Tenapanor for the Control of Serum Phosphate (s-P) in Adults with Chronic Kidney Disease (CKD) on Dialysis

November 16, 2022

Cardiovascular and Renal Drugs Advisory Committee Meeting

Ardelyx, Inc.

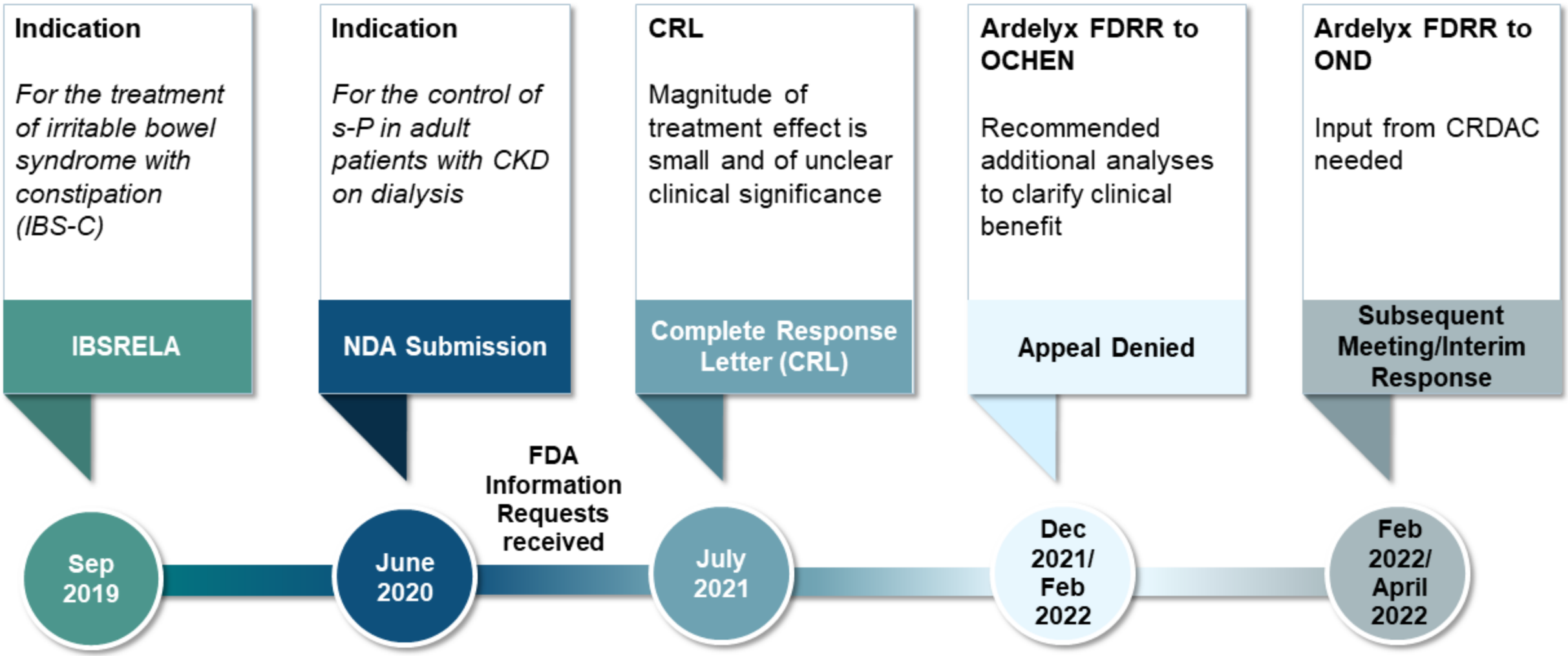
Introduction

Laura A. Williams, MD, MPH

Chief Medical Officer

Ardelyx, Inc.

Tenapanor Regulatory History



Alignment Between FDA and Ardelyx

Alignment

- Hyperphosphatemia is a serious, common complication in patients on maintenance dialysis
- ***"Based on these data [existing data] as well as biological plausibility, FDA has accepted treatment effects on s-P as a valid surrogate endpoint and basis for approval of products intended to treat hyperphosphatemia in patients with CKD on dialysis"***[1]
- Unmet need for safe and effective therapies that lower pill burden and allow more patients to achieve guideline-directed treatment goal

1. FDA Briefing Document (NDA# 213931)

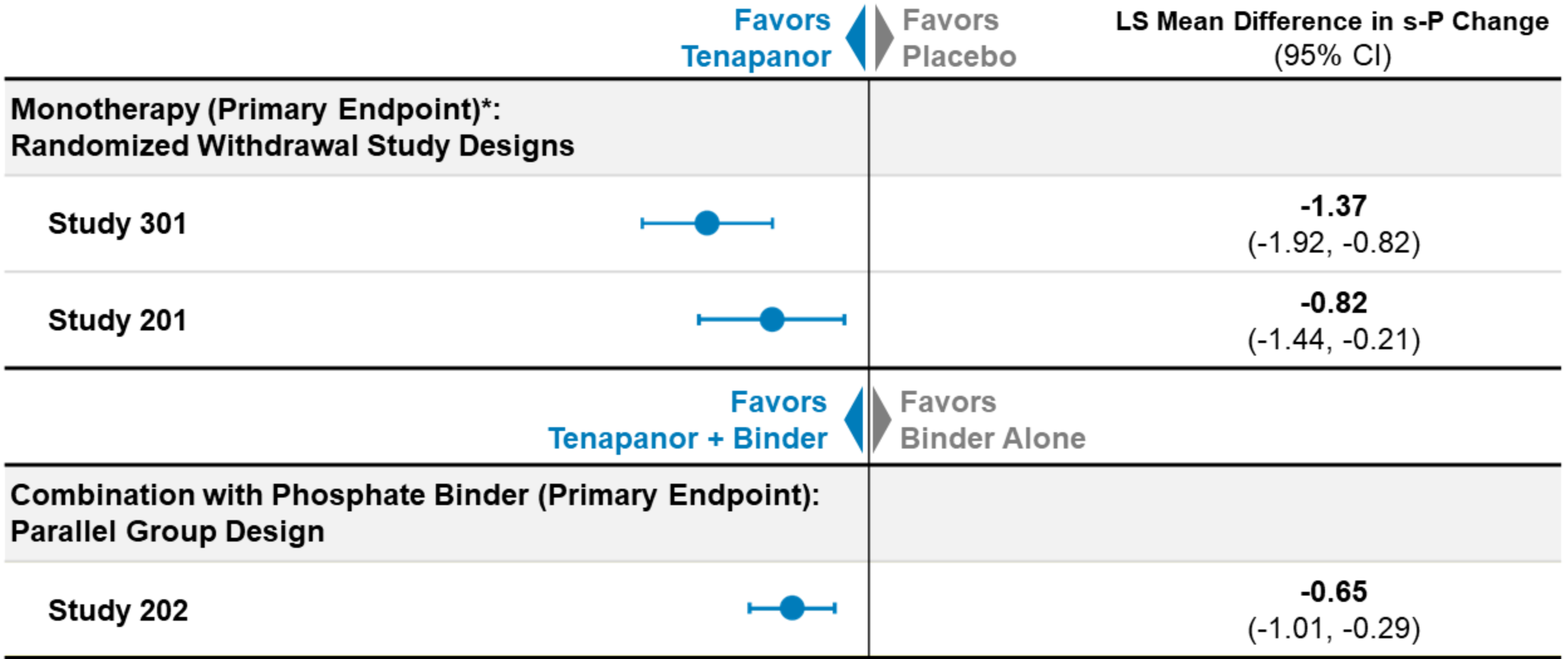
FDA Agrees Tenapanor Demonstrates Efficacy and Safety

FDA CRL and Briefing Document

- Clinical trial designs, study conduct, and results of 3 registration trials in tenapanor clinical development program
- ***"…we agree that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis…"[1]***
- ***"…with the exception of diarrhea and tolerability issues resulting in discontinuation of tenapanor or dose reductions, safety analyses did not raise significant concerns."[2]***

1. Complete Response Letter (CRL); 2. FDA Briefing Document (NDA# 213931)

All Phase 3 Studies Successful, Meeting Prespecified Primary Efficacy Endpoints



LS = least squares

*Studies 301 and 201 data from predefined Efficacy Analysis Population (EAS)

FDA Key Question: Clinical Meaningfulness of s-P Lowering with Tenapanor

Key FDA Question	Ardelyx Position
What is the magnitude of serum phosphorus reduction achieved with tenapanor and is it clinically meaningful? a. As monotherapy? b. In combination with existing phosphate binder treatment?	▪ Prespecified primary analysis yielded mean treatment difference (RWP) of ▪ -0.8 and -1.4 mg/dL (2 monotherapy studies) ▪ -0.7 mg/dL (combination therapy study) ▪ Secondary analysis yielded -0.7 mg/dL treatment difference (RWP responders and non-responders) ▪ RTP (enrichment phase) data showed mean s-P reduction of 1.4 mg/dL, with significant number of patients achieving clinically meaningful s-P reductions and target treatment goals (in setting of positive control) ▪ Novel mechanism of action and simplified dosing regimen (1 small pill twice a day) also clinically meaningful, providing another option for s-P lowering, as monotherapy or in combination with phosphate binders

- Ardelyx agrees with expert nephrologists on clinical relevance of tenapanor's treatment effect

RWP: randomized withdrawal period; RTP: randomized treatment period

FDA Key Discussion Point: Ability to Predict Continued Response or Non-Response

Key Discussion Point	Ardelyx Position
Identifying a responder population to support clinical utility of tenapanor	▪ Early response or non-response predicted continued response or non-response ▪ Allowing nephrologists to assess and optimize benefit relatively early

- Standard practices of monthly s-P monitoring align with ability to effectively manage patients
  - Prolonged use of tenapanor with minimal benefit would be avoided

FDA Key Discussion Point: Most Common Adverse Reaction is Diarrhea

Key Discussion Point	Ardelyx Position
Diarrhea most common adverse reaction in clinical trials	▪ Easily managed tolerability issue; not a major safety concern ▪ Softer stool consistency and diarrhea - expected pharmacodynamic effect of tenapanor that is easily managed ▪ Data, including the long-term safety studies, show that these potential downstream consequences of diarrhea were rarely observed

- Overall safety and tolerability profile is acceptable

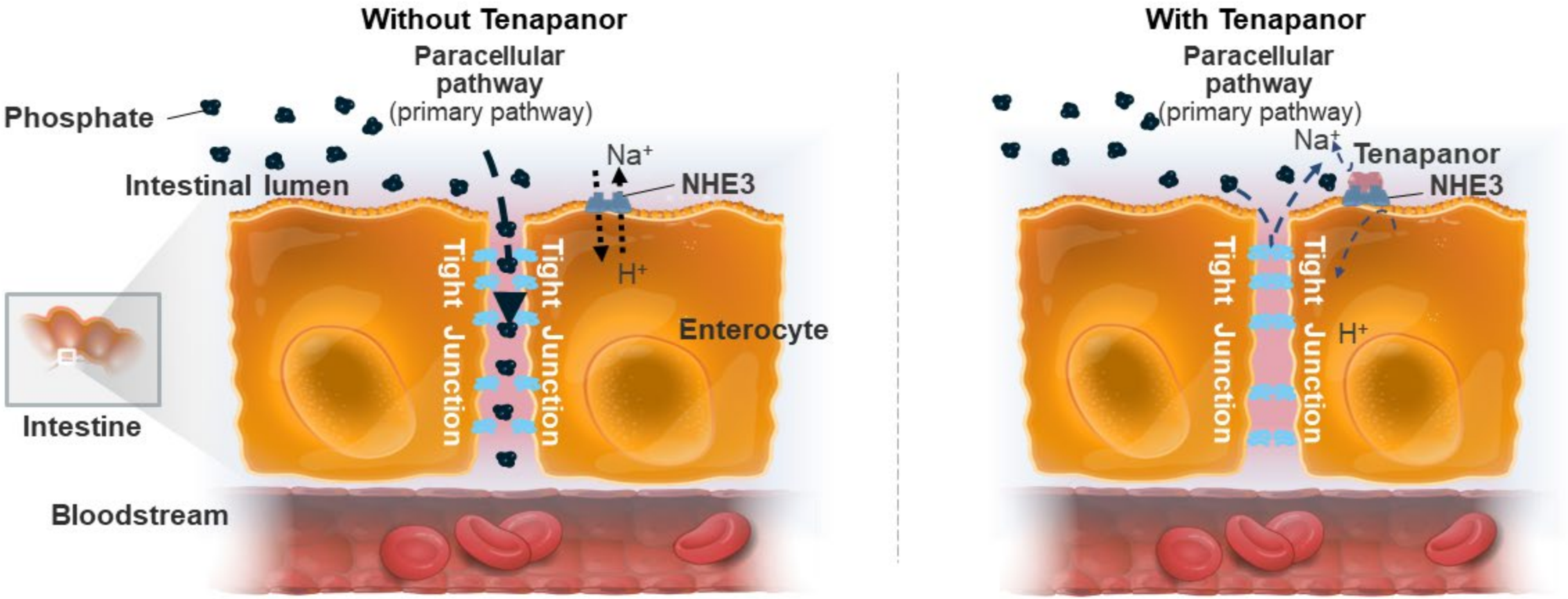
FDA Key Question: Benefit-Risk Assessment

Key FDA Question	Ardelyx Position
Do the benefits of control of s-P with tenapanor in CKD patients on maintenance dialysis outweigh its risk? a. As monotherapy? b. In combination with existing phosphate binder treatment?	▪ **Tenapanor:** first-in-class, phosphate absorption inhibitor demonstrated safety and efficacy in reducing s-P in patients with hyperphosphatemia on maintenance dialysis ▪ Novel treatment option (monotherapy or in combination with phosphate binders) with simplified dosing regimen (fewer, smaller pill; 1 pill twice a day) ▪ Met prespecified efficacy endpoints in 3 controlled registration studies ▪ Demonstrated clinically meaningful effect (in positive control setting), with meaningful number of patients achieving s-P threshold reductions and target treatment goals, consistent with existing phosphate-lowering therapy ▪ Early response predicted continued response ▪ Acceptable safety/tolerability

- Totality of evidence for tenapanor demonstrates positive benefit-risk assessment

Tenapanor Provides a Novel Approach (Non-Binder Option) to Managing Serum Phosphate

Tenapanor is a small molecule that inhibits NHE3, and it is minimally absorbed



NHE3 = sodium hydrogen exchanger isoform 3

Agenda for Sponsor's Presentation

Unmet Need	**Glenn Chertow, MD** Norman S. Coplon/Satellite Healthcare Professor of Medicine Professor of Epidemiology and Population Health Stanford University School of Medicine
Study Design Considerations	**Jason Connor, PhD** President and Lead Statistical Scientist Confluence Stat LLC
Efficacy and Clinical Meaningfulness	**David Spiegel, MD** VP Nephrology Ardelyx, Inc.
Safety	**Laura A. Williams, MD, MPH** Chief Medical Officer Ardelyx, Inc.
Clinical Perspective	**Stuart Sprague, DO** Chairperson, Division of Nephrology and Hypertension NorthShore University Health System

Additional External Responders

Eugene Poggio, PhD
President and Chief Biostatistician
Biostatistical Consulting Inc.

Josephine Torrente
Director
Hyman, Phelps & McNamara, P.C.

