a mean s-P change of -1.27 mg/dL for the ITT analysis set of the RTP (LOV). The early onset of s-P lowering effect of tenapanor was observed as early as 1 week on treatment, as shown in Figure 30.

Figure 30: Study 301: Change in s-P from Study Baseline by Visit During the 26-Week RTP (RTP ITT)



ITT=Intention-to-Treat; s-P=serum phosphorus.

5.2.5.2 Proportion of Patients Reaching s-P ≤ 5.5 mg/dL at Week 26

Among the 248 ITT patients with an observed s-P at Week 26, 43% (107/248) achieved an s-P of ≤ 5.5 mg/dL at Week 26 and 55% (137/248) achieved an s-P reduction of ≥ 1.2 mg/dL at Week 26. By treating patients with missing Week 26 s-P as non-responders (i.e., the worst-case imputation), 26% (107/407) and 34% (137/407) of the 407 ITT patients achieved an s-P of ≤ 5.5 mg/dL and an s-P reduction of ≥ 1.2 mg/dL at Week 26, respectively; in addition, 21% (84/407) of the ITT patients achieved both response criteria at Week 26. These indicate that among the 107 patients reaching an s-P of ≤ 5.5 mg/dL at Week 26, the majority (84/107; 79%) also achieved an s-P reduction of ≥ 1.2 mg/dL at Week 26 (Table 12).

Table 12: Study 301: Proportion of Patients Reaching Target s-P at Week 26 (RTP ITT)

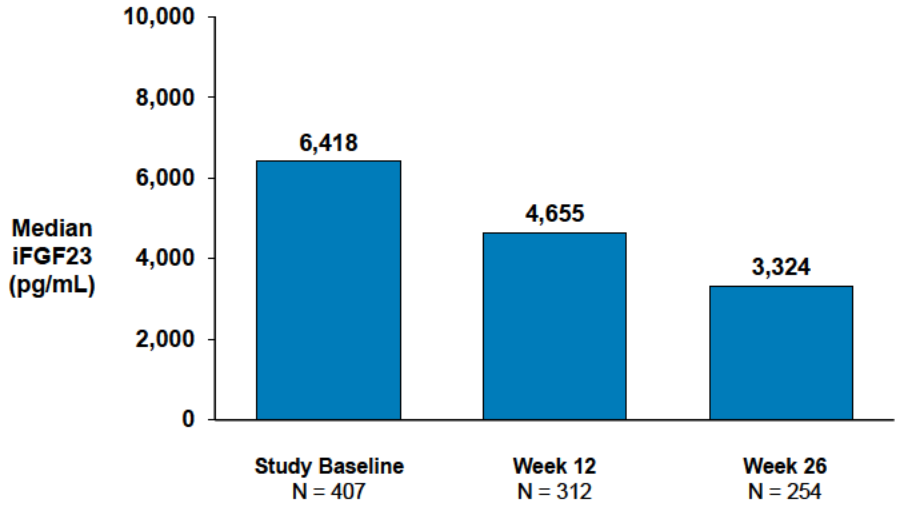
	Proportion of Patients, n (%)
1. *Randomized Treatment Period (ITT with Observed s-P at Week 26)*	**Observed Cases N=248**
• Reaching s-P ≤ 5.5 mg/dL at Week 26	107 (43%)
• Achieving s-P reduction of ≥ 1.2 mg/dL from study baseline to Week 26	137 (55%)
• Achieving s-P reduction of ≥ 1.0 mg/dL from study baseline to Week 26	149 (60%)
• Achieving s-P reduction of ≥ 0.8 mg/dL from study baseline to Week 26	160 (65%)
2. *Randomized Treatment Period (ITT)*	**ITT N=407**
• Reaching s-P ≤ 5.5 mg/dL at Week 26	107 (26%)
• Achieving s-P reduction of ≥ 1.2 mg/dL from study baseline to Week 26	137 (34%)
• Reaching s-P ≤ 5.5 mg/dL **AND** achieving ≥ 1.2 mg/dL s-P reduction from study baseline at Week 26	84 (21%)
• With s-P > 5.5 mg/dL **BUT** achieving ≥ 1.2 mg/dL s-P reduction from study baseline at Week 26	53 (13%)

EAS=Efficacy Analysis Set; ITT=Intention-to-Treat; RTP=Randomized Treatment Period; s-P=serum phosphorus.

5.2.5.3 Relative Change in iFGF23

FGF23 is a major regulator of phosphate homeostasis. Serum FGF23 concentration is an independent predictor of increased mortality and cardiovascular disease in patients receiving maintenance dialysis (Gutierrez et al 2008; Jean et al 2009; Stohr et al 2018). Median iFGF23 decreased by nearly 50% from period-level baseline to the end of the 26-week RTP for patients randomized to tenapanor (Figure 31).

Figure 31: Study 301: Relative Change in iFGF23 During 26-Week RTP (RTP ITT)



iFGF23=intact fibroblast growth factor 23; ITT=Intention-to-Treat; RTP=Randomized Treatment Period.

5.2.6 Subgroup Analysis of Primary Efficacy Endpoint

The LS mean difference of tenapanor treatment relative to placebo was statistically significant for all subgroups in the EAS except the baseline s-P ≥ 7.5 mg/dL (n=6) and age < 45 years subgroups (n=24) (Figure 32). However, both subgroup sizes were small, limiting data interpretation.

Figure 32: Study 301: Subgroup Analysis of Change in s-P from Period-Level Baseline to End of 12-Week RWP (EAS)

	Tenapanor N = 63	Placebo N = 68	Favors Tenapanor / Favors Placebo	LS Mean Difference (95% CI)	p-value
Overall				**-1.37** (-1.92, -0.82)	**< 0.0001**
Age					
< 45 years	**13**	**11**		**-1.39** (-2.90, 0.11)	**0.0675**
≥ 45 – < 65 years	**35**	**32**		**-1.66** (-2.47, -0.84)	**0.0001**
≥ 65 years	**15**	**25**		**-1.18** (-2.12, -0.23)	**0.0163**
Sex					
Male	**41**	**40**		**-1.00** (-1.63, -0.38)	**0.0019**
Female	**22**	**28**		**-1.96** (-3.03, -0.88)	**0.0006**
Race					
White	**33**	**26**		**-1.45** (-2.32, -0.59)	**0.0014**
Black or African American	**29**	**37**		**-1.36** (-2.15, -0.57)	**0.0010**
Baseline s-P Level (RWP)					
< 7.5 mg/dL	**60**	**65**		**-1.34** (-1.92, -0.77)	**< 0.0001**
≥ 7.5 mg/dL	**3**	**3**		**-1.75** (-7.50, 4.00)	**0.3206**

CI=confidence interval; EAS=Efficacy Analysis Set; RWP=Randomized Withdrawal Period; s-P=serum phosphorus.

At the end of RWP, the mean change from study baseline in s-P was -2.16 mg/dL for the group re-randomized to tenapanor and -0.86 mg/dL for the for the group re-

randomized to placebo Table 13. Most importantly, approximately 46% of patients re-randomized to tenapanor reached the target goal of s-P ≤ 5.5 mg/dL and 44% of high-risk patients with s-P ≥ 7.5 mg/dL achieved this s-P target goal.

Table 13: Study 301: Change in s-P from Study Baseline and Proportion of Patients Reaching Target s-P at End of RWP (EAS)

At End of RWP	RTP TEN – RWP TEN	RTP TEN – RWP PBO
All patients in EAS (Responders entering RWP)	N=63	N=68
Mean change from study baseline (SE)	-2.16 (0.24)	-0.86 (0.22)
Achieving ≤ 5.5 mg/dL s-P	29 (46%)	16 (24%)
Mean change from study baseline (SE) in responders	n=29 -3.48 (0.28)	n=16 -2.29 (0.27)
Achieving ≤ 5.5 mg/dL s-P AND ≥ 1.2 mg/dL s-P reduction from study baseline	28 (44%)	14 (21%)
High-risk patients (≥ 7.5 mg/dL s-P at study baseline) in EAS	N=36	N=41
Achieving ≤ 5.5 mg/dL s-P	16 (44%)	7 (17%)

Note: Change from study baseline at end of RWP is an LOV-type endpoint, derived as the last observed s-P in RWP – s-P at study baseline.
EAS=Efficacy Analysis Set; LOV=last observed value; PBO=placebo; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

5.3 Study 202: Tenapanor Treatment in Combination With Phosphate Binders

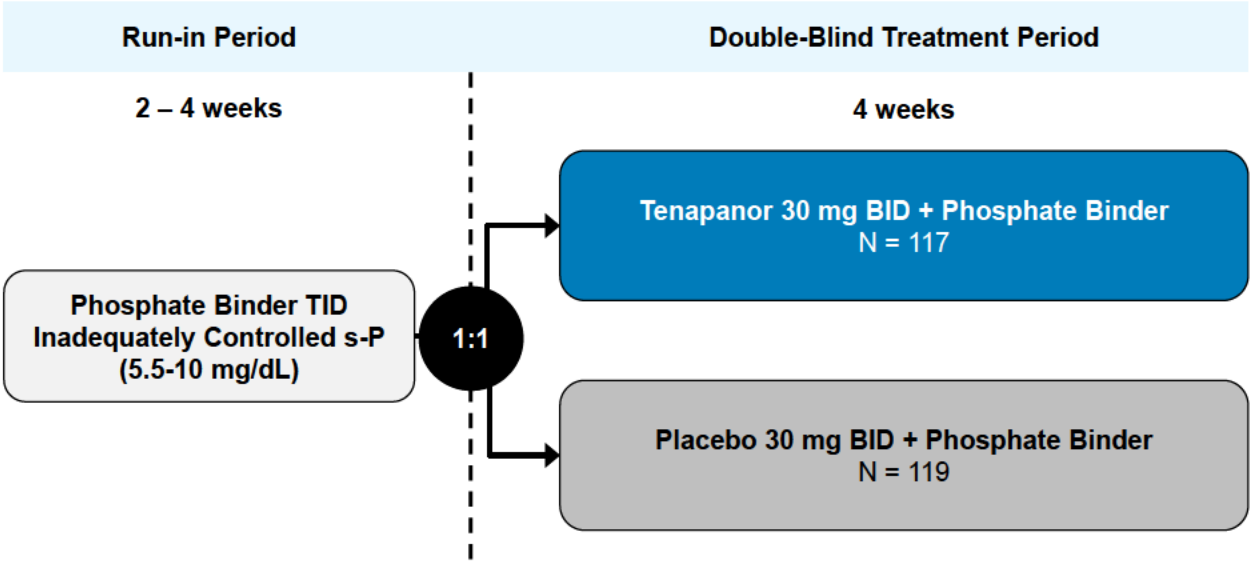
5.3.1 Study Design

TEN-02-202 (Study 202) was a randomized, double-blind, placebo-controlled study to evaluate the efficacy of tenapanor in combination with PB therapy for inadequately controlled HP in more difficult-to-treat patients receiving maintenance dialysis.

The study comprised a screening visit, a run-in period of ≥ 2 weeks and ≤ 4 weeks, and a 4-week double-blind RTP (Figure 33). At screening, patients were required to be on TID daily PB therapy and to have s-P ≥ 5.5 and ≤ 10.0 mg/dL to enter the study. Patients were told to continue their existing PB treatment throughout the study without any change to the dose. During the run-in period, s-P was measured at each visit (pre-dialysis after a short interval) to enable evaluation of the s-P randomization criteria. To be randomized at Day 1 (Visit 4), patients were required to have s-P ≥ 5.5 and ≤ 10.0 mg/dL at Visit 3.

During the double-blind RTP, patients received tenapanor or placebo starting at a dose of 30 mg BID. Investigators were permitted to decrease or increase the dose of study medication based on s-P and/or GI tolerability in 10-mg increments to a minimum of 10 mg BID or a maximum of 30 mg BID after randomization (Visit 4) to Day 15 (Visit 6). Doses could be adjusted between visits.

Figure 33: Study 202: Study Design



BID=twice daily; TID=three times daily.

5.3.1.1 Key Enrollment Criteria

Patients in the study were enrolled at 46 study centers in the US. Study 202 included patients ≥ 18 and ≤ 80 years of age receiving chronic maintenance hemodialysis for ≥ 6 months, prescribed and taking PB medication ≥ 3 times per day, and s-P ≥ 5.5 and ≤ 10.0 mg/dL at screening and at the end of the run-in period. Patients were ineligible if they had severe HP, defined as s-P > 10.0 mg/dL on PBs at any time point during routine clinical monitoring for the 3 preceding months prior to screening, a serum/plasma PTH level > 1,200 pg/mL, any clinical signs of hypovolemia at screening as judged by the Sponsor, or a history of inflammatory bowel disease or IBS with diarrhea.

A full list of inclusion and exclusion criteria is provided in Appendix 9.4.3.

5.3.1.2 Endpoint Definitions

The primary efficacy endpoint was the change from baseline in s-P at Week 4. The efficacy of tenapanor in combination with PB therapy was evaluated based on the difference in mean change from baseline in s-P at Week 4 between the tenapanor and placebo groups.

Key secondary efficacy endpoints included:

- s-P response (achieving s-P < 5.5 mg/dL) at Week 4
- Relative change from baseline in iFGF23 at Week 4, derived as "iFGF23 at Week 4/Baseline iFGF23 – 1"

Other secondary efficacy endpoints analyzed included:

- Change from baseline in s-P at Week 1, Week 2, and Week 3

- s-P response at Week 1, Week 2, and Week 3
- Change from baseline in PTH at Week 4

5.3.1.3 Statistical and Analytic Plans

5.3.1.3.1 Determination of Sample Size

Assuming a common SD of 1.0 mg/dL, a sample size of 214 patients, with 107 patients per group, was expected to provide 95% power to detect a treatment difference of -0.5 mg/dL in the primary endpoint between the tenapanor and placebo groups. This calculation was based on a 2-sample t-test with a significance level of 0.05 (2-sided). Based on the same assumption above, the sample size of 214 patients would provide at least 85% power at a 0.01 significance level.

5.3.1.3.2 Data Sets Analyzed

The following analysis sets were defined in Study 202:

- Full Analysis Set (FAS): included all randomized patients who had ≥ 1 post-baseline s-P measurement
- Per Protocol (PP): a subset of the FAS excluding any patient who had a significant protocol deviation that could have altered his/her efficacy outcome to treatment
- Week 4 Completers: included all patients from the FAS who completed the s-P assessment at Week 4

5.3.1.3.3 Primary Endpoint Analysis

The primary efficacy endpoint was the change from baseline in s-P level at Week 4. In the primary analysis, the treatment comparison of the mean change was performed using an MMRM on observed cases of the FAS. The MMRM included the Interactive Response Technology (IRT)-recorded PB type (sevelamer or non-sevelamer), s-P level for eligibility (< 7.5 mg/dL or ≥ 7.5 mg/dL), treatment, visit (Week 1–Week 4), and treatment-by-visit interaction as fixed effects. Baseline s-P and baseline by visit were included as covariates and patients as a random effect.

