Report on the Deliberation Results

August 25, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Phozevel Tablets 5 mg
	Phozevel Tablets 10 mg
	Phozevel Tablets 20 mg
	Phozevel Tablets 30 mg
Non-proprietary Name	Tenapanor Hydrochloride (JAN*)
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	October 28, 2022

Results of Deliberation

In its meeting held on August 21, 2023, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

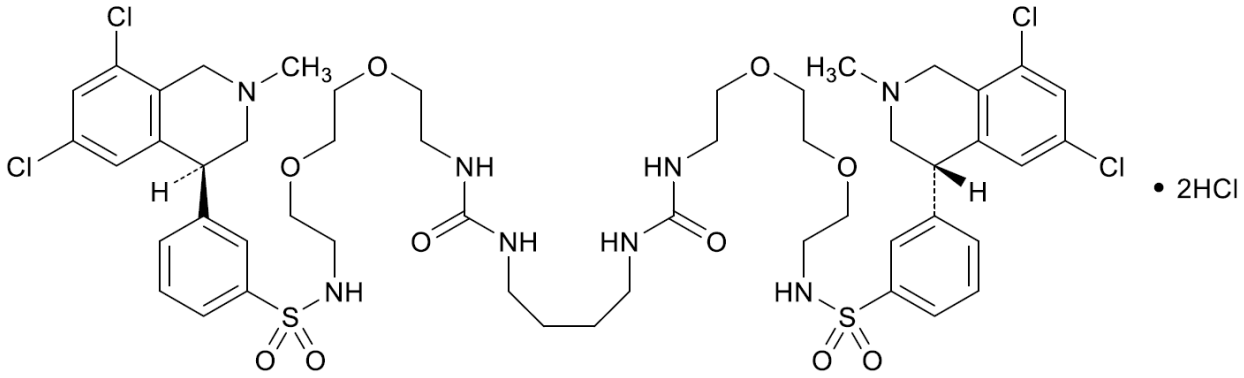
Review Report

August 8, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Phozevel Tablets 5 mg Phozevel Tablets 10 mg Phozevel Tablets 20 mg Phozevel Tablets 30 mg
Non-proprietary Name	Tenapanor Hydrochloride
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	October 28, 2022
Dosage Form/Strength	Film-coated tablets, each containing 5.32, 10.64, 21.28, or 31.92 mg of Tenapanor Hydrochloride (equivalent to 5, 10, 20, or 30 mg, respectively, of tenapanor)
Application Classification	Prescription drug, (1) Drugs with a new active ingredient

Chemical Structure



Molecular formula: $C_{50}H_{66}Cl_4N_8O_{10}S_2 \cdot 2HCl$

Molecular weight: 1,217.97

Chemical name: *N*,*N*'-(10,17-Dioxo-3,6,21,24-tetraoxa-9,11,16,18-tetraazahexacosane-1,26-diyl)bis{3-[(4*S*)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl]benzenesulfonamide} dihydrochloride

Items Warranting Special Mention None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis

Dosage and Administration

The usual adult starting dose is 5 mg of tenapanor orally twice daily, immediately prior to the morning and evening meals. Then, the dose should be adjusted according to the symptoms and serum phosphorus levels. The maximum dose is 30 mg.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

July 14, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Phozevel Tablets 5 mg Phozevel Tablets 10 mg Phozevel Tablets 20 mg Phozevel Tablets 30 mg
Non-proprietary Name	Tenapanor Hydrochloride
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	October 28, 2022
Dosage Form/Strength	Film-coated tablets, each containing 5.32, 10.64, 21.28, or 31.92 mg of Tenapanor Hydrochloride (equivalent to 5, 10, 20, or 30 mg, respectively, of tenapanor)

Proposed Indication

Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis

Proposed Dosage and Administration

The usual adult starting dose is 5 mg of tenapanor orally twice daily, immediately prior to meals. Then, the dose should be adjusted according to the symptoms and serum phosphorus levels. The maximum dose is 30 mg twice daily.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

In patients with chronic kidney disease (CKD), urinary phosphate excretion decreases as the renal function declines. In early CKD, normal serum phosphorus is maintained by compensatory increases in parathyroid hormone and fibroblast growth factor-23, which results in increased phosphate excretion. However, as CKD progresses, phosphate excretion decreases severely, leading to hyperphosphatemia. Persistent hyperphosphatemia results in secondary hyperparathyroidism, extraskeletal calcification, etc., which can cause decreased QOL (*Kidney Int*. 2006; 69: 1945-53), cardiovascular events (*Am J Kidney Dis*. 1998; 31: 607-17), etc. Hyperphosphatemia has also been associated with increased mortality risk (*Journal of Japanese Society for Dialysis Therapy*. 2012; 45: 301-56, *J Am Soc Nephrol*. 2005; 16: 520-8). Against such background, "Clinical Practice Guideline for the Management of Chronic Kidney Disease-Mineral and Bone Disorder" (the Japanese clinical practice guideline) published by the Japanese Society for Dialysis Therapy (a general incorporated association) recommends the proper control of serum phosphorus levels in patients with CKD (*Journal of Japanese Society for Dialysis Therapy*. 2012; 45: 301-56).

The current treatment options for hyperphosphatemia in patients with CKD on dialysis are dietary phosphate restriction, more frequent dialysis to remove phosphorus, and oral phosphate binders (precipitated calcium carbonate, sevelamer hydrochloride, bixalomer, lanthanum carbonate hydrate, ferric citrate hydrate, sucroferric oxyhydroxide), which reduce phosphate absorption from the gastrointestinal tract. However, due to their respective properties, oral phosphate binders have problems such as hypercalcemia, gastrointestinal disorders, mainly constipation, and possible tissue accumulation following long-term administration. Thus, there is an unmet need for new treatments for hyperphosphatemia.

Tenapanor hydrochloride (tenapanor) is an inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) discovered by Ardelyx, Inc. (in the US). Tenapanor inhibits NHE3 expressed on the apical surface of intestinal epithelial cells, reduces sodium ion absorption from the gastrointestinal tract, and increases the intracellular proton concentration. It causes a decrease in the intracellular pH of intestinal epithelial cells and reduces the permeability to phosphate of tight junctions between intestinal epithelial cells, resulting in reduced intestinal phosphate absorption. Thus, tenapanor was considered to have potential as a therapy for hyperphosphatemia, and its development was initiated.