Unmet Need

Glenn Chertow, MD

Norman S. Coplon/Satellite Healthcare Professor of Medicine
Professor of Epidemiology and Population Health
Stanford University School of Medicine

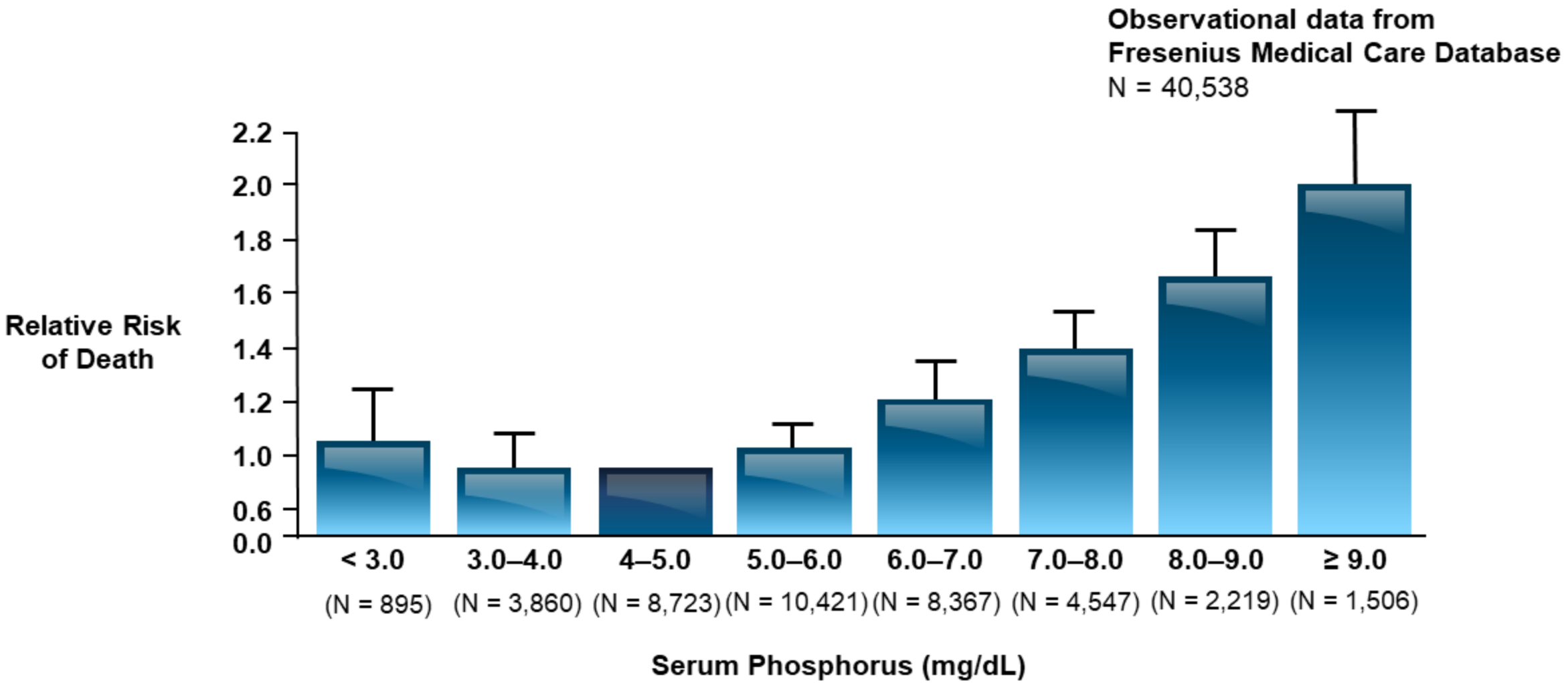
Hyperphosphatemia Matters to Patients and Clinicians

- Condition with tremendous clinical consequences
- High prevalence in patients receiving maintenance dialysis
- Hyperphosphatemia leads to
  - Worsening secondary hyperparathyroidism
  - Increased risk of fracture
  - Vascular and heart valve calcification
  - Calciphylaxis
- Phosphorous not efficiently removed with conventional 3x/week hemodialysis

Associated Risks of Hyperphosphatemia Not Anchored to Specific s-P Threshold

- s-P accepted surrogate
  - No existing randomized controlled trial demonstrates amount of s-P lowering needed to improve clinical outcomes
- Clinical guidelines, standard of care for patients on maintenance dialysis, FDA approval of phosphate binders based on observational studies

Hyperphosphatemia and Mortality in Hemodialysis



Block GA, et al. 2004
Adjusted for case mix and other laboratory values

Fundamental Objective of Nephrologists is to Lower Serum Phosphate Levels Toward Normal Range[1-3]

Kidney Disease

KDIGO

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES – Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD

KDIGO guidelines **(2017)** recommend in patients with CKD stages G3A–G5D, **lowering** elevated serum phosphate levels **toward the normal range[2] (2.5 - 4.5 mg/dL)**[3]

National Kidney Foundation

KDOQI

KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE

KDOQI guidelines **(2003)** recommend that in patients with CKD stage 5, and those treated with dialysis, the serum levels of phosphate should be maintained between **3.5 - 5.5 mg/dL**[1]

1. National Kidney Foundation. 2003; 2. Kidney Disease: Improving Global Outcomes (KDIGO), 2017; 3. Fouque D, et al. 2018

Approaches to Help Control s-P in Patients Receiving Dialysis

Treatment approach	
Reduce dietary phosphate intake	▪ Need to restrict processed foods ▪ Often difficult for patients, especially with limited resources ▪ Can complicate other dietary restrictions imposed by concomitant diabetes, hypertension, and hyperlipidemia
Increase frequency or extend duration of hemodialysis	▪ ≥ 4 times per week for ≥ 4 hours adds to immense dialysis burden already experienced by patients

Most Patients on Maintenance Dialysis Prescribed Phosphate Binders With High Pill Burden

- Binds luminal phosphate in intestine allowing larger fraction to be eliminated
- Patients typically take 3 tablets or capsules with each meal
- Many take 2 types of binders, without achieving s-P targets
- Median overall daily pill burden reported to be 19[1]

Median Daily Phosphate Binder Dose[1,*]

Weekly Phosphate Binder Dose

1. Chiu, Y, et al. 2009; *Sevelamer

Unmet Need for Additional Treatment Option With Alternative Mechanism of Action

- Patients unable to achieve target range on phosphate binders[1]
  - 42% at any given month
  - 77% over 6-month period
- Current binder options are inadequate
- Physicians use multiple agents with different MoA to achieve treatment goals
- Mean values in range of s-P reduction (0.7 – 1.4 mg/dL) clinically meaningful
  - Even modest improvements in s-P can result in higher proportion of patients achieving target

1. Spherix Global Insights RealWorld Dynamix, 2019

What Do We Need?

- More options to manage s-P to help more patients achieve target s-P concentrations recommended by clinical practice guidelines
- Therapies with alternative mechanisms of action that can be used alone or in combination with phosphate binders
- Simplified dosing regimen (fewer pills, smaller pills, BID dosing)
- Favorable safety and tolerability profile

Demonstrated benefits with tenapanor are clinically meaningful and could materially improve management

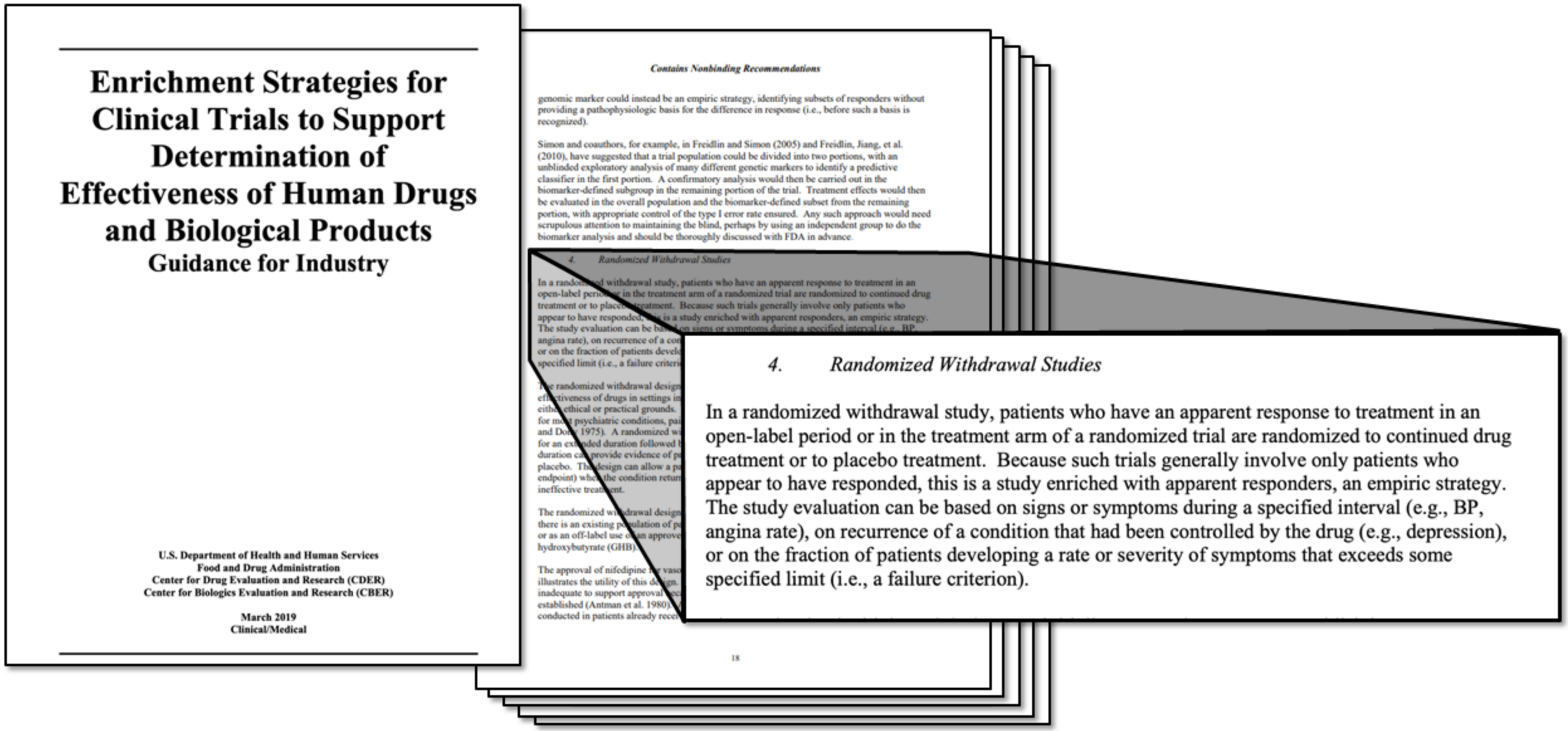
Study Design Considerations

Jason Connor, PhD

President & Lead Statistical Scientist at ConfluenceStat LLC

Assistant Professor of Medical Education University of Central Florida, College of Medicine

Tenapanor Program Relied on FDA Guidance for Enrichment Strategy



Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2019
Clinical/Medical

Contains Nonbinding Recommendations

genomic marker could instead be an empiric strategy, identifying subsets of responders without providing a pathophysiologic basis for the difference in response (i.e., before such a basis is recognized).

Simon and coauthors, for example, in Freidlin and Simon (2005) and Freidlin, Jiang, et al. (2010), have suggested that a trial population could be divided into two portions, with an unblinded exploratory analysis of many different genetic markers to identify a predictive classifier in the first portion. A confirmatory analysis would then be carried out in the biomarker-defined subgroup in the remaining portion of the trial. Treatment effects would then be evaluated in the overall population and the biomarker-defined subset from the remaining portion, with appropriate control of the type I error rate ensured. Any such approach would need scrupulous attention to maintaining the blind, perhaps by using an independent group to do the biomarker analysis and should be thoroughly discussed with FDA in advance.

4. Randomized Withdrawal Studies

In a randomized withdrawal study, patients who have an apparent response to treatment in an open-label period or in the treatment arm of a randomized trial are randomized to continued drug treatment or to placebo treatment. Because such trials generally involve only patients who appear to have responded, this is a study enriched with apparent responders, an empiric strategy. The study evaluation can be based on signs or symptoms during a specified interval (e.g., BP, angina rate), on recurrence of a condition that had been controlled by the drug (e.g., depression), or on the fraction of patients developing a rate or severity of symptoms that exceeds some specified limit (i.e., a failure criterion).

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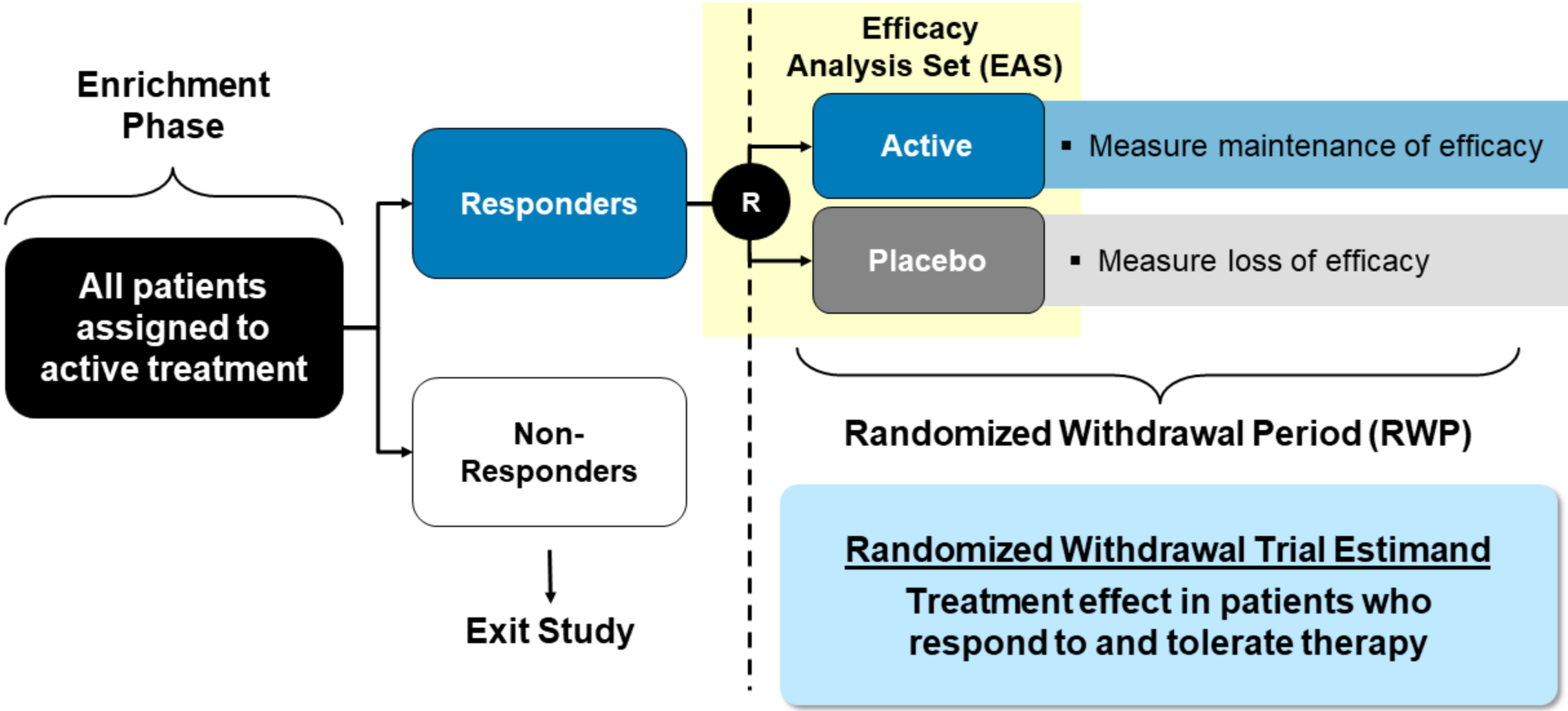
Typical Randomized Withdrawal (RW) Study Offers Straightforward Enrichment Strategy



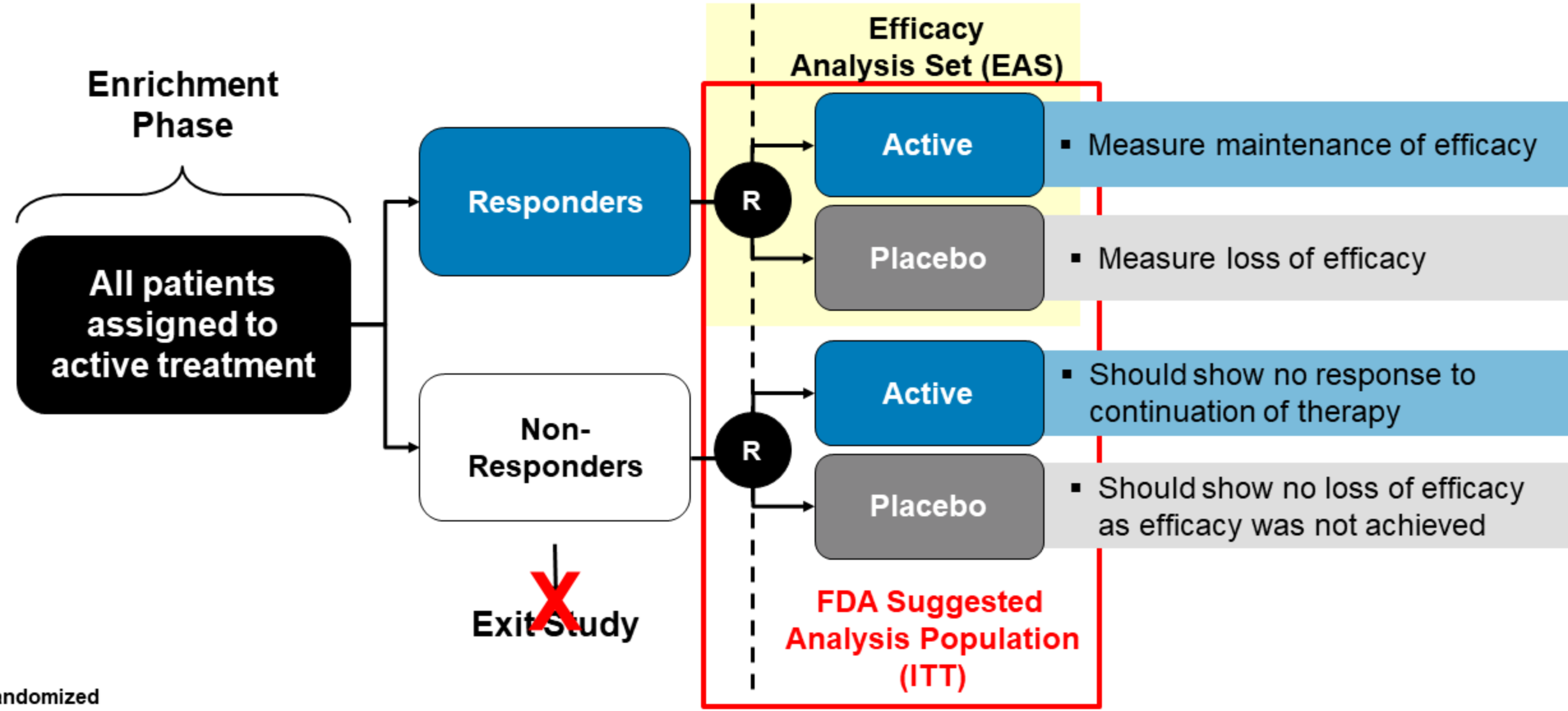
R = randomized

FDA Briefing Document

Analyses based on the ITT population of the RW periods in Study TEN-02-201 and Study TEN-02-301 provide perhaps the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on therapy.

