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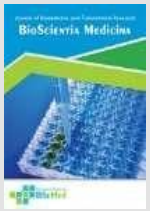

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Beyond Phosphate Binding: A Systematic Review and Meta-Analysis on the Efficacy and Safety of the Novel Paracellular Phosphate Inhibitor, Tenapanor, for Hyperphosphatemia in Dialysis Patients

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A B S T R A C T

Background: Hyperphosphatemia is a critical driver of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) undergoing dialysis. Current management, reliant on phosphate binders, is hampered by high pill burden and poor adherence. Tenapanor, a first-in-class, minimally-absorbed sodium/hydrogen exchanger 3 (NHE3) inhibitor, reduces paracellular phosphate absorption. We performed a systematic review and meta-analysis of all available Phase 3 trials to quantify its efficacy and safety. **Methods:** We searched PubMed, Embase, and Cochrane CENTRAL through October 2025 for Phase 3 clinical trials evaluating tenapanor for hyperphosphatemia in dialysis patients. Data were extracted from 6 eligible studies (N=1573). We conducted separate random-effects meta-analyses for different study designs: 1) parallel-group monotherapy vs. placebo, 2) withdrawal-design monotherapy vs. placebo, 3) parallel-group add-on therapy vs. placebo, and 4) safety (diarrhea incidence) vs. placebo. Efficacy was measured by Mean Difference (MD) in serum phosphate change; safety by Risk Ratio (RR). **Results:** Tenapanor demonstrated significant efficacy across all study designs. In parallel-group monotherapy (1 study, N=167), tenapanor was superior to placebo (MD: -1.89 mg/dL; 95% CI: -2.36 to -1.42). In withdrawal-design studies (2 RCTs, N=373), tenapanor maintained serum phosphate levels significantly better than placebo (Pooled MD: -0.75 mg/dL; 95% CI: -1.05 to -0.45; I^2=0%). As an add-on therapy (1 RCT, N=235), tenapanor provided additional phosphate reduction versus binders alone (MD: -0.65 mg/dL; 95% CI: -0.96 to -0.35). Tenapanor significantly increased the risk of diarrhea versus placebo (3 RCTs, N=521; Pooled RR: 4.10; 95% CI: 2.50 to 6.72; I^2=30%), which was the primary adverse event leading to discontinuation. **Conclusion:** Tenapanor represents a new mechanistic paradigm for hyperphosphatemia management. It is a highly effective phosphate-lowering agent, both as monotherapy and add-on therapy, but is associated with a significant, mechanism-based risk of gastrointestinal side effects.

1. Introduction

Chronic kidney disease (CKD) is a progressive, irreversible condition that has evolved into a formidable public health crisis, affecting an estimated 850 million people worldwide. As kidney function declines, the body's ability to maintain mineral homeostasis is compromised, leading to a complex systemic syndrome known as CKD–mineral and bone disorder (CKD-MBD). This disorder is not merely a skeletal disease but a multisystemic ailment

characterized by abnormalities in calcium, phosphorus (phosphate), parathyroid hormone (PTH), active Vitamin D, and fibroblast growth factor-23 (FGF23), coupled with vascular and soft-tissue calcification.[1,2]

Among these perturbations, hyperphosphatemia—the failure of the diseased kidneys to excrete the daily phosphate load—stands as a central and recalcitrant clinical challenge, particularly in the ~550,000 patients in the United States alone who require maintenance dialysis. The clinical consequences of elevated serum phosphate are profound and life-threatening. Phosphate is not an inert bystander; it is a direct and active uremic toxin. Persistent hyperphosphatemia is a primary driver of secondary hyperparathyroidism, renal osteodystrophy, and, most ominously, extraskeletal calcification.[3-6] Phosphate actively promotes the osteogenic transdifferentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells, a process that deposits hydroxyapatite in the medial layer of arteries. This vascular calcification transforms pliable blood vessels into rigid, calcified tubes, dramatically increasing arterial stiffness, pulse pressure, and left ventricular hypertrophy. Consequently, hyperphosphatemia is one of the strongest independent, modifiable risk factors for cardiovascular morbidity and mortality in the dialysis population, with each 1 mg/dL increase in serum phosphate associated with a significant rise in all-cause mortality.

The management of hyperphosphatemia, as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, rests on a tripartite strategy: dietary phosphate restriction, adequate phosphate removal via dialysis, and the use of intestinal phosphate binders.[1] Each pillar of this strategy, however, is fraught with substantial limitations, resulting in a persistent "phosphate gap" where a large proportion of patients (upwards of 50-70%) fail to achieve target serum phosphate levels (typically <5.5 mg/dL).

