Tenapanor: A New Treatment Option for Hyperphosphatemia in End Stage Kidney Disease

Tiffany Lin[1], Akram Al-Makki[2], Brian Shepler[1]

[1]Department of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette, IN, USA; [2]IU Health Arnett Nephrology, Lafayette, IN, USA

Corresponding author: Brian Shepler, PharmD., Purdue University College of Pharmacy, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, United States; TEL: (765)-494-1365; email:sheplerb@purdue.edu

ABSTRACT -- Purpose: This narrative review explores the currently published studies that have evaluated tenapanor for the treatment of hyperphosphatemia in end-stage kidney disease (ESKD) patients on hemodialysis. This medication's new phosphate lowering mechanism of action reduces intestinal phosphate absorption predominantly through reduction of passive paracellular phosphate flux by inhibition of the sodium/hydrogen exporter isoform 3 (NHE3). Tenapanor additionally prevents active transcellular phosphate absorption compensation by decreasing the expression of sodium phosphorus 2b transport protein (NaPi2b). **Methods:** A comprehensive search of the literature was conducted using PubMed and ClinicalTrials.gov search engines. The search term "tenapanor hyperphosphatemia" was used for study retrieval. Results were limited to studies published in the English language and excluded review articles. Human, animal, and in vitro studies were included. No date range was specified. **Results:** A total of 11 primary studies were identified and included in this review, the largest human study of which enrolled 236 patients. Each study is presented in table format along with measured end points. **Conclusions:** Tenapanor is the first drug in its class that lowers hyperphosphatemia in ESKD patients through a novel mechanism of action involving paracellular inactive transport. Although more studies are needed, early results indicate that tenapanor may have a place in managing hyperphosphatemia in ESKD patients both as monotherapy and as an adjunct to existing phosphate binder therapy.

INTRODUCTION

Hyperphosphatemia is a significant complication that plagues nearly all patients with late-stage chronic kidney disease (CKD) and end-stage kidney disease (ESKD) (1). This is a consequence of the deteriorating kidney's inability to excrete phosphorus from the body thereby allowing dietary phosphorus absorption and serum accumulation. Hyperphosphatemia in ESKD can lead to secondary hyperparathyroidism, renal osteodystrophy, metastatic calcification, and cardiovascular mortality. In addition to dietary restriction of phosphorus and hemodialysis, drugs that bind phosphate in the gut are usually needed as well (2). The Kidney Disease Improving Global Outcomes' (KDIGO) latest hyperphosphatemia guidelines recommend treating hyperphosphatemia by limiting phosphorus intake from the diet and using phosphate-binding medications (1). Phosphate binders continue to be a mainstay of treatment for hyperphosphatemia and exist in several different categories including the oldest calcium-containing binders (calcium carbonate, calcium acetate), the polymer-based binder (sevelamer carbonate), the metal-based binders (lanthanum carbonate, aluminum hydroxide) and the newest additions to the armamentarium, the iron-based binders (sucroferric oxyhydroxide, ferric citrate) (3). These medications all control phosphorus absorption by binding to dietary phosphorus in the gastrointestinal tract and allowing the chelate to pass from the body into the feces. Aluminum hydroxide is no longer recommended for long-term use because of concerns about its toxicity, and calcium citrate should be avoided in all CKD patients since citrate can markedly increase intestinal aluminum absorption (4,5).

Recent developments in the understanding of how phosphorus is absorbed from a mechanistic standpoint have allowed innovative new therapies to be conceptualized. From animal model studies, two distinct mechanisms for phosphorus absorption have been identified. Active transcellular transport

through specific ion transporters and inactive paracellular transport which occurs through tight junctions of cells in the duodenum are new biologic pathways for phosphorus absorption from the gastrointestinal tract (6). Active transcellular transport is facilitated through the sodium phosphorus 2b transport protein (NaPi2b) and is located on the apical side the of the intestinal lumen. This protein is expressed when low serum phosphorus increases parathyroid hormone (PTH) concentrations which then stimulates production of activated vitamin D3. Similarly, high serum phosphorus concentrations increase fibroblast growth factor 23 (FGF23) concentrations and lower PTH concentrations which reduce active vitamin D3 production and decrease NaPi2b production (7). Paracellular phosphorus absorption is an inactive transport that is mediated by the sodium/hydrogen exporter isoform 3 (NHE3) protein. This is thought to be a more potent controller of phosphorus absorption and a better target for directed drug therapy (8).