-FDA Briefing Document

Sponsor's Study Design Efficacy Analysis Set Follows Typical Randomized Withdrawal (RW)



R = randomized
Sponsor's studies 201 and 301 with randomized withdrawal (RW) design

Precedent Established from Randomized Withdrawal Studies

	Approval	Indication	N	% in Efficacy Analysis Set
Veltassa (patiromer sorbitex calcium)	10/21/2015	Hyperkalemia	92	44%
Palynziq (pegvaliase-pqpz)	5/24/2018	Phenylketonuria	164	52%
Lyrica CR (pregabalin)	6/21/2007 10/11/2017	Fibromyalgia Postherpetic neuralgia	256 418	52% 61%
Auryxia (ferric citrate)	9/5/2014	Hyperphosphatemia	192	66%
Jynarque (tolvaptan)	4/23/2018	ADPKD	1519	90%
Hetlioz (tasimelteon)	1/30/2014	Non-24-Hour Sleep-Wake Disorder	20	*Unable to determine*
Stelara (ustekinumab)	9/23/2016	Crohn's disease	388	*Unable to determine*
Velphoro (sucroferric oxyhydroxide)	12/3/2013	Hyperphosphatemia	694	*Unable to determine*
Fosrenol (lanthanum carbonate)	10/26/2004	Hyperphosphatemia	185	*Unable to determine*
Viberzi (eluxadoline)	5/27/2015	IBS with diarrhea	1145	*Unable to determine*

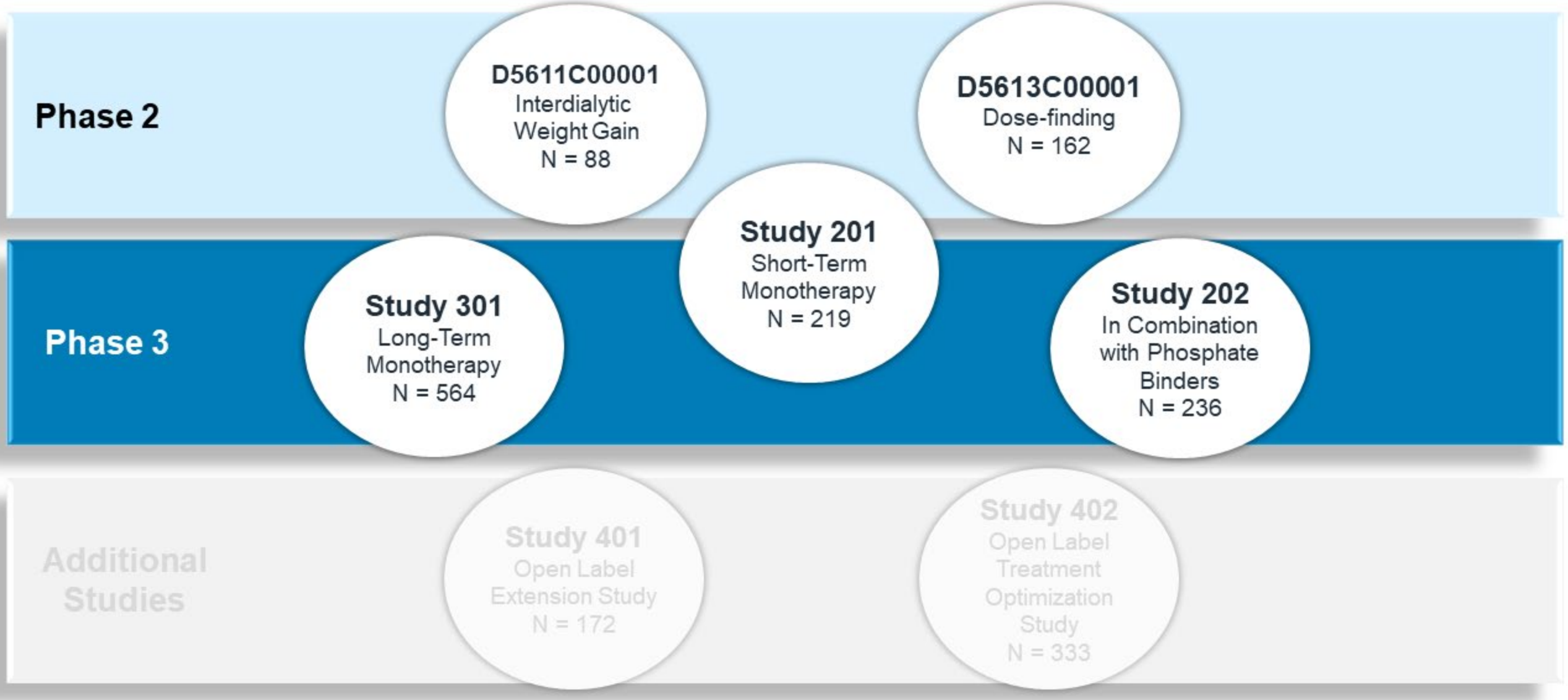
Efficacy

David Spiegel, MD

Vice President of Nephrology

Ardelyx, Inc.

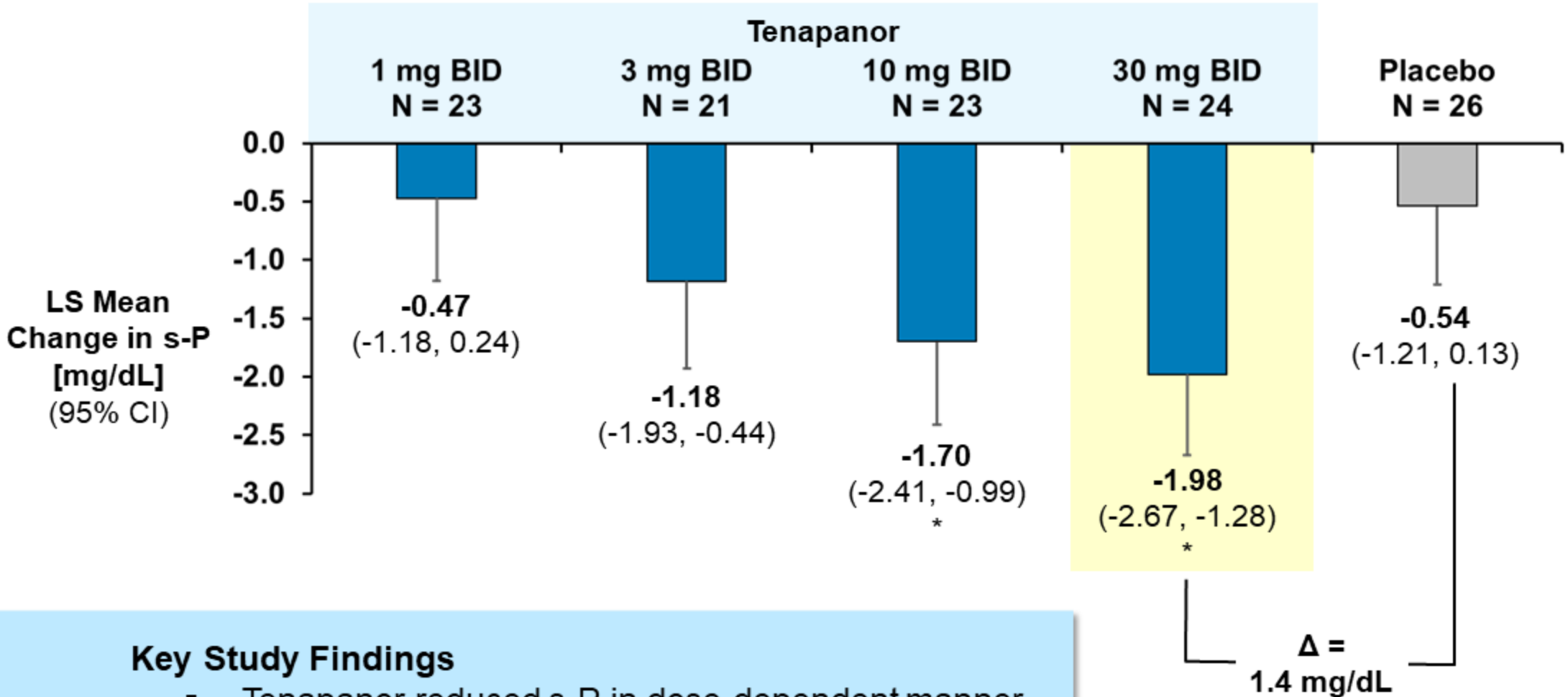
Tenapanor Clinical Development Program



Phase 2b D5613C00001 Dose Selection Study

Randomized, Double-Blind, Placebo-Controlled

Phase 2b Dose Selection Study D5613C00001: Absolute Change from Baseline in s-P



Key Study Findings

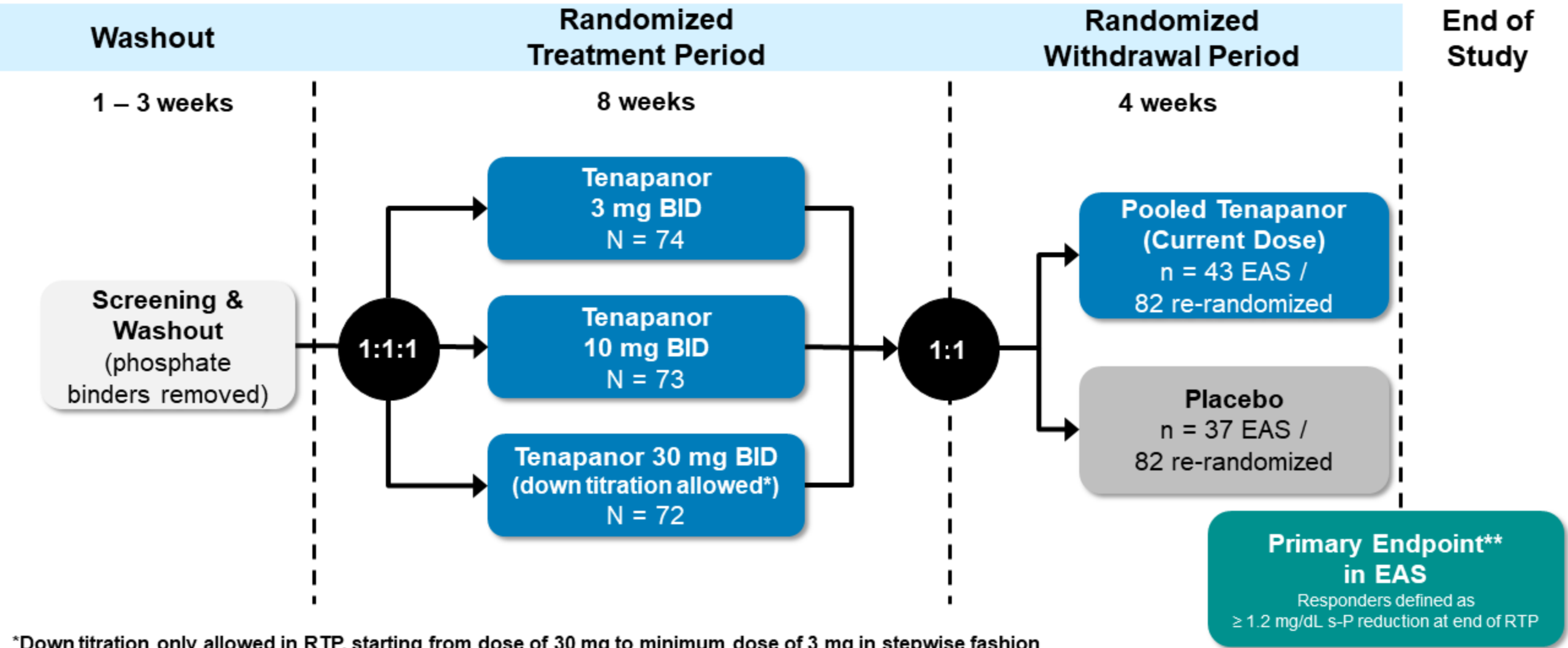
- Tenapanor reduced s-P in dose-dependent manner
- Most pronounced s-P lowering with 30 mg BID

*$p < 0.05$ vs placebo

Phase 3 Study 201: Short-term Monotherapy with Tenapanor

12-week trial with 4-week comparison to placebo with randomized withdrawal design

Study 201: 12-Week Phase 3 Study Design

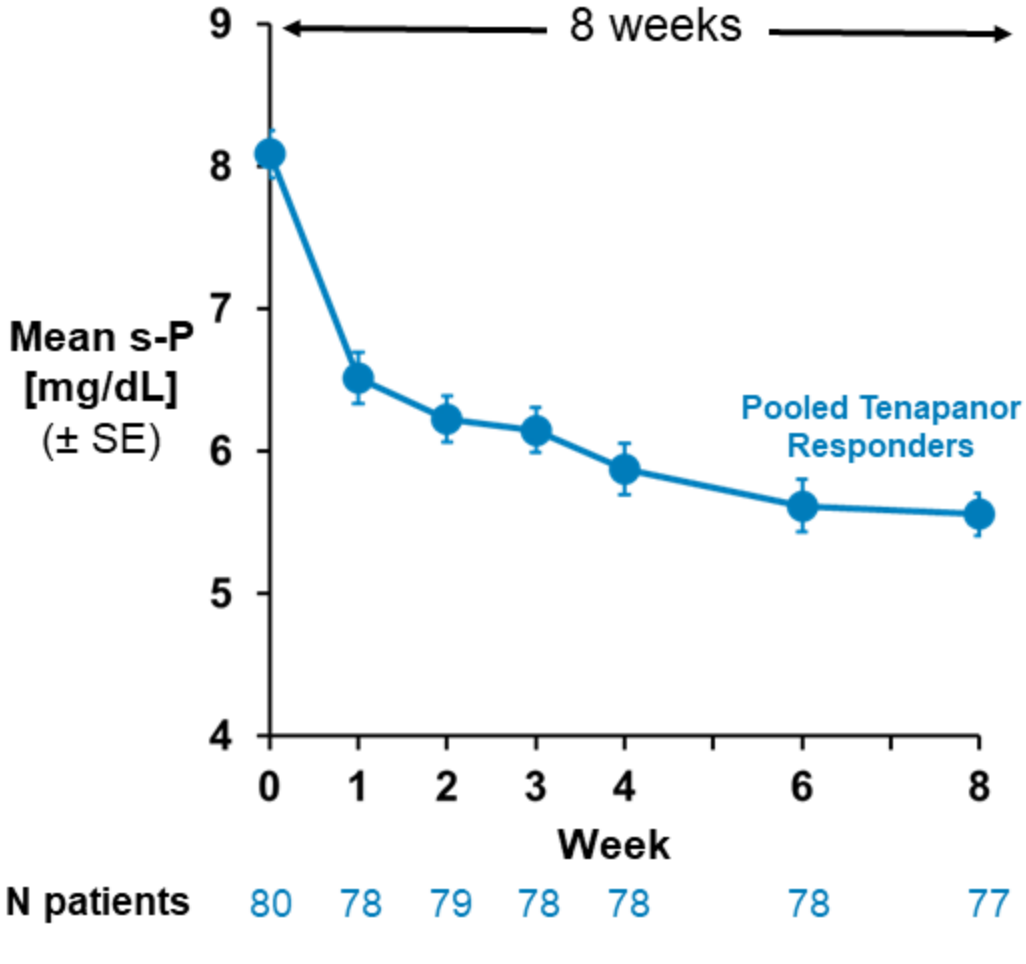


*Down titration only allowed in RTP, starting from dose of 30 mg to minimum dose of 3 mg in stepwise fashion

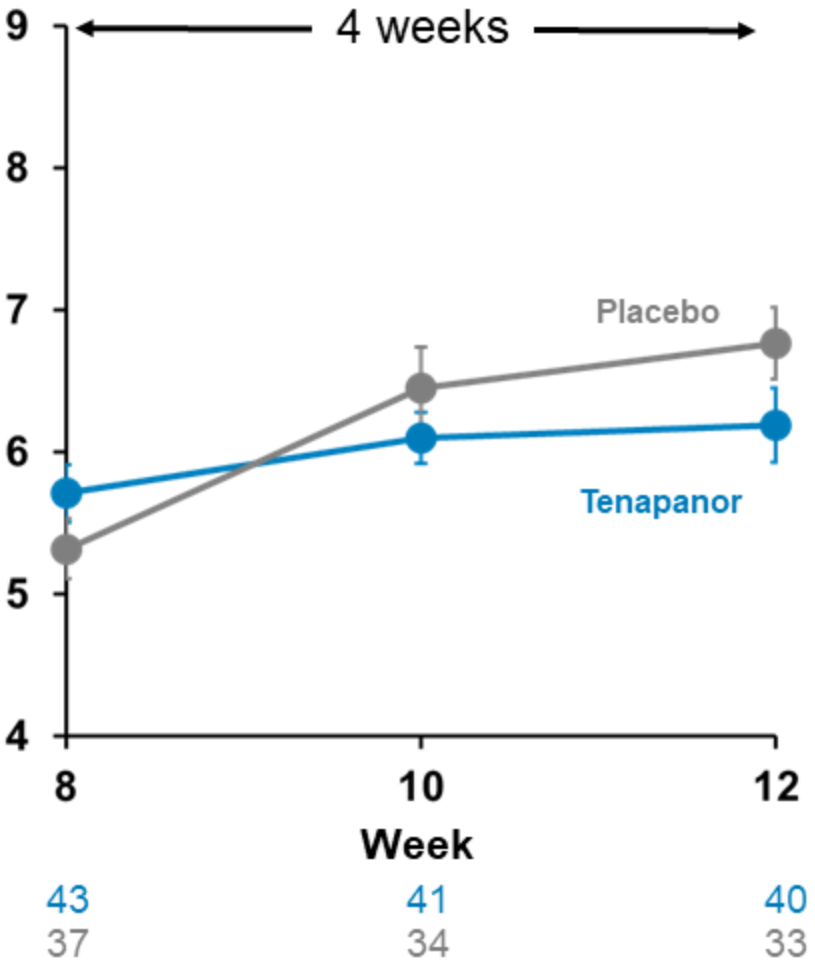
**Difference in s-P change from RWP baseline to end of RWP between pooled tenapanor and placebo in the EAS

