Tenapanor's Efficacy and Safety

Cardiovascular and Renal Drugs Advisory Committee Meeting

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Outline

- Serum phosphorus (s-P) as a surrogate for clinical outcomes and regulatory context/framework
- Efficacy
- Safety

s-P as a Surrogate for Clinical Outcomes in Patients on Dialysis

- FDA accepts effects on s-P as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis.
- As agreed with the FDA, the development program for tenapanor was designed to demonstrate efficacy in lowering s-P in patients with CKD on dialysis.

s-P as a Surrogate for Clinical Outcomes in Patients on Dialysis

- To date, four major classes of agents have been approved in the United States to control s-P levels in adults with CKD on dialysis—calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-based binding agents.

- These agents were approved based on effects on s-P.

- In studies that established the efficacy and safety of these agents, the therapies lowered s-P levels by ~1.5 to 2.2 mg/dL.

s-P as a Surrogate for Clinical Outcomes in Patients on Dialysis

- In epidemiologic studies, elevated s-P levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft-tissue calcification and cardiovascular disease in patients with CKD. In patients on dialysis, higher s-P levels have also been associated with increased mortality.
- Such epidemiologic data and biological plausibility suggest that treating hyperphosphatemia will improve patient outcomes; however, data from randomized controlled trials demonstrating that treatments that lower s-P improve patient outcomes are lacking.

What Constitutes a Clinically Meaningful Change in s-P?

- In some diseases, we have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate endpoint and changes in clinical outcomes. In this disease state, we do not.
- To date, the Division of Cardiology and Nephrology has not stipulated that applicants demonstrate a treatment effect larger than some threshold; however, it has indicated that:
  - the magnitude of the treatment effect should be clinically relevant
  - if the size of the effect on s-P is significantly smaller than the size of the effect of currently approved phosphate binders, then applicants should address the clinical relevance of the effect size.

Comparative Effectiveness Requirement for Drug Approval?

- There is no comparative effectiveness requirement for drug approval.
- However, in considering what might constitute a clinically relevant treatment effect on s-P, the Division of Cardiology and Nephrology considered the precedent set by previously approved treatments and the existing data supporting the use of s-P as a surrogate endpoint.
- The Division also believes that being much less effective than existing therapy means that a drug could delay or possibly prevent patients from reaching their target s-P levels.

A Regulatory Framework: Evidence and Uncertainties

Evidence: The submitted data indicate that tenapanor is effective in reducing s-P when used as monotherapy or in combination with existing agents in CKD patients on dialysis.

Uncertainty:

- Whether the magnitude of tenapanor's effect on s-P is clinically meaningful when administered as monotherapy and in combination with existing agents
- Whether it is possible to use a patient's early response to treatment to identify patients who are "responders" (i.e., assess for a response in a patient at some early time point and discontinue treatment in patients who do not appear to have an adequate response)

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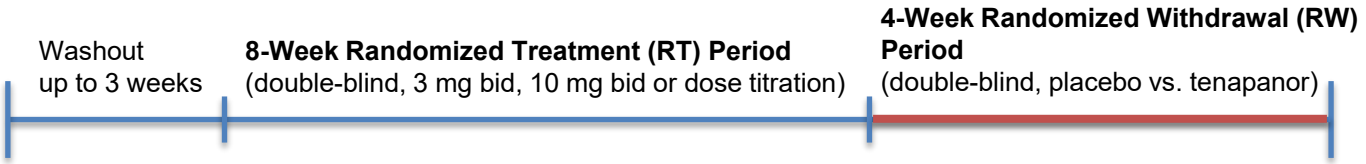
Trial Overview

Two trials to support use as monotherapy:

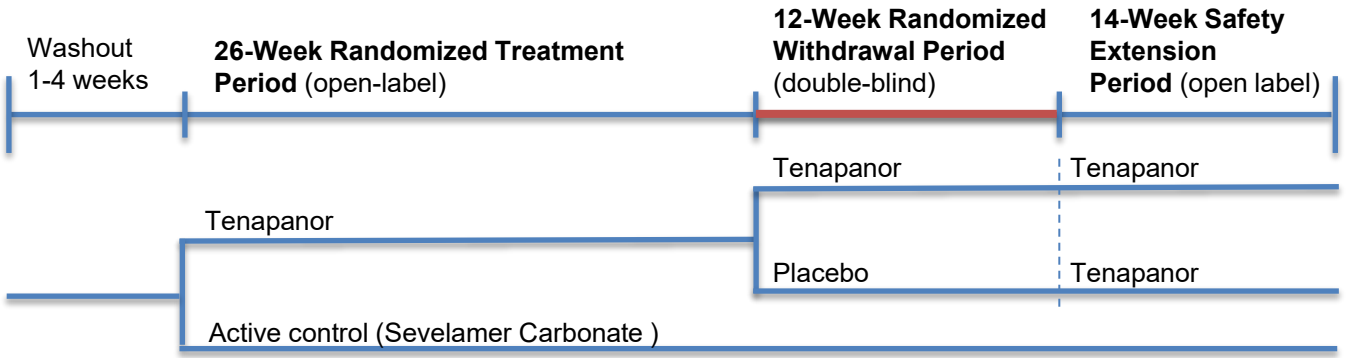
- TEN-02-201

  (Study 201)