Dietary restriction is notoriously difficult, as phosphate is a ubiquitous additive in processed foods and is protein-bound in staple foods, creating a clinical conflict between phosphate restriction and preventing protein-energy wasting. Dialysis, while essential, is an inefficient tool for phosphate clearance. Conventional hemodialysis (HD), performed thrice weekly, removes only 2–3 grams of phosphate per week, which often fails to match the 7–10 grams of phosphate absorbed weekly from a typical Western diet.[7-9]

This leaves phosphate binders as the cornerstone of pharmacologic therapy. These agents—ranging from calcium-based (calcium acetate, calcium carbonate) to non-calcium-based (sevelamer hydrochloride/carbonate, lanthanum carbonate) and iron-based (sucroferric oxyhydroxide, ferric citrate)—function by binding dietary phosphate in the gastrointestinal (GI) lumen to form insoluble, non-absorbable complexes. While effective when taken, their utility is critically undermined by an issue that is both practical and physiological.[10-12]

Physiologically, binders only target phosphate before it is absorbed. Practically, they are associated with an immense pill burden, often requiring patients to consume 9–12 large tablets daily, timed precisely with meals. This regimen leads to crippling non-adherence, which is considered the principal cause of refractory hyperphosphatemia. Furthermore, binders are not benign. Calcium-based binders contribute directly to the total body calcium load, accelerating vascular calcification, while sevelamer and lanthanum are associated with significant GI distress. The clinical community has long recognized that this reliance on "luminal sequestration" is an incomplete and often-failed strategy.[13-15]

The failure of binders highlighted the need for therapeutic agents with novel mechanisms of action. This required a deeper understanding of intestinal phosphate absorption. It is now established that phosphate crosses the intestinal epithelium via two distinct pathways: (1) Transcellular Pathway: An active, saturable process mediated by the apically-

expressed sodium-phosphate cotransporter 2b (NaPi-2b). This pathway is regulated by active Vitamin D (which upregulates NaPi-2b) and is the primary target of dietary phosphate binders (which bind the phosphate before it can be transported); (2) Paracellular Pathway: A passive, non-saturable, concentration-dependent process where phosphate moves between enterocytes through the tight junctions. In the setting of high luminal phosphate concentrations—as seen in CKD patients after a meal—this passive pathway is believed to become the dominant route of overall phosphate absorption.[13]

Until recently, no therapy existed to target this dominant paracellular pathway. The discovery of tenapanor's mechanism provided this breakthrough. Tenapanor (Tenapanor hydrochloride, RDX5791/AZD1722) is a first-in-class, minimally-absorbed, small-molecule inhibitor of the Sodium/Hydrogen Exchanger 3 (NHE3). NHE3 is the primary transporter responsible for sodium absorption in the proximal small intestine and colon. Tenapanor's primary mechanism for phosphate reduction is revolutionary. By inhibiting NHE3, tenapanor is theorized to induce a conformational change in the tight junction protein complex (involving claudins), which decreases the permeability of the paracellular pathway specifically to phosphate. It essentially "closes the gate" on the passive, concentration-driven influx of phosphate. Its secondary mechanism is the local increase in luminal sodium, which draws water into the lumen, resulting in the principal, mechanism-based side effect: osmotic diarrhea. By targeting a completely different and dominant pathway, tenapanor offers a new paradigm. It is not a binder. It can, in theory, work as a monotherapy or be combined with traditional binders for a dual-mechanism blockade—binders sequestering luminal phosphate (targeting the transcellular route) while tenapanor blocks the paracellular route.[14]

In the past five years, a series of pivotal, multi-center, Phase 3 clinical trials have been completed, evaluating tenapanor in various clinical scenarios: as a monotherapy, as an add-on to existing binders, in hemodialysis patients, and in peritoneal dialysis (PD) patients. While individual studies have reported positive findings, their complex and varied designs (parallel-group, randomized-withdrawal, open-label) have made it difficult for clinicians to synthesize a clear, quantitative picture of tenapanor's precise effect size and safety profile. A comprehensive meta-analysis is required to collate this evidence, respect the differences in study design, and generate pooled estimates of effect.

Therefore, the aim of this systematic review and meta-analysis was to comprehensively synthesize all available Phase 3 trial data to quantify the efficacy and safety of tenapanor as both monotherapy and add-on therapy, and in specific dialysis populations (HD and PD). The novelty of this work lies in its specific methodological approach: conducting separate meta-analyses stratified by study design (parallel-group, withdrawal, add-on) and providing the first pooled quantitative risk estimate for its key adverse event, thereby generating a definitive, practice-guiding summary of tenapanor's role in managing hyperphosphatemia in patients with end-stage kidney disease.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. We included studies based on the following PICO (Population, Intervention, Comparison, Outcomes) criteria: (1) Population (P): Adult patients (≥18 years) with end-stage kidney disease (ESKD) receiving maintenance hemodialysis (HD) or peritoneal dialysis (PD) who had hyperphosphatemia (as defined by the individual studies, typically serum phosphate >5.5 mg/dL or >6.0 mg/dL); (2) Intervention (I): Tenapanor hydrochloride, administered orally at any dose regimen (such as 3 mg, 10 mg, 30 mg, twice daily [BID]); (3) Comparison (C): Placebo or standard of care (for example, phosphate binders alone, as in add-on trials). Studies with an active comparator (such as