Study 201: Decrease in s-P Evident in First Few Weeks and Persisted for Tenapanor-Treated Patients; Met Primary Endpoint

RTP s-P by Visit for Responders Entering RWP (EAS)



RWP s-P by Visit for EAS



Primary Endpoint	TEN	PBO
LS mean Δ from RWP baseline	0.56	1.38
LS Mean Difference (95% CI)	-0.82 (-1.44, -0.21)	
p-value	p = 0.010	

EAS: defined as those patients who entered RWP with ≥ 1.2 mg/dL reduction

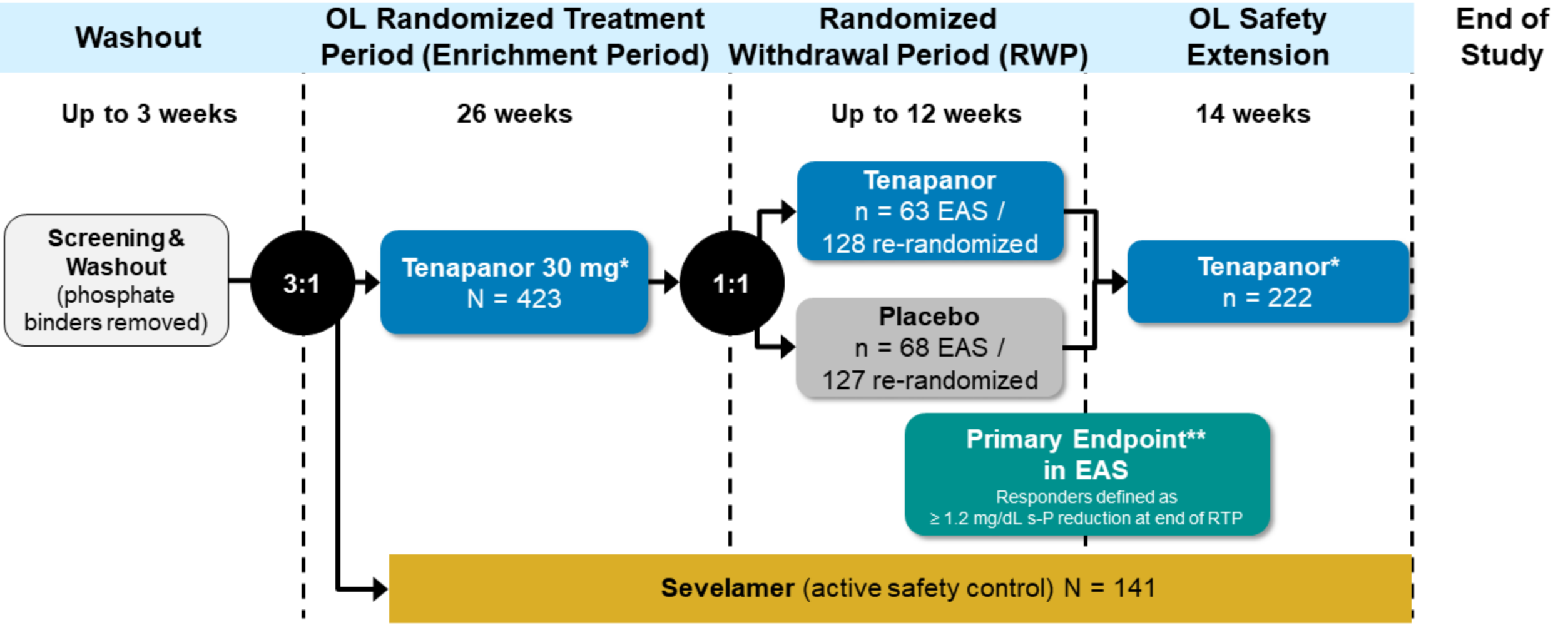
Phase 3 Study 301: Long-term Monotherapy with Tenapanor

52-week trial with 12-week comparison to placebo with randomized withdrawal design

Study 301 and Study 201 Similar, but Study 301 Larger Study with Longer Duration

- Study 301 started all patients on proposed dose of one 30 mg tablet taken twice daily
- Study 301 included active safety control arm
  - Patients treated for 52 weeks with sevelamer (most commonly prescribed phosphate binder)
  - Compared adverse events in patients on maintenance dialysis, a population known to have high event rate
  - No prespecified efficacy comparisons between tenapanor and sevelamer

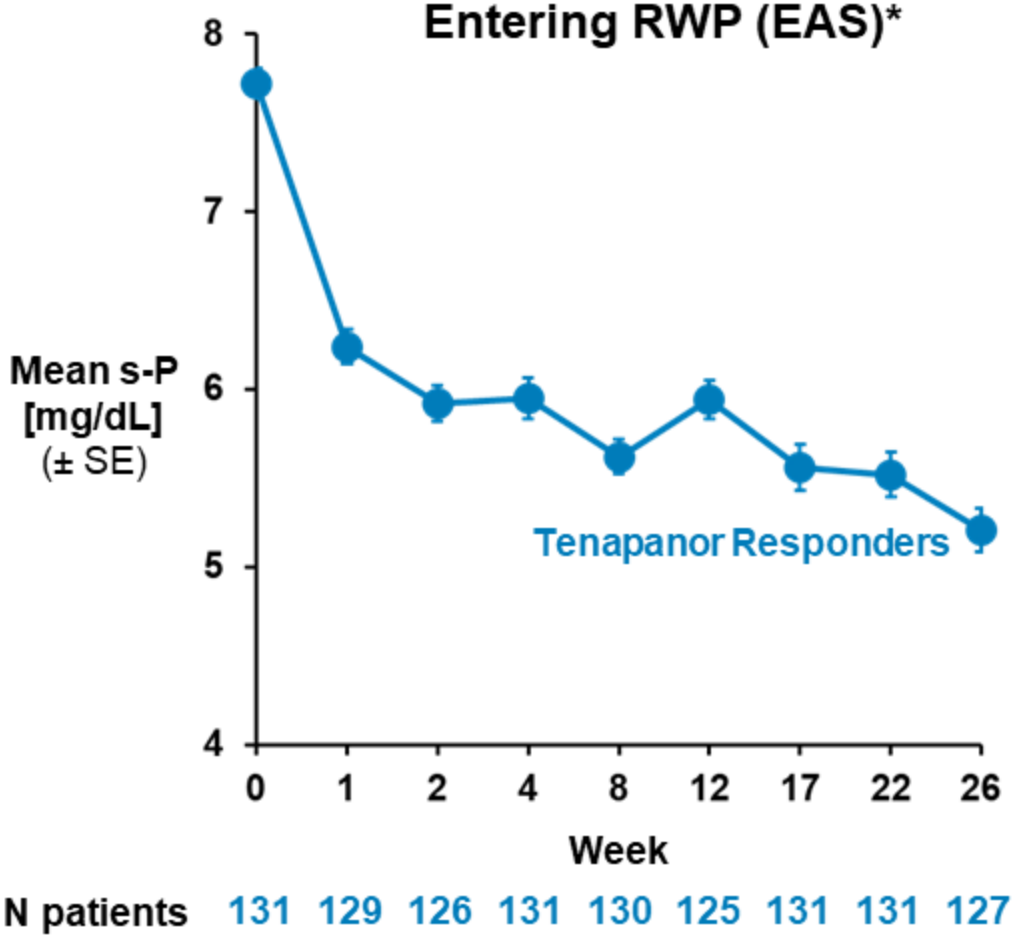
Study 301: 52-Week Pivotal Phase 3 Study



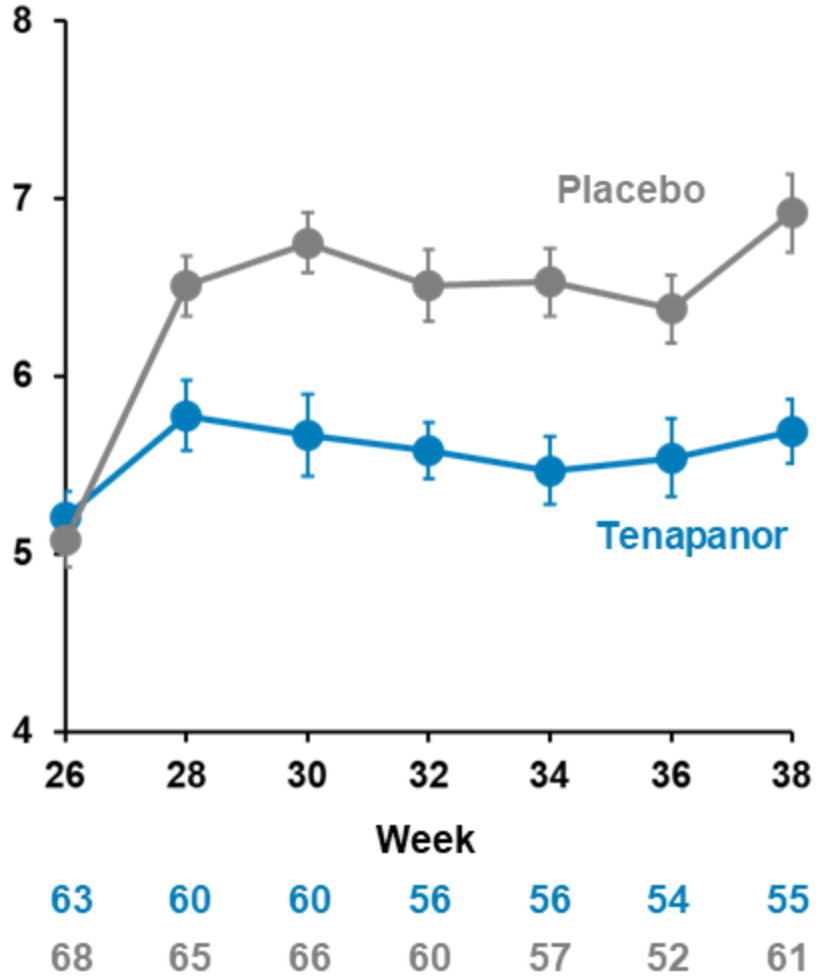
OL = open-label; *Down titration allowed in increments of 10 mg, max dose of 30 mg and min dose of 10 mg
**Difference in s-P change from RWP baseline to end of RWP between tenapanor and placebo in the EAS

Study 301, 12-Week RWP: Primary Endpoint Met Statistically Significant Difference in s-P During RWP in EAS