- TEN-02-301

  (Study 301)

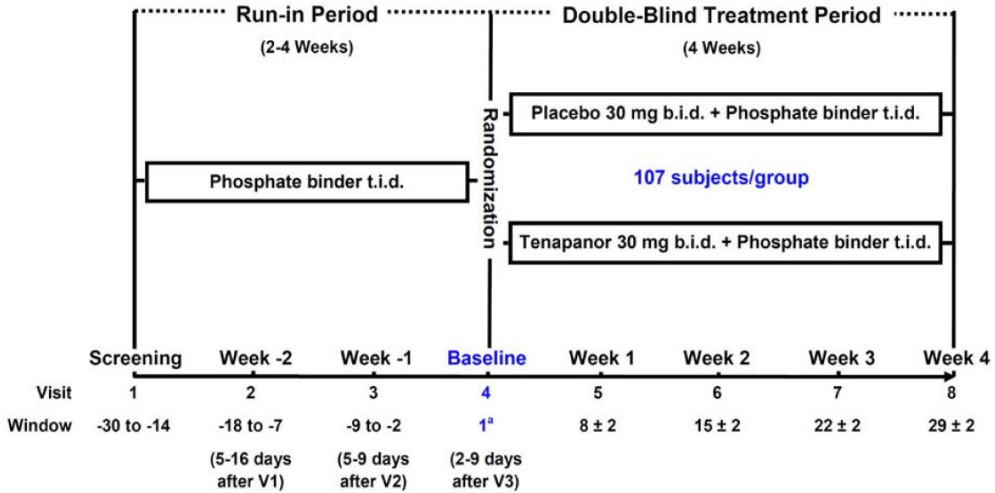


Primary endpoint: Change in s-P from the end of the **RT** period (period-level baseline) to the last visit with a s-P assessment (last observed value) during the **RW** period.

Trial Overview

One trial to support use in combination with existing phosphate binder treatment:

- TEN-02-202: 4-week, randomized, double-blind, placebo-controlled study **(Study 202)**



Primary endpoint: Change from baseline in s-P level at Week 4

TEN-02-301 and TEN-02-202: Key Inclusion Criteria

Both Studies

- Taking at least 3 doses of phosphate binder per day; prescribed dose unchanged during the last 3 weeks (TEN-02-301) or 4 weeks (TEN-02-202) prior to screening.
- s-P levels within specified range:

  TEN-02-301 (phosphate binder washed out after screening)

  – s-P between 4.0 and 8.0 mg/dL at screening analyzed at the central laboratory. For enrollment in the study, s-P of at least 6.0 mg/dL but not more than 10.0 mg/dL and an increase of at least 1.5 mg/dL versus pre wash-out value after 1, 2, or 3 weeks wash-out of phosphate binders.

  TEN-02-202 (phosphate binder continued; not required to be maximal approved/tolerated dose)

  – s-P ≥5.5 and ≤10.0 mg/dL at screening and the end of the run-in period, analyzed at the central laboratory.