5.3.1.3.4 Sensitivity Analyses

The primary MMRM was repeated on the PP Population and Week 4 Completers. Analysis of covariance (factors: IRT-recorded PB type [sevelamer or non-sevelamer], s-P for eligibility [< 7.5 mg/dL or ≥ 7.5 mg/dL], and treatment; covariate: Baseline [Visit 4] s-P) was performed on the following populations:

- FAS using the last observation carried forward (LOCF) approach
- PP Population using LOCF
- Week 4 Completers.

5.3.1.3.5 Secondary Endpoint Analysis

s-P response at Week 4: The s-P response rate (i.e., the proportion of participants achieving s-P < 5.5 mg/dL) at Week 4 was estimated for each treatment group and compared between the tenapanor and placebo groups with 95% CIs. The p-value was obtained from the Cochran-Mantel-Haenszel (CMH) test, adjusting for IRT-recorded PB type (sevelamer or non-sevelamer) and s-P for eligibility (< 7.5 mg/dL or ≥ 7.5 mg/dL).

Change from Baseline in iFGF23 at Week 4: The relative change from baseline in iFGF23 at Week 4 was analyzed using an analysis of variance (ANOVA) model, with the log-transformed relative value at Week 4 (i.e., Week 4 value/Baseline value) as the dependent variable. Factors in the ANOVA model included the IRT-recorded PB type (sevelamer or non-sevelamer), s-P for eligibility (< 7.5 mg/dL or ≥ 7.5 mg/dL), and treatment. The 95% CIs were reported.

Change from Baseline in s-P at Weeks 1, 2, and 3: Mean changes from baseline in s-P at Week 1, Week 2, and Week 3 were estimated for each treatment group and compared between the tenapanor and placebo groups, using the MMRM for the primary analysis of the primary efficacy endpoint.

s-P response at Week 1, Week 2, and Week 3: The s-P response rate (i.e., the proportion of patients achieving s-P < 5.5 mg/dL) at each post-baseline visit prior to Week 4 was estimated for each treatment group and compared between the tenapanor and placebo groups with 95% CIs. The p-value was obtained from the CMH test, adjusting for IRT-recorded PB type (sevelamer or non-sevelamer) and s-P for eligibility (< 7.5 mg/dL or ≥ 7.5 mg/dL).

Change from Baseline in PTH at Week 4: The change from baseline in PTH level at Week 4 was analyzed using an ANCOVA model, with PTH change at Week 4 as the dependent variable. The ANCOVA model included the IRT-recorded PB type (sevelamer or non-sevelamer), s-P for eligibility (< 7.5 mg/dL or ≥ 7.5 mg/dL), and treatment as factors and baseline PTH level as a covariate.

5.3.2 Patient Disposition and Baseline Characteristics

5.3.2.1 Disposition

A total of 236 patients were randomized into the study: 117 were randomized to tenapanor and 119 to placebo (Table 14). Of these patients, 228/236 (96.6%) completed the study, including 112/117 (95.7%) in the tenapanor group. In the tenapanor group, 4 (3.4%) patients prematurely discontinued from study primarily due to an AE and 1 (0.9%) withdrew primarily due to a kidney transplant.

Table 14: Study 202: Study Disposition (All Randomized Patients)

	Tenapanor + Phosphate Binder (N=117) n (%)	Placebo + Phosphate Binder (N=119) n (%)
ITT population	117 (100)	119 (100)
FAS	116 (99.1)	119 (100)
PP population	90 (76.9)	93 (78.2)
Week 4 completers*	112 (95.7)	117 (98.3)
Early withdrawal from study	5 (4.3)	3 (2.5)
Primary reason for withdrawal		
Adverse event	4 (3.4)	1 (0.8)
Withdrawal by patient	0	1 (0.8)
Other	1 (0.9)	1 (0.8)

*Week 4 completers included all FAS patients who completed the s-P assessment at Week 4. In the placebo group, 2 patients prematurely discontinued from the study and their s-P assessment at the Early Termination visit was mapped to Week 4, and 1 patient completed the study without an observed s-P at Week 4.
FAS=Full Analysis Set; ITT=Intention-to-Treat; PP=Per Protocol; s-P=serum phosphorus.

5.3.2.2 Baseline Demographics

The majority of patients were male and white or Black/African American (Table 15). At screening, the mean age of patients at screening was approximately 55 years old.

Table 15: Study 202: Baseline Demographics (Safety Population)

	Tenapanor + Phosphate Binder (N=117)	Placebo + Phosphate Binder (N=119)
Age at screening (years), mean (SD)	55.1 (12.3)	53.9 (12.7)
Male, n (%)	65 (55.6)	74 (62.2)
Race, n (%)		
White	57 (48.7)	60 (50.4)
Black/African American	52 (44.4)	50 (42.0)
Asian	2 (1.7)	4 (3.4)
American Indian or Alaska native	4 (3.4)	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (0.9)	2 (1.7)
Other	1 (0.9)	2 (1.7)
Baseline BMI (kg/m^2), mean (SD)	33.5 (7.7)	30.8 (8.12)
s-P for eligibility, n (%)		
< 7.5 mg/dL	76 (65.0)	77 (64.7)
≥ 7.5 mg/dL	41 (35.0)	42 (35.3)
Randomized type of phosphate binder, n (%)		
Sevelamer	57 (48.7)	58 (48.7)
Non-sevelamer	60 (51.3)	61 (51.3)

BMI=body mass index; SD=standard deviation; s-P=serum phosphorus.

5.3.2.3 Baseline Disease Characteristics

In the Safety Population, across treatment groups, the mean duration since ESKD diagnosis at baseline was approximately 4.4 years. The majority of patients were receiving hemodialysis, and approximately 10% were undergoing peritoneal dialysis. The mean s-P at baseline was 6.83 mg/dL, with the majority of patients (70.8%) having baseline s-P < 7.5 mg/dL (Table 16).

Table 16: Study 202: Baseline Disease Characteristics (Safety Population)

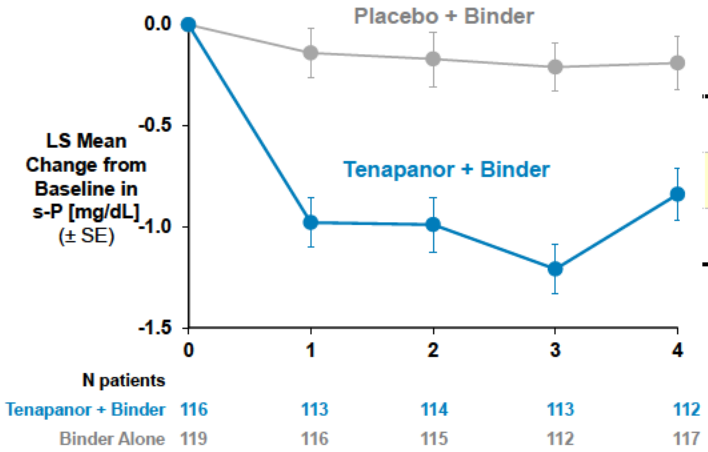
	Tenapanor + Phosphate Binder (N=117)	Placebo + Phosphate Binder (N=119)
Duration since ESKD diagnosis at baseline, years, mean (SD)	4.7 (4.04)	4.1 (4.0)
Type of dialysis		
Hemodialysis	105 (89.7)	107 (89.9)
Peritoneal dialysis	12 (10.3)	12 (10.1)
Duration since first dialysis at baseline, months, mean (SD)	56.6 (48.47)	46.1 (41.37)
Baseline s-P		
< 7.5 mg/dL	87 (74.4)	80 (67.2)
≥ 7.5 mg/dL	30 (25.6)	39 (32.8)
Baseline iFGF23 level (pg/mL), mean (SD)	13,942.3 (15,692.13)	15,436.9 (16,804.22)
Baseline PTH level (pg/mL), mean (SD)	366.5 (231.11)	369.7 (223.17)

BMI=body mass index; ESKD=end-stage kidney disease; iFGF23=intact fibroblast growth factor 23; PTH=parathyroid hormone; SD=standard deviation; s-P=serum phosphorus.

5.3.3 Primary Endpoint – Change from Baseline in s-P at Week 4

Tenapanor treatment in combination with PB met the primary efficacy endpoint, demonstrating a statistically significant (p=0.0004) reduction from baseline in s-P compared with placebo + binder at Week 4. The early onset of s-P lowering effect of tenapanor was observed as early as 1 week (Figure 34).

Figure 34: Study 202: Primary Efficacy Analysis for Primary Endpoint – Change from Baseline in s-P at Week 4 (FAS)

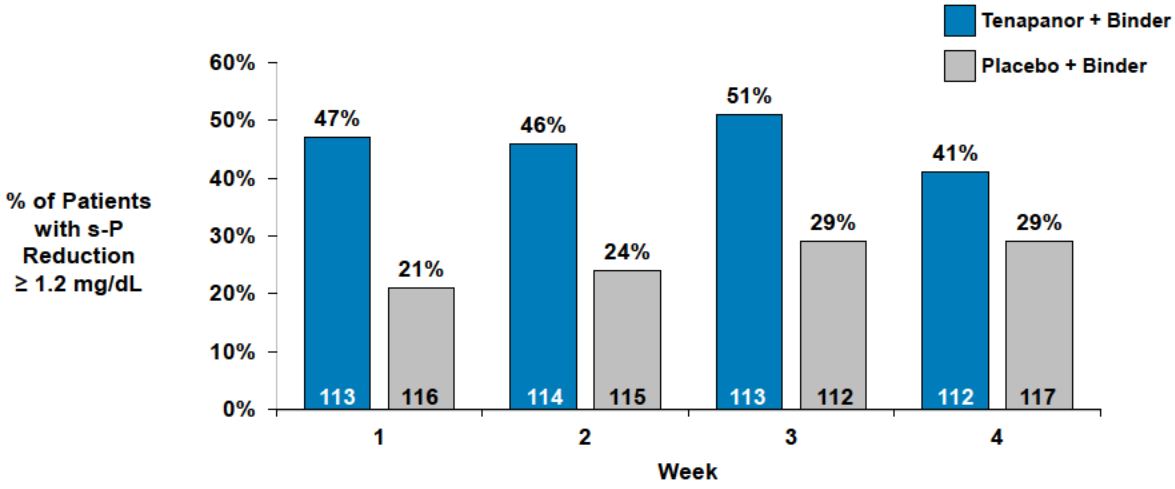


Primary Endpoint	TEN + Binder	PBO + Binder
LS mean Δ from baseline to Week 4	-0.84	-0.19
LS Mean Difference (95% CI)	-0.65 (-1.01, -0.29)	
p-value	p = 0.0004	

The LS means, SEs, CIs, and p-value came from an MMRM model on observed cases.
CI=confidence interval; FAS=Full Analysis Set; LS=least squares; MMRM=mixed-effects model for repeated measures; PBO=placebo; SE=standard error; s-P=serum phosphorus; TEN=tenapanor.

At Week 1 through Week 4, higher proportions of patients achieved an s-P reduction of ≥ 1.2 mg/dL in the tenapanor + binder treatment arm compared with placebo + binder (Figure 35).

Figure 35: Study 202: Proportion of Patients with ≥ 1.2 mg/dL s-P Reduction (FAS)



Note: Patients with missing s-P at a post-baseline visit were excluded from the calculation of the response rate for the corresponding visit.
FAS=Full Analysis Set; s-P=serum phosphorus.

5.3.3.1 Sensitivity Analyses

To assess the robustness of the primary efficacy results, the primary endpoint was also analyzed using the MMRM model applied to the PP Population and Week 4 completers.

Treatment comparisons of the primary efficacy endpoint on the 2 populations were statistically significant in favor of tenapanor (p=0.0002 and p=0.0003, respectively; Table 17), supporting the results of the pre-specified primary efficacy analysis.

Table 17: Study 202: Sensitivity Analyses Using MMRM on Observed Cases for Primary Endpoint – Change from Baseline in s-P at Week 4 (PP and Week 4 Completers)

	LS Mean Estimate (SE)				
	Tenapanor + Phosphate Binder	Placebo + Phosphate Binder	LS Mean Difference (SE)	95% CI	p-value
s-P Change from Baseline at Week 4					
Per Protocol Population	-0.92 (0.136)	-0.20 (0.135)	-0.72 (0.189)	(-1.09, -0.34)	0.0002
Week 4 Completers	-0.85 (0.132)	-0.19 (0.130)	-0.67 (0.183)	(-1.03, -0.31)	0.0003

CI=confidence interval; LS=least squares; MMRM=mixed-effects model for repeated measures; PP=Per Protocol; SE=standard error; s-P=serum phosphorus.

Additional sensitivity analyses were performed to assess the impact of missing data on the primary efficacy results in the FAS, PP population, and Week 4 completers. The reduction from baseline in s-P between the tenapanor and placebo groups was statistically significant across all populations analyzed (Table 18), indicating that missing data were unlikely to have substantially biased the primary results.

Table 18: Study 202: Sensitivity Analyses Using LOCF ANCOVA for Primary Endpoint – Change from Baseline in s-P at Week 4 (FAS, PP, and Week 4 Completers)

	LS Mean Estimate (SE)				
	Tenapanor + Phosphate Binder	Placebo + Phosphate Binder	LS Mean Difference (SE)	95% CI	p-value
s-P Change from Baseline at Week 4					
Full Analysis Set	-0.88 (0.131)	-0.23 (0.131)	-0.66 (0.180)	(-1.01, -0.30)	0.0003
Per Protocol Population	-0.92 (0.137)	-0.20 (0.137)	-0.72 (0.190)	(-1.09, -0.34)	0.0002
Week 4 Completers	-0.88 (0.133)	-0.22 (0.132)	-0.66 (0.183)	(-1.02, -0.30)	0.0004

ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last-observed-carried-forward; PP=Per Protocol; SE=standard error; s-P=serum phosphorus.

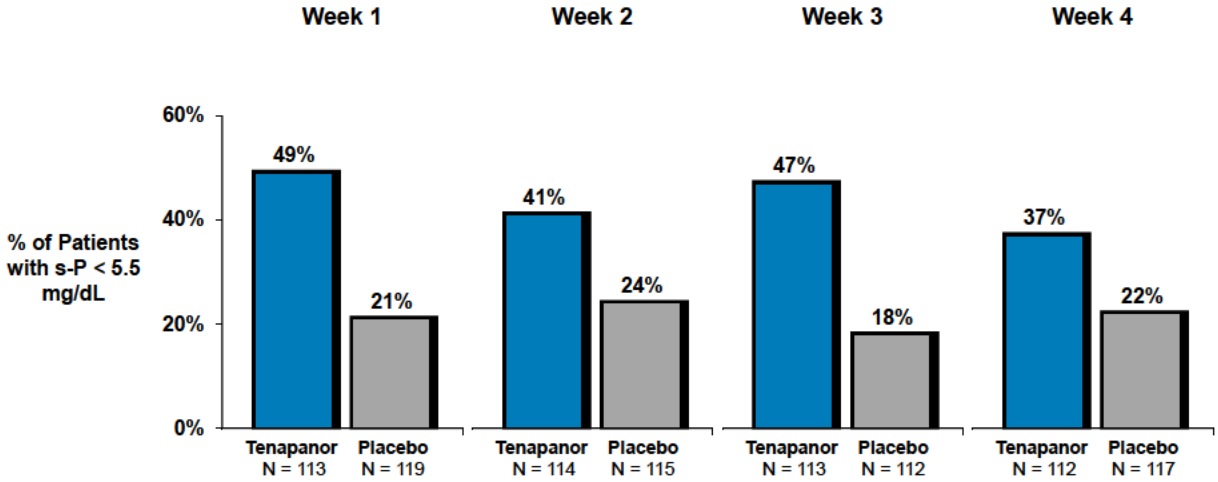
Positive results remained consistent among subgroups defined based on age, sex, race, geographic region, type of maintenance dialysis, baseline s-P, and the type of PB being administered.