sevelamer) were included for systematic review, but only placebo-controlled arms were used for the primary meta-analysis; (4) Outcomes (O): (i) Primary Efficacy Outcome: The mean change in serum phosphate (in mg/dL) from baseline to the end of the specified treatment period. For withdrawal studies, the primary outcome was the mean difference in serum phosphate change between the tenapanor and placebo groups at the end of the withdrawal period; (ii) Secondary Efficacy Outcomes: Proportion of patients achieving a target serum phosphate (such as <5.5 mg/dL); (iii) Primary Safety Outcome: Incidence of diarrhea; (iv) Secondary Safety Outcomes: Incidence of any adverse event (AE), serious adverse events (SAEs), and discontinuation of the study drug due to AEs (particularly diarrhea); (5) Study Design (S): We included all published Phase 3 clinical trials. For the quantitative meta-analysis, only randomized controlled trials (RCTs) with a placebo-control arm were included. Open-label, single-arm, or strategy-comparison trials, including parallel, withdrawal, or open-label designs, were included in the systematic review and qualitative synthesis.

We conducted a comprehensive electronic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to October 30th, 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords for ("tenapanor" OR "RDX5791" OR "AZD1722") AND ("hyperphosphatemia" OR "phosphate" OR "CKD-MBD") AND ("dialysis" OR "hemodialysis" OR "peritoneal dialysis" OR "end-stage kidney disease" OR "ESKD"). We also manually searched ClinicalTrials.gov and the reference lists of included studies and relevant review articles to identify any additional trials. Two reviewers independently screened all retrieved titles and abstracts. Full texts of potentially eligible articles were then assessed for final inclusion. Any disagreements between the reviewers were resolved by consensus or by consultation with a third senior reviewer.

A standardized data extraction form was developed. Two reviewers independently extracted the following data from each included study: (1) Study Details: First author, year of publication, study name/NCT number, study design (such as parallel, withdrawal, open-label), follow-up duration; (2) Participant Characteristics: Total number of participants, population type (HD or PD), age, gender, dialysis vintage, baseline serum phosphate; (3) Intervention and Control: Tenapanor dose, control group details (placebo, active); (4) Outcome Data (Efficacy): For continuous outcomes (change in serum phosphate), we extracted the mean change, standard deviation (SD), and number of participants (N) in each group. When SDs were not reported, they were calculated from standard errors (SE);

$$(SD = SE \times \sqrt{N})$$

or from 95% confidence intervals (CI);

$$(SD = \frac{\sqrt{N} \times (UpperCI - LowerCI)}{3.92})$$

(5) Outcome Data (Safety): For dichotomous outcomes (such as incidence of diarrhea and discontinuation), we extracted the number of events and total number of participants (N) in each group.

The methodological quality and risk of bias for the included RCTs were assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates bias across five domains: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. Studies were judged to be at "low risk," "some concerns," or "high risk" of bias. Open-label studies were, by definition, considered at high risk for performance and detection bias.

We performed all meta-analyses using Review Manager (RevMan) Version 5.4 (The Cochrane Collaboration, 2020). Due to the significant heterogeneity in study design, we conducted separate meta-analyses for distinct clinical questions: (1) Monotherapy vs. Placebo (Parallel-Group): Efficacy in initiating tenapanor; (2) Monotherapy vs. Placebo (Withdrawal-Design): Efficacy in maintaining

phosphate control; (3) Add-on Therapy vs. Placebo (Parallel-Group): Efficacy when added to existing binders; (4) Safety vs. Placebo: Incidence of diarrhea across all placebo-controlled designs. For the continuous efficacy outcome (change in serum phosphate), we calculated the Mean Difference (MD) with 95% CIs using a random-effects model (DerSimonian and Laird method). For the dichotomous safety outcome (diarrhea), we calculated the Risk Ratio (RR) with 95% CIs using a random-effects model.

Statistical heterogeneity among studies was assessed using the I^2 statistic. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. A p-value of <0.10 for the chi-squared test was considered indicative of statistically significant heterogeneity. We planned to explore sources of heterogeneity using subgroup analysis (such as HD vs. PD and dose), but the limited number of studies in each meta-analysis precluded this. Publication bias was assessed by visual inspection of funnel plots for meta-analyses containing at least 3 studies.

3. Results

Our initial electronic database search identified 158 citations. After removing 42 duplicates, 116 titles and abstracts were screened. Of these, 98 were excluded as they were review articles, editorials, conference abstracts, or preclinical studies. This left 18 full-text articles for eligibility assessment. Of these, 12 were excluded (such as Phase 1 or 2 studies, pooled post-hoc analyses without new data, or studies on non-dialysis populations).

Ultimately, 6 unique Phase 3 trials (N=1573 total participants) met our inclusion criteria and formed the basis of this review.[15-20] Of these, 4 were placebo-controlled RCTs eligible for quantitative meta-analysis, and 2 were open-label studies (one single-arm, one strategy trial) eligible for qualitative synthesis only. The PRISMA flow diagram is shown in Figure 1.