The focus of this review and the novelty of this work is on one such drug therapy product, the first novel NHE3 inhibitor to be studied in human subjects for the treatment of hyperphosphatemia, tenapanor hydrochloride. Tenapanor, a minimally systemically absorbed molecule, is an inhibitor of intestinal NHE3 that was developed to treat irritable bowel syndrome with constipation but that also lowers serum phosphorus by blocking its paracellular transport from the intestinal lumen. Tenapanor reduces intestinal phosphate absorption predominantly through reduction of passive paracellular phosphate flux. Tenapanor also prevents active transcellular phosphate absorption compensation by decreasing the expression of NaPi2b (9).

METHODS

To complete this narrative review, a search of the literature was conducted using PubMed and ClinicalTrials.gov search engines. The search term "tenapanor hyperphosphatemia" was used for both search engines. Results were limited to studies published in the English language and excluded review articles. Human, animal, and in vitro studies were included. No date range was specified.

RESULTS

Using the search methods described above, 17 articles were returned. After excluding review articles, 11 primary studies were identified. All phase one through phase three articles were included in our review for completeness. Another 11 studies are currently recruiting patients, underway, or do not have published results. Of the published trials, the largest study in humans enrolled 236 patients. Most studies evaluated the efficacy of tenapanor for hyperphosphatemia while others focused on drug-drug interactions. Table 1 depicts a summary of the details and findings obtained from the described search method.

DISCUSSION

Phase one trials were included in this review to thoroughly examine tenapanor's effect on hyperphosphatemia and potential drug-drug interactions. These drug-drug interactions are a crucial part of clinical practice and in the case of tenapanor involve CYP450 inhibition, phosphate binders, and PepT1. All three drug interaction studies in vivo concluded that there was no difference in serum concentrations of the test drug and tenapanor when both were co-administered (10-12). It is important to note that there is no drug-drug interaction between phosphate binders and tenapanor, as dual therapy with these agents may be warranted with tenapanor in patients with persistent hyperphosphatemia.

A few publications included data from in vitro, animal, and human studies together. Some outcomes from the in vitro and animal studies in those select publications did not translate into the same results in vivo. For example, one study considered that tenapanor, although minimally systemically absorbed, may exhibit drug-drug interactions with CYP450 enzymes since CYP3A4 is also present in the cells of the gut wall. In vitro studies displayed inhibition of CYP3A4 by tenapanor. However, no such interaction was observed from the co-administration of midazolam (a model substrate of CYP3A4) and tenapanor in human studies (10). This phenomenon could possibly be due to a higher concentration of tenapanor used in vitro compared to that found in human intestinal tissue.

All the phase three trials had a primary endpoint of change in serum phosphorus concentrations from baseline in patients suffering from hyperphosphatemia. The proportion of patients that reached a serum phosphorus concentration of < 5.5 mg/dL were only included as a secondary endpoint (13, 14). Normal serum phosphorus concentrations are between 2.5 and 5.5 mg/dL.