The applicant has filed a marketing application for tenapanor, based on the results from Japanese clinical studies that demonstrated the efficacy and safety of tenapanor in patients with CKD on dialysis with hyperphosphatemia, etc.

As of July 2023, tenapanor has been approved for the indication of irritable bowel syndrome with constipation in the US and Canada. Although a new drug application for the indication of hyperphosphatemia has been filed in the US, tenapanor for hyperphosphatemia has not been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to off-white to light brown solid. Its description, crystalline form, particle size, thermal analysis, acid dissociation constant, partition coefficient, hygroscopicity, and solubility have been determined. The drug substance exists in crystalline (crystalline form I) and amorphous forms. The commercial synthesis yields the amorphous form only, which has been demonstrated to be stable at room temperature.

Its chemical structure has been elucidated by elemental analysis, nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR, ^{13}C-NMR), infrared absorption spectrometry (IR), mass spectrometry (MS), and single-crystal X-ray crystallography. The drug substance has 2 chiral centers, and both chiral centers have the *S*-configuration.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting materials.

A control strategy for the drug substance was established based on identification of critical quality attributes (CQAs) and evaluation of process parameters through design of experiments etc. (Table 1).

Table 1. Overview of drug substance control strategy

CQA	Method of control
Impurity profile	Manufacturing process, specification
Chloride content	Manufacturing process, specification
Particle size distribution	Manufacturing process, specification
Water content	Manufacturing process, specification

The manufacturing process for the drug substance consists of the following steps: synthesis of intermediates, synthesis of [redacted], purification of [redacted], preparation of tenapanor hydrochloride (the active substance), packaging, and testing/storage.

Synthesis of intermediates, synthesis of [redacted], purification of [redacted], and preparation of tenapanor hydrochloride (the active substance) have been defined as critical steps. [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR and high performance liquid chromatography [HPLC]), purity tests (metallic elements [inductively coupled plasma mass spectrometry], related substances [HPLC], [redacted] [redacted], [redacted] [redacted]), [redacted] ([redacted]), water content (volumetric titration), residue on ignition, [redacted] ([redacted]), [redacted] ([redacted]), and assay (HPLC).

2.1.4 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2. The drug substance was stable under the long-term conditions, but related substances were increased under the accelerated conditions. Photostability data showed that the drug substance is photostable.

Table 2. Primary stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25 ± 2°C	60 ± 5%RH	[redacted] bag (with desiccant) + [redacted] bag	[redacted] months
Intermediate	3 commercial-scale batches	30 ± 2°C	[redacted]%RH		[redacted] months
Accelerated	3 pilot-scale batches	40 ± 2°C	75 ± 5%RH		[redacted] months

Based on the above, a re-test period of [redacted] months was proposed for the drug substance packaged in [redacted] bag (with desiccant), placed in a heat-sealed [redacted] bag, and stored at room temperature. The long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet containing 5.32, 10.64, 21.28, or 31.92 mg of tenapanor hydrochloride (equivalent to 5, 10, 20, or 30 mg, respectively, of tenapanor) and the following excipients: microcrystalline cellulose, low-substituted hydroxypropyl cellulose, colloidal silicon dioxide, propyl gallate, and stearic acid. It also contains Opadry Yellow [redacted] (5 mg tablet), Opadry Yellow [redacted]10 mg tablet), Opadry Brown [redacted] (20 mg tablet), or Opadry Red [redacted] (30 mg tablet).

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: mixing, [redacted]/[redacted], [redacted], tableting, film-coating, storage, packaging, and testing/storage. Process control items and values have been established for [redacted], [redacted], and [redacted]. A control strategy for the drug product was established based on identification of CQAs and evaluation of process parameters through quality risk assessment, design of experiments, etc. (Table 3).

Table 3. Overview of drug product control strategy

CQA	Method of control
Strength	Manufacturing process, specification
Uniformity of dosage units	Manufacturing process, specification
Dissolution	Specification
Related substances	Manufacturing process, specification
[redacted]	Manufacturing process, specification
Water content	Manufacturing process, specification

[redacted], [redacted], and [redacted] have been defined as critical steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC and ultraviolet-visible spectroscopy [UV/VIS]), purity tests (related substances [HPLC]), water content (volumetric titration), uniformity of dosage units (content uniformity testing [HPLC]), dissolution (HPLC), [redacted] ([redacted]), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. The drug product was stable under the long-term conditions, but intermediate data showed [redacted] over time. Under the accelerated conditions, related substances tended to increase over time, [redacted], and dissolution decreased. The drug product was photostable in the photostability testing, but it was photosensitive when packaged in a blister pack.

Table 4. Primary stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term[a)]	3 commercial-scale batches	25 ± 2℃	60 ± 5%RH	Blister pack + aluminum bag (with desiccant)	12 or 18 months
Intermediate[b)]	3 commercial-scale batches	30 ± 2℃	[redacted]%RH		12 months
Accelerated	3 commercial-scale batches	40 ± 2℃	75 ± 5%RH		6 months

a) The 5 mg tablets only were stored for 12 months.
b) The 30 mg tablets only were tested.

Based on the above, a shelf-life of 24 months (5 and 30 mg tablets) or 30 months (10 and 20 mg tablets) was proposed for the drug product packaged in a blister pack ([redacted]/aluminum foil) stored in an aluminum bag with desiccant to protect from light at room temperature, in accordance with the ICH Q1E guideline. The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Primary pharmacodynamic studies were conducted to evaluate the inhibition of NHE3 and reduction of phosphate absorption by tenapanor. In a secondary pharmacodynamic study, tenapanor was screened for its activity at receptors, ion channels, transporters, and enzymes other than NHE3. Safety pharmacology studies assessed the effects of tenapanor on the central nervous, cardiovascular, respiratory, and gastrointestinal

systems. Unless otherwise specified, 10 mmol/L hydrochloric acid/0.01% Tween 80 solution was used as vehicle in *in vivo* studies.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Inhibition of NHE3 (CTD 4.2.1.1-1 and CTD 4.2.1.1-2)

Using a hamster lung fibroblast cell line (PS120 cells) stably expressing human NHE3 and an opossum kidney cell line (OK cells) transiently transfected with rat NHE3, the inhibition potential of tenapanor (0-1 μmol/L) and its major metabolite M1 (0-10 μmol/L) on human NHE3 and rat NHE3 was evaluated. The IC_{50} values of tenapanor for human NHE3 and rat NHE3 inhibition were 1.3 and 1 nmol/L, respectively. On the other hand, M1 did not inhibit human or rat NHE3.