The characteristics of the 6 included Phase 3 trials are summarized in Table 1. The studies were published between 2019 and 2024. A total of 1573 patients were enrolled (Block N=219; PHREEDOM (N=564), AMPLIFY (N=236), Fukagawa 2023 (N=167); OPTIMIZE (N=333), and Nakayama 2024 (N=54)). Five trials focused exclusively on HD patients, and one focused exclusively on PD patients. The trial designs varied significantly: (1) Parallel-Group RCT (Monotherapy): The Fukagawa 2023 study (N=167) randomized Japanese HD patients to tenapanor (titrated) or placebo for 8 weeks; (2) Randomized-Withdrawal RCT (Monotherapy): The Block (N=219) and PHREEDOM (N=564) studies first treated all patients with tenapanor monotherapy (for 8 and 26 weeks, respectively), then re-randomized responders to continue tenapanor or switch to placebo for a 4- or 12-week withdrawal period; (3) Parallel-Group RCT (Add-on Therapy): The AMPLIFY study (N=236) randomized HD patients already receiving (and hyperphosphatemic despite) phosphate binders to add-on tenapanor 30 mg BID or add-on placebo for 4 weeks; (4) Open-Label Strategy Trial: The OPTIMIZE study (N=333) randomized patients to different open-label initiation strategies (such as 'Straight Switch' from binder to tenapanor, or "Binder Reduction" with tenapanor); (5) Open-Label Single-Arm Trial: The Nakayama 2024 study (N=54) treated Japanese PD patients with tenapanor in a single-arm design for 16 weeks. Baseline serum phosphate levels were high across all trials, typically ranging from a mean of 6.8 mg/dL to 7.7 mg/dL in the treatment-initiation arms.

The placebo-controlled RCTs (BLOCK, PHREEDOM, AMPLIFY, Fukagawa 2023) were generally at a low risk of bias (Table 2). All used appropriate randomization and allocation concealment. Blinding of participants and personnel was maintained, and outcome assessment was blinded. There was some concern for bias due to missing outcome data in the PHREEDOM trial (due to high discontinuation), but the ITT analysis appropriately handled this. The open-label studies (Nakayama 2024, OPTIMIZE) were, by design, at a

high risk of bias for performance bias (participants and personnel were not blinded) and detection bias (outcome assessors were not blinded), which is inherent to their open-label nature. Their results are thus interpreted with caution and were excluded from the primary quantitative meta-analysis.