Table 1. Summary of In Vitro, Animal, and Human Studies for Tenapanor

Authors, Year	Study Designs and Objective(s)	Patients (if applicable)	Treatment Drug(s) and Dose	Outcomes
Labonte et al., 2015 (21)	Animal study Obj: Evaluate the effect of tenapanor on dietary phosphorus absorption in rats	N = 9 male Sprague-Dawley rats	Tenapanor 0.3, 1, and 3 mg/kg	Increased fecal phosphorus elimination and decreased urinary phosphate excretion: reflects a reduced sodium and phosphorus absorption
King et al., 2020 (22)	Animal study Obj: Evaluate the effect of tenapanor and varying doses of sevelamer carbonate on urinary phosphorus excretion in rats	N = 102 8-week-old male Sprague-Dawley rats	Tenapanor 0.15 mg/kg BID + Sevelamer 0.75% to 3% (wt/wt)	Coadministration of tenapanor and sevelamer dose-dependently resulted in a more pronounced reduction in urinary phosphorus than that of either agent alone, directly reflecting a decreased intestinal phosphate absorption.
Johansson et al., 2017 (10)	In vitro study Obj: Determine if tenapanor inhibits various CYP450 enzymes	N/A	Tenapanor 0.1, 0.3, 1.0, 3.0, 10, and 30 µM in the presence of CYP enzyme marker substrates and NADPH	Tenapanor reversibly inhibited 5 of the 7 CYPs tested, being most potent against CYP3A4/5. No evidence of inhibition of CYP1A2 was observed.
	In vitro study Obj: Determine if tenapanor induces CYP1A2, CYP2B6, or CYP3A4 via mRNA expression	N/A	Tenapanor 0.0001 to 50 µM	Tenapanor did not induce CYP1A2 or CYP2B6 mRNA expression in any of the experiments for these enzymes. Induction of CYP3A4 mRNA expression was observed with tenapanor in 1 out of 4 experiments for this enzyme.
	Phase 1: Open label Obj: Determine if tenapanor clinically inhibits or induces CYP3A4	N = 28 healthy volunteers	Midazolam 7.5 mg single dose + Tenapanor 15 mg BID	Similar plasma midazolam concentrations and metabolite concentrations when midazolam was given alone and with tenapanor indicates no effect on CYP3A4.
Johansson et al., 2017 (11)	In vitro study Obj: Determine the pharmacodynamic effects of coadministration of tenapanor with phosphate binders	N/A	Tenapanor 1, 10, 50, 100, and 200 µM + Sevelamer carbonate 1.6 mg/mL, calcium acetate 1 mg/mL, and calcium carbonate 2.4 mg/dL	72-87% of tenapanor was found bound, suggesting an interaction between tenapanor and sevelamer carbonate. No binding was observed between tenapanor and calcium carbonate or calcium acetate.
	Animal Study Obj: Determine the in vivo effects of coadministration of tenapanor with phosphate binders	N = 60 7-week-old male Sprague-Dawley rats	Tenapanor dissolved in water at 0.1, 0.3, 1, or 3 mg/kg + Sevelamer carbonate dissolved in water at 48 mg/kg	Dose-dependent reduction in urinary sodium by tenapanor was unaffected by coadministration of sevelamer 10 minutes later. Reversing the administration order (i.e., tenapanor given 10 minutes after sevelamer) also had no detectable effects on the dose-dependent reduction in urinary sodium.
	Phase 1: Open-label, crossover Obj: Determine the clinical effects of coadministration of tenapanor with phosphate binders	N =16 healthy volunteers	Tenapanor 15 mg BID x 4 days Tenapanor 15 mg BID + sevelamer 800 mg TID x 4 days 2-day washout before crossover with sevelamer or Ca based binder	Phosphorus levels in stool and urine were similar if patients took tenapanor alone or tenapanor with binder. *Table 1. (continued)*