5.3.4 Key Secondary Endpoints

5.3.4.1 Proportion of Patients with s-P Response (< 5.5 mg/dL) at Week 4

A significantly higher proportion of patients achieved s-P response at Week 4 in the tenapanor + binder group (37.1%) compared with placebo + binder (21.8%), with a rate difference of 15.2% and a statistically significant association between treatment and s-P response status at Week 4, after adjusting for 2 randomization stratification factors (p=0.0097; Figure 36).

Figure 36: Study 202: Proportion of Patients with s-P Response (< 5.5 mg/dL) (FAS)



FAS=Full Analysis Set; s-P=serum phosphorus.

5.3.4.2 Relative Change from Baseline in iFGF23 at Week 4

The estimated mean relative change from baseline was -24.4% for the tenapanor + binder group and -6.9% for the placebo + binder group, indicating that the addition of tenapanor to existing PB treatment significantly reduced iFGF23 at Week 4 as compared to PB treatment alone. The geometric LS mean value of the ratio of the Week 4 value/Baseline value was 0.756 for tenapanor and 0.931 for placebo, and the ratio of the geometric means (tenapanor/placebo) was estimated as 0.813. The treatment comparison was statistically significant (p=0.0027), supporting the efficacy of tenapanor in reducing iFGF23.

5.3.5 Other Secondary Endpoints

5.3.5.1 Change in s-P at Weeks 1, 2, and 3

Similar to the primary efficacy endpoint of the change from baseline in s-P at Week 4, treatment comparisons of the change from baseline in s-P at Weeks 1, 2, and 3 were all statistically significant, favoring the efficacy of tenapanor in reducing s-P compared to placebo (Figure 34).

5.3.5.2 Change in PTH at Week 4

The LS mean reduction in PTH from baseline in the tenapanor group (-9.3 pg/mL) was numerically greater than in the placebo group (-0.8 pg/mL) at Week 4. However, the treatment difference of 8.5 pg/mL in LS mean reduction between the tenapanor and placebo groups was not statistically significant (p=0.6411).

5.4 Study 401: Long-Term Treatment of Patients Receiving Maintenance Dialysis with Hyperphosphatemia with Tenapanor Alone or in Combination With Sevelamer

Study 401 (NORMALIZE) was an open-label study in eligible patients who completed Study 301 to assess tenapanor alone or in combination with sevelamer to treat to target s-P in patients receiving maintenance dialysis with HP for up to an additional 18 months.

Patients who ended Study 301 on tenapanor could add sevelamer to their regimen if their s-P remained above the normal (4.5 mg/dL) and likewise, patients who ended the study on sevelamer could add tenapanor to their sevelamer dose if the s-P was above the target of 4.5 mg/dL. As the s-P dropped, the sevelamer dose was then lowered based on their s-P following a protocol specified dose-titration schedule.

Study Objectives

The primary objective of Study 401 was to evaluate the ability of tenapanor alone or in combination with sevelamer to achieve s-P concentration within the population reference range of ≥ 2.5 and ≤ 4.5 mg/dL.

Secondary objectives included:

- To compare the s-P lowering effect of tenapanor and sevelamer alone in patients with s-P of > 4.5 mg/dL to patients treated with tenapanor and sevelamer
- To evaluate the effect of tenapanor alone and with sevelamer on the proportion of patients reaching s-P targets, defined as ≤ 4.5 mg/dL
- To evaluate the effect of the addition of tenapanor to patients taking sevelamer on the percentage reduction in the sevelamer dose

Patient Disposition, Demographics, and Baseline Characteristics

A total of 172 patients were enrolled into Study 401 from Study 301: 61 patients from the TEN-02-301 sevelamer carbonate arm and 111 patients from the TEN-02-301 tenapanor arm. A total of 48 patients (27.9%) discontinued from the study: 26 patients (42.6%) in the sevelamer group and 22 patients (19.8%) in the tenapanor group. The most common primary reasons for discontinuation from the study were death, withdrawal by patient, and “other” reasons (12–14 [7–8%] patients each). Three patients in each group discontinued due to an AE.

Demographics and baseline characteristics were similar to Study 301 (as described in Sections 5.2.2.2 and 5.2.2.3) and generally well balanced between treatment groups. The mean s-P improved from 7.27 mg/dL at the baseline of Study 301 to 5.81 mg/dL prior to entering Study 401, with a mean reduction of 1.46 mg/dL on average after 1 year of treatment in Study 301 (tenapanor: 1.53 mg/dL; sevelamer carbonate: 1.34 mg/dL).

Efficacy Results

The proportion of patients achieving s-P ≤ 4.5 mg/dL consistently doubled from baseline to Week 1 through Month 6 post-baseline visits, ranging between 38.7% and 47.4% of patients. Based on the last s-P assessment during the study, 34.5% (59/171) of patients achieved s-P ≤ 4.5 mg/dL, including 39.1% treated with tenapanor alone, 36.4% treated with tenapanor with ≤ 3 sevelamer carbonate tablets daily, and 32.3% treated with tenapanor with > 3 sevelamer carbonate tablets daily.

The proportion of patients achieving s-P < 5.5 mg/dL increased from baseline by approximately 50% at Week 1 through Month 6 post-baseline visits, ranging between 61.3% and 68.6%. Based on the last s-P assessment during the study, 52.0% of patients (89/171) achieved s-P < 5.5 mg/dL, including 52.2% taking tenapanor alone, 50.9% taking tenapanor combined with ≤ 3 sevelamer carbonate tablets, and 52.7% taking tenapanor combined with > 3 sevelamer carbonate tablets.

5.5 Study 402: Long-Term Treatment of Patients Receiving Maintenance Dialysis with Hyperphosphatemia with Tenapanor Treatment Alone or in Combination With Phosphate Binder

Study 402 (OPTIMIZE) was a randomized, open-label study to evaluate different methods of initiating tenapanor therapy in patients receiving maintenance dialysis with HP, when patients were either PB-naïve or on PB therapy (Edelstein et al 2022a; Edelstein et al 2022b). The primary objective was to evaluate the effect of tenapanor alone or in combination with PB to achieve target s-P of ≤ 5.5 mg/dL. The proportion of patients achieving s-P ≤ 4.5 mg/dL and patient-reported outcomes were also investigated.

After 10 weeks of treatment, mean change from baseline in s-P was -0.93 mg/dL for patients who initiated tenapanor 30 mg BID and stopped PB therapy (Cohort 1) and -0.98 mg/dL for patients who initiated tenapanor 30 mg BID and reduced PB treatment by ≥ 50% (Cohort 2), with > 35% of patients achieving target s-P (≤ 5.5 mg/dL) and > 10% achieving normal s-P (≤ 4.5 mg/dL) in each cohort.

Moreover, the mean (SD) number of PB pills taken per day was reduced from 8.8 (3.8) and 9.3 (4.0) at baseline for cohorts 1 and 2, respectively, to 5.5 (3.6) and 8.0 (4.2) at Week 10. Patients from Cohort 3 were PB-naïve and after 10 weeks of treatment with tenapanor, mean change from baseline in s-P was −0.93 mg/dL, with > 60% achieving target s-P and 40% achieving normal s-P. Among the 243 patients in Cohort 1 and 2 combined, 205 reported an improved s-P management routine during

the study vs previous therapy. The primary reasons for this improved perception of s-P management were reduced medication burden and bowel movement changes (e.g., bowel movement form and frequency). Although increased stool frequency and consistency were observed, a low percentage of patients (< 7%) prematurely discontinued tenapanor due to diarrhea.

5.6 Summary of Clinical Efficacy and Clinical Utility of Tenapanor

The results from the clinical development program have demonstrated that tenapanor lowers s-P in patients receiving maintenance dialysis, which is an accepted surrogate endpoint upon which several PBs have been approved. The Phase 2B study identified the appropriate dose of tenapanor for Phase 3, and all 3 tenapanor Phase 3 studies met their pre-specified primary efficacy endpoint:

- In the FAS of the Phase 2B dose-selection study (D5613C00001), tenapanor reduced s-P in a dose-dependent manner, with the most pronounced effect, a placebo-adjusted mean sP reduction of 1.4 mg/dL seen with 30 mg BID.
- In the EAS of the 12-week monotherapy RW study (201), the mean s-P reduction was 2.6 mg/dL during the RTP and the placebo-adjusted LS mean s-P change during the RWP was -0.82 mg/dL, supporting the efficacy of tenapanor.
- In the EAS of the 52-week monotherapy RW study (301), the mean s-P reduction was 2.6 mg/dL during the RTP and the placebo-adjusted LS mean s-P change during the RWP was -1.37 mg/dL, supporting the efficacy of tenapanor.
- In the FAS of the 4-week study of tenapanor in combination with PB(s) (202), the LS mean change from baseline in s-P was 0.65 mg/dL lower for the tenapanor + binder group compared to the placebo + binder group, and nearly twice as many patients achieved s-P < 5.5 in the tenapanor + binder group compared with the placebo + binder group.
- The onset of s-P lowering effect of tenapanor was observed as early as 1 week on treatment and was sustained throughout the RTP in each pivotal study.

Additional analyses support the conclusion that tenapanor provides clinically meaningful s-P lowering, showing that patients who respond to tenapanor can be identified early in treatment, and the treatment response achieved is typically maintained with continued treatment. As shown in Section 1.5.5, 53% of tenapanor patients achieved a ≥ 1.2 mg/dL reduction in s-P, and 46% achieved a ≥ 1.5 mg/dL reduction in Study 301 (Figure 10), which is in the range FDA has referenced for PBs (Figure 2). These results were consistent across the Phase 3 studies (Figure 11). Furthermore, tenapanor-treated patients had reductions in iFGF23, demonstrating the biological significance of the s-P lowering of tenapanor (Figure 31).

Although sevelamer was included in Study 301 as a safety comparator, analysis of the change from baseline in s-P showed that more sevelamer-treated patients than tenapanor-treated patients achieved ≥ 1.2 mg/dL s-P reduction at Week 26. However,

for patients who responded to either therapy, the magnitude of s-P lowering was very similar between groups (Figure 12). These findings confirm that patients who have a biologic response to tenapanor achieve s-P lowering similar to that seen with sevelamer, an FDA-approved PB.

Finally, the majority (79%) of patients identified as early responders (i.e., s-P reduction ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4) were also identified as late responders (i.e., s-P reduction ≥ 1.2 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26), and 66% of those determined not to respond early also did not respond later in treatment (Figure 17). These data support that patients who respond to tenapanor can generally be identified early and tend to remain responsive, while patients who do not respond can also be identified early in treatment. These data, coupled with well-established clinical guidelines and practice, will allow nephrologists to identify patients who respond to tenapanor therapy and avoid unnecessary prolonged use.

Taken together, these efficacy findings indicate that tenapanor can be an important additional therapeutic tool that fits into the current treatment paradigm for managing patients with HP requiring maintenance dialysis.

6 CLINICAL SAFETY

Summary

- In the integrated safety summary, 934 patients receiving maintenance dialysis have received daily tenapanor at any dose, and 632 patients receiving maintenance dialysis have received tenapanor at the dosage intended for clinical use.
- In Study 301, a higher percentage of patients in the tenapanor group experienced AEs and AEs leading to treatment discontinuation compared to the sevelamer group during the 26-week RTP; however, the sevelamer group is an enriched group, as these patients were treated with sevelamer prior to the start of study treatment such that most had already demonstrated tolerance for sevelamer.
- Diarrhea was the most commonly reported AE during the 26-week RTP of Study 301, occurring in 53% of patients randomized to tenapanor and 7% of sevelamer patients. In patients randomized to tenapanor:
    - Diarrhea was predominantly mild to moderate in severity and was not treatment-limiting in the majority of cases, with 16% discontinuing tenapanor due to diarrhea reported during the 26-week RTP.
    - Of patients who discontinued treatment due to AEs of diarrhea, approximately 75% started to experience diarrhea within the first 2 weeks of treatment.
    - During the 26-week RTP, 6% of patients experienced severe diarrhea, and 1 patient had a temporally associated event of dehydration leading to hospitalization.
    - The incidence of diarrhea decreased during the 12-week RWP and 14-week safety extension period.
- The overall incidence of SAEs was higher in the sevelamer group than the tenapanor group for all periods of Study 301.
- In Study 202, where tenapanor was assessed in combination with PBs, a higher overall incidence of AE was observed in patients treated with tenapanor, while the overall incidence rates of SAEs and AEs leading to discontinuation were comparable between groups.
- As in Study 301, the most commonly reported AE in Study 202 was diarrhea, although only 3% of patients in the tenapanor group and 2% in the placebo group experienced AEs of diarrhea leading to discontinuation.
- In the integrated safety summary, 15 (1.6%) deaths occurred in patients randomized to tenapanor, none of which were considered by the Investigator to be related to study treatment, and 5 (2.0%) deaths occurred in PB-treated patients.

6.1 Safety Presentation

Safety is presented for Study 301 (26-week RTP, 12-week RWP, and 14-week safety extension), Study 202, and all tenapanor-treated patients separately due to the differences in study designs and treatment administration. Study 301 provides the most relevant active-controlled comparison between tenapanor and PB, during the 26-week RTP and vs placebo in the RWP. It is important to note, however, that the sevelamer group is considered to be enriched, as 63.5% of the group were treated with sevelamer prior to the start of study treatment and therefore most patients in the sevelamer arm had already demonstrated tolerance for sevelamer. Overall, Study 301 provides 52 -weeks of long-term comparison of tenapanor to sevelamer.

Study 202 provides safety data for tenapanor when used with a PB compared to PB alone (i.e., placebo plus PB).

Finally, the CKD on Maintenance Dialysis Safety Set provides data for all patients who received any dose(s) of tenapanor in the Phase 2 and Phase 3 studies (i.e., D5611C00001, D5613C00001, Study 201, Study 301, and Study 202). To account for differences in treatment duration among the 5 studies above, safety data collected up to the first 12 weeks of treatment were pooled for integrated summaries of safety data by pooled treatment group.

Unless specified otherwise, AE summaries presented in this document are for treatment-emergent AEs (TEAEs).

6.2 Treatment Exposure

Overall, in the CKD on Maintenance Dialysis Safety Set, 632 patients receiving maintenance dialysis have been treated with tenapanor at the dosage intended for clinical use, with 607 of these patients coming from the pivotal Phase 3 studies. Based on the integrated data from the analysis period of up to 12 weeks, 934 patients receiving maintenance dialysis have been treated with daily tenapanor doses of 2–30 mg, 60 mg (administered as 30 mg BID), or 90–120 mg for a total of 141.3 person-years (Table 19). The number of patients receiving maintenance dialysis with at least 6-month and 12-month exposure to tenapanor is approximately 263 and 83, respectively. As of March 2020, 172 patients from Study 301 have entered Study 401, and 18 patients had discontinued from Study 401. Of the 172 enrolled patients, 62 patients were treated with sevelamer in Study 301 and started the treatment with tenapanor in Study 401.