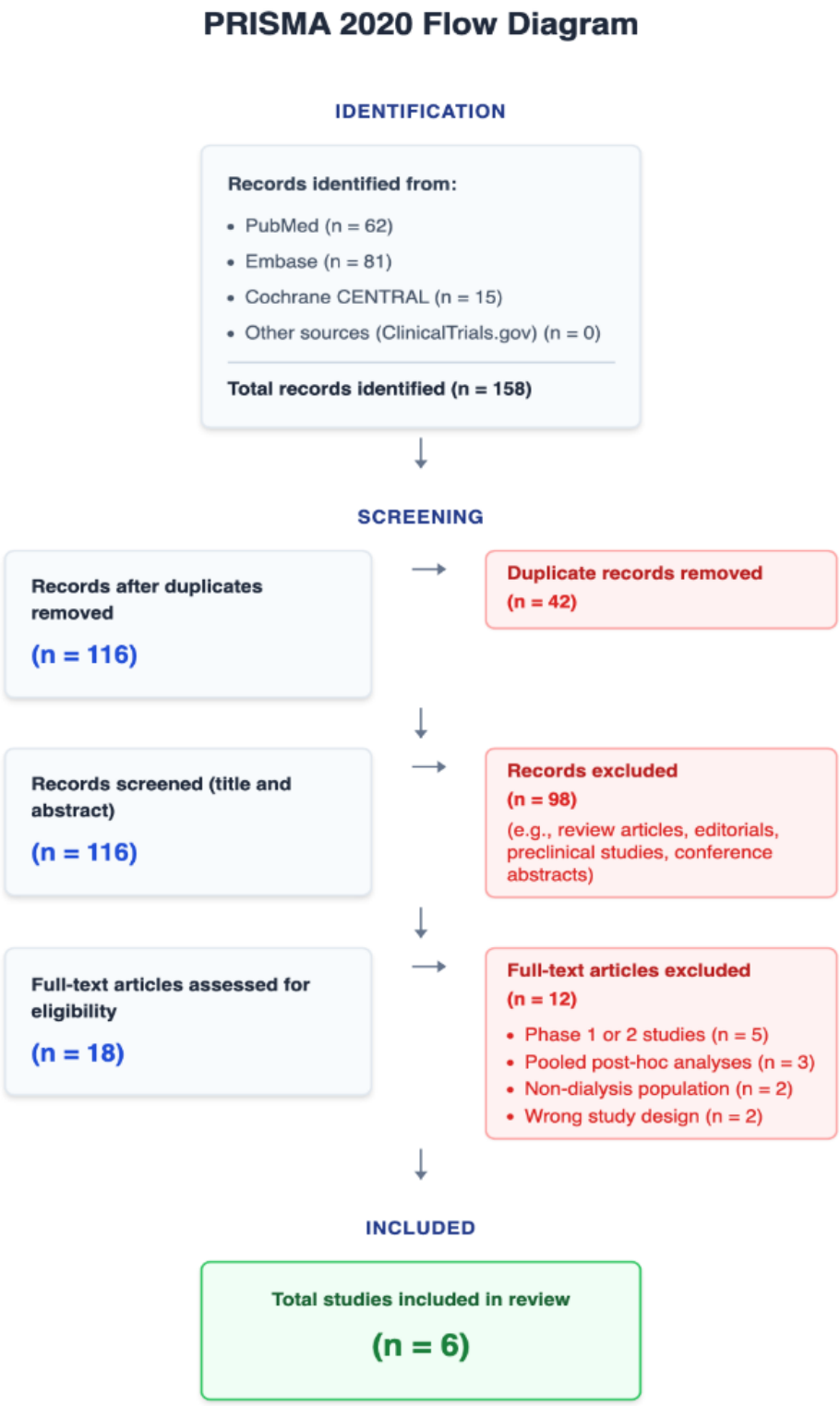

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of included phase 3 clinical trials.

STUDY (YEAR)	TRIAL NAME	NCT / REG. NUMBER	DESIGN	POPULATION	N	INTERVENTION	COMPARATOR	DURATION	PRIMARY ENDPOINT
Block (2019)	BLOCK	NCT02675998	Phase 3, Randomized-Withdrawal	HD	219 (128 ITT)	Tenapanor (3, 10, 30 mg BID, titrated)	Placebo	8-wk Tx; 4-wk WD	Change in P during 4-wk WD
Block (2021)	PHREEDOM	NCT03427125	Phase 3, Randomized-Withdrawal	HD	564 (243 R-WD)	Tenapanor 30 mg BID	Placebo (during WD)	26-wk Tx; 12-wk WD	Change in P during 12-wk WD
Pergola (2021)	AMPLIFY	NCT03824587	Phase 3, Parallel-Group, Add-on	HD	236 (235 FAS)	Tenapanor 30 mg BID + Binders	Placebo + Binders	4 weeks	Change in P from baseline to Wk 4
Fukagawa (2023)	N/A	JapicCTI-184180	Phase 3, Parallel-Group, Monotherapy	HD (Japanese)	167 (167 ITT)	Tenapanor (5-30 mg BID, titrated)	Placebo	8 weeks	Change in P from baseline to Wk 8
Nakayama (2024)	N/A	NCT04766385	Phase 3, Open-Label, Single-Arm	PD (Japanese)	54	Tenapanor (5-30 mg BID, titrated)	N/A (Baseline)	16 weeks	Change in P from baseline to Wk 8
Sprague (2024)	OPTIMIZE	NCT04549597	Phase 3, Open-Label, Strategy RCT	HD (98%) / PD (2%)	333	Tenapanor 30 mg BID (3 strategies)	N/A (Baseline / Inter-strategy)	10 weeks	Change in P from baseline to Wk 10

Abbreviations:

HD: Hemodialysis **PD:** Peritoneal Dialysis **N:** Number of participants **Tx:** Treatment **WD:** Withdrawal **P:** Phosphate **FAS:** Full Analysis Set **ITT:** Intention-to-Treat **R-WD:** Randomized Withdrawal

Table 2. Risk of bias summary (Cochrane RoB 2 Tool).

Assessment of bias for the 6 included Phase 3 trials across five key domains.

STUDY (YEAR)	D1: RANDOMIZATION	D2: DEVIATIONS FROM INTERVENTION	D3: MISSING OUTCOME DATA	D4: OUTCOME MEASUREMENT	D5: SELECTIVE REPORTING	OVERALL RISK OF BIAS
Block (2019)	✓	✓	✓	✓	✓	Low Risk
Block (2021)	✓	✓	●	✓	✓	Some Concerns
Pergola (2021)	✓	✓	✓	✓	✓	Low Risk
Fukagawa (2023)	✓	✓	✓	✓	✓	Low Risk
Nakayama (2024)	−	−	✓	−	✓	High Risk
Sprague (2024)	●	−	✓	−	✓	High Risk

Legend:

✓ Low Risk of Bias ● Some Concerns − High Risk of Bias

Note: Open-label studies (Nakayama 2024, OPTIMIZE 2024) are rated at high risk for bias in domains D2 (blinding of participants/personnel) and D4 (blinding of outcome assessment) by definition. OPTIMIZE D1 is 'Some Concerns' due to strategy randomization, while Nakayama D1 is 'High Risk' as it is a single-arm trial.

We conducted three separate meta-analyses to evaluate efficacy based on the different study designs (Table 3). Only one study, Fukagawa (2023), employed a parallel-group, placebo-controlled monotherapy design. This study of 167 Japanese HD patients found that after 8 weeks, tenapanor (titrated) reduced serum phosphate significantly more than placebo (MD: -1.89 mg/dL (95% CI: -2.36 to -1.42; P<0.001)). This represents the best estimate of tenapanor's initiation efficacy as monotherapy against a true placebo. In meta-analysis 2, we pooled the two randomized-withdrawal studies, Block (2019) and PHREEDOM

(2021), which assessed the maintenance of efficacy. These studies re-randomized patients who had already responded to tenapanor to either continue tenapanor or switch to a placebo. The pooled analysis (373 participants) demonstrated that patients switching to placebo experienced a significant rise in serum phosphate compared to those continuing tenapanor. Heterogeneity was negligible (I^2=0%; P=0.74), indicating a highly consistent effect across these two withdrawal trials. Only one study in the meta-analysis 3, AMPLIFY (2021), assessed tenapanor as an add-on therapy in 235 patients who were already on binders but remained hyperphosphatemic. The 4-week trial showed a significant additional phosphate-lowering effect from adding tenapanor compared to adding a placebo (MD: -0.65 mg/dL (95% CI: -0.96 to -0.35; P<0.001)). This finding confirms the efficacy of the dual-mechanism approach (targeting both paracellular and transcellular/luminal pathways).