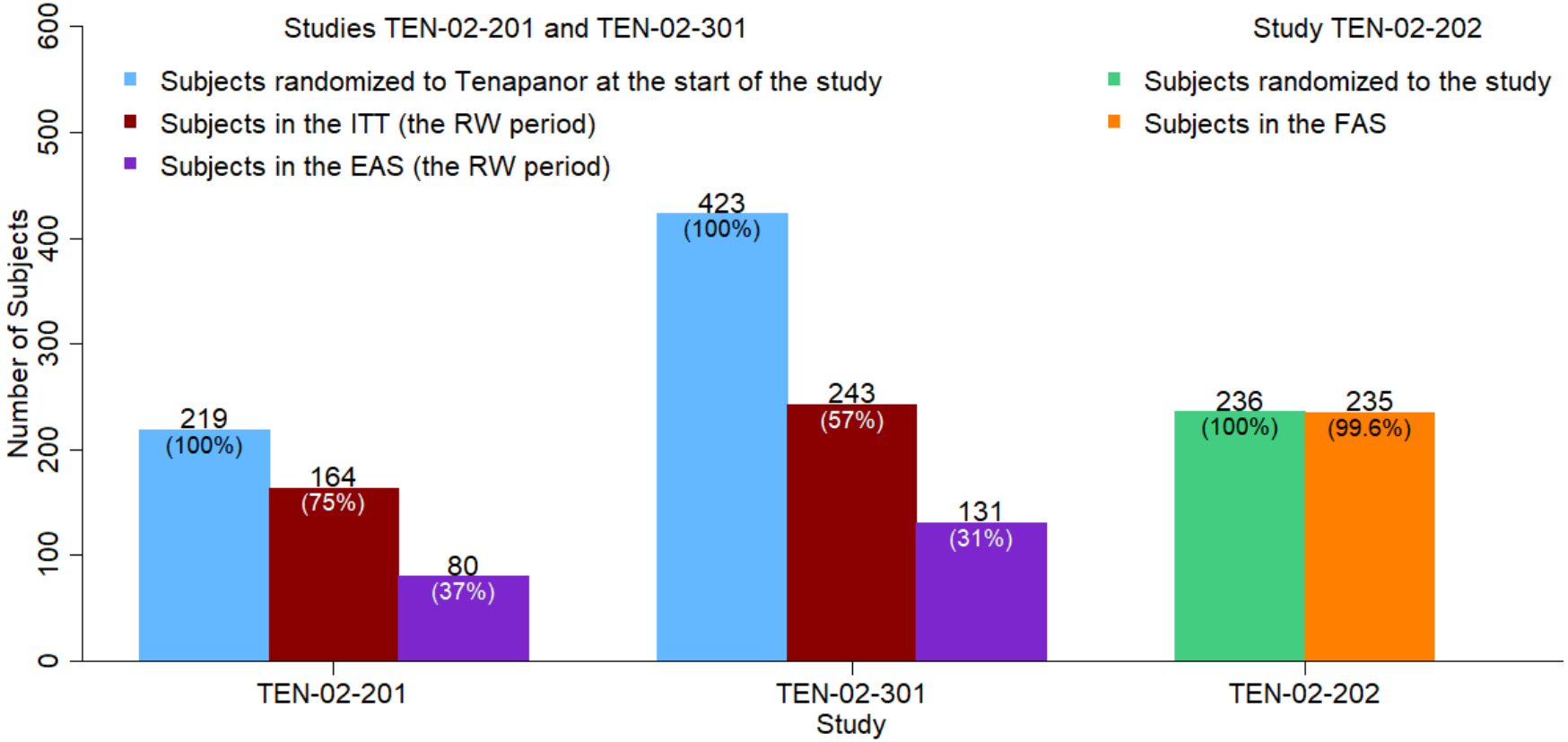
TEN-02-301 and TEN-02-202: Administration of Tenapanor

- Participants randomized to tenapanor initiated 30 mg taken twice daily taken just prior to breakfast and dinner.
- Tenapanor supplied as 10 mg tablets in trials. Dose could be down titrated or up titrated in a stepwise fashion to a maximum of 30 mg twice a day based on s-P levels and/or gastrointestinal tolerability; participants took one to three tablets twice a day to achieve total daily doses of 20, 40, or 60 mg tenapanor.
- On dialysis days, patients on hemodialysis instructed not to take study drug at the meal prior to dialysis and instead to take it before another meal.
- If a meal was skipped, dose was to be taken with another meal during the day or at around the time that the meal would have been consumed.

Key Datasets Defined by the Applicant

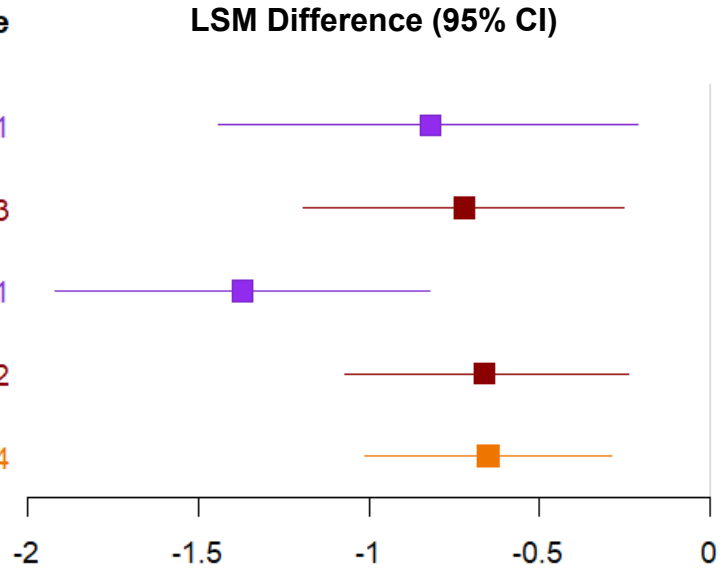
- For TEN-02-201 and TEN-02-301:
  - Intent-to-Treat (ITT): All subjects who
    - met the study entry inclusion/exclusion criteria, and
    - completed the RT period, entered the RW period, and
    - received at least 1 dose of study drug during the RW period, and
    - had at least 1 post-treatment s-P measurement during the RW period
  - Efficacy Analysis Set (EAS): All ITT subjects who achieved **a reduction of ≥1.2 mg/dL** in s-P level from baseline to the end of the RT period
- For TEN-02-202:
  - Intent-to-treat (ITT): All randomized subjects
  - Full Analysis Set (FAS): All ITT subjects who had at least one post-baseline s-P measurement during the study