Table 19: Integrated Summary of Overall Exposure to Tenapanor During Analysis Period (Up to the First 12 Weeks of Treatment) (CKD on Maintenance Dialysis Safety Analysis Set)

	Tenapanor					
	2–30 mg[a] (N=257)	60 mg[b] (N=515)	90–120 mg[c] (N=45)	60 mg[b] + Phosphate Binders (N=117)	Phosphate Binders (N=256)	Placebo (N=69)
Mean duration of exposure (weeks ± SD)	6.23 ± 3.4	9.99 ± 3.8	3.78 ± 0.8	3.93 ± 0.5	8.3 ± 4.2	3.97 ± 0.5
Duration of exposure category, n (%)						
≤ 2 weeks	21 (8.2)	27 (5.2)	3 (6.7)	3 (2.6)	2 (0.8)	0
> 2 – ≤ 4 weeks	36 (14.0)	36 (7.0)	28 (62.2)	83 (70.9)	83 (32.4)	32 (46.4)
> 4 – ≤ 8 weeks	145 (56.4)	75 (14.6)	14 (31.1)	31 (26.5)	37 (14.5)	37 (53.6)
> 8 weeks	55 (21.4)	377 (73.2)	0	0	134 (52.3)	0
Overall exposure, person-years	30.67	98.56	3.26	8.8	40.74	5.25

[a] Patients received either 1 mg BID, 3 mg QD, 3 mg BID, 10 mg BID, or 30 mg QD
[b] All patients received 30 mg BID, from 30 mg BID (max) to ≥ 10 mg BID
[c] Patients received 45–90 mg BID
Patient data from study TEN-02-301 are restricted to the first 12 weeks in the 26-week RTP to better align treatment exposure with that of the other studies in the Core pooling group.
Overall exposure in person-years is defined as the sum of duration of exposure during on-treatment period in days (for all treated patients)/365.25.
The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
SD=standard deviation

6.2.1 Exposure in Study 301

During the 26-week RTP, mean exposure was 171.4 days for sevelamer and 137.2 days for tenapanor (Table 20). During the 12-week RWP, mean exposure was 83.8 days for sevelamer and 74.7 days for tenapanor. During the 14-week safety extension period, mean exposure was 98.2 days for sevelamer and 94.4 days for tenapanor.

Table 20: Study 301: Summary of Study Drug Exposure (Safety Analysis Sets)

	26-Week Randomized Treatment Period		12-Week Randomized Withdrawal Period			14-Week Safety Extension Period	
	Tenapanor (N=419)	Sevelamer (N=137)	Tenapanor (N=125)	Placebo (N=126)	Sevelamer (N=116)	Tenapanor (N=220)	Sevelamer (N=110)
Exposure (Days)[a]							
n	419	137	125	126	116	220	110
Mean	137.2	171.4	74.7	74.8	83.8	94.4	98.2
SD	67.87	35.31	23.32	22.03	11.18	17.81	10.94
Median	182.0	182.0	84.0	84.0	85.0	98.0	98.0
Minimum	1	1	1	1	10	1	37
Maximum	215	199	112	104	99	121	137
Exposure category, n (%)							
≤ 2 weeks	37 (8.8)	3 (2.2)	5 (4.0)	2 (1.6)	2 (1.7)	3 (1.4)	0 (0.0)
> 2 – ≤ 4 weeks	20 (4.8)	0 (0.0)	5 (4.0)	9 (7.1)	0 (0.0)	3 (1.4)	0 (0.0)
> 4 – ≤ 8 weeks	34 (8.1)	0 (0.0)	14 (11.2)	12 (9.5)	1 (0.9)	8 (3.6)	2 (1.8)
> 8 weeks	-	-	101 (80.8)	103 (81.7)	113 (97.4)	-	-
> 8 – ≤ 12 weeks	19 (4.5)	4 (2.9)	-	-	-	7 (3.2)	2 (1.8)
> 12 weeks	309 (73.7)	130 (94.9)	-	-	-	199 (90.5)	106 (96.4)

[a] Exposure=treatment end date of the study period – treatment start date of the study period + 1. If the date of the last dose of study drug during the study period was missing, the treatment end date of the study period was the last visit date in the study period - 1. Note that the exposure calculation was intended to describe the length of time a patient was exposed to study drug, and therefore, did not take study drug interruptions into account.
SD=standard deviation.

6.2.2 Exposure in Study 202

In the Safety Population of Study 202, 117 patients received tenapanor for a mean of 27.5 days. The mean final dose of tenapanor at the end of the RTP for the tenapanor group was 24.1 mg BID.

6.3 Safety in Study 301

Table 21 presents an overall summary of AEs for the Safety Analysis Sets of the 26-week RTP, the 12-week RWP, and the 14-week safety extension period (for a total of 52 weeks). Patients were randomized (3:1) to tenapanor vs sevelamer. Overall, a larger proportion of patients experienced AEs during the 26-week RTP than during the 12-week RWP or the 14-week safety extension period.

During the 26-week RTP, 80% of patients in the tenapanor group and 64% of patients in the sevelamer group experienced AEs, 17% of patients in the tenapanor group and 23% of patients in the sevelamer group experienced SAEs, and 24% of patients in the tenapanor group and about 1% of patients in the sevelamer group experienced AEs that led to study drug discontinuation. Seven patients (1.7%) in the tenapanor group experienced an AE leading to death and 3 patients (2.2%) in the sevelamer group experienced an AE leading to death during the 26-week RTP (additional details on deaths are provided in Section 6.5.4).

During the 12-week RWP, 46% of patients in the tenapanor group, 56% of patients in the placebo group, and 41% of patients in the sevelamer group experienced AEs, 11% of patients in the tenapanor group, 10% of patients in the placebo group, and 16% of patients in the sevelamer group experienced SAEs, and 9% of patients in the tenapanor group, 13% of patients in the placebo group, and 1% of patients in the sevelamer group experienced AEs leading to study drug discontinuation. One (0.8%) patient in the tenapanor group, 1 (0.8%) patient in the placebo group and 1 patient (0.9%) in the sevelamer group experienced an AE leading to death during the 12-week RWP (additional details on deaths are provided in Section 6.5.4).

During the 14-week safety extension period, 46% of patients in the tenapanor group and 39% of patients in the sevelamer group experienced AEs, 16% of patients in the tenapanor group and 20% of patients in the sevelamer group experienced SAEs, and 1% of patients in the tenapanor group and no patients in the sevelamer group experienced AEs that led to study drug discontinuation. Four patients (1.8%) in the tenapanor group and 1 patient (0.9%) in the sevelamer group experienced an AE leading to death during the 14-week safety extension period (additional details on deaths are provided in Section 6.5.4). No deaths were considered related to study drug by Investigators.

Overall, although a larger proportion of patients experienced AEs in the tenapanor group than the sevelamer group, the tenapanor group had a lower rate of SAEs.

Table 21: Study 301: Overall Summary of Adverse Events (Safety Analysis Set)

	26-Week Randomized Treatment Period		12-Week Randomized Withdrawal Period			14-Week Safety Extension Period	
Patients with any, n (%)	Tenapanor (N=419)	Sevelamer (N=137)	Tenapanor (N=125)	Placebo (N=126)	Sevelamer (N=116)	Tenapanor (N=220)	Sevelamer (N=110)
AE	337 (80.4)	88 (64.2)	58 (46.4)	70 (55.6)	48 (41.4)	102 (46.4)	43 (39.1)
AE leading to study drug discontinuation	102 (24.3)	2 (1.5)	11 (8.8)	17 (13.5)	1 (0.9)	3 (1.4)	0 (0.0)
SAE	73 (17.4)	32 (23.4)	14 (11.2)	13 (10.3)	19 (16.4)	35 (15.9)	22 (20.0)
AE leading to hospitalization	73 (17.4)	32 (23.4)	13 (10.4)	13 (10.3)	19 (16.4)	34 (15.5)	21 (19.1)
Death[a]	7 (1.7)	3 (2.2)	1 (0.8)	1 (0.8)	1 (0.9)	4 (1.8)	1 (0.9)

[a] All deaths, treatment-emergent or not, are included in the summary.
SAE=serious adverse event.

6.3.1 Common Adverse Events

Table 22 presents a summary of AEs (that occurred in ≥ 5% of patients overall in any treatment group) for the Safety Analysis Sets of the 26-week RTP, the 12-week RWP, and the 14-week safety extension period.

Overall, the most common AEs in either treatment arm occurred more frequently during the 26-week RTP and included diarrhea (53% of patients in the tenapanor group and 7% of patients in the sevelamer group), HP (6% of patients in the tenapanor group and 2% of patients in the sevelamer group), and hypertension (4% of patients in the tenapanor group and 5% of patients in the sevelamer group). It is important to note that HP was recorded as an AE due to worsening of the underlying condition as opposed to an adverse reaction due to study drug.

During the first 3 months of the 26-week RTP, diarrhea was reported in 50% of patients in the tenapanor group and 5% of patients in the sevelamer group. Comparatively, during the second 3 months of the 26-week RTP, diarrhea was reported in 5% of patients in the tenapanor group and 3% of patients in the sevelamer group. The incidence of diarrhea decreased during the 12-week RWP (4% of patients in the tenapanor group, 2% in the placebo group, and 4% of patients in the sevelamer group) and during the 14-week safety extension period (7% of patients in the tenapanor group and no patients in the sevelamer group).

Importantly, the remaining most common AEs, including hypertension and falls, occurred more frequently in the sevelamer arm vs tenapanor during the 26-week RTP.

Table 22: Study 301: Summary of Adverse Events (≥ 5% of Patients Overall in Any Treatment Group) (Safety Analysis Set)

	26-Week Randomized Treatment Period		12-Week Randomized Withdrawal Period			14-Week Safety Extension Period	
Preferred Term	Tenapanor (N=419) n (%)	Sevelamer (N=137) n (%)	Tenapanor (N=125) n (%)	Placebo (N=126) n (%)	Sevelamer (N=116) n (%)	Tenapanor (N=220) n (%)	Sevelamer (N=110) n (%)
Patients with any AE	337 (80.4)	88 (64.2)	58 (46.4)	70 (55.6)	48 (41.4)	102 (46.4)	43 (39.1)
Diarrhea	222 (53.0)	10 (7.3)	5 (4.0)	2 (1.6)	5 (4.3)	15 (6.8)	0 (0.0)
Hyperphosphatemia	27 (6.4)	3 (2.2)	7 (5.6)	15 (11.9)	0 (0.0)	3 (1.4)	0 (0.0)
Hypertension	15 (3.6)	7 (5.1)	2 (1.6)	0	2 (1.7)	3 (1.4)	2 (1.8)
Fall	11 (2.6)	10 (7.3)	2 (1.6)	2 (1.6)	1 (0.9)	2 (0.9)	4 (3.6)
Cough	9 (2.1)	9 (6.6)	1 (0.8)	1 (0.8)	0 (0.0)	3 (1.4)	2 (1.8)
Fluid overload	8 (1.9)	7 (5.1)	0 (0.0)	1 (0.8)	3 (2.6)	4 (1.8)	1 (0.9)
AV fistula thrombosis	6 (1.4)	7 (5.1)	1 (0.8)	1 (0.8)	2 (1.7)	0 (0.0)	2 (1.8)
Pneumonia	4 (1.0)	7 (5.1)	1 (0.8)	0	2 (1.7)	3 (1.4)	4 (3.6)

AE=adverse event; AV=arteriovenous fistula.

6.3.2 Serious Adverse Events

Table 23 presents a summary of SAEs (≥ 1% of patients overall in any treatment period) for the Safety Analysis Sets of the 26-week RTP, the 12-week RWP, and the 14-week safety extension period.

Overall, the incidence of SAEs, including those leading to hospitalizations, was generally similar across treatment groups and slightly higher in the sevelamer group for all 3 treatment periods. During the 26-week RTP, 17% of patients in the tenapanor group and 23% of patients in the sevelamer group experienced SAEs. During the 12-week RWP, 11% of patients in the tenapanor group, 10% of patients in the placebo group, and 16% of patients in the sevelamer group experienced SAEs. During the 14-week safety extension period, 16% of patients in the tenapanor group and 20% of patients in the sevelamer group experienced SAEs.

Table 23: Study 301: Summary of Serious Adverse Events (≥ 1% Patients Overall in Any Treatment Period) (Safety Analysis Set)

	26-Week Randomized Treatment Period		12-Week Randomized Withdrawal Period			14-Week Safety Extension Period	
Preferred Term, n (%)	Tenapanor (N=419)	Sevelamer (N=137)	Tenapanor (N=125)	Placebo (N=126)	Sevelamer (N=116)	Tenapanor (N=220)	Sevelamer (N=110)
Patients with any SAE	73 (17.4)	32 (23.4)	14 (11.2)	13 (10.3)	19 (16.4)	35 (15.9)	22 (20.0)
Acute respiratory failure	7 (1.7)	1 (0.7)	0 (0.0)	1 (0.8)	3 (2.6)	1 (0.5)	1 (0.9)
Fluid overload	5 (1.2)	4 (2.9)	0 (0.0)	1 (0.8)	1 (0.9)	2 (0.9)	1 (0.9)
Hyperkalemia	5 (1.2)	3 (2.2)	0 (0.0)	0 (0.0)	2 (1.7)	NA	NA
Cellulitis	4 (1.0)	2 (1.5)	0 (0.0)	1 (0.8)	3 (2.6)	2 (0.9)	0 (0.0)
Pneumonia	3 (0.7)	5 (3.6)	1 (0.8)	0 (0.0)	1 (0.9)	2 (0.9)	2 (1.8)
Acute myocardial infarction	3 (0.7)	3 (2.2)	0 (0.0)	0 (0.0)	2 (1.7)	0 (0.0)	2 (1.8)
Sepsis	2 (0.5)	2 (1.5)	0 (0.0)	1 (0.8)	0 (0.0)	4 (1.8)	0 (0.0)
Atrial fibrillation	2 (0.5)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.8)	0 (0.0)

NA=not applicable; SAE=serious adverse event.

6.3.3 Adverse Events Leading to Discontinuation

A higher proportion of patients randomized to tenapanor experienced AEs leading to study drug discontinuation compared to sevelamer during the 52-week study period, and most occurred during the 26-week RTP (Table 24). This difference in rate of AEs leading to discontinuation was expected, as approximately 65% of patients had been treated with sevelamer prior to the start of study treatment and would be expected to have a higher tolerability to side effects.

Diarrhea was the most common AE leading to treatment discontinuation during the 26-week RTP (16% of patients in the tenapanor group and 1% in the sevelamer group).