Johansson et al., 2017 (12)	Phase 1: Open-label, crossover Obj: Determine tenapanor's effect on PepT1 activity in healthy volunteers	N = 28 healthy volunteers	Single dose cefadroxil 500 mg in AM for 1 day + Tenapanor 15 mg BID x 4 days, followed by single doses of both tenapanor 15 mg and cefadroxil 500 mg on day 5 4-day washout between treatments	Cefadroxil plasma concentration-time curves were similar whether cefadroxil was administered alone or in combination with tenapanor. PK parameters also similar when cefadroxil was given alone or with tenapanor indicating no effect on PepT1's absorption activity.
Johansson et al., 2017 (23)	Phase 1: RCT Obj: To report on the safety and efficacy of tenapanor on healthy subjects	N = 83 healthy adults	Tenapanor 180 mg single dose or 15, 30, 60, or 90 mg BID x 7 days	Diarrhea and abdominal pain were the most common AEs related to treatment. Repeated doses of tenapanor resulted in increased stool phosphorus and decreased urine phosphorus. All tenapanor doses *Table 1. (continued)* resulted in plasma concentrations below lower limit of quantification suggesting low systemic absorption.
King et al., 2018 (8)	Animal Studies Obj: Determine the mechanism by which tenapanor reduces gastrointestinal phosphate uptake	N = 5 to 7 healthy rats per group in each experiment	Various tenapanor doses based on the experiment performed	Tenapanor produces its effect by tight-junction modulation which increases transepithelial electrical resistance and reduces permeability to phosphate, reducing paracellular phosphate absorption. Tenapanor prevents active transcellular phosphate transport by decreasing NaPi2b expression.
	Phase 1: Open-label, crossover Obj: Determine the effect of tenapanor on intestinal phosphate absorption	N = 18 healthy volunteers	Tenapanor 15 mg BID x 4 days	Significantly increased mean daily stool phosphorus excretion and significantly decreased mean daily urinary phosphorus excretion. Significantly reduced mean daily urinary sodium excretion. No effect on potassium excretion.
Block et al., 2017 (16)	Phase 2: RCT, dose-ranging Obj: Evaluate the effect of tenapanor on serum phosphate concentration in HD patients with hyperphosphatemia	N = 162 CKD stage 5D adults on maintenance HD and with hyperphosphatemia	Tenapanor 3 or 30 mg daily; or 1, 3, 10, or 30 mg twice daily for 4 weeks	Statistically significant dose-dependent reduction in serum phosphate with largest reductions in the tenapanor 10 and 30 mg BID groups No significant difference in serum PTH
Block et al., 2019 (24)	Phase 2b: RCT Obj: Evaluate the effect of tenapanor on serum FGF23	N = 162 CKD stage 5D patients receiving HD on stable dose of phosphate binders with hyperphosphatemia	Tenapanor 3 or 30 mg daily; or 1, 3, 10, or 30 mg twice daily	Tenapanor treatment decreased serum FGF concentrations from post-phosphate binder washout. FGF23 continued to rise in patients receiving placebo after washout.

Table 1. (continued)

Block et al., 2019 (13)	Phase 3: RCT Obj: Evaluate the efficacy and safety of tenapanor in HD patients with hyperphosphatemia	N = 219 CKD stage 5D adults on maintenance HD and with hyperphosphatemia	Tenapanor 3 or 10 mg BID; or 30 mg BID down titrated if needed	RTP: Significant decrease in serum phosphate levels in all three treatment groups RWP: Serum phosphate increase was significantly lower among tenapanor group No difference in serum PTH Significant decrease in FGF23 concentrations in all 3 treatment groups
Pergola et al., 2021 (14)	Phase 3: RCT Obj: Evaluate the safety and efficacy of tenapanor combined with a phosphate binder	N = 236 CKD stage 5D adults on maintenance HD and with hyperphosphatemia	Existing binder and strength + Tenapanor 30 mg BID, down titrated to minimum 10 mg BID based on GI tolerability	Tenapanor + binder had a significantly larger decrease in serum phosphate from baseline compared to placebo + binder. Significantly larger proportion of tenapanor + binder patients achieved serum phosphorus concentrations < 5.5 mg/dL. Significant reductions in FGF23 levels in tenapanor + binder group. Diarrhea was the most common AE.

BID: twice daily; TID: three times daily; PK: pharmacokinetic; RCT: randomized controlled trial; AE: adverse event; HD: hemodialysis; RTP: randomized treatment period; RWP: randomized withdrawal period

Reducing a patient's serum phosphorus levels to < 5.5 mg/dL would be what is clinically significant rather than merely recognizing a change in serum phosphorus from baseline. The ongoing NORMALIZE (NCT03988920) trial is studying this clinical significance, as its primary endpoint is the proportion of patients who reach a normal serum phosphorus concentration (2.5-5.5 mg/dL) (15).

Only one clinical study, AMPLIFY, has tested the combination of tenapanor with phosphate binder therapies. Phosphate binders tested included sevelamer and non-sevelamer binders. The study investigators did not include which binders comprised the non-sevelamer group. Tenapanor + binder resulted in a significantly larger decrease in serum phosphorus compared to placebo + binder (-0.84 vs. -0.19 mg/dL; P < 0.001) (14). No tenapanor monotherapy group was included in the study design and no definitive statement can be made regarding the additive or synergistic effect of tenapanor. It is likely that given the complementary mechanism of action that some degree of synergy may exist.