RTP s-P by Visit for Responders Entering RWP (EAS)*



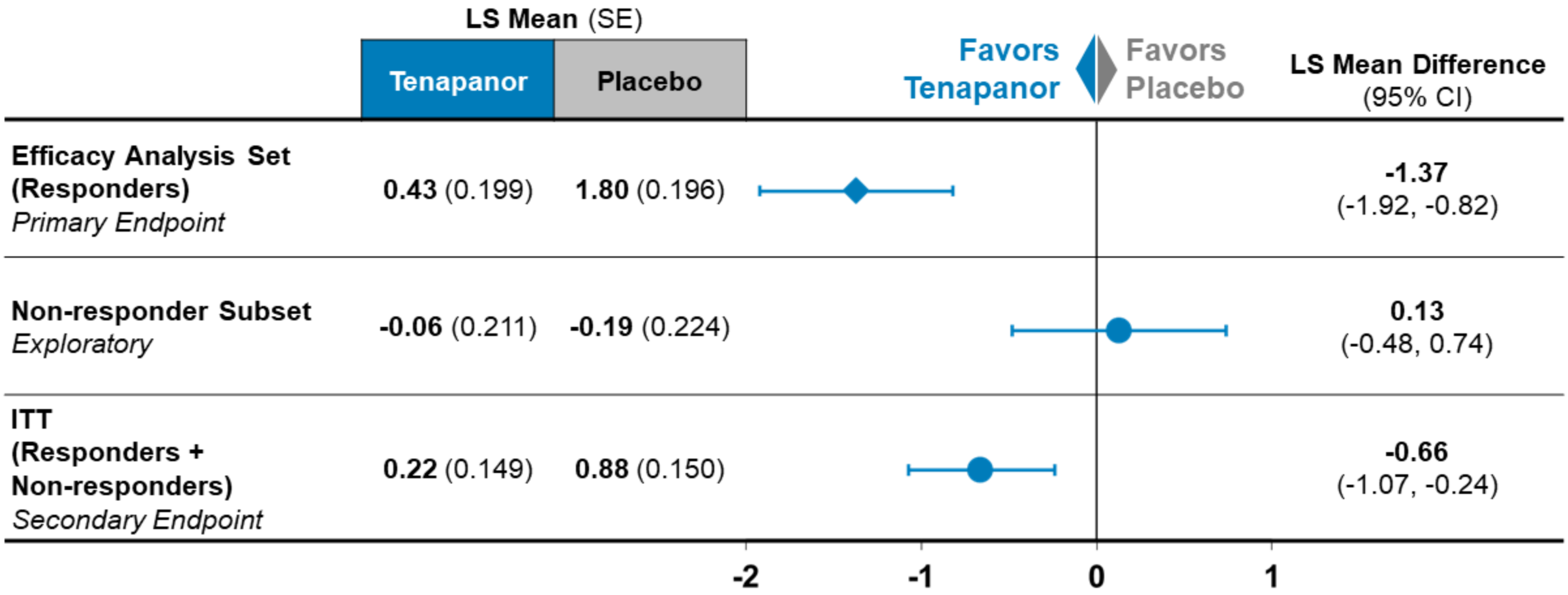
RWP s-P by Visit for EAS



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	

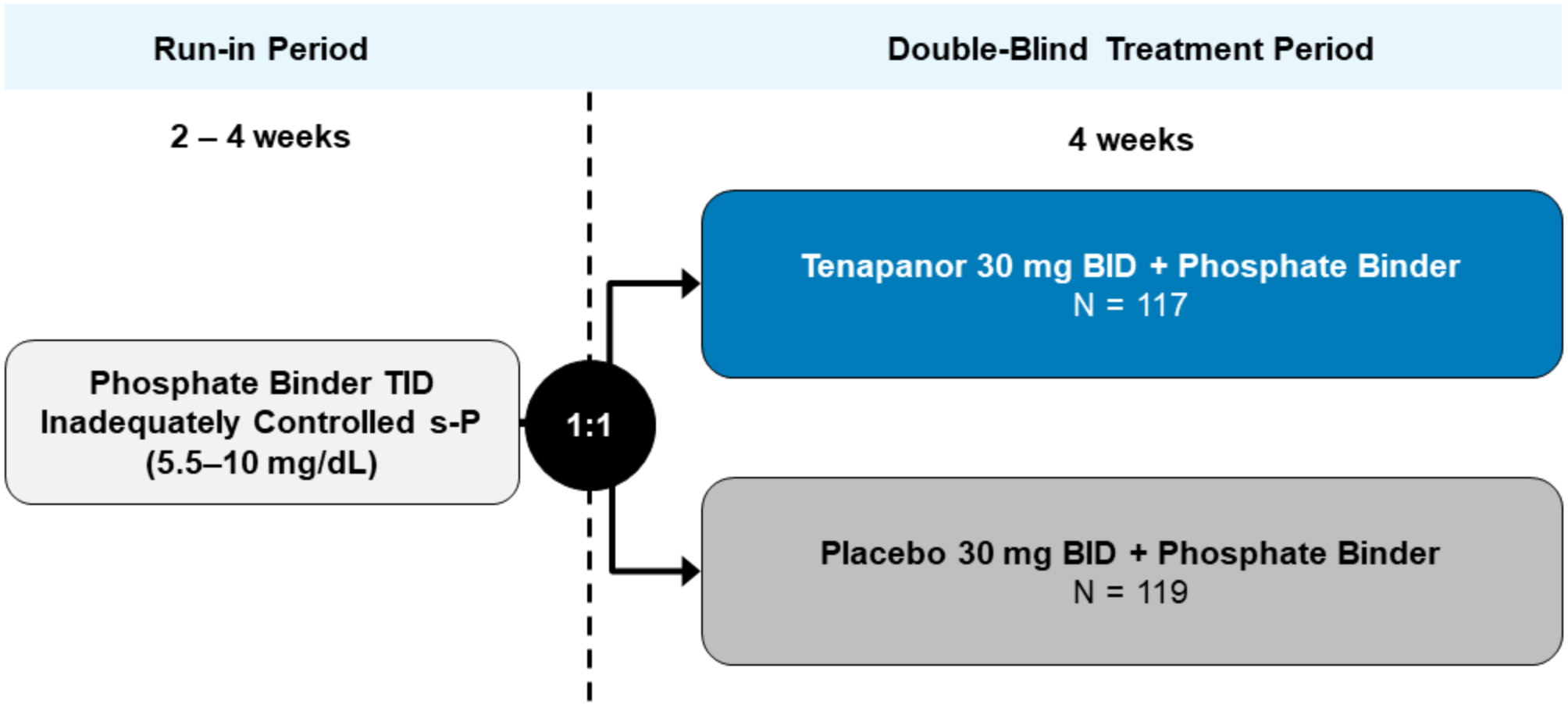
*pre-specified exploratory endpoint

Study 301, 12-Week RWP: Treatment Difference in Responders and Non-Responders

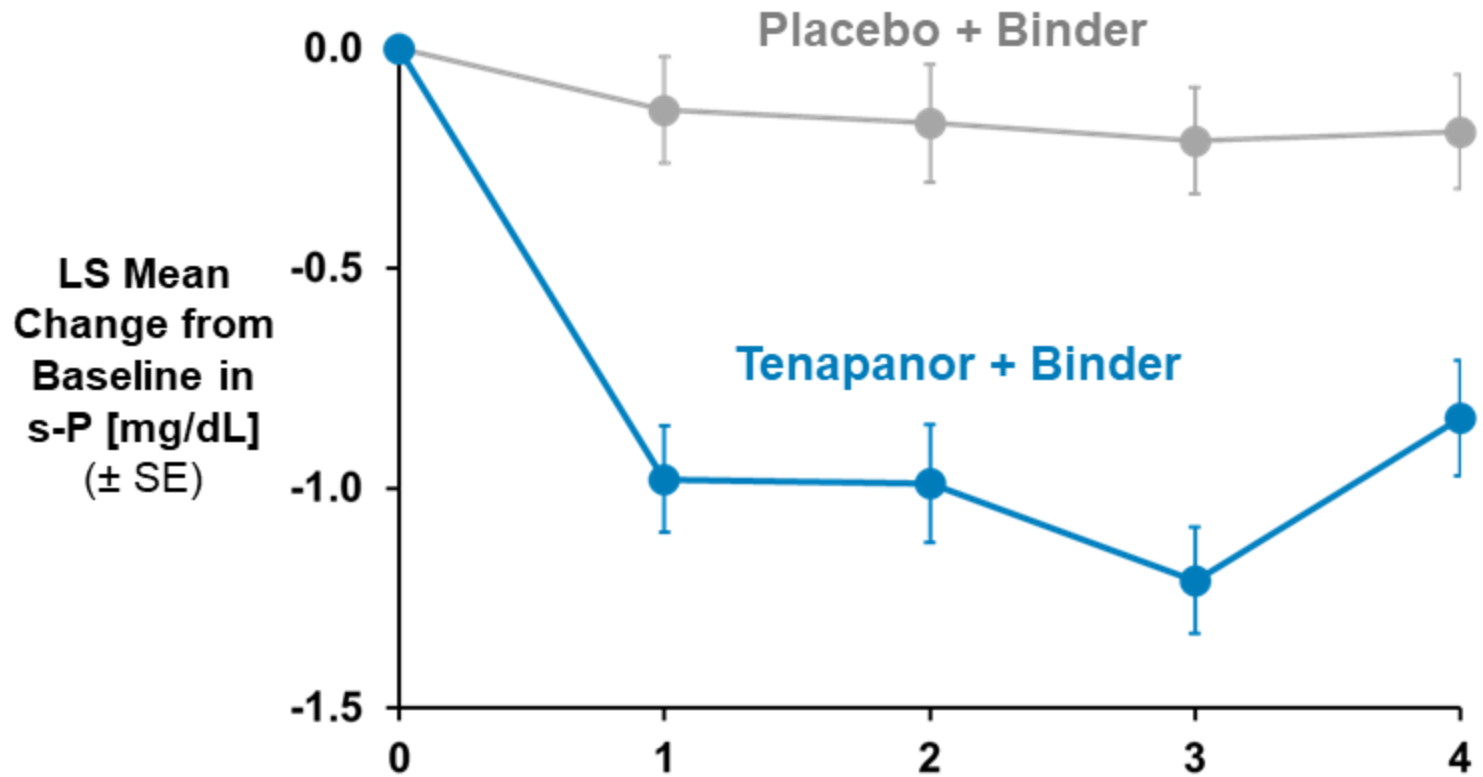


Phase 3 Study 202:
In Combination with Phosphate Binders

Study 202 Design: 4-Week Pivotal Study for Treatment in Combination with Phosphate Binders



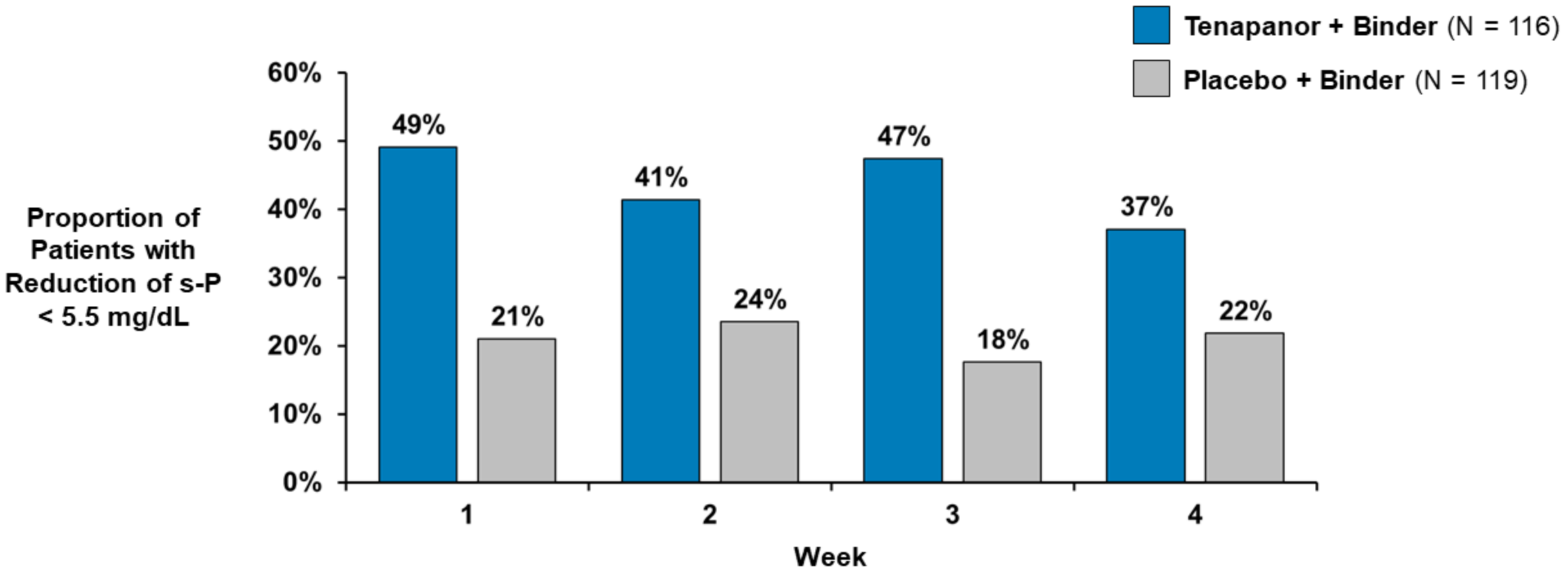
Study 202: Tenapanor in Combination with Binders Demonstrated Statistically Significant Reduction of s-P vs. Binders Alone



N patients					
Tenapanor + Binder	116	113	114	113	112
Placebo + Binder	119	116	115	112	117

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	**0.0004**	

Study 202: Percent of Patients Achieving s-P Reduction to < 5.5 mg/dL Over Time



p<0.01 at all visits

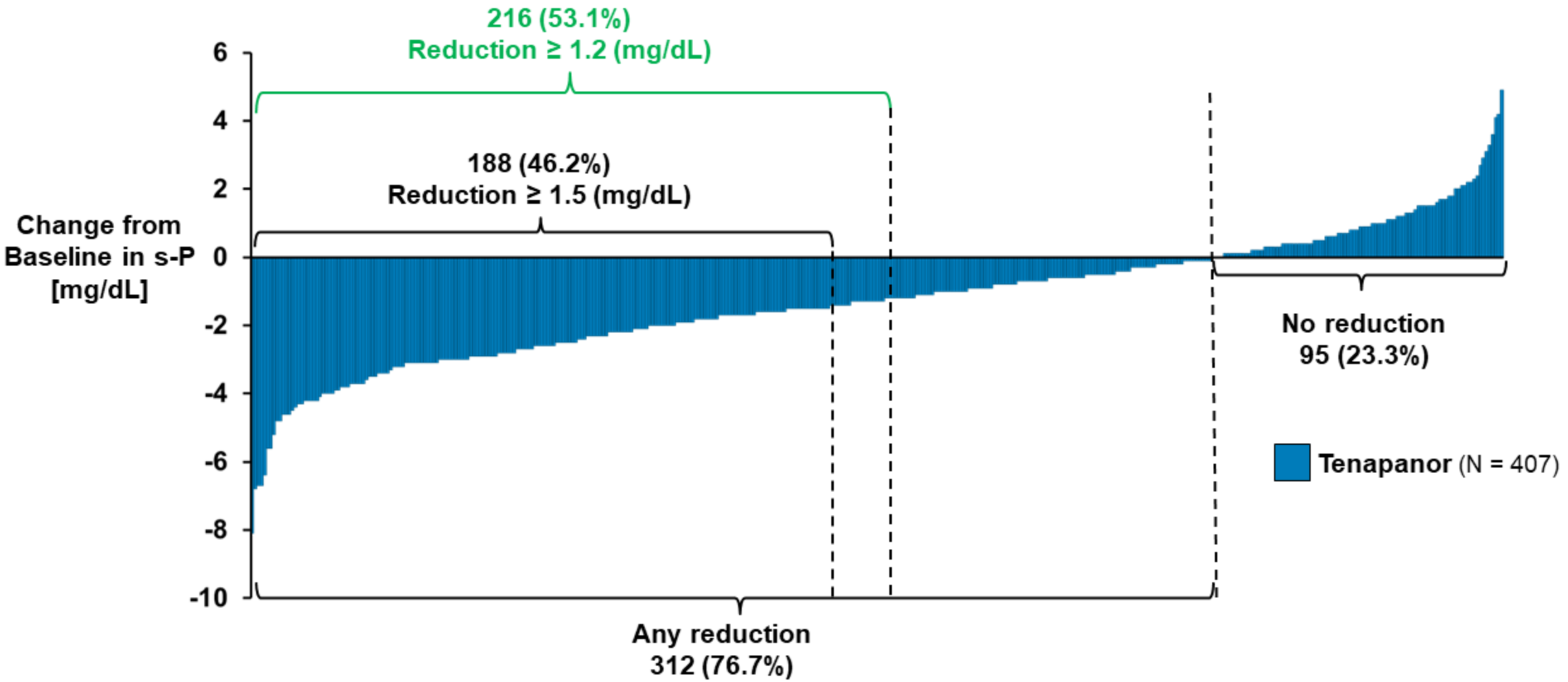
Clinical Meaningfulness of Tenapanor

Tenapanor Provides Clinically Meaningful s-P Lowering Effect for a Meaningful Subset of Patients

Focusing on the mean effect ignores the fact that some patients may have a larger and clinically relevant response to treatment.

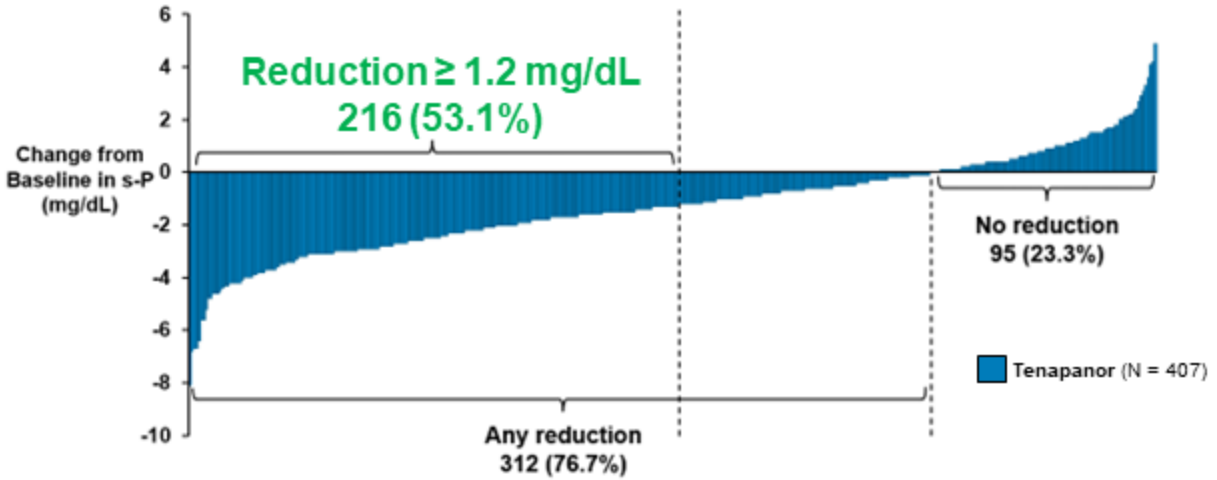
-FDA Briefing Document

Study 301, 26-Week RTP: 53% of All Tenapanor-Treated Patients Achieved Reduction of ≥ 1.2 mg/dL