3.1.1.2 Reduction of phosphate absorption (CTD 4.2.1.1-3)

Using human small intestinal epithelial cell monolayer cultures, the effect of tenapanor on intestinal phosphate absorption was evaluated. Tenapanor 1 μmol/L or vehicle (0.01% dimethyl sulfoxide [DMSO]) and phosphate at physiological luminal concentrations in humans (1, 3, or 10 mmol/L) were added to the apical side of the monolayer, and apical and basolateral phosphate concentrations were determined. After treatment with vehicle, the basolateral phosphate concentration increased in a linear fashion with increasing apical phosphate concentrations, showing apical-to-basolateral paracellular phosphate flux. Tenapanor reduced apical to basolateral phosphate flux.

Using human duodenum or ileum epithelial cell monolayer cultures, acidic apical media were replaced with fresh neutral pH apical media, and at the same time, tenapanor (1 μmol/L) or vehicle (0.01% DMSO) was added to the apical side of the monolayer, and transepithelial electrical resistance (TEER), a measure of paracellular permeability, was measured. After treatment with vehicle, NHE3-mediated proton efflux (from intracellular to apical) resulted in a reduction in TEER. This effect was blocked by tenapanor.

Using human duodenum epithelial cell monolayer cultures, acidic apical media were replaced with fresh apical media at different pH, and at the same time, tenapanor 1 μmol/L or vehicle (0.01% DMSO) was added to the apical side of the monolayer, and TEER was measured. Compared with vehicle, tenapanor increased TEER at neutral or alkaline luminal pH. On the other hand, after the change to acidic apical media, tenapanor did not increase TEER. In NHE3-knockout human ileum epithelial cells, basolateral phosphate flux was inhibited, and no change in TEER was observed after the change from acidic apical media to neutral apical media.

3.1.2 *In vivo* studies

3.1.2.1 Reduction of phosphate absorption in rats (CTD 4.2.1.1-8)

In male rats fasted overnight (6/group) pre-treated with a single oral dose of tenapanor 0 (vehicle) or 0.5 mg/kg, urinary phosphate content was determined at 4 hours after an oral bolus of 1 mL of a phosphate solution containing 0, 0.15, 0.5, or 1.5 mol/L sodium dihydrogenphosphate. The urinary phosphate content increased in a phosphate concentration-dependent manner in the vehicle group, indicating passive intestinal phosphate

absorption via the paracellular pathway. Compared with vehicle, tenapanor 0.5 mg/kg reduced the urinary phosphate content across all phosphate concentrations.

Urinary phosphate and sodium contents were determined at 4 hours after a high-phosphate (1.2%) meal in male rats[1)] (8/group) treated with a single oral dose of tenapanor 0 (vehicle), 0.15, 0.3, or 0.5 mg/kg. Tenapanor at all dose levels decreased the urinary phosphate and sodium contents, compared with vehicle.

Cecal water volume, phosphate content, and sodium content were determined in male rats[1)] (6/group) fed a high-phosphate (1.2%) meal and treated with a single oral dose of tenapanor 0 (vehicle) or 0.15 mg/kg. Compared with vehicle, tenapanor 0.15 mg/kg increased the cecal water volume, phosphate content and concentration, and sodium content and concentration at 1 and 2 hours post-dose.

Tenapanor reduced urinary phosphate content and increased cecal phosphate content, suggesting that tenapanor reduces intestinal phosphate absorption.

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors, ion channels, transporters, and enzymes (CTD 4.2.1.2-1 and CTD 4.2.1.2-6)

Tenapanor (10 μmol/L or 0.003-300 μmol/L) was screened for its activity at 181 receptors, ion channels, transporters, and enzymes. The neurokinin 1 (NK1) receptor and the 5-hydroxytryptamine 1D ($5\text{-}HT_{1D}$) receptor were identified with functional IC_{50} or EC_{50} values of <1 μmol/L, and the IC_{50} and EC_{50} values of tenapanor were 0.35 and 0.070 μmol/L, respectively.

Its metabolite M1 (0.003-100 μmol/L) was screened for its activity at 82 receptors, ion channels, transporters, and enzymes. M1 at concentrations up to 1 μmol/L had no functional activity at these molecular targets.

Since plasma tenapanor concentrations were below the lower limit of quantification (LLOQ) (0.437 pmol/L) in most subjects in clinical studies of tenapanor in healthy volunteers [see Section 6.2], and the C_{max} of M1 following twice daily oral administration of tenapanor 30 mg was 0.039 μmol/L in a foreign phase III study in dialysis patients (Study TEN-02-301), the applicant explained that tenapanor and M1 are unlikely to affect these receptors, ion channels, transporters, and enzymes in a clinical setting.

3.3 Safety pharmacology

Table 5 shows an overview of safety pharmacology studies.

[1)] Rats were trained to eat a phosphate (0.6%) meal over ≤4 hours once a day for 6 days. Tenapanor was administered after 6 days of intake.

Table 5. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Tenapanor doses or concentrations	Route, duration	Findings	Attached document CTD
CNS	Rat (10 males/group)	Modified Irwin's test	100, 300, 1,000 mg/kg	Single oral dose	1,000 mg/kg: a decrease in body temperature[a)]	4.2.1.3-1
Cardiovascular system	HEK293 cells (n = 5-9/group)	hERG current	1, 3, 10 μmol/L	*In vitro*	10 μmol/L: 17.9% inhibition	4.2.1.3-2
	CHO cells (n = 4/group) HEK293 cells for hCav3.2 only (n = 4/group)	Human recombinant voltage-gated cardiac ion channels (hCav1.2/β2/α2δ, hCav3.2, hHCN4, hKv1.5, hKv4.3/hKChIP2.2, hKv7.1/hKCNE1, hNav1.5)	Highest concentration of 33.3 or 100 μmol/L[b)]	*In vitro*	Inhibition of hCav1.2/β2/α2δ (IC_{50} = 4.67 μmol/L)	Reference data 4.2.1.3-3
	Dog (4 males/group)	Heart rate, blood pressure, ECG	100, 300, 1,000 mg/kg	Single oral dose	No effects	4.2.1.3-4
	Dog (4/sex/group)	Heart rate, ECG	50, 300, 1,000 mg/kg	Multiple oral doses	No effects	4.2.1.3-11
	Dog (4/sex/group)	Heart rate, ECG	50, 300, 1,000 mg/kg	Multiple oral doses	No effects	4.2.1.3-12
Respiratory system	Rat (4 males/group)	Tidal volume, minute volume, respiratory rate	100, 300, 1,000 mg/kg	Single oral dose	No effects	4.2.1.3-5
Gastrointestinal system	Rat (10 males/group)	Gastrointestinal motility	100, 300, 1,000 mg/kg	Single oral dose	No effects	4.2.1.3-6

a) This finding was not considered of toxicological significance because the change in body temperature was <0.5°C.
b) The highest concentration tested was 33.3 μmol/L for hCav1.2/β2/α2δ, hKv4.3/hKChIP2.2, hKv7.1/hKCNE1, and hNav1.5, and 100 μmol/L for hCav3.2, hHCN4, and hKv1.5.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacologic effects