All clinical trials in human subjects published to date have been conducted in ESKD patients receiving maintenance hemodialysis. There is evidence that tenapanor as monotherapy as well as given concomitantly with phosphate binders lowers serum phosphorus levels. Hemodialysis patients currently taking phosphate binders with uncontrolled hyperphosphatemia may benefit from tenapanor to reduce the pill burden of phosphate binders. Adherence with phosphate binders was low at 38% and phosphate binders accounted for half of a patient's total pill burden (16). 70% of patients on hemodialysis continued to experience elevated serum phosphorus despite efforts to control levels through diet and phosphate binder therapy (14). Tenapanor has been dosed between 10-30 mg twice daily without regard to meals in the studies presented here. This dosing schedule and pill burden could be considerably less than those for phosphate binders since phosphate binders require administration three times daily with meals. This drug's twice daily dosing can be a benefit for patients suffering from excessive pill burden. Although not specifically studied in humans, cardiovascular calcification would not be expected with tenapanor compared to other calcium-containing phosphate binders such as calcium carbonate as it does not contain calcium.

From the evidence presented, it appears tenapanor as an adjunct therapy to phosphate binders produces the greatest decrease in serum phosphorus concentrations (14). Monotherapy with tenapanor also lowers serum phosphorus although not to the same degree as dual therapy. The ongoing NORMALIZE trial is evaluating the ability of

tenapanor alone or in combination with sevelamer to achieve normal serum phosphorus concentrations in patients with ESKD (15). Once published, this information will further guide clinicians in the appropriate use of tenapanor.

It is important for prescribers to know and share with patients that diarrhea (16%), flatulence, and abdominal distention (3% each) have been the most common adverse effects of tenapanor. The drug is contraindicated for use in children < 6 years old and in patients with intestinal obstruction (17-19).

In July 2021, the Food and Drug Administration (FDA) issued a Complete Response Letter to the pharmaceutical company Ardelyx, the makers of tenapanor, and stated that more significant clinical data was needed before approval could be granted for the indication of hyperphosphatemia. Although the current data does show a reduction in phosphorus serum concentrations, the magnitude of this effect requires more investigation (20).

CONCLUSION

In conclusion, tenapanor has shown a unique mechanism of action to reduce phosphate absorption from the intestines, thus further reducing serum phosphorus concentrations in patients. Published data to date show efficacy as monotherapy and a greater effect when combined with phosphate binders. When used as monotherapy, this may reduce excessive pill burden from phosphate binders. No significant drug interactions have been observed clinically, and tenapanor can be administered without regard to meals. The long-term safety of tenapanor is unknown as well as its efficacy in CKD patients who are not on hemodialysis. More large, randomized trials regarding the use of tenapanor, powered for cardiovascular and/or mortality outcomes, in CKD as well as ESKD patients, are needed, especially for subpopulations that have not been adequately represented in previous trials. In addition, more data demonstrating the magnitude of the phosphorus lowering effect will be needed before FDA approval is granted to tenapanor for treating hyperphosphatemia.

ACKNOWLEDGEMENTS

REFERENCES

1. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD). Kid Int Suppl. 2017 Jul;7(1):1-59. DOI: 10.1016/j.kisu.2017.04.001

2. Phosphate Binders. Med Lett Drugs Ther. 2006 Feb;48(1228):15-6.

3. Floego J. Phosphate binders in chronic kidney disease: a systematic review of recent data. J Nephrol. 2016 Jun;29(3):329-40. DOI: 10.1007/s40620-016-0266-9

4. Molitoris BA, Froment DH, Mackenzie TA, Huffer WH, Alfrey AC. Citrate: a major factor in the toxicity of orally administered aluminum compounds. Kidney Int. 1989 Dec;36(6):949-53. DOI: 10.1038/ki.1989.286

5. Nolan CR, Califano JR, Butzin CA. Influence of calcium acetate or calcium citrate on intestinal aluminum absorption. Kidney Int. 1990 Nov;38(5):937-41. DOI: 10.1038/ki.1990.294.