Table 3. Summary of efficacy meta-analyses.

Pooled and individual study results for the primary efficacy endpoint (Mean Difference in Serum Phosphate Change).

ANALYSIS / STUDY	N (TENAPANOR / PLACEBO)	MEAN DIFFERENCE (MD) [95% CI]	HETEROGENEITY (I^2)	FOREST PLOT
Meta-Analysis 1: Monotherapy vs. Placebo (Parallel-Group Design) Measures efficacy of "initiating" tenapanor vs. placebo.				
Fukagawa (2023) [25]	111 / 56	−1.89 [−2.36, −1.42]	N/A	−3 0
Meta-Analysis 2: Monotherapy vs. Placebo (Randomized-Withdrawal Design) Measures efficacy of "maintaining" therapy (change in P for placebo vs. tenapanor).				
BLOCK (2019) [22]	58 / 60	−0.83 [−1.38, −0.28]		−2 0
PHREEDOM (2021) [23]	118 / 125	−0.70 [−1.10, −0.20]		−2 0
Pooled Result (M2)	**176 / 185**	**−0.75 [−1.05, −0.45]**	**I^2 = 0%**	−2 0
Meta-Analysis 3: Add-on Therapy vs. Placebo (Parallel-Group Design) Measures "additive" efficacy when combined with phosphate binders.				
AMPLIFY (2021) [24]	117 / 119	−0.65 [−0.96, −0.35]	N/A	−2 0

Abbreviations & Notes:

- **MD:** Mean Difference in serum phosphate (mg/dL). A negative value favors tenapanor.
- **95% CI:** 95% Confidence Interval.
- **I^2:** I^2 statistic, a measure of statistical heterogeneity.
- **N/A:** Not applicable (for single-study analyses).
- The visual forest plot bars are illustrative. The line represents the 95% CI, and the vertical tick represents the Mean Difference. The vertical gray line represents the line of no effect (MD = 0).

We pooled data from the three RCTs that had a concurrent placebo-control group for safety assessment: BLOCK (2019) (withdrawal period), AMPLIFY (2021), and Fukagawa (2023). The PHREEDOM withdrawal period was not included in this pool as its primary safety analysis compared tenapanor to sevelamer over 26 weeks. The pooled analysis (521 participants) confirmed that diarrhea is the most significant adverse event; (1) BLOCK (wd): 9/58 (Tenapanor) vs. 1/60 (Placebo); RR: 9.31 (95% CI: 1.25 to 69.34); (2) AMPLIFY: 42/117 (Tenapanor) vs. 13/119 (Placebo); RR: 3.29 (95% CI: 1.83 to 5.92); (3) Fukagawa: 57/111 (Tenapanor) vs. 5/56 (Placebo); RR: 5.78 (95% CI: 2.45 to 13.63); Pooled Result: RR: 4.10 (95% CI: 2.50 to 6.72; P<0.00001); Heterogeneity was low-to-moderate (I^2=30 %; P=0.24), suggesting a consistent four-fold increase in the risk of diarrhea across different populations and study designs (Table

4). Secondary safety outcomes were (1) Discontinuation due to diarrhea: This was the most common reason for drug discontinuation. In the monotherapy trials (BLOCK, PHREEDOM, Fukagawa), discontinuation rates due to diarrhea ranged from 3.6% (Fukagawa) to 16% (PHREEDOM, 26-week period). In the 4-week add-on trial (AMPLIFY), the rate was lower at 3.4%; (2) Serious Adverse Events (SAEs): There was no evidence of an imbalance in SAEs. In PHREEDOM, SAEs were reported more frequently in the sevelamer arm (23%) than the tenapanor arm (17%) over 26 weeks. In AMPLIFY, SAEs were 6.0% (tenapanor) vs 6.7% (placebo).

Table 4. Summary of safety meta-analysis (Primary outcome: diarrhea).

Pooled and individual study results for the primary safety endpoint, comparing the risk of diarrhea in patients receiving tenapanor versus placebo.