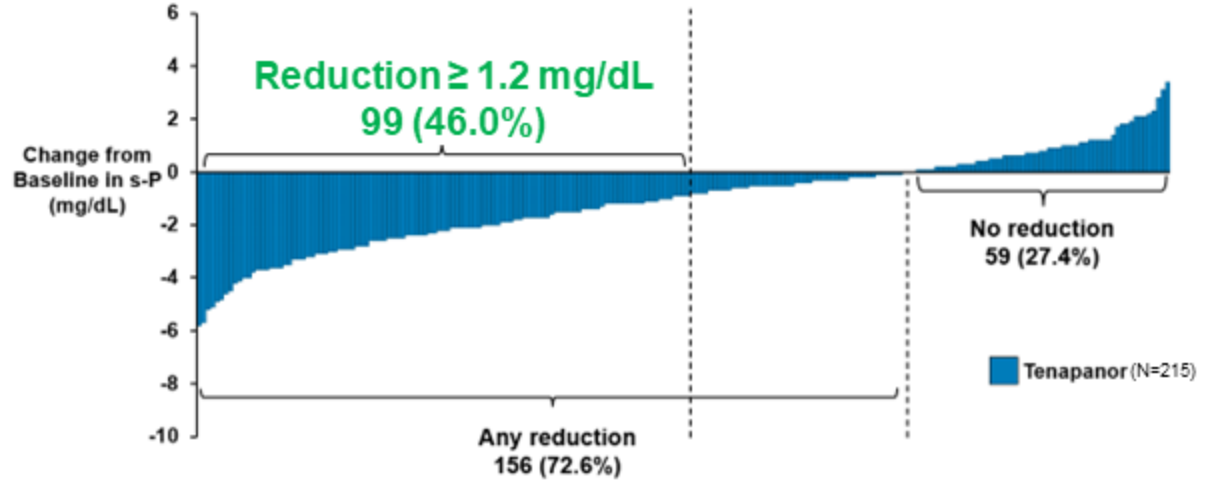


Consistent Trends Across Monotherapy and Combination Therapy Studies

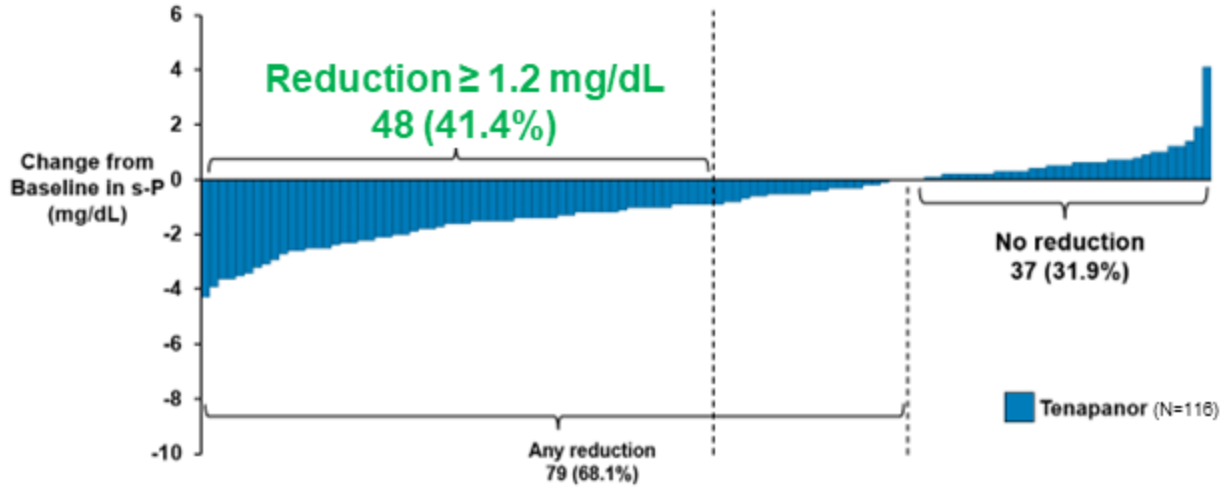
Study 301, End of 26-Week RTP



Study 201, End of 8-Week RTP

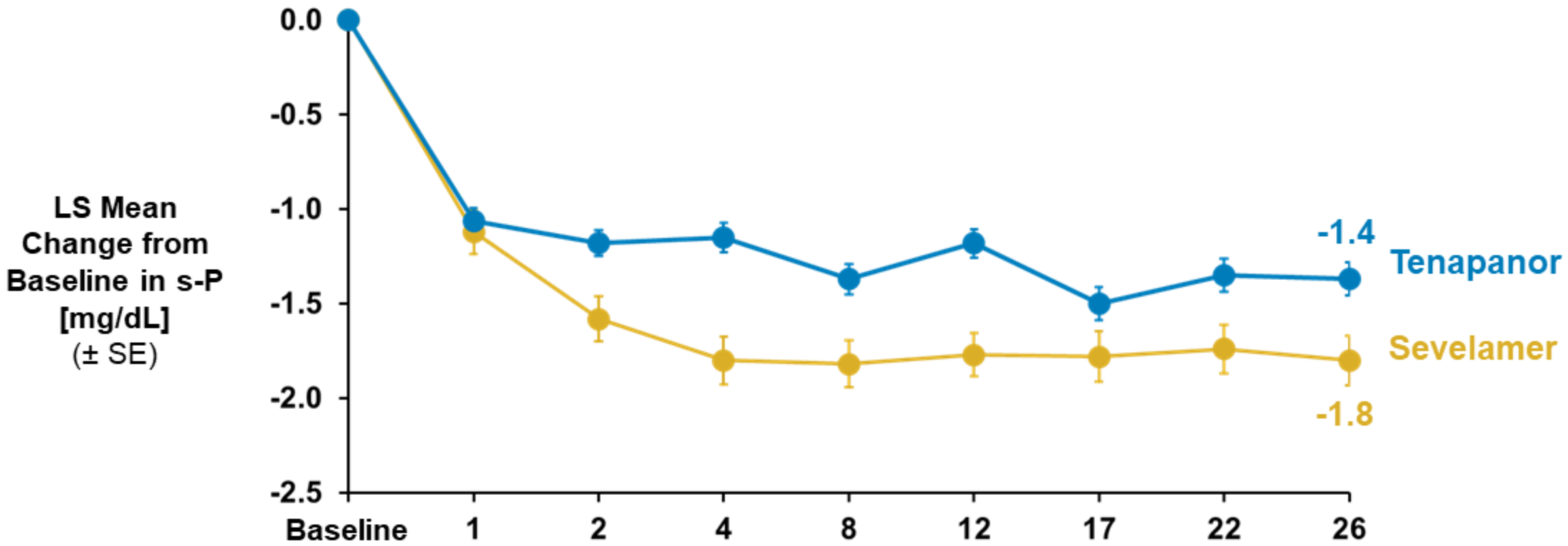


Study 202, End of 4-Week RTP (Combination with Phosphate Binders)



All Tenapanor-Treated Patients

Study 301: s-P Change for Tenapanor vs. Sevelamer During First 26 Weeks of Open-Label Treatment Period

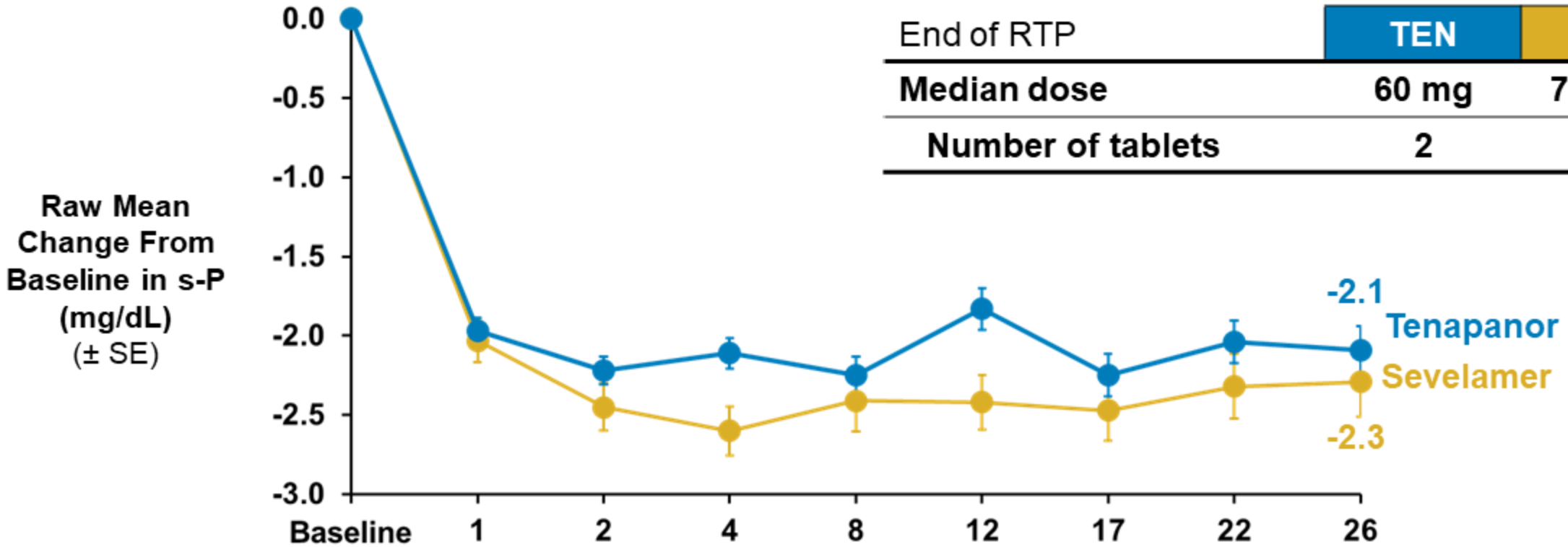


N	Baseline	1	2	4	8	12	17	22	26
Tenapanor	407	399	385	366	332	311	298	271	248
Sevelamer	137	129	132	134	132	130	122	122	113

Observed Cases (ANCOVA)

Study 301: s-P Change During RTP (Early Responders: Achieving ≥ 1.2 mg/dL s-P Reduction at ≥ 2 Visits at Weeks 1, 2, and 4)

End of RTP	TEN	SEV
Median dose	60 mg	7200 mg
Number of tablets	2	9

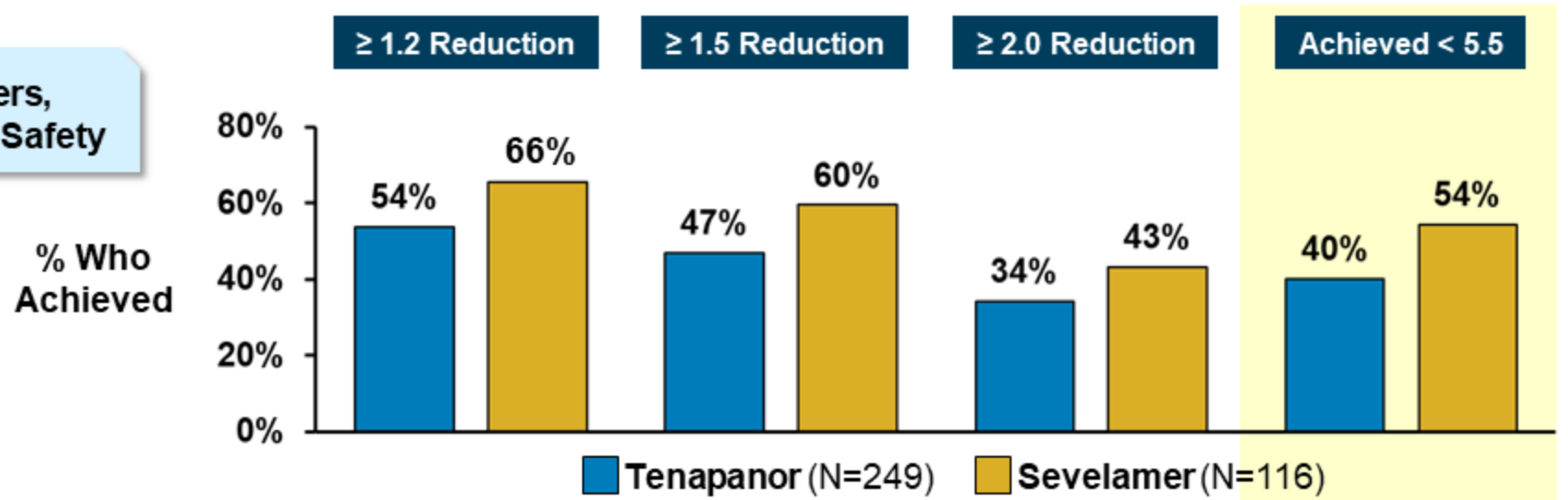


N	Baseline	1	2	4	8	12	17	22	26
Tenapanor	189	188	184	181	167	157	155	139	129
Sevelamer	72	68	69	71	70	69	67	67	66

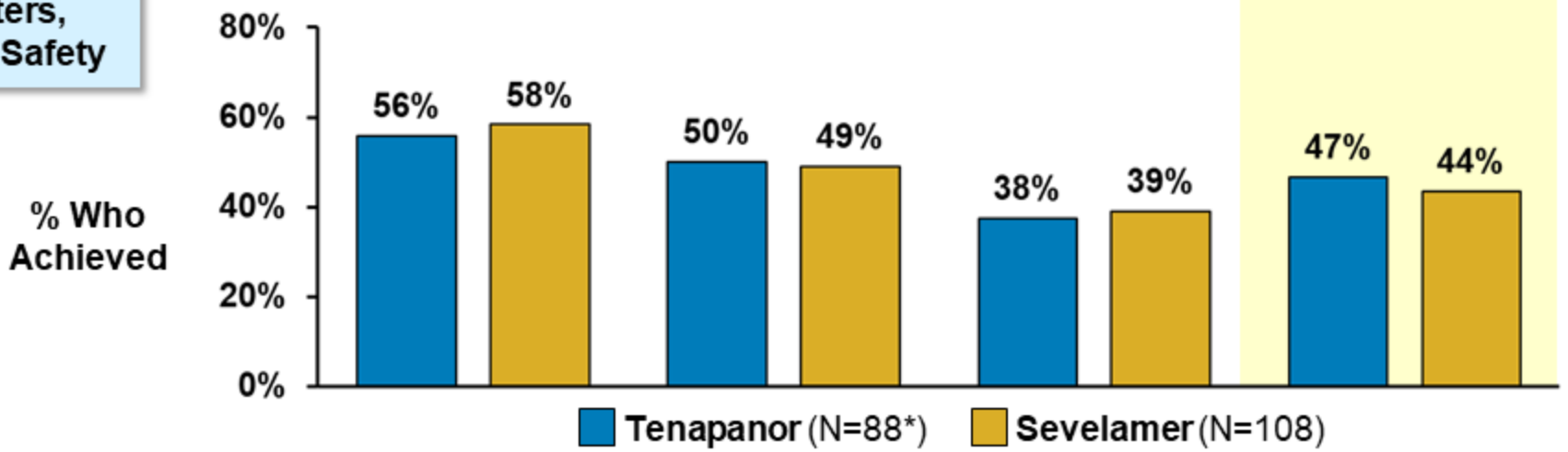
Descriptive summaries are based on observed data

Study 301: Additional Indicators of Tenapanor's Clinically Relevant Treatment Effect

26-Week RTP Completers, Tenapanor ITT, Sevelamer Safety



52-Week Study Completers, Tenapanor ITT, Sevelamer Safety

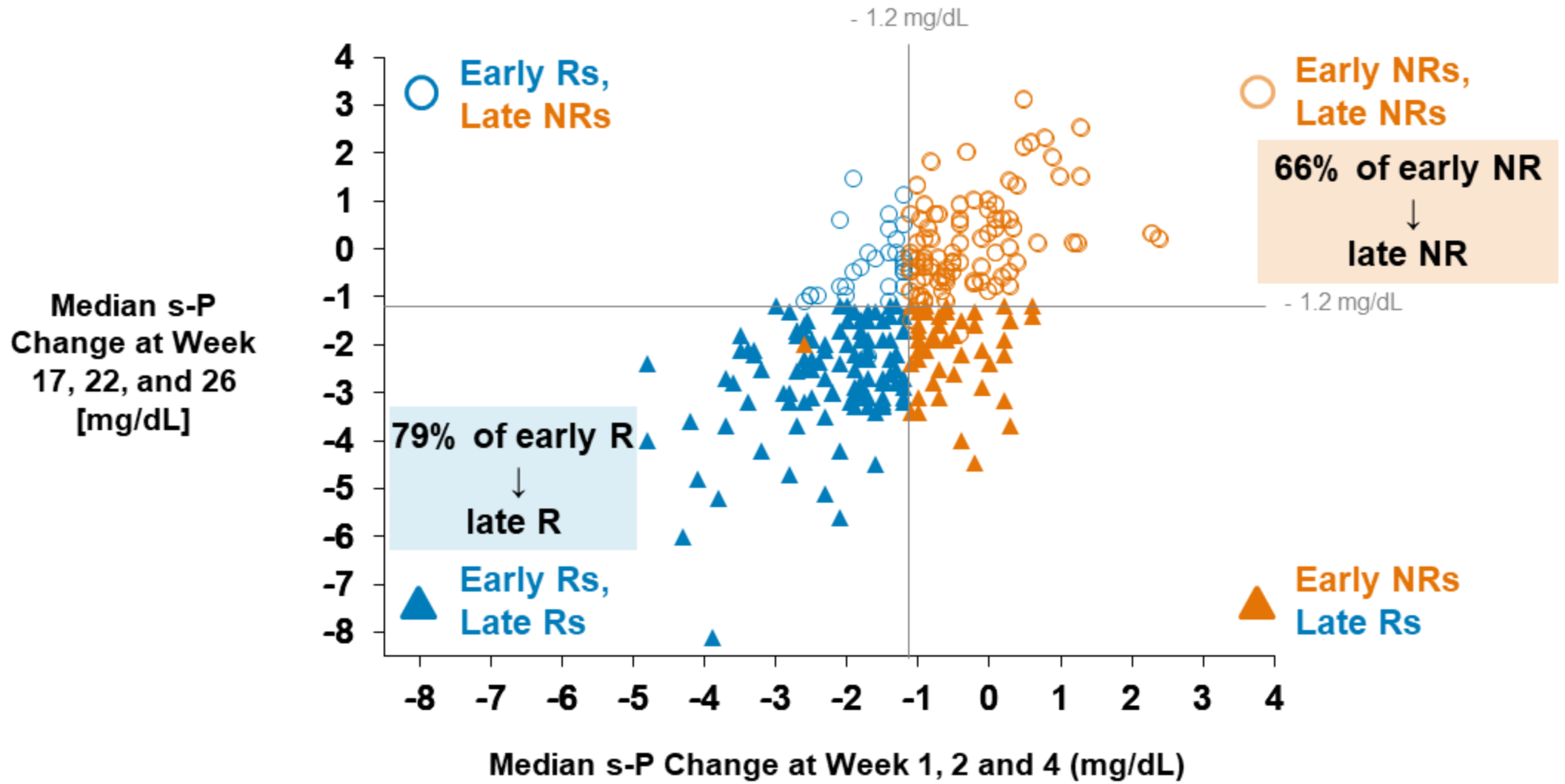


*52-Week Completers excludes those re-randomized to placebo in 12-week RWP

Early Response Predicts Late Response

- FDA feedback from NDA review: analyses must account for intrasubject variability by using multiple measurements of s-P over time
- FDA analysis does not use multiple timepoints and is based on single measures