Subject Disposition for Three Studies



Primary Efficacy Results for Change in s-P from Period-Level Baseline to End of Study

Study	Dataset	Placebo (N)	Tenapanor (N)	LSM Difference (v.s. Placebo)	P-value
TEN-02-201[1,2]	EAS	37	43	-0.8	0.01
	ITT	82	82	-0.7	0.003
TEN-02-301[1,3]	EAS	68	63	-1.4	<0.0001
	ITT	123	120	-0.7	0.002
TEN-02-202[1]	FAS	119	116	-0.7	0.0004



1. Primary analysis method: the ANCOVA model for TEN-02-201 and TEN-02-301; the MMRM approach for TEN-02-202
2. Sensitivity analyses using MMRM for TEN-02-201: -0.9 and -0.8 for the EAS and the ITT, respectively
3. Sensitivity analyses using MMRM for TEN-02-301: -1.4 and -0.7 for the EAS and the ITT, respectively

Abbrev.: LSM: least squares mean; EAS: efficacy analysis set; ITT: intent-to-treat; CI: confidence interval; ANCOVA: analysis of covariance; MMRM: mixed model for repeated measures

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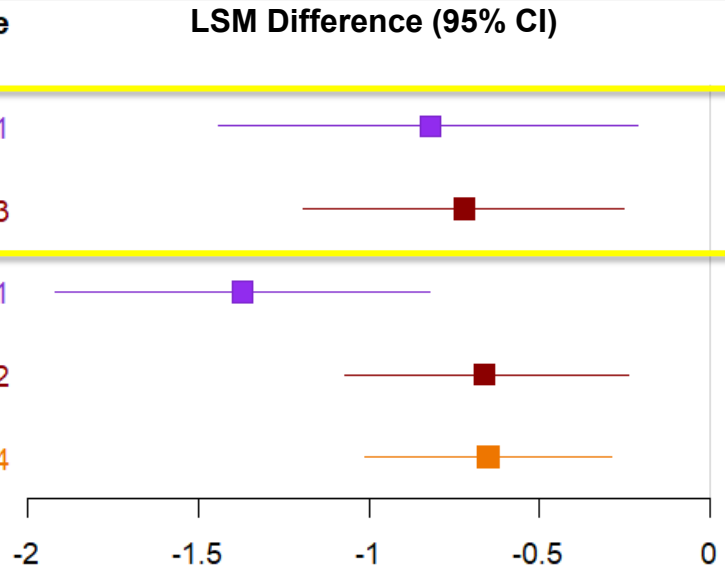

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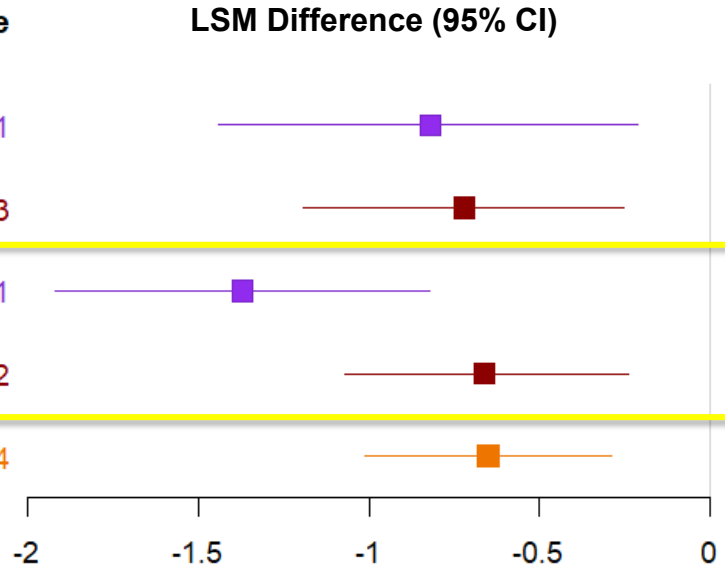

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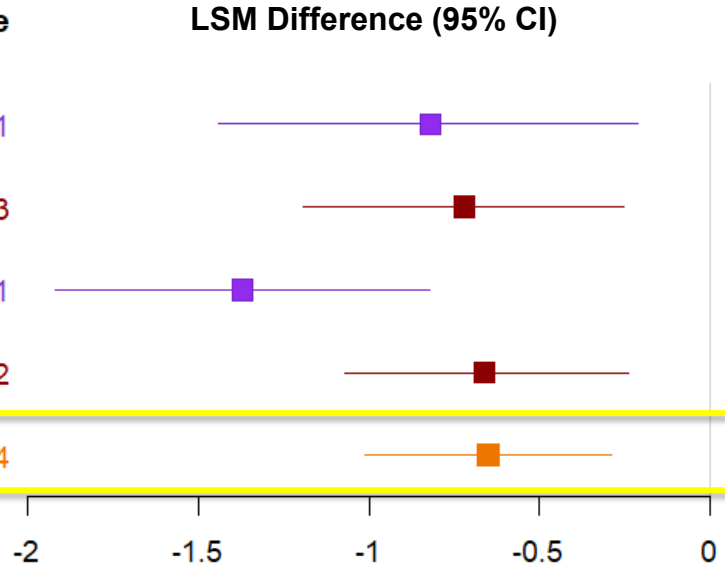