Table 24: Study 301: Summary of Most Common Adverse Events (Events in > 2 Patients in Any Treatment Period) Leading to Study Drug Discontinuation (Safety Analysis Set)

	26-Week Randomized Treatment Period		12-Week Randomized Withdrawal Period			14-Week Safety Extension Period	
Preferred Term, n (%)	Tenapanor (N=419)	Sevelamer (N=137)	Tenapanor (N=125)	Placebo (N=126)	Sevelamer (N=116)	Tenapanor (N=220)	Sevelamer (N=110)
Patients with any AE leading to study drug discontinuation	102 (24.3)	2 (1.5)	11 (8.8)	17 (13.5)	1 (0.9)	3 (1.4)	0
Diarrhea	65 (15.5)	1 (0.7)	1 (0.8)	0	0	0	0
Hyperphosphatemia	25 (6.0)	1 (0.7)	7 (5.6)	15 (11.9)	0	1 (0.5)	0
Hypophosphatemia	5 (1.2)	0	1 (0.8)	1 (0.8)	0	0	0
Abdominal discomfort	2 (0.5)	0	0	0	0	0	0

AE=adverse event.

6.4 Safety in Study 202

In total, 51% of patients in the tenapanor group and 28% of patients in the placebo group experienced AEs, 3% of patients in the tenapanor group and 4% of patients in the placebo group experienced SAEs, and 4% of patients in the tenapanor group and 2% of patients in the placebo group discontinued study medication due to AEs. No patients died during the study.

Table 25: Study 202: Overall Summary of Adverse Events (Safety Population)

Patients with any, n (%)	Tenapanor (N=117)	Placebo (N=119)
AE	60 (51.3)	33 (27.7)
SAE[a]	3 (2.6)	5 (4.2)
AE leading to study drug discontinuation[b]	5 (4.3)	2 (1.7)
Death	0	0

[a] Serious adverse events discussed in the safety analysis refer to treatment-emergent AEs only, not those that occurred prior to the treatment period.
[b] Adverse events leading to study medication discontinuation were those with "Drug Withdrawn" as the action taken with study medication.
AE=adverse event; SAE=serious adverse event.

6.4.1 Common Adverse Events

The most common System Organ Class (SOC) of AEs was GI disorders, affecting 44% of patients in the tenapanor group and 14% of patients in the placebo group. The most frequently reported AEs in the tenapanor group were diarrhea (43%) and nausea (5%).

Table 26: Study 202: Summary of Adverse Events (≥ 3% of Patients in any Treatment Group) (Safety Population)

System Organ Class Preferred Term, n (%)	Tenapanor (N=117)	Placebo (N=119)
Patients with any AE	60 (51.3)	33 (27.7)
Gastrointestinal disorders	51 (43.6)	17 (14.3)
Diarrhea	50 (42.7)	8 (6.7)
Nausea	6 (5.1)	3 (2.5)
Vomiting	3 (2.6)	4 (3.4)

AE = adverse event.

6.4.2 Serious Adverse Events

In total, 3% of patients in the tenapanor group and 4% of patients in the placebo group experienced an SAE during the study. The SOC of respiratory, thoracic, and mediastinal disorders was the only SOC with > 1 patient. In the tenapanor group, 1 (0.9%) patient experienced acute pulmonary edema and 1 (0.9%) patient experienced pulmonary edema.

Table 27: Study 202: Summary of Serious Adverse Events (Safety Population)

System Organ Class Preferred Term, n (%)	Tenapanor (N=117)	Placebo (N=119)
Patients with any SAE	3 (2.6)	5 (4.2)
Respiratory, thoracic, and mediastinal disorders	2 (1.7)	2 (1.7)
Acute pulmonary edema	1 (0.9)	1 (0.8)
Acute respiratory failure	0 (0.0)	1 (0.8)
Dyspnea	0 (0.0)	1 (0.8)
Pneumothorax	0 (0.0)	1 (0.8)
Pulmonary edema	1 (0.9)	0 (0.0)
Cardiac disorders	1 (0.9)	1 (0.8)
Angina pectoris	0 (0.0)	1 (0.8)
Cardiorespiratory arrest	1 (0.9)	0 (0.0)
Nodal arrhythmia	0 (0.0)	1 (0.8)
Infections and infestations	1 (0.9)	1 (0.8)
Diverticulitis	1 (0.9)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.8)
Gastrointestinal disorders	1 (0.9)	0 (0.0)
Vomiting	1 (0.9)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (0.8)
Noncardiac chest pain	0 (0.0)	1 (0.8)
Injury, poisoning, and procedural complications	0 (0.0)	1 (0.8)
Arteriovenous fistula aneurysm	0 (0.0)	1 (0.8)
Investigations	1 (0.9)	0 (0.0)
Troponin increased	1 (0.9)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.8)
Fluid overload	0 (0.0)	1 (0.8)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.8)
Myalgia	0 (0.0)	1 (0.8)
Nervous system disorders	0 (0.0)	1 (0.8)
Lacunar infarction	0 (0.0)	1 (0.8)

6.4.3 Adverse Events Leading to Discontinuation

The most common AE that led to study drug discontinuation was diarrhea in both treatment groups (2 patients (1.7%) in the placebo group and 3 patients (2.6%) in the tenapanor group). Additionally, 2 patients in the tenapanor group reported AEs of myocardial infarction and hypotension that led to study drug discontinuation.

6.5 Safety in the CKD on Maintenance Dialysis Safety Set

Overall, among the 934 tenapanor-treated patients in the CKD on Maintenance Dialysis Safety Set, 67% experienced AEs (Table 28). Most AEs were mild to moderate in severity, and 14% of tenapanor-treated patients experienced severe AEs. Nine percent of tenapanor-treated patients experienced SAEs, and 17% discontinued study drug due to AE(s). Six (0.6%) tenapanor-treated patients experienced a TEAE leading to death (details in Section 6.5.4**).**

Table 28: Integrated Overall Summary of Adverse Events (CKD on Maintenance Dialysis Safety Analysis Set)

Patients with any, n (%)	All Tenapanor Patients[a] (N=934)
AE	628 (67.2)
Severe AE	128 (13.7)
SAE	81 (8.7)
AE Leading to Death	6 (0.6)
AE Leading to Study Drug Discontinuation	158 (16.9)

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202 AEs occurring during the on-treatment phase are summarized. The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
AE=adverse event; CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period; SAE=serious adverse event.

6.5.1 Common Adverse Events

Diarrhea was the most common AE reported in 46% of the 934 tenapanor-treated patients in the CKD on Maintenance Dialysis Safety Set. Details on diarrhea are provided in Section 6.6.1. Nausea, vomiting, and hyperphosphatemia were the only other AEs reported in ≥ 2% of tenapanor-treated patients.

Table 29: Integrated Summary of Common Adverse Events Reported by ≥ 2% Tenapanor-Treated Patients (CKD on Maintenance Dialysis Safety Analysis Set)

System Organ Class Preferred Term, n (%)	All Tenapanor Patients[a] (N=934)
Patients with any AE	628 (67.2)
Gastrointestinal Disorders	474 (50.7)
Diarrhea	428 (45.8)
Nausea	26 (2.8)
Vomiting	25 (2.7)
Metabolism and nutrition disorders	100 (10.7)
Hyperphosphatemia	35 (3.7)

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202 AEs occurring during the on-treatment phase are summarized. The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
AE=adverse event; CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period.

6.5.2 Serious Adverse Events

SAEs were recorded in 81 (8.7%) of the 934 tenapanor-treated patients in the CKD on Maintenance Dialysis Safety Set. The most frequently reported SAEs were classified in the Infections and infestations SOC (2.9% of tenapanor-treated patients).

Table 30: Integrated Summary of Serious Adverse Events (≥ 3 Tenapanor-Treated Patients) (CKD on Maintenance Dialysis Safety Analysis Set)

Preferred Term, n (%)	All Tenapanor Patients[a] (N=934)
Patients with any SAE	81 (8.7%)
Fluid overload	8 (0.9)
Osteomyelitis	5 (0.5)
Pneumonia	5 (0.5)
Acute respiratory failure	4 (0.4)
Cardiac arrest	4 (0.4)
Acute myocardial infarction	3 (0.3)
Cardiac failure, congestive	3 (0.3)
Diarrhea	3 (0.3)
Sepsis	3 (0.3)
Septic shock	3 (0.3)

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202
SAEs occurring during the on-treatment phase are summarized. The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period
SAE=serious adverse event.

6.5.3 Adverse Events Leading to Discontinuation

AEs leading to study drug discontinuation were recorded in 16.9% of the 934 tenapanor-treated patients in the CKD on Maintenance Dialysis Safety Set. The most commonly reported AE leading to study drug discontinuation was diarrhea (11%) followed by hyperphosphatemia (3%). Additional details on AEs of diarrhea are provided in Section 6.6.1.

Table 31: Integrated Summary of Adverse Events Leading to Study Drug Discontinuation (≥ 2 Tenapanor-Treated Patient) (CKD on Maintenance Dialysis Safety Analysis Set)

System Organ Class Preferred Term, n (%)	All Tenapanor Patients[a] (N=934)
Patients with any AE leading to study drug discontinuation	158 (16.9)
Gastrointestinal Disorders	112 (12.0)
Diarrhea	102 (10.9)
Abdominal pain	4 (0.4)
Anal incontinence	3 (0.3)
Nausea	3 (0.3)
Abdominal pain	2 (0.2)
Hemorrhoidal hemorrhage	2 (0.2)
Metabolism and nutrition disorders	37 (3.0)
Hyperphosphatemia	28 (3.0)
hypophosphatemia	6 (0.6)
Cardiac disorders	5 (0.5)
Cardiac arrest	3 (0.3)
General disorders and administration site conditions	4 (0.4)
Asthenia	2 (0.2)
Nervous System disorders	4 (0.4)
Respiratory, thoracic and mediastinal disorders	3 (0.3)
Skin and subcutaneous tissue disorders	3 (0.3)
Pruritus	2 (0.2)
Vascular disorders	3 (0.3)
Infections and infestations	2 (0.2)
Septic shock	2 (0.2)
Investigations	2 (0.2)

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202.
AEs occurring during the on-treatment phase which led to study drug discontinuation are summarized. The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
AE=adverse event; CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Withdrawal Period.

6.5.4 Deaths

A total of 20 deaths occurred to the CKD on Maintenance Dialysis Safety Set, with 15 (1.6%) deaths in tenapanor-treated patients (Table 32) and 5 (2.0%) deaths in sevelamer-treated patients. Causes of death were primarily due to cardiovascular and

infectious etiology and in line with common causes of death in patients receiving maintenance dialysis. One patient died in the Phase 2 dose-finding study, D5613C00001, and one patient died in Study 201. Thirteen patients treated with tenapanor died during the 52-week, long-term Study 301. None of the deaths were considered drug related.

Table 32: Integrated Listing of Adverse Events Leading to Death in Tenapanor-Treated Patients (CKD on Maintenance Dialysis Safety Analysis Set)

Study	Age/Sex/Race	Days from Last Study Treatment[a]	Cause of Death
Treatment: Tenapanor 2-30 mg[b]			
D5613C00001	66/M/WH	24	Cardiac failure
TEN-02-201	71/F/WH	18	Intestinal perforation
			Small intestinal obstruction
			End-stage renal disease
Treatment: Tenapanor 60 mg[c]			
TEN-02-301	65/M/WH	13	Basal ganglia hemorrhage
TEN-02-301	51/M/AM	2	Cardiac arrest
TEN-02-301	75/M/BL	9	Cardiac arrest
TEN-02-301	58/M/BL	5	Hemorrhage intracranial
TEN-02-301	50/M/BL	35	Unknown reason
TEN-02-301	75/F/BL	15	Sepsis
TEN-02-301	36/M/WH	3	Cardiac arrest
TEN-02-301	67/M/WH	26	Sepsis
TEN-02-301	66/M/WH	23	Respiratory failure
TEN-02-301	49/M/WH	12	Cardiogenic shock
			Septic shock
TEN-02-301	62/M/WH	17	Pulseless electrical activity
TEN-02-301	69/F/WH	12	Sepsis
TEN-02-301	85/F/WH	5	Cardiac arrest
			Septic shock

[a] Date of Last Dose – Date of Death + 1.
[b] Patients received either 1 mg BID, 3 mg QD, 3 mg BID, 10 mg BID, or 30 mg QD
[c] All patients received 30 mg BID, from 30 mg BID (max) to ≥ 10 mg BID
Note: All deaths, treatment-emergent or not, are included in the summary
All patients with tenapanor are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202.
AM=American Indian/Alaska Native; BL=Black/African American; F=Female; M=Male; WH=White.

6.6 Adverse Events of Special Interest

6.6.1 Non-Infectious Diarrhea

Stool softening is an expected PD effect caused by sodium retention in the intestinal lumen producing an osmotically driven increase in stool fluid content, thus diarrhea was an anticipated AE. For reference, MedDRA classifies any report of "bothersome" loose stool(s), loose bowels, and/or mushy stool(s) as "diarrhea" events, with or without increased "stool frequency."

During the 26-week RTP of Study 301, in which most events of diarrhea occurred, nearly 90% of cases were mild to moderate in intensity, and 11% were reported as severe (Table 33). Among patients randomized to tenapanor who reported diarrhea intensity as severe, the majority noted resolution within 14 days (Table 34).

Table 33: Study 301: Occurrence of Non-Infectious Diarrhea by Severity During 26-Week RTP (Safety Analysis Set)

	26-Week RTP	
Severity, n (%)	Tenapanor N=419	Sevelamer N=137
Noninfectious Diarrhea	222 (53.0)	10 (7.3)
Mild	53 (12.6)	5 (3.6)
Moderate	143 (34.1)	5 (3.6)
Severe	26 (6.2)	0

RTP=Randomized Treatment Period.

Table 34: Study 301: Time to Resolution of First-Reported Severe Non-Infectious Diarrhea Case During 26-Week RTP (Safety Analysis Set)

	≤ 2 Weeks	> 2 Weeks	Ongoing at Exit	Total
Severe, n (%)	17 (65)	7 (27)	2 (8)	26

Time to resolution = AE end date – AE start date + 1.
RTP=Randomized Treatment Period.

In the tenapanor group of Study 301 during the 26-week RTP, 222 patients reported diarrhea; the median onset of their first-reported diarrhea event was 4.5 days within the first dose of tenapanor and 74% started to experience diarrhea within 14 days of the first dose of tenapanor (Table 35 and Figure 37). Among the 200 patients with a reported diarrhea end date, 49% had their first-reported diarrhea resolved within 14 days from onset. Among the 24 patients experiencing severe diarrhea with a reported diarrhea end date, 17 (71%) had their severe diarrhea resolved within 14 days from onset (Table 34).

Diarrhea AEs did not appear to be treatment-limiting in the majority of patients (16% discontinued study drug due to diarrhea at any time), and most events were mild to moderate in intensity. In the 26-week RTP of Study 301, 75% of the 65 tenapanor-

treated patients who discontinued treatment due to AEs of diarrhea started to experience diarrhea within the first 2 weeks of treatment (Table 34 and Figure 38). While diarrhea was the most common GI side effect resulting in down titration of dose, 56%–62% of patients remained on the proposed starting dose (tenapanor 30 mg BID; 60 mg daily) in Studies 201, 202, and 301.