The applicant's explanation about the pharmacologic effects of tenapanor:

Tenapanor is an NHE3 inhibitor. NHE3 is expressed mainly on the apical surface of intestinal epithelial cells and plays a central role in maintaining sodium and water balances.

As most of dietary phosphate absorbed is excreted into the urine, renal phosphate excretion and reabsorption are considered to play a central role in maintaining phosphate homeostasis in the body (*J Bone Miner Metab*. 2016; 34: 1-10). As CKD progresses, the capacity for renal phosphorus excretion declines, leading to hyperphosphatemia (*Kidney Int*. 2011; 79: 1370-8). Phosphate absorption occurs in the small intestine via paracellular and transcellular pathways. Paracellular phosphate absorption occurs passively through tight junctions between intestinal epithelial cells, and phosphorus passage through the intercellular spaces is dependent on the electrochemical gradients. On the other hand, transcellular phosphate absorption is mediated predominantly by sodium-dependent phosphate co-transporter type 2b (NaPi2b). At normal luminal phosphate

concentrations, NaPi2b-mediated transport would be saturated, and the paracellular transport would be the dominant route for phosphate absorption in the gastrointestinal tract (*Sci Transl Med*. 2018; 10: 1-38, *Pflugers Arch*. 2019; 471: 165-73, etc.). Tenapanor inhibits NHE3 expressed on the apical surface of intestinal epithelial cells, reduces sodium ion absorption from the gastrointestinal tract, and increases the intracellular proton concentration. It causes a decrease in the intracellular pH of intestinal epithelial cells and reduces the permeability to phosphate of tight junctions between intestinal epithelial cells, resulting in reduced paracellular intestinal phosphate absorption. Thus, tenapanor is considered to have potential as a therapy for hyperphosphatemia.

As primary pharmacodynamic studies demonstrated that tenapanor inhibits NHE3 and reduces phosphate absorption, tenapanor has potential as a therapy for hyperphosphatemia.

Based on the submitted results from the primary pharmacodynamic studies and the applicant's discussion, PMDA considers that tenapanor is expected to improve hyperphosphatemia.

3.R.2 Safety pharmacology studies

The applicant's explanation about the findings observed in safety pharmacology studies:
There were no relevant effects on the respiratory and gastrointestinal (gastrointestinal motility) systems in safety pharmacology studies.

As CNS effects, a decrease in body temperature was observed in rats at 1,000 mg/kg. This finding was considered of little toxicological significance because the change in body temperature was <0.5℃.

As cardiovascular effects, tenapanor inhibited the hERG current (17.9% inhibition at 10 μmol/L) and hCav1.2/β2/α2δ (IC_{50} = 4.67 μmol/L) *in vitro*. On the other hand, there were no effects of tenapanor on heart rate, blood pressure, and ECG in safety pharmacology studies in dogs, and plasma tenapanor concentrations were below the LLOQ (0.437 pmol/L) in most subjects in clinical studies of tenapanor [see Section 6.2]. Thus, tenapanor is unlikely to affect the cardiovascular system in clinical use.

PMDA considers that tenapanor is unlikely to pharmacologically affect the central nervous, cardiovascular, respiratory, and gastrointestinal (gastrointestinal motility) systems in clinical use.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Following administration of tenapanor hydrochloride, its metabolite M1, or [^{14}C]-tenapanor hydrochloride in mice, rats, or dogs, pharmacokinetics were determined. Plasma concentrations of unchanged tenapanor and M1 were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS). Plasma concentrations of tenapanor hydrochloride were calculated based on the measured plasma concentrations of unchanged tenapanor. The LLOQ for tenapanor hydrochloride was 0.5 ng/mL in all animal species, and the LLOQ for M1 was 0.5 ng/mL in rat, rabbit, and dog plasma and 1.0 ng/mL in mouse plasma. [^{14}C]-tenapanor hydrochloride-derived radioactivity was determined using liquid scintillation counter and quantitative whole-

body autoradiography.

4.1 Absorption

4.1.1 *In vitro* cell permeability (CTD Reference data 4.2.2.2-1)

The permeability of tenapanor across Madin-Darby canine kidney (MDCK) cell monolayers was determined when cells were incubated with tenapanor (10 μmol/L). Table 6 shows the apparent permeability coefficients in the apical (pH = 6.5 or 7.4) to basolateral (pH = 7.4) direction (P_{app} A→B) of different compounds. The P_{app} A→B value of tenapanor was lower than the P_{app} A→B values of atenolol and colchicine, which were selected as compounds with low permeability, and the permeability of tenapanor was considered to be low.

Table 6. Permeability across MDCK cell monolayers

Compound	Apical pH	P_{app} A→B ($\times 10^{-6}$ cm/s)
Tenapanor	7.4	BLQ
	6.5	BLQ
Propranolol[a)]	7.4	28
	6.5	7
Atenolol[b)]	7.4	0.5
	6.5	0.5
Colchicine[b)]	7.4	0.3
	6.5	0.3

BLQ: below the quantification limit (0.01×10^{-6} cm/s)
a) Selected as a compound with high permeability.
b) Selected as a compound with low permeability.

4.1.2 Single-dose studies

4.1.2.1 Single-dose study of M1 in mice (CTD Reference data 4.2.2.2-2)

Table 7 shows the plasma pharmacokinetic parameters of M1 following a single oral dose of M1 in male mice, which suggested that M1 is rapidly absorbed from the gastrointestinal tract.