6. Fouque D, Vervloet M, Ketteler M. Targeting gastrointestinal transport proteins to control hyperphosphatemia in chronic kidney disease. Drugs. 2018 Aug;78(12):1171-86. DOI: 10.1007/s40265-018-0950-2

7. Cozzolino M, Ketteler M, Wagner CA. An expert update on novel therapeutic targets for hyperphosphatemia in chronic kidney disease: preclinical and clinical innovations. Expert Opin Ther Targets. 2020 May;24(5):477-88. DOI: 10.1080/14728222.2020.1743680

8. King AJ, Siegel M, He Y, et al. Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability. Sci Transl Med. 2018 Aug;10(456):eaam6474. DOI: 10.1126/scitranslmed.aam6474

9. Saurette M, Alexander RT. Intestinal phosphate absorption: the paracellular pathway predominates? Exp Biol Med (Maywood). 2019 May;244(8):646-54. DOI: 10.1177/1535370219831220

10. Johansson S, Rosenbaum DP, Ahlqvist M, et al. Effects of tenapanor on cytochrome P450-mediated drug-drug interactions. Clin Pharmacol Drug Dev. 2017 Sep;6(5):466-75. DOI: 10.1002/cpdd.346

11. Johansson S, Leonsson-Zachrisson M, Knutsson M, et al. Preclinical and healthy volunteer studies of potential drug-drug interactions between phosphate binders. Clin Pharmacol Drug Dev. 2017 Sep;6(5):448-56. DOI: 10.1002/cpdd.307

12. Johansson S, Rosenbaum DP, Palm J, et al. Tenapanor administration and the activity of the H^+ -coupled transporter PepT1 in healthy volunteers. Br J Clin Pharmacol. 2017 Sep;83(9):2008-14. DOI: 10.1111/bcp.13313

13. Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. J Am Soc Nephrol. 2019 Apr;30(4):641-52. DOI: 10.1681/ASN.2018080832

14. Pergola PE, Rosenbaum DP, Yang Y, Chertow GM. A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). J Am Soc Nephrol. 2021 Jun;32(6):1465-73. DOI: 10.1681/ASN.2020101398

15. NIH U.S. National Library of Medicine. A long-term study to evaluate the ability of tenapanor alone or in combination with sevelamer to treat to goal serum phosphorus in patients with end-stage kidney disease on dialysis (NORMALIZE). Accessed June 8, 2021. https://clinicaltrials.gov/ct2/show/NCT03988920?term=nct03988920&draw=2&rank=1

16. Block GA, Rosenbaum DP, Leonsson-Zachrisson M, et al. Effect of tenapanor on serum phosphate in patients receiving hemodialysis. J Am Soc Nephrol. 2017 Jun;28(6):1933-42. DOI: 10.1681/ASN.2016080855

17. Munjal A, Dedania B, Cash B. Update on pharmacotherapy for irritable bowel syndrome. Curr Gastroenterol Rep. 2019 Apr;21(6):25. DOI: 10.1007/s11894-019-0692-7

18. Chey WD, Lembo AJ, and Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol 2020 Feb;115(2):281-293. DOI: 10.14309/ajg.0000000000000516

19. Drugs for Irritable Bowel Syndrome. Med Lett Drugs Ther. 2020 Mar;62(1594):41-8.

20. Melville NA. Medscape. FDA Rejects tenapanor for control of phosphorus in kidney disease. Accessed October 12, 2021. https://www.medscape.com/viewarticle/956066

21. Labonte ED, Carreras CW, Leadbetter MR, et al. Gastrointestinal inhibition of sodium-hydrogen exchanger 3 reduces phosphorus absorption and protects against vascular calcification in CKD. J Am Soc Nephrol. 2015 May;26(5):1138-49. DOI: 10.1681/ASN.2014030317

22. King AJ, Kohler J, Fung C, et al. Combination treatment with tenapanor and sevelamer synergistically reduces urinary phosphorus excretion in rats. Am J Physiol Renal Physiol. 2021 Jan 1;320(1):F133-F144. DOI: 10.1152/ajprenal.00137.2020

23. Johansson S, Rosenbaum DP, Knutsson M, Leonsson-Zachrisson, M. A phase 1 study of the safety, tolerability, pharmacodynamics and pharmacokinetics of tenapanor in healthy Japanese volunteers. Clin Exp Nephrol. 2017 Jun;21(3):407-16. DOI: 10.1007/s10157-016-1302-8

24. Block GA, Rosenbaum DP, Yan A, Greasley PJ, Chertow GM, Wolf M. The effects of tenapanor on serum fibroblast growth factor 23 in patients receiving hemodialysis with hyperphosphatemia. Nephrol Dial Trans. 2019 Feb;34(2):339-46. DOI: 10.1093/ndt/gfy061