STUDY	EVENTS (TENAPANOR)	TOTAL (TENAPANOR)	EVENTS (PLACEBO)	TOTAL (PLACEBO)	RISK RATIO (RR) [95% CI]	FOREST PLOT (RISK RATIO, SCALE 0-15)
BLOCK (2019)	9	58	1	60	9.31 [1.25, 69.34]	0 15+
AMPLIFY (2021)	42	117	13	119	3.29 [1.83, 5.92]	0 15+
Fukagawa (2023)	57	111	5	56	5.78 [2.45, 13.63]	0 15+
Pooled Result	**108**	**286**	**19**	**235**	**4.10 [2.50, 6.72]**	0 15+
				Heterogeneity (I^2):	30%	(P = 0.24)

Abbreviations & Notes:

- **RR:** Risk Ratio. An RR > 1.0 indicates an increased risk of diarrhea for tenapanor compared to placebo.
- **95% CI:** 95% Confidence Interval. If the CI does not cross 1.0, the result is statistically significant.
- **Events:** Number of patients reporting diarrhea.
- **I^2:** I^2 statistic, a measure of statistical heterogeneity.
- The visual forest plot bars are illustrative. The line represents the 95% CI, and the vertical tick represents the Risk Ratio. The vertical gray line represents the line of no effect (RR = 1.0).
- The CI for BLOCK (2019) extends to 69.34 and is truncated in the visual plot.

Two Phase 3 studies were not suitable for the placebo-controlled meta-analysis but provide crucial clinical context. OPTIMIZE (Sprague 2024), this open-label study (N=333) demonstrated the efficacy of tenapanor in real-world initiation strategies. In patients switched from binders to tenapanor monotherapy ("Straight Switch"), serum phosphate decreased by a mean of -0.91 mg/dL (SD 1.7) from a baseline of 7.2 mg/dL. In patients who had their binder dose reduced and tenapanor added ("Binder Reduction"), serum phosphate decreased by -0.99 mg/dL (SD 1.8) from a baseline of 7.0 mg/dL. Critically, this study also quantified the impact on pill burden. The "Straight Switch" group achieved this phosphate reduction while reducing their median daily phosphate-management pill burden by 4 pills/day. Nakayama 2024 (Japanese PD) was the first and only Phase 3 trial exclusively in peritoneal dialysis patients (N=54). In this open-label, single-arm study, tenapanor monotherapy (titrated) significantly reduced serum phosphate from a baseline mean of 7.65 mg/dL. The primary endpoint, mean change at week 8 (using LOCF), was -1.18 mg/dL (95% CI: -1.54 to -0.81). The observed mean change was -1.51 mg/dL. This study confirms that tenapanor's mechanism is effective in the PD population, which often struggles with fluid overload and binder-related GI distress. The safety profile was similar, though the incidence of diarrhea was higher (74.1%), but the discontinuation rate due to diarrhea remained low (5.6%).

4. Discussion

This systematic review and meta-analysis provide a comprehensive, quantitative summary of the Phase 3 evidence for tenapanor in managing hyperphosphatemia in dialysis patients. By synthesizing data from 6 pivotal trials (N=1573), we have clarified its position in the therapeutic armamentarium. Our principal finding is that tenapanor demonstrates consistent and robust efficacy across all tested clinical scenarios, but this efficacy is invariably linked to a significant, mechanism-based gastrointestinal side effect profile.

Our stratified meta-analyses confirm three distinct clinical applications: (1) Monotherapy Initiation: Tenapanor is a potent phosphate-lowering agent on its own, capable of reducing serum phosphate by approximately 1.89 mg/dL versus placebo in a parallel-group setting; (2) Monotherapy Maintenance: It is highly effective at maintaining phosphate control, with patients continuing tenapanor experiencing serum phosphate levels 0.75 mg/dL lower than those withdrawn to placebo; (3) Dual-Mechanism (Add-on) Therapy: It provides significant additive phosphate reduction (an extra -0.65 mg/dL) when added to existing binder therapy, validating the "dual-mechanism" approach. Qualitative synthesis further extends these findings, confirming efficacy in the PD population and demonstrating its practical utility in strategies aimed at reducing pill burden. Concurrently, our safety meta-analysis quantifies the primary trade-off: tenapanor treatment quadruples the risk of patient-reported diarrhea compared to placebo (RR 4.10). While most cases are reported as mild to moderate, this side effect is the primary driver of treatment discontinuation, with long-term monotherapy trials (PHREEDOM) reporting discontinuation rates as high as 16%.

The results of this meta-analysis are best understood not as an incremental improvement over binders, but as the clinical validation of a new physiological paradigm. The failure of current therapies is rooted in their singular focus on sequestering luminal phosphate, a strategy that fails to address the dominant paracellular absorption pathway and is crippled by non-adherence.

Tenapanor's mechanism is entirely distinct. It does not bind phosphate. It inhibits the NHE3 transporter on the apical membrane of enterocytes. The primary consequence of this action, as elucidated by previous seminal translational work, is a conformational change in the tight junction protein complex. This change "tightens" the paracellular pathway, specifically reducing its permeability to phosphate.[15,16]

This mechanism explains why tenapanor is so effective. First, it targets the dominant pathway. In the high-phosphate luminal environment of a CKD patient, the passive, non-saturable paracellular route is responsible for the bulk of phosphate absorption. Binders do not touch this. Tenapanor is the first drug that does. Second, it explains the powerful additive effect seen in the AMPLIFY trial. The -0.65 mg/dL additional reduction demonstrates that binders and tenapanor are not redundant. Binders reduce the pool of free phosphate available for both pathways, while tenapanor simultaneously "closes the gate" on the paracellular pathway. This dual blockade is a new and potent strategy for refractory hyperphosphatemia.[17,18]