Table 7. Plasma pharmacokinetic parameters of M1 following a single dose of M1 in mice

M1 dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24\ h}$ (ng·h/mL)
100	41,063	0.5	104,819
300	85,419	2.0	801,778

Calculated from mean plasma concentration data (n = 3/time point)

4.1.2.2 Single-dose study of tenapanor hydrochloride in rats (CTD Reference data 4.2.2.2-4)

Following a single oral dose of 1 or 10 mg/kg of tenapanor hydrochloride in male rats, plasma concentrations of tenapanor hydrochloride at 0 to 24 hours post-dose were determined. Almost all of the plasma samples were below the LLOQ, and the highest concentration detected was 1.97 ng/mL.

4.1.2.3 Single-dose study of tenapanor hydrochloride in dogs (CTD Reference data 4.2.2.2-7)

Following a single oral dose of 1 or 10 mg/kg of tenapanor hydrochloride capsules in male dogs, plasma concentrations of tenapanor hydrochloride at 0 to 24 hours post-dose were determined. Almost all of the plasma samples were below the LLOQ, and the highest concentration detected was 3.3 ng/mL.

4.1.2.4 Single-dose study of tenapanor hydrochloride in portal vein cannulated dogs (CTD 4.2.2.2-8)

Pharmacokinetics were determined in portal vein cannulated male dogs following a single oral dose of tenapanor hydrochloride capsules. Table 8 shows the plasma pharmacokinetic parameters of tenapanor and M1. M1 was detected in plasma collected from the portal vein, and tenapanor exposure was higher in plasma collected from the portal vein than in plasma collected from the jugular vein, indicating that tenapanor hydrochloride can potentially be metabolized in the small intestine and liver.

Table 8. Plasma pharmacokinetic parameters following a single oral dose of tenapanor hydrochloride in portal vein canulated dogs

Dose (mg/kg)	Analyte	Plasma collected from	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24\ h}$ (ng·h/mL)	$t_{1/2}$ (h)
1,000	Tenapanor	Jugular vein	4.3 ± 0.6	2.7 ± 1.2	18.9 ± 5.1	—
		Portal vein	17.4 ± 8.6	3.3 ± 1.2	90.4 ± 35.6	—
	M1	Jugular vein	13.0 ± 2.5	5.3 ± 2.3	152 ± 44	6.1 [a)]
		Portal vein	9.5 ± 2.3	5.3 ± 2.3	118 ± 43	—

Mean ± SD (n = 3); —, Not calculated
a) Mean (n = 2)

4.1.3 Repeated-dose studies

4.1.3.1 Repeated-dose study of tenapanor hydrochloride in mice (CTD 4.2.3.2-2)

Tenapanor hydrochloride was administered orally once daily for 28 days to male and female mice, and pharmacokinetics were determined. Table 9 shows the plasma pharmacokinetic parameters of tenapanor. The $AUC_{0\text{-}t}$ largely increased with increasing dose, but there was no clear dose-response relationship for the C_{max} of tenapanor. The applicant explained that inter-individual differences in the amount absorbed from the gastrointestinal tract and the time needed for absorption due to its poor solubility and permeability may have resulted in no dose-response relationship for the C_{max}.

The C_{max} and $AUC_{0\text{-}t}$ on Day 1 were higher in males than in females, and the C_{max} and $AUC_{0\text{-}t}$ on Day 28 tended to be higher in females than in males. In both males and females, the C_{max} and $AUC_{0\text{-}t}$ tended to be higher on Day 28 than on Day 1. The applicant explained that the gender-related differences may have been caused by gender-related differences in the amount of tenapanor hydrochloride dissolved in the intestinal lumen due to its pharmacological effects, inter-individual differences in plasma tenapanor concentrations, etc.

Table 9. Plasma pharmacokinetic parameters of tenapanor following multiple oral dosing in mice

Tenapanor hydrochloride dose (mg/kg)	Sex	Sampling time point (Day)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)
10	M	1 [a)]	1.3	24	10.8
		28	14.1	0.5	19.0
	F	1 [a)]	1.1	2	0.7
		28	60.8	1	64.4
50	M	1	18.3	1	36.6
		28	14.0	4	93.0
	F	1	1.5	1	3.5
		28	79.5	1	152
200	M	1	12.0	0.5	61.3
		28	34.1	0.5	143
	F	1	7.9	0.5	14.9
		28	79.0	0.5	332

Calculated from mean plasma concentration data (n = 2-3/time point)
a) Data at 2 time points

4.1.3.2 Repeated-dose study of tenapanor hydrochloride and M1 in rats (CTD Reference data 4.2.2.2-6)

Tenapanor hydrochloride or M1 was administered orally once daily for 4 days to male and female rats, and pharmacokinetics were determined. Table 10 shows the plasma pharmacokinetic parameters of M1. Plasma tenapanor concentrations following oral administration of tenapanor hydrochloride were all below the LLOQ.

Following oral administration of tenapanor hydrochloride, the C_{max} and AUC_{0-t} of M1 were higher in females than in males, and the C_{max} and AUC_{0-t} of M1 tended to be higher on Day 4 than on Day 1 in both males and females.

Following oral administration of M1, the C_{max} and AUC_{0-t} of M1 tended to be higher in females than in males. The C_{max} and AUC_{0-t} of M1 tended to be higher on Day 4 than on Day 1.

Table 10. Plasma pharmacokinetic parameters of M1 following multiple oral dosing of tenapanor hydrochloride or M1 in rats

Test article	Dose (mg/kg)	Sex	Sampling time point (Day)	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)
Tenapanor hydrochloride	5	M	1	2.0 ± 0.5	1	27 ± 4	—
			4	5.8 ± 1.6	1	82 ± 19	7.4 [b)]
		F	1	7.6 ± 2.2	8	117 ± 22	—
			4	16.5 ± 15.0	4	145 ± 64	—
	10	M	1	4.1 ± 0.8	1	45 ± 6	—
			4	6.2 ± 1.5	2	89 ± 19	7.1 ± 1.4
		F	1	9.1 ± 2.0	8	150 ± 23	—
			4	12.3 ± 8.0	1	108 ± 61	—
M1	5	M	1	1,620 ± 282	1	9,490 ± 1,660	3.6 ± 1.2
			4	2,550 ± 633	0.25	11,200 ± 1,360	3.0 ± 0.9
		F	1	2,300 ± 332	1	15,400 ± 175	5.0 ± 3.0
			4	2,520 ± 452	0.5	18,600 ± 1,750	3.0 ± 0.2
	30	M	1	9,880 ± 1,320	0.5	66,100 ± 1,750	2.7 [b)]
			4	12,500 ± 704	0.5	116,000 ± 24,500	2.5 ± 0.7
		F	1	13,200 ± 1,150	1	122,000 ± 5,530	4.7 ± 1.0
			4	17,800 ± 1,100	1.25	176,000 ± 4,010	3.9 ± 1.0

Mean ± SD (n = 3); —, Not calculated
a) Median
b) Individual value for n = 1

4.1.3.3 Repeated-dose study of tenapanor hydrochloride in rats (CTD 4.2.3.2-6)

Tenapanor hydrochloride was administered orally once daily for 16 days to male and female rats, and pharmacokinetics were determined. Table 11 shows the plasma pharmacokinetic parameters of tenapanor. The C_{max} and AUC_{0-t} of tenapanor largely increased with increasing dose.