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Concluding Remarks

TEN-02-201 and TEN-02-301:

- Although the estimate of the average treatment effect in the 2 studies was similar in the ITT population, the average treatment effect differs in the EAS

Study	ITT	EAS
TEN-02-201	-0.7 (0.24)	-0.8 (0.31)
TEN-02-301	-0.7 (0.21)	-1.4 (0.28)

- Only about 1/3 of the subjects who started tenapanor were included in the EAS

Study	Randomized to Tenapanor initially	ITT (RW period)	EAS (RW period)
TEN-02-201	219	164 (75%)	80 (37%)
TEN-02-301	423	243 (57%)	131 (31%)

Concluding Remarks

- Analyses of the ITT populations provide perhaps the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on therapy

- Tenapanor's average treatment effect on s-P when used in patients who tolerate and remain on therapy is about -0.7 mg/dL
  - TEN-02-201 for ITT population: -0.7 mg/dL, 95% CI: (-1.19, -0.25)
  - TEN-02-301 for ITT population: -0.7 mg/dL, 95% CI: (-1.07, -0.24)
  - TEN-02-202 for FAS: -0.7 mg/dL, 95% CI: (-1.01, -0.29)

- The magnitude of tenapanor's effect appears to be less than that observed with approved agents, which lowered s-P levels by ~1.5 to 2.2 mg/dL.

Is it possible to use a patient's early response to treatment to identify patients who are "responders"?

Exploration in Usage of s-P Early Response

- Ideally, the strategy used to identify patients with a meaningful response to tenapanor would identify these patients early in the course of treatment, so that patients with a poor response can switch to a more effective therapy
- FDA explored this issue from several perspectives
  - Whether the strategy used in Studies TEN-02-301 and TEN-02-201 can identify patients with a meaningful response to tenapanor
  - Whether patients who responded well to tenapanor in the early weeks would likely also respond well in the later weeks

Strategy Used in Studies TEN-02-301 and TEN-02-201

- Primary analysis in Studies TEN-02-301 and TEN-02-201 used a subset of subjects who entered the RW period: Subjects who achieved a reduction of ≥1.2 mg/dL in s-P level from baseline to the end of the RT period (EAS)

- The treatment effect in this subset of population was inconsistent between Studies TEN-02-201 and TEN-02-301

Study	ITT	EAS
TEN-02-201	-0.7	-0.8
TEN-02-301	-0.7	-1.4

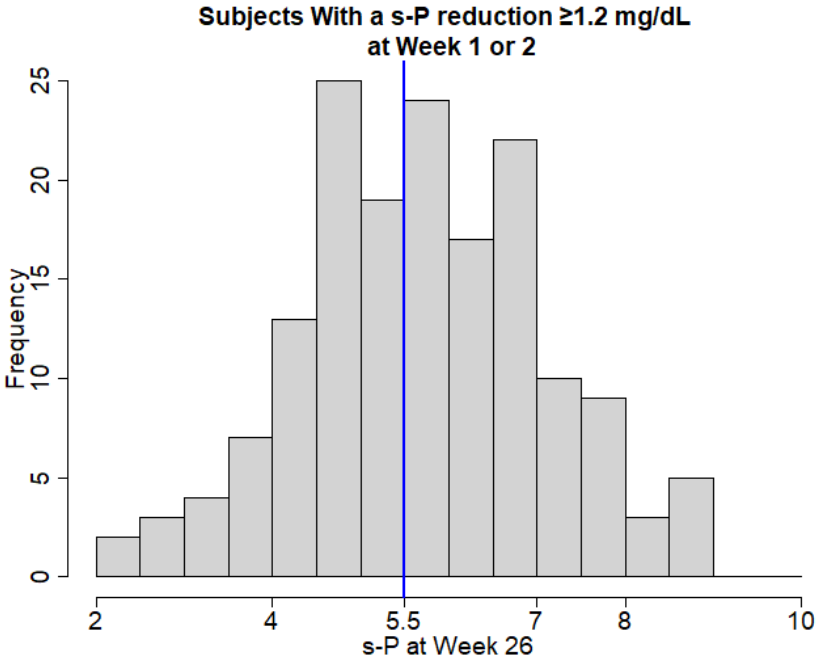
Exploratory Analysis: 26-Week RT Period, TEN-02-301