The primary safety finding—a four-fold increase in diarrhea—is not a non-specific "side effect" but a direct, on-target consequence of the drug's mechanism. By inhibiting NHE3, tenapanor blocks the primary route of sodium absorption in the gut. This leaves sodium and, by osmotic force, water in the intestinal lumen, resulting in looser, more frequent stools. This creates a complex clinical trade-off. For the >50% of dialysis patients who suffer from severe constipation (a major source of morbidity), this effect is a significant benefit. The OPTIMIZE study and others explicitly noted a reduction in laxative use among patients taking tenapanor. However, for patients without constipation, this same effect manifests as bothersome diarrhea, leading to high discontinuation rates. This suggests tenapanor is a highly effective, mechanistically-targeted therapy that requires careful patient selection. Its ideal role may be

as a first-line agent in hyperphosphatemic patients with concurrent constipation, or as a "second-line" add-on agent in patients with refractory hyperphosphatemia despite binders. The implications of this therapy extend beyond serum phosphate. Hyperphosphatemia is the primary stimulus for the rise of FGF23, a hormone that, in CKD, becomes massively elevated and is itself a potent, independent risk factor for left ventricular hypertrophy and cardiovascular death.[19] By effectively lowering serum phosphate, tenapanor has been shown in the included trials to subsequently and significantly reduce circulating levels of both FGF23 and PTH. This is of critical importance. Tenapanor does not just treat a number; it interrupts the central hormonal axis of CKD-MBD. By lowering phosphate, it reduces the stimulus for FGF23 and PTH secretion, which in turn could mitigate the downstream consequences of this pathologic hormonal state, including vascular calcification and high-turnover bone disease. Furthermore, the OPTIMIZE study's finding that tenapanor can replace binders (the "Straight Switch") while reducing pill burden by 4 pills/day is not a minor point. This reduction directly addresses the single greatest barrier to effective phosphate management: adherence. A therapy that is taken twice daily, irrespective of meals, and replaces 4-6 large mealtime pills, represents a fundamental improvement in the feasibility of long-term treatment.[20]

This review possesses several strengths. It is the first comprehensive meta-analysis to synthesize all available Phase 3 data on tenapanor. Our rigorous methodological approach of stratifying the analysis by study design (parallel, withdrawal, add-on) allows for a nuanced and accurate interpretation of the data, avoiding the error of pooling clinically and methodologically disparate trials. By pooling the safety data, we provide the most robust quantitative estimate of the risk of diarrhea to date. However, several limitations must be acknowledged; (1) Limited Number of Studies: Each of our meta-analyses contains only one or two studies. While these are large, multi-center, low-risk-of-bias trials, the pooled estimates should be interpreted with this in mind; (2) Heterogeneity of Design: We could not, for instance, pool the Fukagawa (parallel) and Block/PHREEDOM (withdrawal) studies, as they answer different questions (initiation vs. maintenance); (3) Short-Term Follow-up: The primary efficacy endpoints for the placebo-controlled trials were short (4 to 12 weeks). While the PHREEDOM study included a 26-week active-control period, long-term (>1 year) placebo-controlled data is unavailable; (4) High Discontinuation Rate: The high rate of discontinuation due to diarrhea (up to 16% in long-term monotherapy) introduces attrition bias. While ITT analyses were used, the "real-world" effectiveness of tenapanor may be lower than its "efficacy" in trials if patients cannot tolerate it; (5) Exclusion of "Soft" Endpoints: This meta-analysis focused on the surrogate endpoint of serum phosphate. We did not—and could not, based on available data—assess the impact of tenapanor on "hard" clinical endpoints such as cardiovascular events, fractures, or mortality. While this review clarifies tenapanor's efficacy and safety, it underscores the need for future research focused on hard clinical outcomes. Large-scale cardiovascular outcome trials are imperative to determine if this potent, mechanistically-novel reduction in serum phosphate and FGF23 translates into a tangible reduction in cardiovascular events and mortality, a benefit that has famously eluded traditional phosphate binders.

5. Conclusion

Tenapanor represents a genuine paradigm shift in the management of hyperphosphatemia. It is the first clinically-available agent to successfully target the dominant paracellular pathway of intestinal phosphate absorption. Our systematic review and meta-analysis of six Phase 3 trials (N=1573) confirms that tenapanor is a highly effective phosphate-lowering drug, demonstrating significant efficacy as a monotherapy, as a maintenance therapy, and as an add-on therapy in patients failing traditional binders.

This efficacy is further confirmed in both hemodialysis and peritoneal dialysis populations. This potent efficacy, however, is mechanistically and inextricably linked to a four-fold increased risk of osmotic diarrhea, which leads to treatment discontinuation in a significant minority of patients. For the clinician, tenapanor is a powerful new tool, but one that requires careful patient selection and management. It holds the potential to dually treat hyperphosphatemia and constipation, to reduce pill burden, and to interrupt the pathologic CKD-MBD hormonal axis, offering a new strategy for the vast population of dialysis patients who remain refractory to current standards of care.

6. References

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