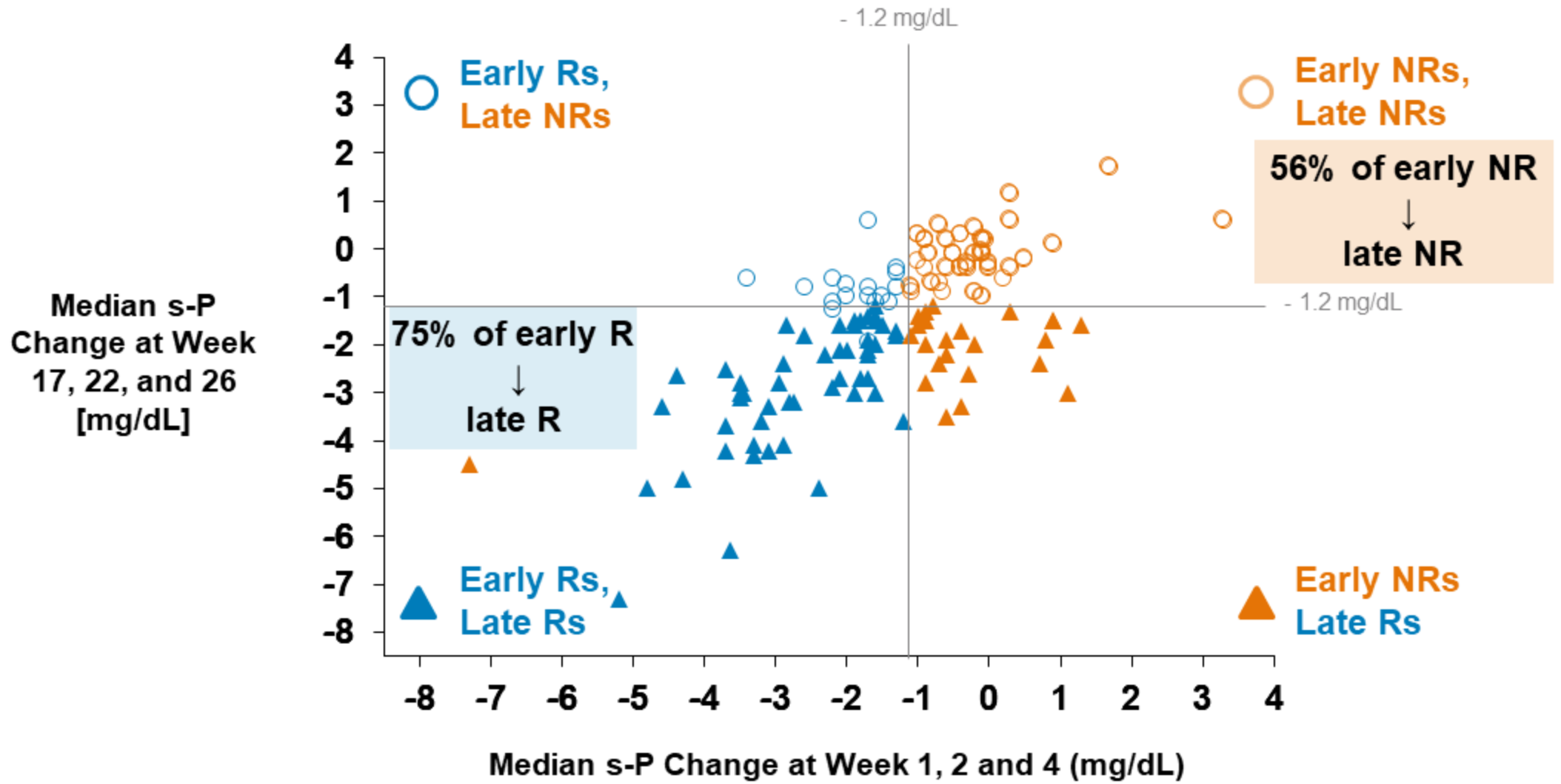
Study 301, RTP: 79% of Tenapanor Patients with Early Response Also Identified as Having a Late Response (Using Multiple Timepoints)



Observed Cases

R = response to treatment; NR = non-response to treatment; response defined as having ≥ 2 of 3 s-P measurements decreased by ≥ 1.2 mg/dL from baseline

Study 301, RTP: Sevelamer Early Response Also Identified a Late Response (Using Multiple Timepoints)



Observed Cases

R = response to treatment; NR = non-response to treatment; response defined as having ≥ 2 of 3 s-P measurements decreased by ≥ 1.2 mg/dL from baseline

Tenapanor Clinically Meaningful Treatment Effect: Phase 2 and 3 Trials

D5613C00001 (Phase 2b) Dose-Selection Monotherapy	▪ Primary analysis (placebo-corrected): -1.4 mg/dL
Study 201 (Phase 3) Monotherapy	▪ EAS RWP (placebo-corrected): -0.8 mg/dL ▪ 8-week RTP: -1.1 mg/dL ▪ 8-week RTP (responders): -2.6 mg/dL
Study 301 (Phase 3) Monotherapy	▪ EAS RWP (placebo-corrected): -1.4 mg/dL ▪ 26-week RTP: -1.4 mg/dL ▪ 26-week RTP (responders): -2.6 mg/dL
Study 202 (Phase 3) Combination Therapy	• 4-week double-blind period: -0.7 mg/dL

Tenapanor Clinical Meaningfulness Conclusion

Additional Support: Clinical Meaningfulness

- Tenapanor s-P lowering effect varies across patients; meaningful proportion of patients have large reduction in s-P
- Study 301 RTP: significant number of patients had clinically relevant reductions in s-P resulting in achieved target treatment goals
- Tenapanor and sevelamer responders have similar s-P reduction
  - Lower pill burden with tenapanor: 2 pills/day (TEN) vs median of 9 tablets/day (SEV)

Identifying Responders

Early Response Predicts Late Response

- Patients responding early tend to have a continued response

Tenapanor: an important therapeutic option fitting into current treatment paradigm

Safety

Laura A. Williams, MD, MPH

Chief Medical Officer

Ardelyx, Inc.

Study 301

Tenapanor vs Sevelamer (52 weeks)

> 1,200 patients from CKD on-dialysis safety analysis set

> 930 tenapanor-treated patients

> 140 patient-years of tenapanor exposure

65% of patients in sevelamer arm treated with sevelamer prior to enrollment

Study 301: Overall Safety of Tenapanor vs. Sevelamer

	26-Week RTP		12-Week RWP			14-Week Safety Ext.	
	TEN N = 419	SEV N = 137	TEN N = 125	Placebo N = 126	SEV N = 116	TEN N = 220	SEV N = 110
Any AE	80%	64%	46%	56%	41%	46%	39%
Moderate	42%	27%	24%	29%	19%	21%	21%
Severe	20%	15%	6%	9%	10%	11%	9%
AE Leading to Study Drug Discontinuation	24%	1%	9%	13%	< 1%	1%	0
SAE	17%	23%	11%	10%	16%	16%	20%
AE Leading to Hospitalization	17%	23%	10%	10%	16%	15%	19%
Overall deaths, N (%)	7 (2%)	3 (2%)	1 (< 1%)	1 (< 1%)	1 (< 1%)	4 (2%)	1 (< 1%)

Study 301: Diarrhea Most Common Adverse Event

Preferred term	26-Week RTP		12-Week RWP			14-Week Safety Ext.	
	TEN N = 419	SEV N = 137	TEN N = 125	Placebo N = 126	SEV N = 116	TEN N = 220	SEV N = 110
Any AE	80%	64%	46%	56%	41%	46%	39%
Diarrhea	53%	7%	4%	2%	4%	7%	0
Mild	13%	4%	2%	0	< 1%	3%	-
Moderate	34%	4%	2%	< 1%	3%	4%	-
Severe	6%	0	0	< 1%	0	0	-
Any discontinuation	24%	1%	9%	13%	< 1%	1%	0
Diarrhea	16%	< 1%	< 1%	0	0	0	0

- Most reported a single diarrhea event
- Most events occurred early and resolved in median of 14 days

MedDRA classifies "bothersome" loose stool(s), loose bowels, and/or mushy stool(s) as "diarrhea," with or without increase in "stool frequency"

Comparison of Other GI-Related Adverse Events with Tenapanor vs. Sevelamer

	Study 301*							SEV Ph3 Study
	26-Week RTP		12-Week RWP			14-Week Safety Ext.		52-Week
	TEN N = 419	SEV N = 137	TEN N = 125	PBO N = 126	SEV N = 116	TEN N = 220	SEV N = 110	SEV USPI N = 99
Any AE	80%	64%	46%	56%	41%	46%	39%	88%
Diarrhea	53%	7%	4%	2%	4%	7%	0	19%
Other GI Events								
Nausea	4%	3%	< 1%	2%	3%	< 1%	< 1%	20%
Vomiting	3%	4%	2%	3%	3%	3%	< 1%	22%
Dyspepsia	0	1%	0	0	0	0	0	16%
Abd. Pain	2%	2%	0	0	2%	< 1%	< 1%	9%
Constipation	< 1%	4%	< 1%	2%	3%	< 1%	0	8%
Flatulence	1%	0	0	< 1%	0	0	0	8%
Discontinuation Due to GI Events	16%	< 1%	2%	0	0	0	0	16%

*65% of patients in Study 301 were SEV-experienced (on sevelamer prior to study initiation)

Study 301 (52 Weeks*): Diarrhea and Temporally Associated** Adverse Events of Special Interest***

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

*Events under placebo treatment in RWP are included in tenapanor group.
**An adverse event (AE) was considered temporally associated with diarrhea event if 1) AE started at or after diarrhea start date and within 3 days of diarrhea end date, if diarrhea ended by End of Study, or 2) AE started at or after diarrhea start date if diarrhea was ongoing at End of Study
*** Adverse events of special interest (AESIs): AEs mapped to preferred terms of Fall, Hypotension, Orthostatic hypotension, Syncope, Presyncope, Dizziness, Dehydration and Hypovolemia

Tenapanor Offers Acceptable Safety and Tolerability Profile

Exposures

- Robust assessment of safety with more than 1,200 patients
- > 930 patients representing > 140 patient-years of tenapanor exposure

Diarrhea: Most Common AE

- Most cases occurred early; mild-to-moderate in intensity; not treatment-limiting and resolved in median of 14 days
- More potentially worrisome downstream consequences of diarrhea rarely seen

Comparison to Binders

- In largest Phase 3 study, safety profile comparable to active safety comparator, sevelamer

Clinical Perspective

Stuart Sprague, DO

Clinical Professor of Medicine
University of Chicago, Pritzker School of Medicine
Chief Emeritus, Division of Nephrology and Hypertension
NorthShore University Health System

Treatment of Hyperphosphatemia Focused Solely on Binding Phosphate for Decades

- Most patients do not consistently achieve target s-P concentrations despite phosphate binder use
- Patients can become frustrated with phosphate binder treatment burden and continued high s-P concentrations
  - Frustration can influence patient motivation to adhere to burdensome regimen
- We need more options

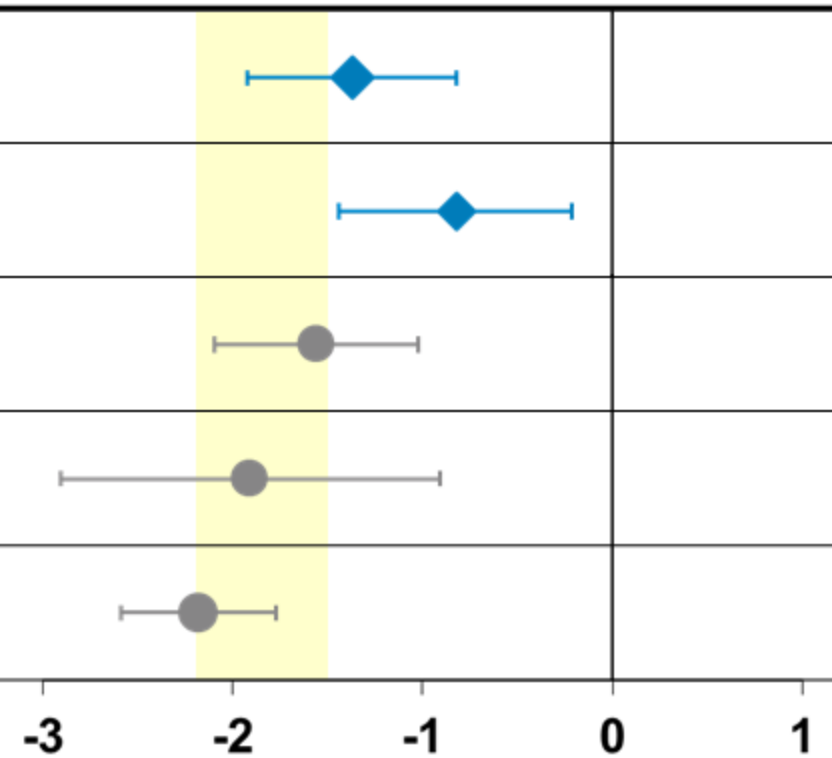
Tenapanor Effectively Lowers s-P via a Novel MoA

- Can be used alone or in combination with phosphate binders
- Simplified dosing
  - Fewer and smaller pills
  - BID dosing
- Large proportion of patients have meaningful s-P reductions
- Treatment response can be identified early with standard clinical practice of monthly s-P monitoring

One-day dose of Tenapanor vs Sevelamer

Tenapanor Treatment Effect Aligns With Benchmark Set by Approved Phosphate Binders

	Endpoint	LS Mean Difference (95% CI)
Tenapanor Study 301	Δ s-P from period-level baseline to end of 12-week RWP (enriched)	**-1.37** (-1.92, -0.82)
Tenapanor Study 201	Δ s-P from period-level baseline to end of 4-week RWP (enriched)	**-0.82** (-1.44, -0.21)
Velphoro[1]	Δ s-P from period-level baseline to end of 3-week RWP (enriched)	**-1.56** (-2.10, -1.02)
Fosrenol[2]	Δ s-P from period-level baseline to end of 4-week RWP	**-1.91** (-2.60, -1.23)
Auryxia[3]	Δ s-P from period-level baseline to end of 4-week RWP	**-2.18** (-2.59, -1.77)



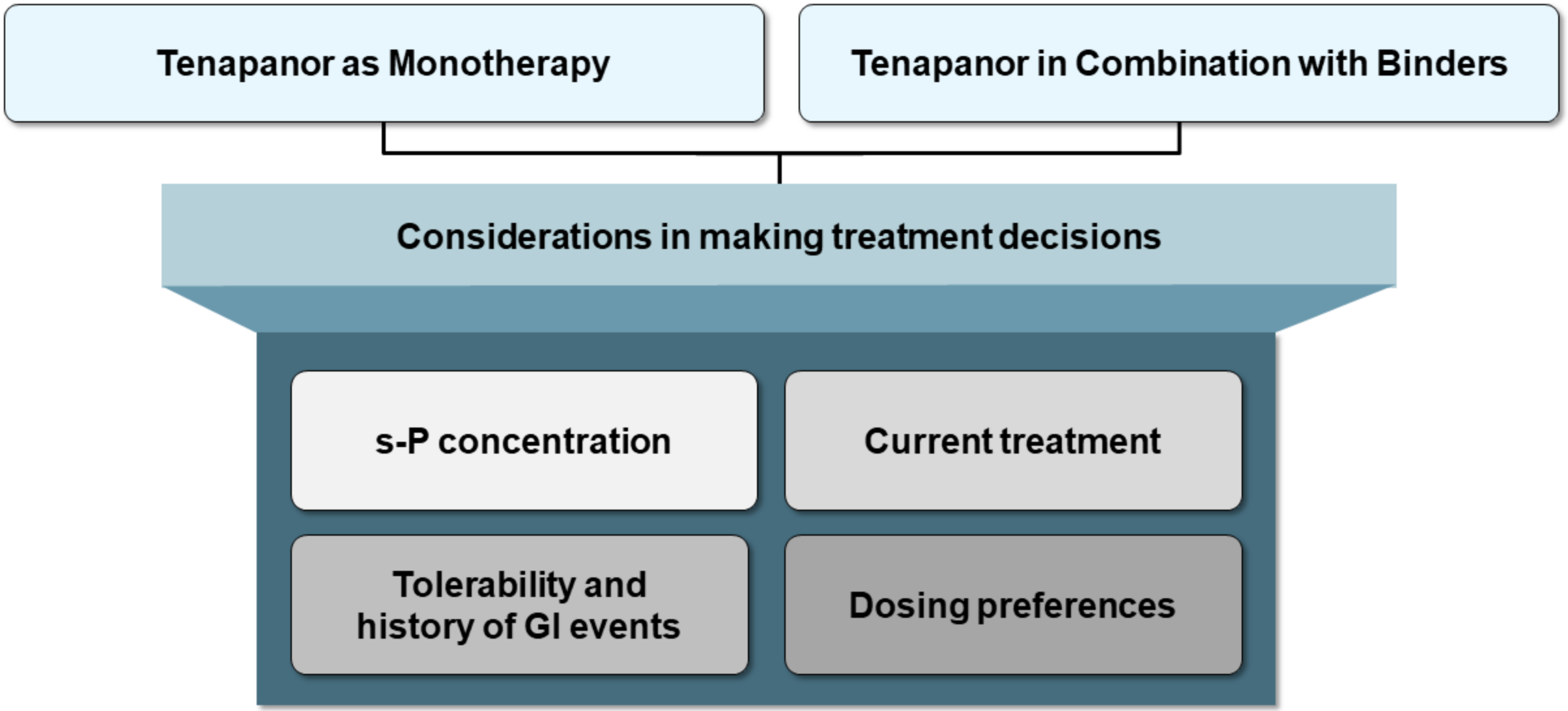
1. Velphoro FDA Review Report (24-week enrichment period) , 2. Fosrenol FDA Review Report, adjusted for multiplicity; 3. Auryxia USPI (52-week enrichment period)

Overall Safety & Tolerability of Tenapanor is Comparable to Approved Phosphate Binders in Phase 3 Studies

	Phase 3 Phosphate Binder Studies			Study 301
	Lanthanum Carbonate (Fosrenol) N = 533	Sucroferric Oxyhydroxide (Velphoro) N = 707	Ferric Citrate (Auryxia) N = 289	Tenapanor N = 419
Study Number Treatment Period	LAM-IV-301 25 Weeks	PA-CL-05A 24 Weeks	KRX-0502-304 52 Weeks	Study 301 26 Weeks / 52 Weeks*
Any AE	78%	83%	90%	80% / 89%
All GI events	Data not Available	45%	56%	58% / 64%
Discontinuations due to AE	25%	16%	21%	24% / 32%
SAE	21%	18%	39%	17% / 25%
Deaths	2%	2%	4%	2% / 3%

Data from registration trials with treatment naïve patients. *Events under placebo treatment in RWP are included.