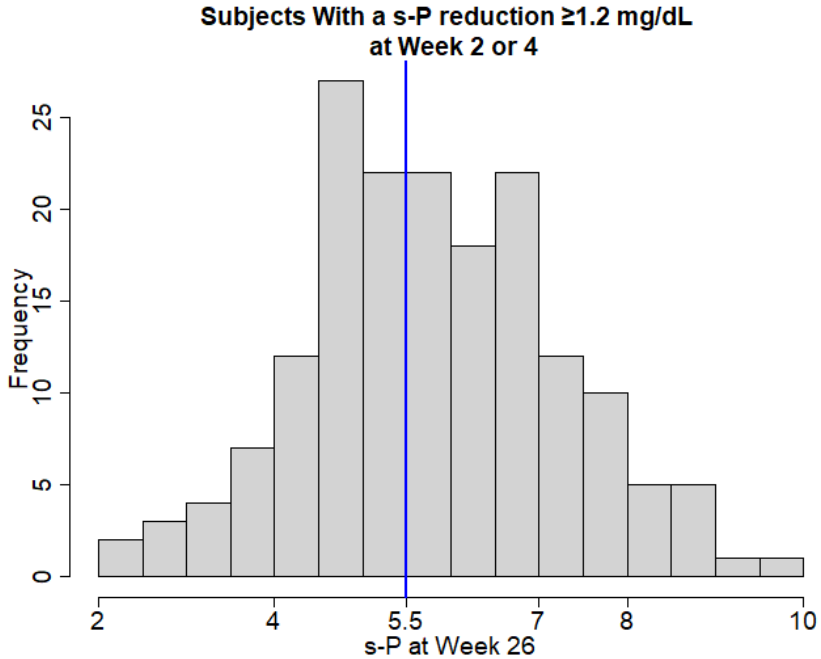
- Focused on subjects who achieved a s-P reduction ≥1.2 mg/dL in early weeks
  - Less than 50% of these subjects also maintained the s-P reduction level ≥1.2 mg/dL at Week 26
  - Less than 30% of these subjects had a s-P <5.5 mg/dL at Week 26

Group	Subjects reached a s-P reduction ≥1.2 mg/dL at Week 1 or Week 2		Subjects reached a s-P reduction ≥1.2 mg/dL at Week 2 or Week 4	
	Yes (N=250)	No (N=157)	Yes (N=258)	No (N=149)
Week 26 a s-P reduction ≥1.2 mg/dL	110 (44%)	24 (15%)	116 (45%)	18 (12%)
Week 26 s-P <5.5 mg/dL	68 (27%)	32 (20%)	72 (28%)	28 (19%)

*Patients with missing data at a particular visit were treated as not reaching a ≥1.2 mg/dL reduction in s-P (worst-case imputation approach)

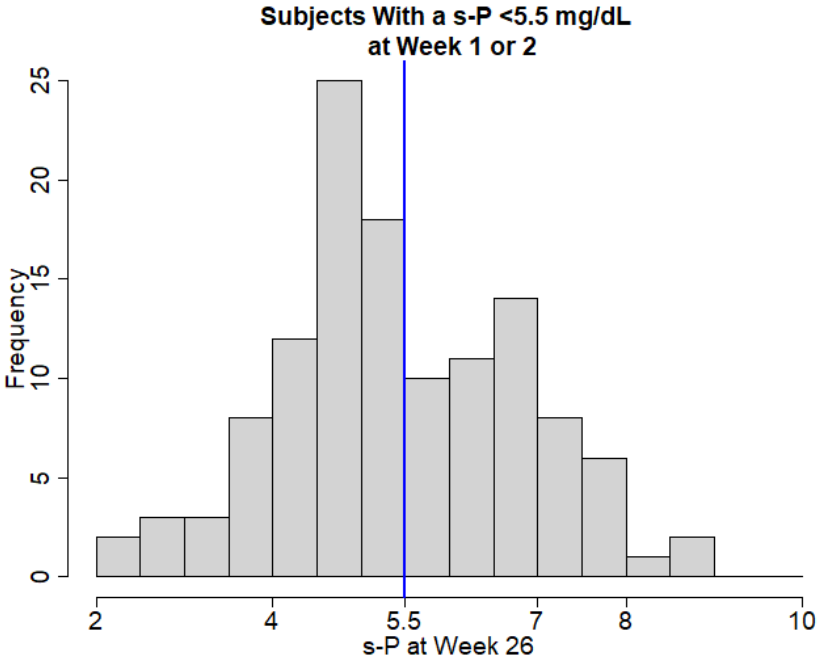
Distributions of s-P at Week 26 for Subjects Achieving a s-P Reduction ≥1.2 mg/dL in the Early Weeks of the 26-Week RT Period, TEN-02-301