Table 35: Study 301: Summary of Diarrhea During 26-Week RTP in Tenapanor-Treated Patients (Safety Analysis Set)

	Tenapanor (N=419)
Diarrhea event rate, n (%)	222 (53%)
Median time to onset of first-reported diarrhea event, study days	4.5
% Reporting first diarrhea within first 2 weeks of treatment (≤ 14 days)	74%
Treatment Discontinuation due to diarrhea, n (%)	65 (16%)
Median time from onset of diarrhea to treatment discontinuation, study days	10
Median time from onset of diarrhea to treatment discontinuation by ending dose at RTP, study days	
30 mg BID (n=26)	4.5
20 mg BID (n=13)	9
10 mg BID (n=26)	22.5

BID=twice daily.

Figure 37: Study 301: First Onset of Adverse Events of Diarrhea in Tenapanor-Treated Patients During 26-Week RTP (Safety Analysis Set)

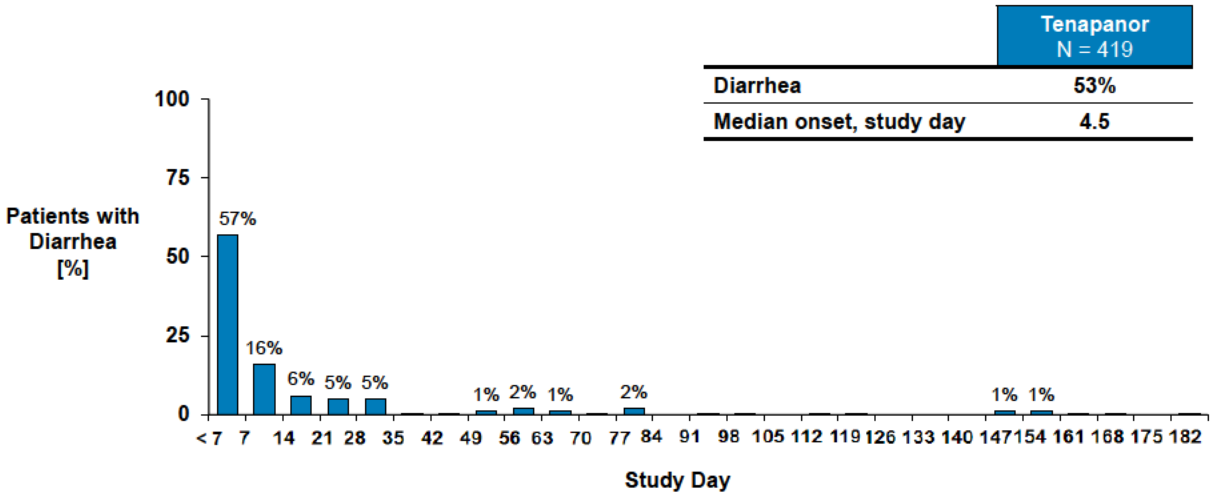
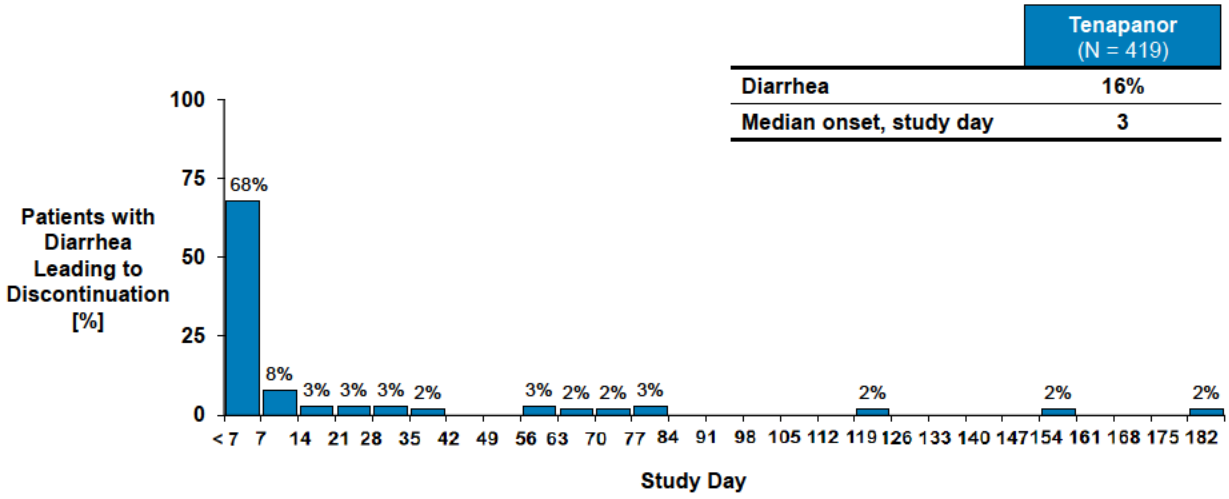


Figure 38: Study 301: Onset of Adverse Events of Diarrhea Leading to Discontinuation in Tenapanor-Treated Patients During 26-Week RTP (Safety Analysis Set)



The decreasing incidence of diarrhea with longer tenapanor exposure is further evident from the long-term safety extension of Study 301. In the first 3 months of treatment, 50% of patients in the tenapanor group and 5% of patients in the sevelamer group reported AEs of diarrhea, whereas 5% of patients in the tenapanor group and 3% of patients in the sevelamer group reported AEs of diarrhea in the second 3 months of treatment. The impact that an enriched population can have on diarrhea adverse events is evident when assessing this early difference between tenapanor and sevelamer treatment arms.

While the reduced incidence of diarrhea over time with tenapanor may be partially due to patient discontinuation, the rate of discontinuation of study drug due to diarrhea is far less than the actual incidence of diarrhea in tenapanor group during 26-week RTP, suggesting that diarrhea is manageable in most cases and tolerability improves with time.

Accordingly, the percentage of tenapanor-treated patients who discontinued study drug due to an AE during the RWP of the pivotal Phase 3 monotherapy studies (1% in Study 201 and 9% in Study 301) was lower than that in the RTP (16% in Study 201 and 24% in Study 301). Based on the integrated summary of safety, the incidence of diarrhea reported for patients treated with tenapanor when combined with PB therapy (42.7%) was slightly lower than that of patients treated with tenapanor 30 mg BID alone (50.9%), but higher than PB alone (5.9%). For patients who did experience diarrhea when tenapanor was dosed with a PB, the diarrhea tended to resolve more rapidly than with tenapanor 30 mg BID alone (median of 5 days vs 13 days, respectively). Two (1.7%) patients receiving placebo and 5 (4.3%) patients receiving tenapanor discontinued due to AEs, and of those, 2 of the 2 placebo patients and 3 of 5 tenapanor patients discontinued due to diarrhea.

Table 36: Integrated Time to First Onset and Duration of Non-Infectious Diarrhea (CKD on Maintenance Dialysis Safety Analysis Set)

Noninfectious Diarrhea	All Tenapanor Patients[a] (N=934)
Patients with at least 1 event, n (%)	432 (46.3)
Time to first onset, n (%)[b]	
≤ 7 days	284 (65.7)
> 7 – ≤ 14 days	73 (16.9)
> 14 – ≤ 21 days	24 (5.6)
> 21 – ≤ 28 days	21 (4.9)
> 28 – ≤ 56 days	18 (4.2)
> 56 days	12 (2.8)
Number of events[c]	472
Duration of event, n (%)[d]	
≤ 7 days	215 (45.6)
> 7 – ≤ 14 days	76 (16.1)
> 14 – ≤ 28 days	68 (14.4)
> 28 – ≤ 56 days	53 (11.2)
> 56 days	60 (12.7)

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets of the following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202.
[b] Time to first onset is Date of first onset – Date of first dose of study drug + 1 for patients with ≥ 1 event, and End date of on-treatment phase – Date of first dose of study drug + 1 for censored patients. For patients with ≥ 1 event. Percent is out of total number of patients with ≥ 1 event.
[c] Number of events where duration can be derived (both start and end date are available).
[d] Percent is out of total number of events
The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Treatment Period.

When assessing GI-related events more broadly, there were few other GI-related AEs beyond diarrhea in either treatment arm. For context, an evaluation of GI-related AEs from the sevelamer USPI was completed. The AE profile in the sevelamer-naïve population from the USPI showed a higher overall AE rate; the rate of diarrhea was 19%, with higher rates of other non-diarrhea GI-related AEs compared to either treatment arm in the tenapanor trials. Additionally, the sevelamer USPI lists an incidence of discontinuations due to GI Events of 16%.

An additional analysis of the temporal association between severe diarrhea and any AESIs leading to hospitalization identified one patient out of the 26 (6%) tenapanor-

treated patients who experienced severe diarrhea during the 26-week RTP with a temporally associated event of dehydration leading to hospitalization.

6.6.2 Dehydration

Based on the integrated summary of safety, AEs of dehydration were infrequently reported, with only 5 patients (< 1%) treated with tenapanor 30 mg BID experiencing an AE of dehydration. Two of these events occurred during the first 7 days of treatment, and the other 3 events occurred between Days 28 and 56 (Table 37).

Table 37: Integrated Summary of Time to First Onset of Dehydration (CKD on Maintenance Dialysis Safety Analysis Set)

Dehydration	All Tenapanor Patients[a] (N=934)
Patients with at least 1 event, n (%)	5 (0.5)
Time to first onset, n (%)[b]	
≤ 7 days	2 (40.0)
> 7 – ≤ 14 days	0
> 14 – ≤ 21 days	0
> 21 – ≤ 28 days	0
> 28 – ≤ 56 days	3 (60.0)
> 56 days	0

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets of the following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202.
[b] Time to first onset is Date of first onset – Date of first dose of study drug + 1 for patients with ≥ 1 event, and End date of on-treatment phase – Date of first dose of study drug + 1 for censored patients. For patients with ≥ 1 event. Percent is out of total number of patients with ≥ 1 event.
The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, and TEN-02-202. For TEN-02-201 on-treatment phase is the total time in the RWP and RTP combined for patients randomized to tenapanor in the RTP and as the total time in the RWP for patients randomized to placebo in the RTP. For TEN-02-301 on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Treatment Period.

6.6.3 Hyponatremia

Based on the integrated summary of safety, AEs of hyponatremia were also infrequently reported. Six patients (< 1%) treated with tenapanor experienced AEs of hyponatremia. Four of these patients received tenapanor 30 mg BID, 1 of which experienced hyponatremia between Days 21 and 28, and the other 3 experienced hyponatremia between Days 28 and 56. Two additional patients receiving tenapanor 90–120 mg experienced hyponatremia within the first 7 days of treatment (Table 38).

Table 38: Integrated Summary of Time to First Onset of Hyponatremia (CKD on Maintenance Dialysis Safety Analysis Set)

Hyponatremia, n (%)	All Tenapanor Patients[a] (N=934)
Patients with at least 1 event, n (%)	6 (0.6)
Time to first event, n (%)[b]	
≤ 7 days	2 (33.3)
> 7 – ≤ 14 days	0
> 14 – ≤ 21 days	0
> 21 – ≤ 28 days	1 (16.7)
> 28 – ≤ 56 days	3 (50.0)
> 56 days	0

[a] All tenapanor patients are individual patients who received any dose(s) of tenapanor in the CKD on Maintenance Dialysis Safety Analysis Set. CKD on Maintenance Dialysis Safety Analysis Set includes patients from the study-level Safety Analysis Sets of the following studies: D5611C00001, D5613C00001, TEN-02-201, TEN-02-301, and TEN-02-202.
[b] Time to first onset is Date of first onset – Date of first dose of study drug + 1 for patients with ≥ 1 event, and End date of on-treatment phase – Date of first dose of study drug + 1 for censored patients. For patients with ≥ 1 event. Percent is out of total number of patients with ≥ 1 event.
The on-treatment phase is defined as the time from first dose through the end of study/early withdrawal visit for studies D5611C00001, D5613C00001, TEN-02-201 (not for patients on placebo during the RW period), and TEN-02-202. For TEN-02-201 patients on placebo during the RW period, on-treatment phase ends at the end of the RT period. For TEN-02-301, on-treatment phase is the time from first dose through the minimum of the date of Week 12 visit and date of early withdrawal.
CKD=chronic kidney disease; RTP=Randomized Treatment Period; RWP=Randomized Treatment Period.

6.7 Adverse Events of Special Interest Temporally Associated with Diarrhea

For Study 301, 234 (56%) patients treated with tenapanor reported diarrhea throughout the entire study. Among those 234 patients, 3% had a temporally associated AESI and the specific AESI rates were ≤ 1% and similar to sevelamer (Table 39).

Table 39: Study 301: Adverse Events of Special Interest Temporally Associated with Diarrhea During the Entire Study (Safety Analysis Set)

Preferred Term, n (%)	Tenapanor (N=419)	Sevelamer (N=137)
Patients with diarrhea	234 (55.8)	14 (10.2)
Patients with diarrhea and without any temporally associated AESI[a,b c]	228 (97.4)	13 (92.9)
Patients with diarrhea and with any temporally associated AESI[a,b c]	6 (2.6)	1 (7.1)
Dehydration[c]	2 (0.9)	0
Hypovolemia[c]	0	0
Hypotension[c]	3 (1.3)	0
Orthostatic hypotension[c]	0	0
Presyncope[c]	1 (0.4)	0
Syncope[c]	2 (0.9)	0
Dizziness[c]	0	1 (7.1)
Fall[c]	1 (0.4)	1 (7.1)

a. An AE was considered temporally associated with a diarrhea event If 1) the AE started at or after the diarrhea start date and within 3 days of the diarrhea end date, if the diarrhea ended by the End of Study or 2) the AE started at or after the diarrhea start date if the diarrhea was ongoing at the End of Study.
b. AESIs: AEs mapped to preferred terms of fall, hypotension, orthostatic hypotension, syncope, presyncope, dizziness, dehydration, and hypovolemia.
c. Percentages were calculated using the number of patients with diarrhea as the denominator
Note: A
AE(s)=adverse event(s); AESI(s)=adverse event(s) of special interest.

6.8 Laboratory Findings

There were no clinically significant changes in electrolytes or other laboratory findings in patients treated with tenapanor across the Safety Analysis Set in Study 301, and more specifically, in those patients who reported severe diarrhea (Table 40).

Table 40: Study 301: Summary of Changes in Serum Electrolytes During 26-Week RTP in Tenapanor-Treated Patients (Safety Analysis Set)

Electrolyte Analysis Visit	Tenapanor with No Diarrhea (N=185)	Tenapanor with Mild/Moderate Diarrhea (N=208)	Tenapanor with Severe Diarrhea (N=26)
Na^+, mmol/L, mean (SD)			
Baseline	136.7 (3.3)	137.1 (3.3)	137.6 (2.5)
Change from Baseline to Week 26	0.3 (3.5)	-0.60 (3.0)	-1.4 (1.2)
Cl^-, mmol/L, mean (SD)			
Baseline	97.6 (3.8)	97.5 (3.8)	97.1 (3.4)
Change from Baseline to Week 26	0.4 (3.3)	0.1 (3.4)	-1.3 (3.2)
K^+, mmol/L, mean (SD)			
Baseline	4.7 (0.7)	4.7(0.7)	4.7 (0.6)
Change from Baseline to Week 26	0.1 (0.6)	0.1 (0.9)	0.3 (0.6)
HCO^{3-}, mmol/L, mean (SD)			
Baseline	23.7 (3.2)	24.1 (2.9)	25.3 (3.2)
Change from Baseline to Week 26	0.5 (3.4)	0.4 (3.5)	-0.1 (3.4)
Ca^{2+}, mg/dL, mean (SD)			
Baseline	8.4 (0.7)	8.4 (0.8)	8.4 (0.6)
Change from Baseline to Week 26	0.1 (0.8)	0.3 (0.9)	0.3 (0.6)
Mg^{2+}, mg/dL, mean (SD)			
Baseline	2.5 (0.3)	2.4 (0.3)	2.3 (0.3)
Change from Baseline to Week 26	0.0 (0.4)	0.0 (0.3)	0.1 (0.3)

SD: standard deviation.