The C_{max} and AUC_{0-t} of tenapanor tended to be higher on Day 16 than on Day 1.

Table 11. Plasma pharmacokinetic parameters of tenapanor following multiple oral dosing in rats

Tenapanor hydrochloride dose (mg/kg)	Sex	Sampling time point (Day)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)
30	M	1	0.6	8	3.5
		16	11.3	1	135
	F	1	0.7	2	1.7
		16	30.5	4	387
100	M	1	2.2	0.5	9.3
		16	22.5	1	164
	F	1	5.3	1	58.6
		16	50.0	2	413
300	M	1	2.6	0.5	14.6
		16	76.0	8	959
	F	1	1.3	4	19.4
		16	34.0	0.5	560
1,000	M	1	9.8	1	79.4
		16	107	0.5	1317
	F	1	45.3	0.5	182
		16	202	4	2759

Calculated from mean plasma concentration data (n = 3/time point); －, Not calculated

4.1.3.4 Repeated-dose study of tenapanor hydrochloride in dogs (CTD 4.2.2.2-9)

Tenapanor hydrochloride capsules were administered orally once daily for 9 months to male and female dogs, and the pharmacokinetics of M1 were determined. Table 12 shows the plasma pharmacokinetic parameters of M1, and there were no clear gender-related differences. There was no evident accumulation after multiple dosing.

Table 12. Plasma pharmacokinetic parameters of M1 following multiple oral dosing of tenapanor hydrochloride in dogs

Dose (mg/kg)	Sex	Sampling time point (Week)	C_{max} (ng/mL)	t_{max} a) (h)	AUC_{0-t} (ng·h/mL)
1,000	M	4	21.3 ± 2.8	8	347 ± 42
		38	19.3 ± 2.7	8	334 ± 51
	F	4	19.4 ± 2.5	8	317 ± 32
		38	22.3 ± 3.1	4	346 ± 27

Mean ± SD (n = 4/time point)
a) Median

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.2-5)

Following a single oral dose of [^{14}C]-tenapanor hydrochloride 1 mg/kg in male albino rats, radioactivity concentrations in different tissues[2)] were determined up to 72 hours post-dose. Maximum concentrations of radioactivity were measured at 0.5 to 8 hours post-dose. The radioactivity levels in the liver, cecum, kidney cortex, kidney, small intestine, kidney medulla, stomach, and spleen were higher than the plasma level at 4 hours post-dose, i.e., 8.4-, 7.3-, 5.2-, 4.5-, 3.3-, 2.7-, 2.1-, and 1.6-fold higher, respectively. Radioactivity in all tissues was below the LLOQ by 48 hours post-dose.

Following a single oral dose of [^{14}C]-tenapanor hydrochloride 1 mg/kg in male pigmented rats, radioactivity concentrations in different tissues[3)] were determined up to 168 hours post-dose. Maximum concentrations of radioactivity were measured in most tissues at 0.5 to 8 hours post-dose. The radioactivity levels in the small intestine, liver, uveal tract, stomach, kidney cortex, kidney, cecum, adrenal gland, kidney medulla, and spleen were higher than the plasma level at 4 hours post-dose, i.e., 20.0-, 16.7-, 10.1-, 8.2-, 7.6-, 6.8-, 5.6-, 3.2-, 3.1-, and 2.2-fold higher, respectively. Radioactivity in all tissues was below the LLOQ by 168 hours post-dose.

The applicant's explanation about accumulation in melanin-containing tissues:
Radioactivity was detected in the uveal tract at 2 to 72 hours post-dose, but not at 168 hours post-dose, i.e., radioactivity concentrations in the uveal tract declined below measurable levels by 168 hours post-dose. In the melanin-containing tissues, i.e., Harderian glands, pigmented skin, meninges, and ocular tissues excluding the uveal tract, radioactivity was below the LLOQ or was undetected at all time points. Thus, unchanged tenapanor and its metabolites are unlikely to accumulate in high concentrations in melanin-containing tissues.

4.2.2 Protein binding (CTD 4.2.2.3-2, 4.2.2.3-3, and 4.2.2.3-5, Reference data 4.2.2.3-1 and 4.2.2.3-4)

Using the plasma from mouse, rat, rabbit, dog, and human, the protein binding of unchanged tenapanor (100 μmol/L) and M1 (0.01-10 μmol/L) was determined. The percentage of unchanged tenapanor bound to protein was >99.99% in all species. The percentages of M1 bound to mouse, rat, rabbit, dog, and human plasma proteins were 95.48% to 97.58%, 97.09% to 98.04%, 94.97% to 95.54%, 94.42% to 95.07%, and 96.57% to 96.80%, respectively.

4.2.3 Distribution in blood cells (CTD 4.2.2.3-5, Reference data 4.2.2.3-4)

Using human whole blood, the distribution of M1 (0.03-10 μmol/L) in blood cells was determined. The blood to plasma partition ratio (R_b) at 0.03 to 3 μmol/L of M1 was 5.13 to 5.87, and R_b at 10 μmol/L of M1 was 16.7.