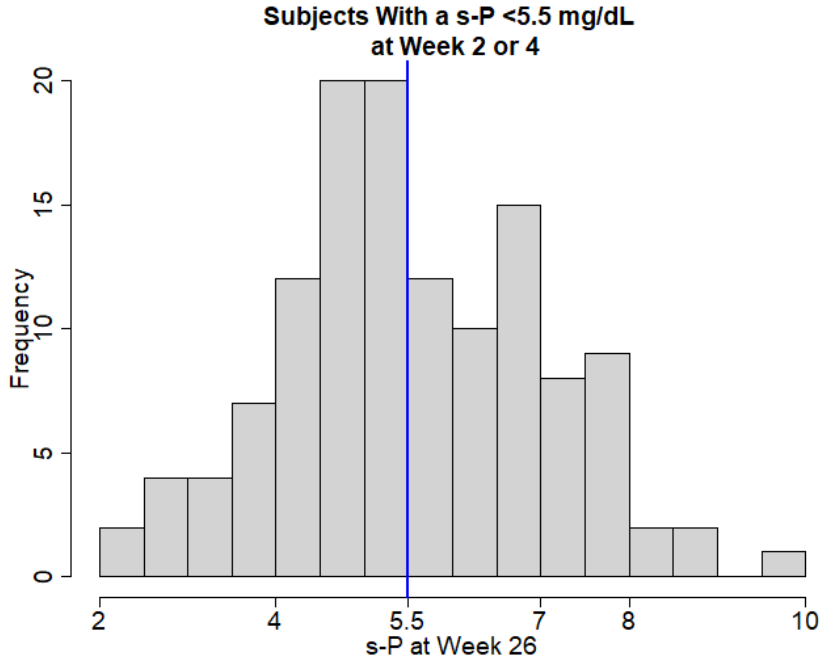




*Observed valves were used at Week 26

Distributions of s-P at Week 26 for Subjects Reaching a s-P <5.5 mg/dL in the Early Weeks of the 26-Week RT Period, TEN-02-301





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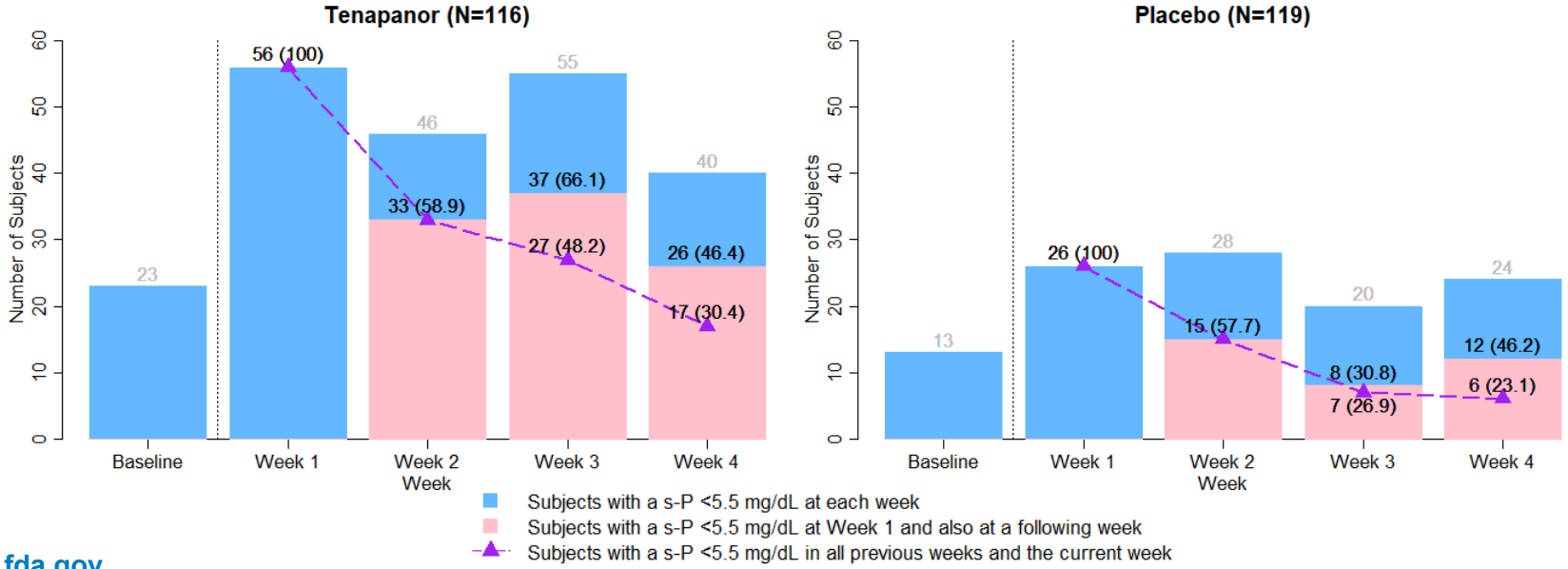
Exploration for s-P Lowering in TEN-02-202 (4-Week, Placebo-Control)

- Focused on subjects who <u>achieved a s-P <5.5 mg/dL in Week 1 of RW period</u>
  - 30% of these subjects on tenapanor (and 23% on placebo) had a s-P <5.5 mg/dL at each weekly assessment (purple triangle with dashed lines)



Concluding Remarks

- It may be possible to individualize treatment based on a patient's early response to tenapanor. However, further data are needed to support the efficacy of a specific strategy.