Tenapanor Could Help Many Patients



Tenapanor Provides Clinically Meaningful s-P Reductions with Positive Benefit-Risk Assessment

- Can be used as monotherapy or in combination with phosphate binders
- Represents important advance for patients and nephrologists in condition where current therapies not able to consistently achieve targets
- Tenapanor has potential to change hyperphosphatemia treatment paradigm

Tenapanor for the Control of Serum Phosphate (s-P) in Adults with Chronic Kidney Disease (CKD) on Dialysis

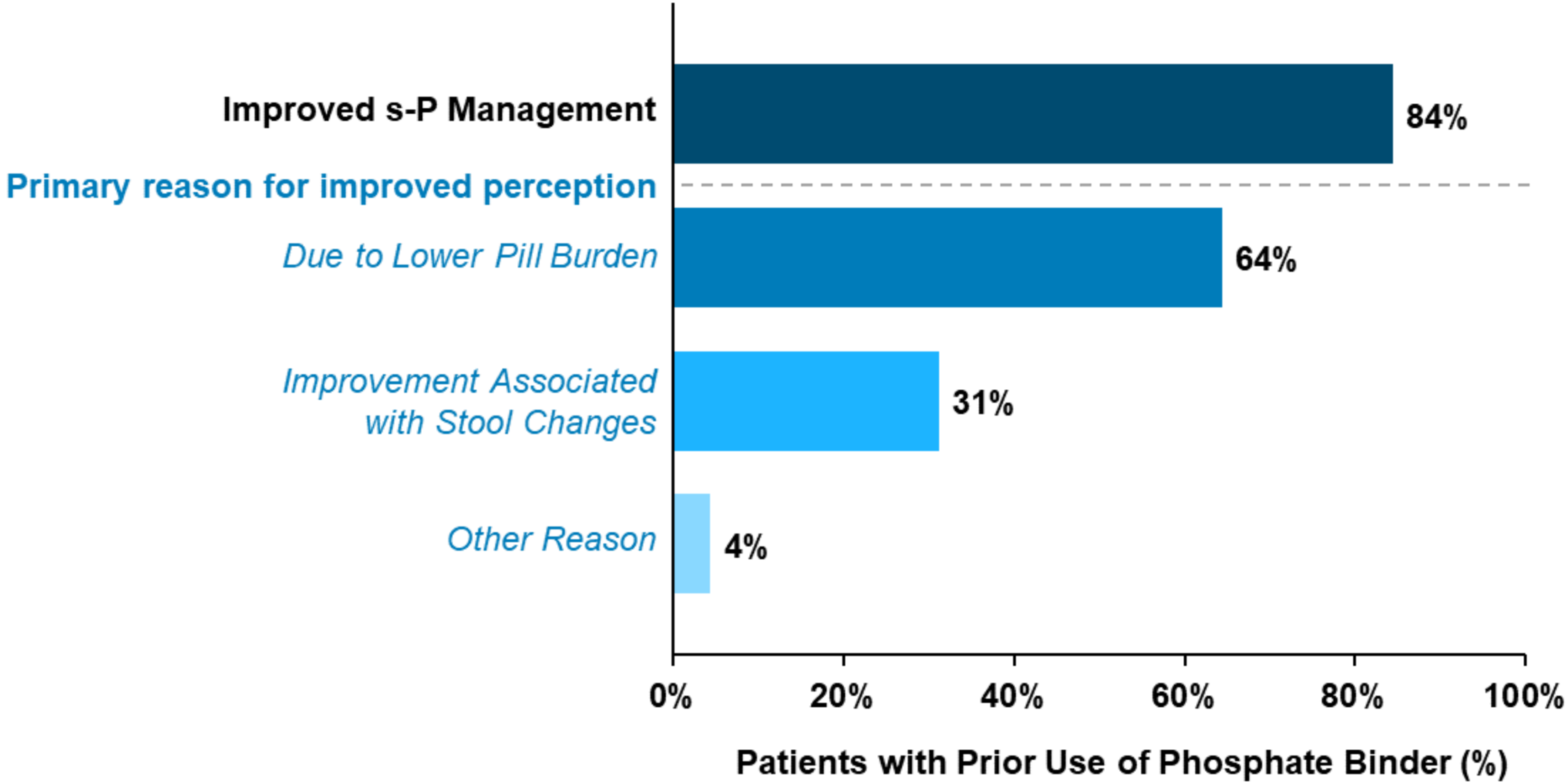
November 16, 2022

Cardiovascular and Renal Drugs Advisory Committee Meeting

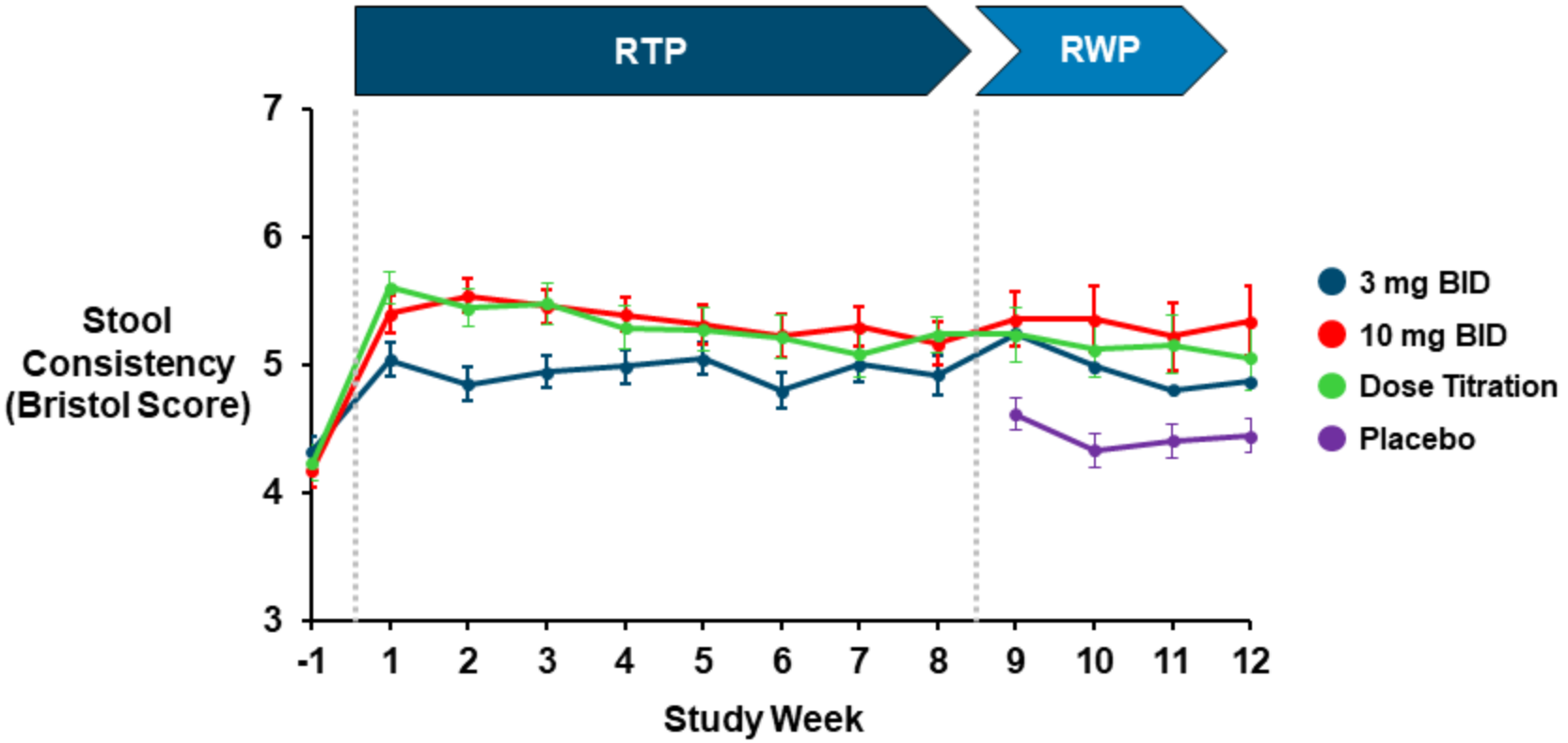
Ardelyx, Inc.

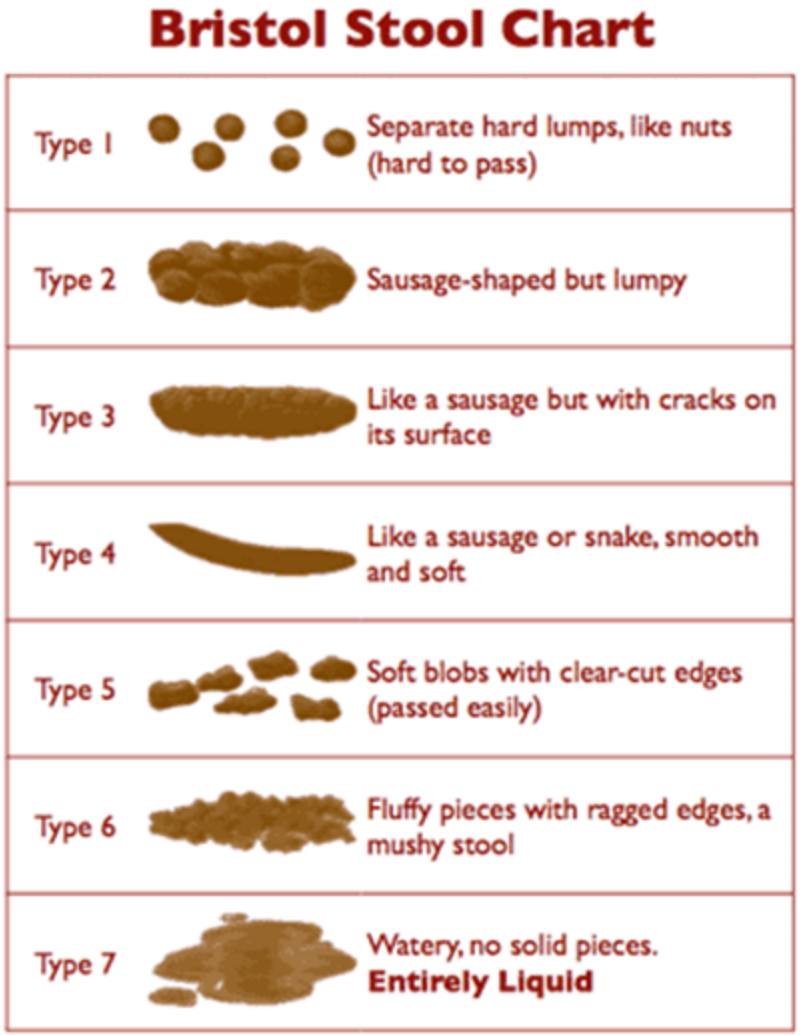
BACKUP SLIDES SHOWN

Study 402 (OPTIMIZE): 84% of Patients with Prior Use of Binder Reported an Improved Perception of Their Phosphate Management Routine With Tenapanor



Study 201, 12 Weeks: Stool Consistency





- Normal stool is 3, 4, or 5 on Bristol scale
- Diarrhea is 6 or 7 on Bristol scale
- No patients discontinued during the RWP despite higher stool frequency and consistency

Study D5613C00001 (Phase 2b): Overall Safety

	1 mg BID N = 23	3 mg BID N = 21	10 mg BID N = 23	30 mg BID N = 25	3 mg OD N = 22	30 mg OD N = 21	Placebo N = 26
Any AE	43%	57%	70%	76%	59%	62%	42%
AE Leading to Study Drug Discontinuation	13%	14%	13%	36%	5%	33%	8%
SAE	9%	10%	13%	8%	5%	0	15%
AEs Leading to Deaths	4%	0	0	0	0	0	0

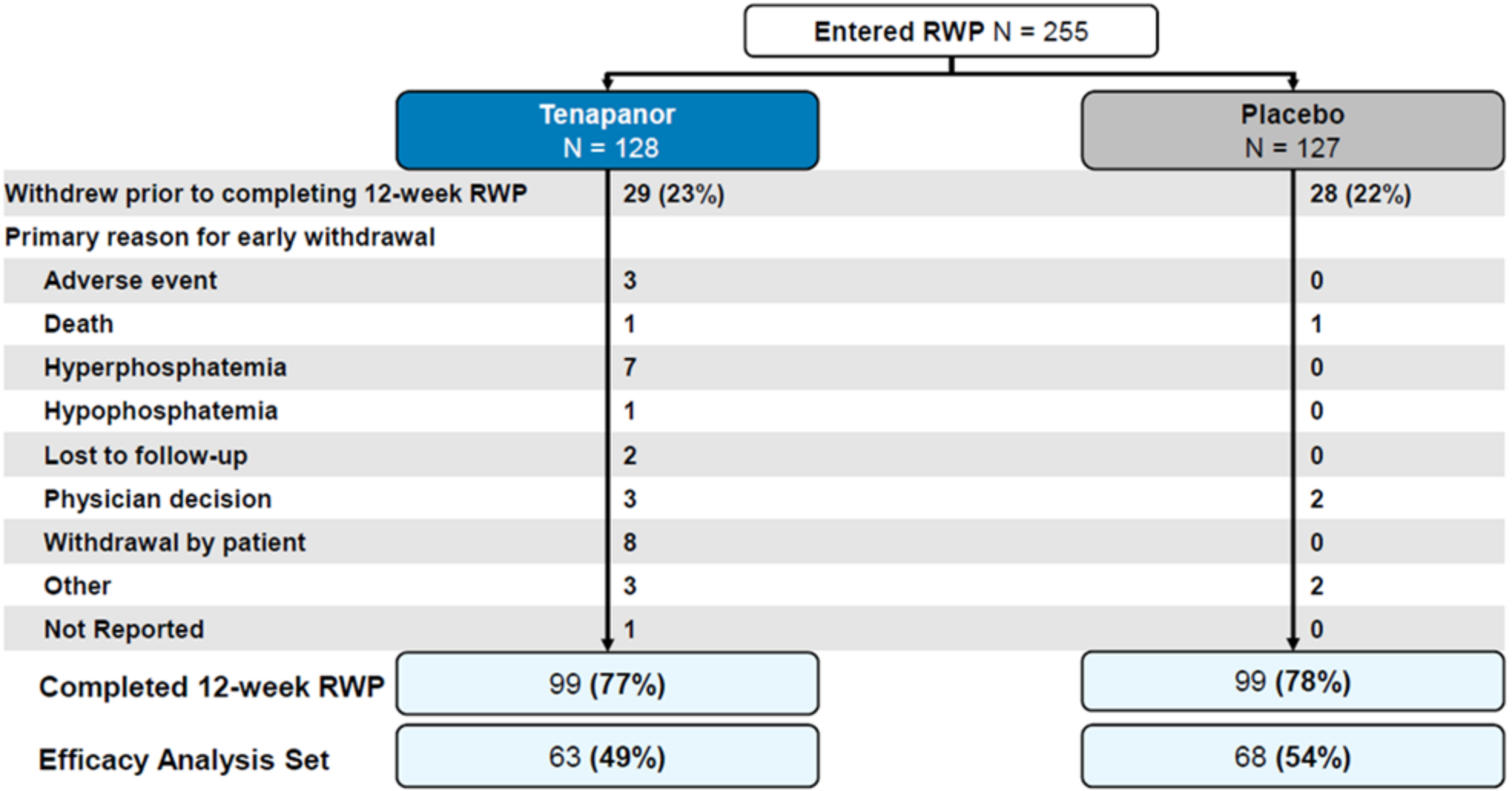
BID = twice daily, OD = once daily

Study 301: Change in s-P from Period-Level Baseline to End of 12-Week RWP by RTP Ending Dose

	Dose	Tenapanor N	Tenapanor LS Mean Change in s-P (mg/dL)	Placebo N	Placebo LS Mean Change in s-P (mg/dL)	LS Mean Difference
EAS	30 mg	35	0.11	40	1.73	-1.62
	20 mg	22	0.85	17	2.03	-1.18
	10 mg	6*	0.78	11	1.77	-0.99
ITT	30 mg	74	0.10	72	0.88	-0.78
	20 mg	32	0.35	32	1.00	-0.64
	10 mg	14*	0.55	19	0.69	-0.13

*Did not meet pre-specified sample size requirement for testing (N ≥ 15)
Patients that entered RWP and remained on dose at which they ended RTP

Study 301: Study Disposition – 12-Week RWP (Adapted from Ardelyx Figure 28)



Study protocol criteria: if s-P reached ≥ 9.0, patient required to stop treatment

Study 301, 12-week RWP: 3 of 7 Patients On Tenapanor Who Discontinued RWP Due to Hyperphosphatemia Met Responder Criteria Upon Entry of RWP

Tenapanor (ITT)	Patients Who Discontinued RWP Due to Hyperphosphatemia N = 7	Mean (Median) s-P at Discontinuation* (mg/dL)
Responder	**3**	**7.47 (6.5)**
Non-responder	**4**	**9.13 (8.9)**

*Last observed value during RWP