6.9 Vital Signs

6.9.1 Blood Pressure

In the CKD on Maintenance Dialysis Safety Set, minimal changes in systolic and diastolic pressure were observed over time (Table 41). Consistent results were observed in patients during the 26-week RTP of Study 301 (Table 42).

Table 41: Integrated Summary of Changes in Systolic and Diastolic Blood Pressure (CKD on Maintenance Dialysis Safety Analysis Set)

Parameter Analysis Visit	All Tenapanor (N=934)	Sevelamer (N=256)	Placebo (N=69)

Systolic Blood Pressure, mmHg, mean (SD)			
Baseline	146.1 (24.8)	143.9 (23.0)	136.4 (14.2)
Week 6	144.5 (24.4)	147.1 (13.3)	137.0 (19.4)
Week 12	144.9 (25.0)	145.8 (23.9)	-
Change from Baseline to Week 12	-1.1 (25.5)	5.6 (24.6)	-
Diastolic Blood Pressure, mmHg, mean (SD)			
Baseline	78.0 (14.7)	79.2 (14.4)	74.7 (10.3)
Week 6	77.8 (15.7)	80.5 (13.7)	76.8 (10.6)
Week 12	76.2 (14.6)	78.9 (13.7)	-
Change from Baseline to Week 12	-1.5 (14.1)	1.9 (13.9)	-

CKD: Chronic Kidney Disease; SD: standard deviation.

Table 42: Study 301: Summary of Changes in Systolic and Diastolic Blood Pressure During 26-Week RTP (Safety Analysis Set)

Parameter Analysis Visit	All Tenapanor (N=419)	Sevelamer (N=137)
Systolic Blood Pressure, mmHg, mean (SD)		
Baseline	146.3 (24.0)	140.2 (21.8)
Week 8	147.8 (24.6)	143.8 (22.3)
Week 17	147.4 (25.4)	143.6 (23.5)
Week 26	146.4 (25.1)	141.4 (22.7)
Change from Baseline to Week 26	0.5 (28.1)	1.5 (24.5)
Diastolic Blood Pressure, mmHg, mean (SD)		
Baseline	77.6 (14.5)	76.7 (14.0)
Week 8	78.2 (14.8)	77.1 (14.3)
Week 17	78.6 (14.9)	76.9 (13.7)
Week 26	79.0 (15.8)	75.3 (14.3)
Change from Baseline to Week 26	1.1 (16.1)	-1.5 (16.1)

SD: standard deviation.

6.10 Post-Marketing Safety in IBS-C

Tenapanor was approved for the treatment of IBS-C in adults, under the tradename Ibsrela, in the US on 12 September 2019, with a recommended dose of 50 mg BID. However, as it was only recently launched in April 2022, there are limited post-marketing surveillance data available. In this limited time, there have been no new safety signals identified and diarrhea has been the major AE reported consistent with Ibsrela's label.

6.11 Summary of Clinical Safety

In summary, tenapanor offers an acceptable safety and tolerability profile based on findings from more than 930 patients exposed to tenapanor throughout the clinical development program for HP. Diarrhea was the most common AE in patients treated

with tenapanor in Study 301, occurring in 53% of patients who received tenapanor at the proposed daily dose of 30 mg BID and 7% of patients administered sevelamer during the 26-week RTP. Most AEs of diarrhea occurred early, were mild to moderate in intensity, and were not treatment-limiting. Importantly, events of severe diarrhea were less frequent, and potential downstream consequences of diarrhea including dehydration, syncope, falls and hospitalizations were uncommon. In Study 301, which employed an active safety comparator, sevelamer, SAEs were slightly higher in the sevelamer group, despite approximately 65% of patients being treated with sevelamer prior to study initiation. Rates of death were low and comparable between tenapanor and sevelamer, and no deaths were deemed related to study treatment by Investigators.

7 BENEFIT-RISK CONCLUSIONS

Hyperphosphatemia is a serious and common complication in patients with ESKD who receive maintenance dialysis. PBs are currently the only class of therapy available to treat HP in this patient population. Despite significant use of PBs, most patients are unable to consistently achieve target s-P goals (Robinson et al 2020), which is likely due in part to the treatment burden associated with PBs (large pills with frequent dosing).

Tenapanor is a first-in-class, oral therapy with minimal systemic absorption that provides clinically meaningful s-P reductions in a significant number of patients with HP who are receiving maintenance dialysis. Tenapanor has a novel mechanism of action, utilizes a twice daily dosing regimen, and its reduction of s-P can be identified relatively early. Tenapanor has an acceptable safety and tolerability profile and coupled with its efficacy across a number of clinical parameters has a positive benefit-risk assessment.

Tenapanor provides benefit as monotherapy for those patients who are unable to achieve significant reductions in s-P with a much smaller pill burden and as combination therapy with PBs who are not able to move their s-P closer to normal with PB therapy alone. In the tenapanor clinical development program, both monotherapy studies under a RW design met the pre-specified primary efficacy endpoint. While the placebo-adjusted mean s-P lowering with tenapanor during the RWP was 0.8 and 1.4 mg/dL in the enriched population (i.e., patients who entered the RWP with at least 1.2 mg/dL s-P reduction at the end of RTP [the enrichment phase]), the range of response was broad, and the mean s-P lowering in the enriched population was 2.6 mg/dL at the end of RTP in both monotherapy trials. In addition, patients who responded to tenapanor had a mean s-P lowering similar to patients who responded to sevelamer. Even the more modest s-P lowering of 0.8 mg/dL will benefit those whose s-P needs to only be minimally reduced to achieve the desired target range. Importantly, this s-P reducing benefit was achieved by taking one small pill twice per day compared to a median of 9 sevelamer pills at the end of study. Additionally, a higher proportion of patients who were previously inadequately controlled on PB therapy alone were able to achieve guideline-recommended target values with combination therapy (tenapanor + PBs).

While empirically derived, responders can be identified through the current treatment paradigm used with PBs, and 79% of those identified as responders to tenapanor continue to respond, as shown in Study 301. Based on the ability to identify responders and the frequent monitoring of these patients, there is little risk that patients will stay on tenapanor without benefit. For those patients who cannot achieve meaningful s-P reductions with tenapanor alone, Study 202 showed that the addition of a PB to tenapanor allowed more patients to achieve target s-P levels, and for some, there was a reduction in the number of PB pills.

As with any drug, some patients will not tolerate or derive benefit from tenapanor. However, the only significant risk that has been seen to date is diarrhea, which has not been associated with significant more worrisome sequelae. This side effect is easily

recognized by patients, and health care professionals (who are in frequent contact) can easily managed, typically, with dose reduction or discontinuation of treatment.

Overall, the tenapanor clinical development program provided substantial evidence for the safety and efficacy of tenapanor to support its use as a novel s-P lowering agent for patients with HP receiving maintenance dialysis. Based on the totality of the results summarized in Table 43, the benefit-risk assessment for tenapanor is positive in patients with HP receiving maintenance dialysis.

Table 43: Summary of Benefit-Risk of Tenapanor

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: Control of s-P in patients with CKD on Maintenance Dialysis	• Observational studies show that increase in s-P increases morbidity and mortality risk • No prospective clinical outcome studies	• FDA has accepted s-P lowering as an endpoint for HP despite no clinical outcome studies that show any level of s-P lowering leads to reduced morbidity or mortality.
Current Treatment Options	• Diet: rarely sufficient given high level of phosphate in processed foods and in protein sources and dairy products • Dialysis: Normally occurs 3 times, additional dialysis or longer dialysis a week • PBs: lower s-P from 1.5 to 2.2 mg/mL; have to be taken with every meal (typical 9–10 large pills per day) in addition to other medications, poor GI tolerability including diarrhea, constipation, and nausea	• 40% of patients still do not meet target s-P (DOPPS 2019).
Benefit	**Pre-Specified Analysis** Monotherapy (EAS): • 201: -0.82 mg/dL (95% CI: -1.44, -0.21) • 301: -1.37 mg/dL (95% CI: -1.92, -0.82) Combination Therapy (Patients with inadequately controlled s-P; FAS): • 202: -0.65 (95% CI: -1.01, -0.29) Monotherapy trials are enrichment trials, not randomized parallel-group placebo-controlled studies. **ITT analysis** Monotherapy (only): • 201: -0.72 mg/dL • 301: -0.66 mg/dL **Other Analyses** Combination Therapy: • 202: 41% had a ≥ -1.2 mg/dL s-P reduction at Week 4 • Twice the number of patients achieved < 5.5 mg/dL in the placebo+binder group	• Placebo-adjusted mean s-P reductions in the RWP of the monotherapy studies were 0.8 mg/dL and 1.4 mg/dL. High end is similar to current therapies. • KDIGO guidelines recommend lowering patient s-P towards normal. Tenapanor will lower s-P using a different mechanism than current therapies with 2 small pills, for some as monotherapy, and for others as combination therapy. • In clinical practice, HCPs can identify those patients who respond to tenapanor as they would a PB regimen and patients who do not respond will not stay

	Mechanism of Action MOA allows for: 1) sufficient treatment effect in some patients with 2 small pills per Day 2) combination therapy (only randomized placebo-controlled trial with 2 HP treatments to show additive effect). **Identification of Responders** • Those who respond to tenapanor continue to respond (79%)	on tenapanor but discontinue or use in combination with a PB.
Risk and Risk Management	• Major risk is diarrhea (53% in Study 301 RTP) consistent with mechanism of action. Diarrhea led to 16% of treatment discontinuations in tenapanor-treated patients in Study 301, and 2.6% of tenapanor-treated patients in Study 202 • During the enrichment phase, 0.5% had serious diarrhea in Study 301 and 0% in the combination therapy study • Rare occurrence of AEs associated with diarrhea (e.g. dehydration) • Diarrhea occurred early and a majority were mild to moderate in severity • Diarrhea is the only significant AE above 5% in the integrated safety summary • In Study 201, bowel habit changed monitored by BSFS, mean change was a single score increase in stool softness and a mean frequency of one bowel habit per week • SAE equivalent in sevelamer control arm vs tenapanor arm in 301 study	• Diarrhea in clinical trials is defined by change in bowel habits as any loose stooks. Loose bowel or mushy stool is classified as diarrhea without regard to stool frequency. • Numerous patients with CKD on dialysis are constipated. • Tenapanor taken away diarrhea resolves quickly. • Patients with CKD on dialysis are seen frequently by a health care professional (normally thrice a week for dialysis).

AE(s)=adverse event(s); BSFS=Bristol stool form scale; CI=confidence interval; CKD=chronic kidney disease; EAS=Efficacy Analysis Set; GI=gastrointestinal; HCPs=healthcare professionals; HP=hyperphosphatemia; ITT=Intention-to-Treat; MoA=mechanism of action; PB(s)=phosphate binder(s); SAE=serious adverse event; s-P=serum phosphorus.

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9 APPENDICES

9.1 Patient Satisfaction Data

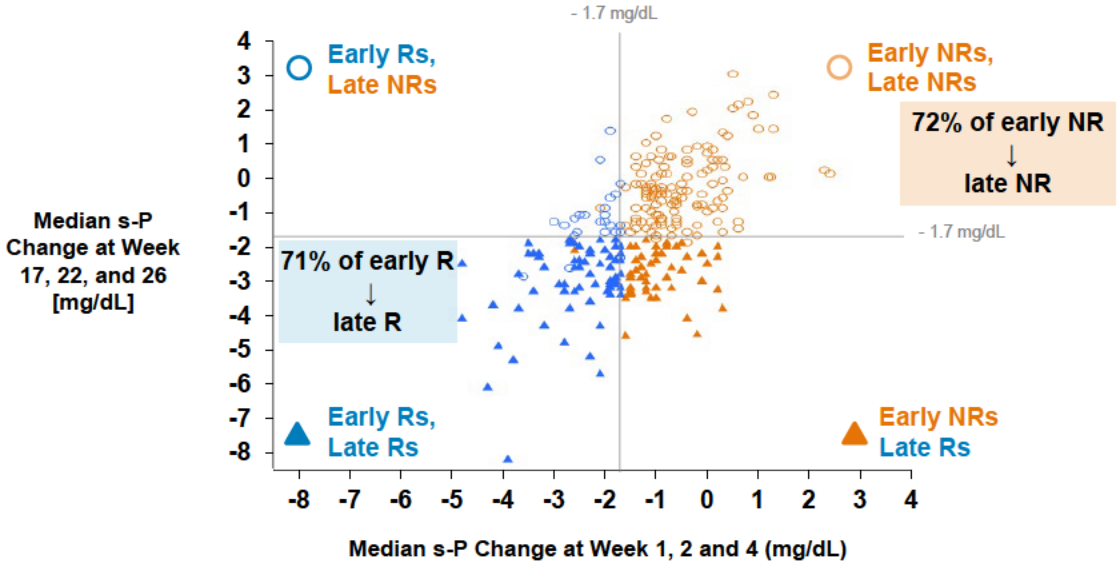
Table 44: Study 402: Patient-Reported Overall Perception Responses

Primary reason for change in perception (Question 2), n (%)	Overall perception response (Question 1)	
	Improved (N=205)	Worsened (N=8)[a]
Medication burden related	132 (64.4)	0
Size of phosphate lowering pills	37 (18.0)	0
Number of phosphate lowering pills	38 (18.5)	0
Number of times per day I had to take phosphate lowering pills	40 (19.5)	0
Number of phosphate lowering medicines I had to take	17 (8.3)	0
Bowel movement related	64 (31.2)	7 (87.5)
Frequency of bowel movements	53 (25.9)	2 (25.0)
Form of bowel movements	11 (5.4)	5 (62.5)
Other	9 (4.4)	1 (12.5)
Other stomach/GI changes (e.g., nausea, bloating, etc.)	5 (2.4)	1 (12.5)
Other	4 (2.0)	0

[a]Percentages in this column may not be conclusive due to the small number of patients in this group.
GI=gastrointestinal.