- If such a strategy were to be implemented, it would likely need to take into consideration the variability in s-P measurements.

Outline

- s-P as a surrogate for clinical outcomes and regulatory context/framework
- Efficacy
- Safety

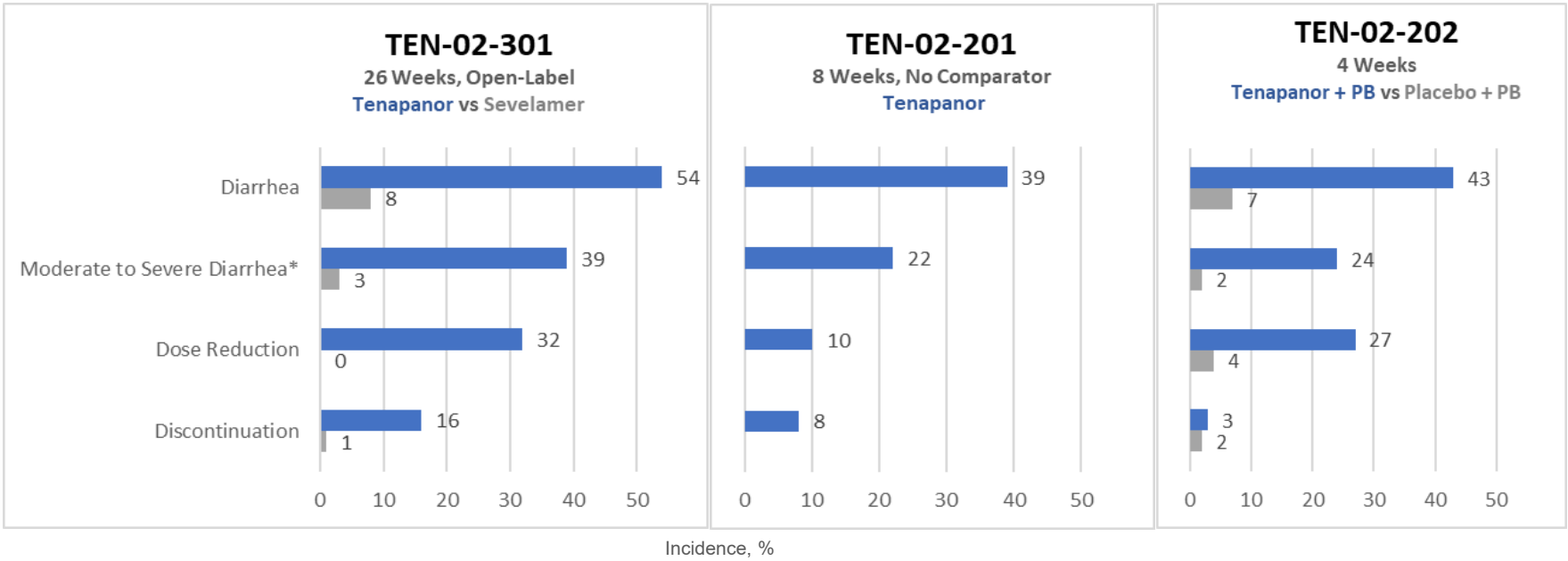
Overview of Safety

- Tenapanor is designed to act locally in the gastrointestinal (GI) tract and is minimally absorbed
- Tenapanor is already approved in the United States (US) at a higher dose in adults with irritable bowel syndrome with constipation (IBS-C), and has a labeled warning for severe diarrhea
- The overall safety analysis did not identify significant safety concerns for patients with CKD on dialysis, other than diarrhea

Overview of Safety for Diarrhea

- The safety analysis for diarrhea focused on the initial treatment periods of the studies -301 and -201, and all of -202
  - High incidence of early withdrawal for diarrhea limited interpretability of data collected later in the trials
  - There were no blinded initial treatment periods comparing tenapanor monotherapy to placebo
- The safety analysis for diarrhea focused on the moderate to severe cases

Diarrhea for Tenapanor



* Moderate: The patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
Severe: The patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

Abbreviations: PB, phosphate-binder (existing treatment was maintained)

Diarrhea Case Characteristics

- Most moderate to severe cases were reported within the first week and continued for a mean duration of 43 days
- Serious cases of diarrhea included intractable diarrhea and dehydration resulting in hospitalizations
- Most cases resolved after dose modification or discontinuation of tenapanor
- Predictive baseline characteristics for severity (such as age, weight, s-P) could not be identified

Safety: Conclusions

- Tenapanor is associated with moderate to severe diarrhea in CKD patients on dialysis
- Diarrhea is associated with significant dose modification and discontinuations of tenapanor monotherapy
- There is uncertainty regarding whether the safety profile observed in the studies underestimates the magnitude and severity of clinical sequelae in the real-world setting, and whether diarrhea and its impact on tolerability will limit adherence to long-term treatment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