[2)] Adrenal gland, arterial wall, bile, blood, bone, bone marrow, cerebellum, cerebrum, brain medulla, olfactory lobe, bulbo-urethral gland, cecum, diaphragm, epididymides, esophagus, exorbital lacrimal gland, lens, uveal tract, eye, abdominal fat, brown fat, Harderian gland, intraorbital lacrimal gland, kidney cortex, kidney medulla, kidney, large intestine, liver, lung, lymph node, meninges, muscle, myocardium, nasal turbinate, pancreas, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (non-pigmented), small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid, urinary bladder, urine

[3)] Adrenal gland, arterial wall, bile, blood, bone, bone marrow, cerebellum, cerebrum, brain medulla, olfactory lobe, bulbo-urethral gland, cecum, diaphragm, epididymides, esophagus, exorbital lacrimal gland, lens, uveal tract, eye, abdominal fat,, brown fat, Harderian gland, intraorbital lacrimal gland, kidney cortex, kidney medulla, kidney, large intestine, liver, lung, lymph node, meninges, muscle, myocardium, nasal turbinate, pancreas, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin (non-pigmented), skin (pigmented), small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid, urinary bladder, urine

4.3 Metabolism

4.3.1 Identification of metabolites *in vitro* (CTD Reference data 4.2.2.4-2)

Rat, dog, and human liver microsomes were incubated with tenapanor (20 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) for 1 hour, which suggested that tenapanor is metabolized primarily by oxidative *N*- or *O*-dealkylation in all species. No human-specific metabolites were detected.

Based on the results of a mass balance study [see Section 6.2.3], the primary metabolites in plasma were considered to be oxidative *N*- (M1, M2, and M12) or *O*-dealkylated metabolites (M12 and M15).

4.3.2 Determination of metabolizing enzymes *in vitro* (CTD 4.2.2.4-4, Reference data 4.2.2.4-5)

Tenapanor (2 μmol/L) was incubated with 100 pmol/mL human recombinant CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), and the relative contributions of these CYP isoforms to the metabolism of tenapanor were estimated. The relative contribution of CYP3A4 was highest (56.8%) followed by CYP3A5 (39.8%). The relative contributions of CYP isoforms other than CYP3A4 and CYP3A5 were all ≤3%. With respect to CYP isoforms involved in the formation of M1 from unchanged tenapanor (CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5), the mean M1 formation velocity was 33.5 to 339 pmol/min/nmol CYP with CYP3A4 and 110 to 245 pmol/min/nmol CYP with CYP3A5, which were higher than those with other CYP isoforms (1.13-27.8 pmol/min/nmol CYP). Thus, CYP3A4 and CYP3A5 were considered to be the primary CYP isoforms involved in the metabolism of tenapanor to M1.

Using human liver microsomes, the contribution of flavin-containing monooxygenases (FMOs) in the metabolism of tenapanor (1 μmol/L) was evaluated. Since a decrease in the CL_{int} of tenapanor (approximately 48% decrease) by inactivation of FMOs[4)] was smaller than that by CYP inhibitor[5)] (approximately 86% decrease), the contribution of FMOs in the metabolism of tenapanor was considered to be lower than that of CYPs.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.2-5)

Following a single oral dose of [^{14}C]-tenapanor hydrochloride 0.3 mg/kg in male rats, 0.335% and 122% of the administered radioactivity were recovered in urine and feces, respectively, over 168 hours. Unchanged tenapanor only was detected in feces.

Following a single oral dose of [^{14}C]-tenapanor hydrochloride 0.3 mg/kg in bile duct cannulated male rats, 1.78%, 95.3%, and 2.51% of the administered radioactivity were recovered in urine, feces, and bile, respectively, over 120 hours.

[4)] Preincubation at 50℃

[5)] 1-aminobenzotriazole

Based on the above, orally administered tenapanor hydrochloride was considered to be primarily excreted in feces in unchanged form.

4.5 Pharmacokinetic interactions

4.5.1 Induction of human liver drug metabolizing enzymes by tenapanor and M1 (CTD 4.2.2.4-13, Reference data 4.2.2.4-9)

A human hepatic cell line was incubated with tenapanor (0.0001-50 μmol/L) to evaluate the induction properties of tenapanor on CYP1A2, CYP2B6, and CYP3A4. At concentrations up to 20 μmol/L of tenapanor,[6] there were no concentration-dependent increases in CYP3A4 mRNA, and the maximal induction was 15.5% of the positive control[7] response. Tenapanor at concentrations up to 20 μmol/L [6] caused no evident induction of CYP1A2 and CYP2B6.

Cryopreserved human hepatocytes were incubated with M1 (0.03-10 μmol/L) to assess the induction potential of CYP1A2, CYP2B6, and CYP3A4 by M1. The EC_{50} and E_{max} of M1 (mean ± standard deviation [SD] [n = 3]) for CYP2B6 were not calculable and >4.27, respectively, and the EC_{50} and E_{max} of M1 for CYP3A4 were 0.99 ± 0.23 μmol/L and 15.9 ± 0.59, respectively. M1 caused no evident induction of CYP1A2. The results of investigations in accordance with the guideline for drug interaction studies showed that M1 has the potential to cause drug interactions via CYP3A4 induction. For the effect of tenapanor on CYP3A4 activity, see Section 6.2.6.

4.5.2 Inhibition of human liver drug metabolizing enzymes by tenapanor and M1 (CTD 4.2.2.4-10 to 4.2.2.4-12 and 4.2.2.4-14 to 4.2.2.4-16)

Human liver microsomes were incubated with tenapanor (0.1-30 μmol/L) to assess the inhibition potential of tenapanor on the activities of CYP isoforms.[8] Tenapanor inhibited CYP2B6 (IC_{50} = 15.4 μmol/L), CYP2C8 (IC_{50} = 10.4 μmol/L), CYP2C9 (IC_{50} = 14.2 μmol/L), CYP2C19 (IC_{50} >30 μmol/L), CYP2D6 (IC_{50} = 3.26 μmol/L), and CYP3A (IC_{50} = 0.402 or 0.68 μmol/L). Tenapanor caused no evident inhibition of CYP1A2 over the concentration range tested.

Human liver microsomes were incubated with M1 (0.1-30 μmol/L) to assess the inhibition potential of M1 on the activities of CYP isoforms.[9] M1 inhibited CYP2B6 (IC_{50} >30 μmol/L), CYP2C19 (IC_{50} >30 μmol/L), CYP2D6 (IC_{50} = 1.95 μmol/L), and CYP3A (IC_{50} = 0.0813 or 0.110 μmol/L). M1 caused no evident inhibition of other CYP isoforms over the concentration range tested.

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[6] Cytotoxicity was observed at 50 μmol/L of tenapanor.

[7] Omeprazole; phenobarbital and 6-(4-chlorophenyl) imidazo [2,1-b] [1,3] thiazole-5-carboaldehyde *O*-(3,4-dichlorobenzyl) oxime; and rifampicin were used as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.