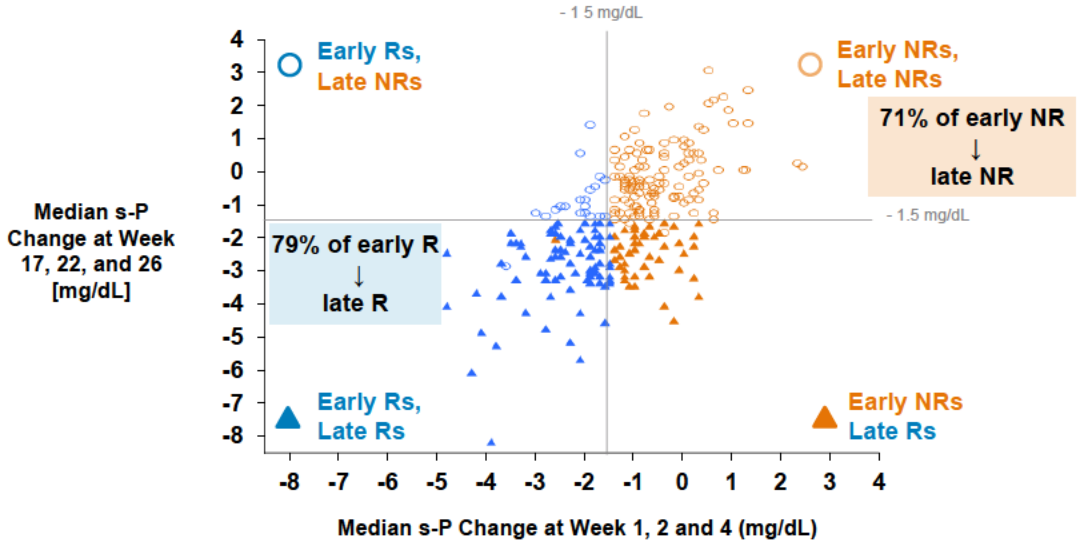
9.2 Early and Late Responder Analysis in Study 301

Figure 39: Study 301: Early Response to Tenapanor Predicts Late Response using Cutoff of 1.7 mg/dL (RTP ITT Patients with Observed Late Response Status)



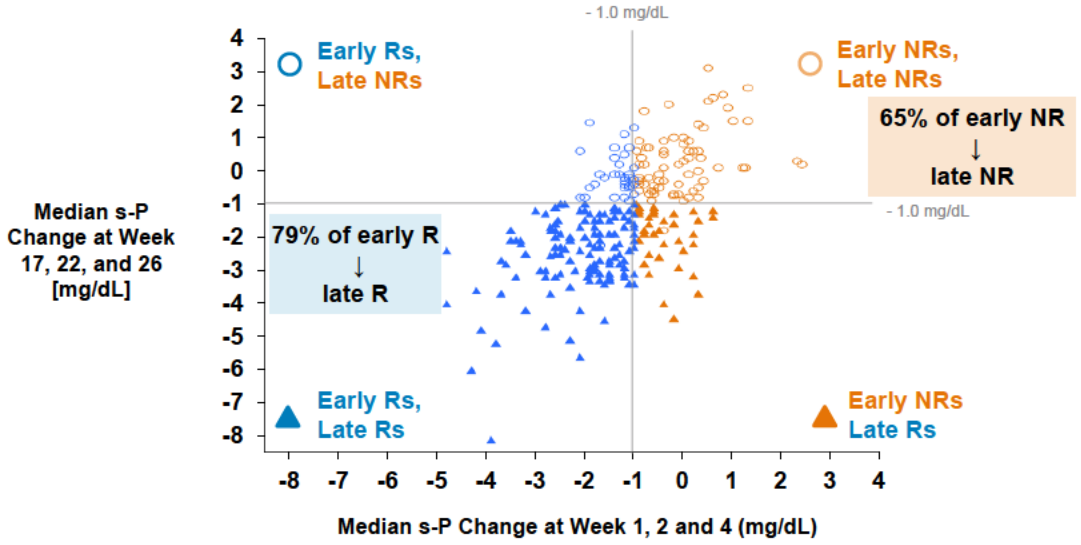
Early responders (Early Rs): patients who had s-P reduction of ≥ 1.7 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4 within the first month of the RTP.
Late responders (Late Rs): patients who had s-P reduction of ≥ 1.7 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26 within the second half of the RTP.
ITT=Intention-to-Treat; s-P=serum phosphorus.

Figure 40: Study 301: Early Response to Tenapanor Predicts Late Response using Cutoff of 1.5 mg/dL (RTP ITT Patients with Observed Late Response Status)



Early responders (Early Rs): patients who had s-P reduction of ≥ 1.5 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4 within the first month of the RTP.
Late responders (Late Rs): patients who had s-P reduction of ≥ 1.5 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26 within the second half of the RTP.
ITT=Intention-to-Treat; s-P=serum phosphorus.

Figure 41: Study 301: Early Response to Tenapanor Predicts Late Response using Cutoff of 1.0 mg/dL (RTP ITT Patients with Observed Late Response Status)



Early responders (Early Rs): patients who had s-P reduction of ≥ 1.0 mg/dL on ≥ 2 of 3 measures collected at Weeks 1, 2, and 4 within the first month of the RTP.
Late responders (Late Rs): patients who had s-P reduction of ≥ 1.0 mg/dL on ≥ 2 of 3 measures collected at Weeks 17, 22, and 26 within the second half of the RTP.
ITT=Intention-to-Treat; s-P=serum phosphorus.

9.3 Randomized Withdrawal Studies of Approved Phosphate Binders and Most Common Adverse Reactions

9.3.1 Velphoro

Study-05 A was a 55-week, open-label, active-controlled, parallel-group trial. A total of 1,055 patients on maintenance hemodialysis (N=968) or peritoneal dialysis (N=87) with s-P ≥ 6 mg/dL following a 2–4-week PB wash-out period, were randomized 2:1 to receive velphoro at a starting dose of 1,000 mg/day (doses up to 3,000 mg/day; N=707) or sevelamer carbonate (N=348) for 24 weeks (Velphoro PI 2013). At the end of Week 24, 93 patients on dialysis whose s-P was controlled (< 5.5 mg/dL) with velphoro, were re-randomized to either continue treatment with their Week 24 maintenance dose (N=44) or a non-effective low dose control of 250 mg/day dose (N=49) of velphoro for a 3-week RWP. A superiority analysis of the velphoro maintenance dose vs low dose was performed at Week 27.

The most common adverse reactions (> 1%) leading to withdrawal were diarrhea (4%), product taste abnormal (2%), and nausea (2%) (Velphoro PI 2013).

9.3.2 Fosrenol

In 2 placebo-controlled, RW studies, a total of 185 patients with ESKD on hemodialysis (N=146) or peritoneal dialysis (N=39) were enrolled (Fosrenol PI 2011). Patients received up-titrated doses of lanthanum carbonate to achieve s-P in the range of 4.2–5.6 mg/dL in one study (doses up to 2,250 mg/day) or < 5.9 mg/dL in the second study (doses up to 3,000 mg/day) followed by maintenance treatment through 6 weeks. After 6 weeks, patients were re-randomized to lanthanum or placebo. During the 4-week placebo-controlled, RWP, s-P increased in the placebo group by 1.9 mg/dL in both studies relative to patients who remained on lanthanum carbonate therapy.

The most common adverse reactions were gastrointestinal events, including nausea, vomiting, and abdominal pain (Fosrenol PI 2011). These events generally abate over time with continued dosing.

9.3.3 Auryxia

Study KRK-0502-304 was a long-term, randomized, 56-week trial consisting of a 52-week active-controlled phase and a 4-week, placebo-controlled, RWP (Auryxia PI 2014). A total of 441 patients receiving maintenance dialysis (hemodialysis > 96%) with s-P of 7.5 mg/dL during a wash-out period, were randomized 2:1 to 6 tablets/day of Auryxia (up to 12 tablets/day; N=292) or active control (calcium acetate and/or sevelamer carbonate; N=149) to maintain s-P within a range of 3.5–5.5 mg/dL. Auryxia-treated patients were re-randomized in a 1:1 ratio to receive Auryxia (N=96) or placebo (N=96) during the 4-week RWP. During the RWP, s-P increased by 2.2 mg/dL in the placebo group relative to patients who remained on Auryxia.

Approximately, 289 patients from Study KRK-0502-304 and 322 patients from 3 short-term studies were treated with Auryxia (Auryxia PI 2014). During the 52-week, active

control period of Study KRK-0502-304, 61 patients (21%) on Auryxia discontinued study drug due to an adverse reaction, as compared to 21 patients (14%) in the active control group. The most common reason for discontinuing Auryxia was GI adverse reactions (14%).

9.4 Study 201, 301, and 202 Inclusion and Exclusion Criteria

9.4.1 Study 201

For inclusion into the trial, patients were required to fulfill all of the following criteria. Patients must:

1. Be male or female and ≥ 18 and ≤ 80 years of age
2. Have chronic maintenance hemodialysis 3× per week for ≥ 3 months
3. Have Kt/V ≥ 1.3 at most recent measurement prior to screening
4. Have prescribed and taken ≥ 3 doses of PB per day and dose was unchanged during the last 3 weeks prior to screening
5. Have s-P of ≥ 4.0 and ≤ 7.0 mg/dL at screening, analyzed at the central laboratory used in the study
6. Have, if on any vitamin D or calcimimetics regimen, the dose unchanged for the last 4 weeks prior to screening
7. Have, for randomization in the study, after 1 week wash-out of PBs, had s-P ≥ 9.0 mg/dL and ≤ 10.0 mg/dL, and an increase of ≥ 1.5 mg/dL vs pre-wash-out value
8. Have, for randomization in the study, after 2 or 3 weeks wash-out of PBs, had s-P of ≥ 6.0 mg/dL and ≤ 10.0 mg/dL and an increase of ≥ 1.5 mg/dL vs pre-wash-out value
9. Have signed and dated informed consent prior to any study-specific procedures
10. Have been able to understand and comply with the protocol
11. Have daily access to a touch tone telephone

And the following was regarded as criterion for exclusion from the trial. Patients must not:

1. Have severe hyperphosphatemia, defined as s-P > 10.0 mg/dL on PBs, at any time point during clinical routine monitoring for the 3 preceding months before Screening Visit
2. Have serum/plasma PTH > 1,200 pg/mL
3. Have persistent metabolic acidosis, defined as serum carbon dioxide < 18 mmol/L from 2 consecutive measurements, during screening and wash-out periods

4. Have clinical signs of hypovolemia at randomization as judged by the Sponsor
5. Have history of inflammatory bowel disease (IBD) or diarrhea predominant IBS
6. Have scheduled living donor kidney transplant, changed to peritoneal dialysis, home HD, or planned to relocate to another center during the study period
7. Have diarrhea or loose stools during the week before randomization defined as BSFS ≥ 6 and frequency ≥ 3 for 2 or more days
8. Have any evidence of or treatment of malignancy within 1 year, excluding non-melanomatous malignancies of the skin
9. Have positive serology hepatitis C/B infection, or HIV with evidence of significant hepatic impairment or white blood cell elevation according to the Investigator
10. Have history of alcohol abuse, illicit drug use, significant mental illness, or any history of drug abuse or addiction ≤ 12 months of study enrollment
12. Have life expectancy < 6 months
13. Have use of an investigational agent within 30 days prior to screening
14. Have previous randomization into this study
15. Have previous exposure to tenapanor
16. Have been involved in the planning and/or conduct of the study
17. Have, in the opinion of the Investigator, been unable or unwilling to fulfill the requirements of the protocol or had a condition which would have rendered the results uninterpretable

9.4.2 Study 301

For inclusion into the trial, patients were required to fulfill all of the following criteria. Patients must:

1. Be male or female and ≥ 18 years of age
2. Have chronic maintenance hemodialysis 3× per week for ≥ 3 months or chronic maintenance PD for a minimum of 6 months
    a. If modality of dialysis had changed, patient must have met 1 of the dialysis criteria above and been on the new modality of dialysis for ≥ 1 month
3. Have stable vascular access, if on HD, as assessed by Sponsor
4. Have Kt/V ≥ 1.2 at most recent measurement within 30 days prior to screening
5. Have prescribed and was taking ≥ 3 doses of PB per day
    a. The prescribed dose should have been unchanged during the last 3 weeks prior to screening

6. Have s-P ≥ 4.0 and ≤ 8.0 mg/dL at screening analyzed at the central laboratory used in the study
7. Have, for enrollment in the study, s-P of ≥ 6.0 mg/dL and ≤ 10.0 mg/dL, and must have had an increase of at least 1.5 mg/dL vs pre-wash-out value after 1, 2, or 3 weeks wash-out of PBs
8. Have signed and dated informed consent prior to any study-specific procedures
9. Have been able to understand and comply with the protocol

And the following was regarded as criterion for exclusion from the trial. Patients must not:

1. Have severe hyperphosphatemia, defined as s-P > 10.0 mg/dL on PBs, at any time point during clinical monitoring for the 3 preceding months before the screening visit
2. Have serum/plasma PTH > 1,200 pg/mL
3. Have clinical signs of hypovolemia at enrollment as judged by the Sponsor
4. Have history of IBD or diarrhea predominant IBS
5. Have scheduled living donor kidney transplant, had plans to change to a different method of dialysis, home HD, or plans to relocate to another center during the study period
6. Have any evidence of or treatment of malignancy within 1 year, excluding non-melanomatous malignancies of the skin
7. Have positive serology for hepatitis C/B infection, or HIV with evidence of significant hepatic impairment or white blood cell elevation according to the Sponsor
8. Have history of alcohol abuse, illicit drug use, significant mental illness, or any history of drug abuse or addiction within 12 months of study enrollment
9. Have life expectancy < 12 months
10. Have use of an investigational agent within 30 days prior to screening
11. Have previous enrollment into this study
12. Have previous exposure to tenapanor
13. Have been involved in the planning and/or conduct of the study
14. Have, in the opinion of the Sponsor, been unable or unwilling to fulfill the requirements of the protocol or had a condition which would have rendered the results uninterpretable

9.4.3 Study 202

For inclusion into the trial, patients were required to fulfill all of the following criteria. Patients must:

1. Be male or female and ≥ 18 and ≤ 80 years of age
2. Have chronic maintenance hemodialysis 3 times per week for at least 3 months or chronic maintenance peritoneal dialysis for a minimum of 6 months
    a. If modality of dialysis had changed, patient must have met 1 of the 2 dialysis criteria above and been on the new modality of dialysis for a minimum of 1 month
3. If receiving active vitamin D or calcimimetics, have been unchanged for the last 4 weeks prior to Screening
4. Have Kt/V ≥ 1.2 at most recent measurement prior to Screening
5. Have prescribed and taking PB medication ≥ 3 times per day
    a. The prescribed dose should have been unchanged during the last 4 weeks prior to Screening
6. Have s-P ≥ 5.5 and ≤ 10.0 mg/dL at Screening and at the end of the Run-in Period, analyzed at the central laboratory used in the study
7. Have signed and dated informed consent prior to any study-specific procedure
8. Have been able to understand and comply with the protocol

And the following was regarded as criterion for exclusion from the trial. Patients must not:

1. Have severe hyperphosphatemia, defined as having s-P > 10.0 mg/dL on PBs, at any time point during routine clinical monitoring for the 3 preceding months before Screening
2. Have serum/plasma PTH > 1,200 pg/mL
3. Have clinical signs of hypovolemia at Screening as judged by the Sponsor
4. Have history of IBD or IBS with diarrhea
5. Have scheduled living donor kidney transplant or planned to relocate to another center during the study period
6. Have use of an investigational agent within 30 days prior to Screening
7. Have been involved in the planning and/or conduct of the study
8. Have, in the opinion of the Sponsor, the patient was unable or unwilling to fulfill the requirements of the protocol or had a condition which would have rendered the results uninterpretable.