[8] The following substrates were used for assessment.
phenacetin for CYP1A2, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, (S)-mephenytoin for CYP2C19, bufuralol for CYP2D6, midazolam and nifedipine for CYP3A

[9] The following substrates were used for assessment.
phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, (S)-mephenytoin for CYP2C19, bufuralol for CYP2D6, chlorzoxazone for CYP2E1, midazolam and nifedipine for CYP3A

Human liver microsomes were incubated with tenapanor (0.03-10 μmol/L) or M1 (0.03-10 μmol/L) in the presence or absence of NADPH to evaluate their time-dependent inhibition of CYP isoforms.[10)] The IC_{50} values of tenapanor for CYP3A were 5.92 μmol/L following a 0-minute pre-incubation and 6.82 and 8.41 μmol/L following a 30-minute pre-incubation with and without NADPH, respectively. The IC_{50} values of M1 for CYP3A were 4.70 μmol/L following a 0-minute pre-incubation and 5.28 and 4.84 μmol/L following a 30-minute pre-incubation with and without NADPH, respectively. The applicant explained that as all IC_{50} values were similar, tenapanor or M1 is not a time-dependent inhibitor of CYP3A4. Tenapanor and M1 caused no evident inhibition of other CYP isoforms over the concentration range tested.

The applicant's explanation:
The results of investigations in accordance with the guideline for drug interaction studies showed that tenapanor and M1 have the potential to cause drug interactions via CYP3A inhibition. Tenapanor and M1 are unlikely to cause drug interactions mediated by other CYP isoforms (CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 for tenapanor, CYP2B6, CYP2C19, and CYP2D6 for M1).

For the effect of tenapanor on CYP3A activity, see Section 6.2.6.

4.5.3 Transporter substrate assessment (CTD 4.2.2.6-1 to 4.2.2.6-6)

Using human colon adenocarcinoma (Caco-2) cell monolayers, breast cancer resistance protein (BCRP)-mediated transport of tenapanor (10 μmol/L) was evaluated. In the absence and presence of a BCRP inhibitor (novobiocin, 30 μmol/L), the efflux ratios of tenapanor were >30.8 and >31.5, respectively, and the P_{app} B→A values (the mean [n = 3]) were 1.05×10^{-6} and 1.10×10^{-6} cm/s, respectively. The applicant explained that as the efflux ratio or P_{app} B→A of tenapanor was not affected by the inhibitor, tenapanor is not a substrate of BCRP. Using Caco-2 cell monolayers, BCRP-mediated transport of M1 (5 μmol/L) was evaluated, which indicated that M1 is not a substrate of BCRP.

Using Madin-Darby canine kidney II (MDCKII) cell monolayers expressing P-glycoprotein (P-gp) (MDCKII-MDR1 cells), P-gp-mediated transport of tenapanor (10 μmol/L) and M1 (5 μmol/L) was evaluated. The efflux ratios of tenapanor across MDCKII-MDR1 cells in the absence and presence of a P-gp inhibitor (zosuquidar, 10 μmol/L) were >10.7 and 1.91, respectively, and the P_{app} B→A values (the mean [n = 3]) were 0.38×10^{-6} and 0.73×10^{-6} cm/s, respectively. The efflux ratios of tenapanor across un-transfected MDCKII cells in the absence and presence of the P-gp inhibitor were 14.5 and 2.39, respectively, and the P_{app} B→A values (the mean [n = 3]) were 0.79×10^{-6} and 0.98×10^{-6} cm/s, respectively. The applicant explained that as the change in the efflux ratio of tenapanor due to the presence of the P-gp inhibitor was similar between MDCKII-MDR1 and MDCKII cells, and the P_{app} B→A value of tenapanor was slightly increased by the P-gp inhibitor, tenapanor is not a substrate of P-gp. The efflux ratios of M1 across MDCKII-MDR1 cells in the absence and presence of a P-gp inhibitor (verapamil, 100 μmol/L) were 2.39 and 0.615, respectively, and the efflux ratios of M1 across

[10)] The following substrates were used for assessment.
phenacetin for CYP1A2, bupropion for CYP2B6, amodiaquine for CYP2C8, diclofenac for CYP2C9, (S)-mephenytoin for CYP2C19, bufuralol for CYP2D6, midazolam for CYP3A

MDCKII cells in the absence and presence of the P-gp inhibitor were 0.931 and 1.06, respectively. The net ER[11] was 2.57, and transport was affected by the P-gp inhibitor, indicating that M1 is a substrate of P-gp.

Using human embryonic kidney 293 (HEK293) cells expressing organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3, the uptake of tenapanor (10 μmol/L) was evaluated, which indicated that tenapanor is not a substrate of OATP1B1 or OATP1B3.

Using HEK293 cells expressing organic anion transporter 1 (OAT1), OAT3, organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), or MATE2-K, the uptake of M1 (5 μmol/L) was evaluated, which indicated that M1 is not a substrate of OAT1, OAT3, OCT2, MATE1, or MATE2-K.

4.5.4 Transporter inhibition (CTD 4.2.2.6-7 to 4.2.2.6-14)

Using MDCK-BCRP cell monolayers expressing BCRP, the effect of tenapanor (1-300 μmol/L) on the transport of a probe substrate of BCRP[12] was evaluated. Tenapanor caused no evident inhibition of BCRP over the concentration range tested. Using Caco-2 cell monolayers, the effect of M1 (0.3-100 μmol/L) on the transport of a probe substrate of BCRP[13] was evaluated. M1 inhibited BCRP with an IC_{50} value of 43.7 μmol/L.

Using MDCKII-MDR1 cell monolayers expressing P-gp, the effects of tenapanor (0.3-100 μmol/L) and M1 (0.3-100 μmol/L) on the transport of probe substrates of P-gp[14] were evaluated. While tenapanor caused no evident inhibition of P-gp, M1 inhibited P-gp with an IC_{50} value of 80.7 μmol/L.

Using HEK293 cells expressing OATP1B1 or OATP1B3, the effect of tenapanor (0.01-10 μmol/L) on the transport of a probe substrate of OATP1B1 and OATP1B3[15] was evaluated. Tenapanor inhibited OATP1B1 and OATP1B3 with IC_{50} values of 0.658 and 1.43 μmol/L, respectively.

Using HEK293 cells expressing OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K, the effects of M1 (0.3-100 μmol/L) on the transport of probe substrates[16] were evaluated. M1 inhibited OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K with IC_{50} values of 23.6, 46.7, >100, 16.9, and 21.9 μmol/L, respectively. M1 caused no evident inhibition of OCT2[17] and OAT3.

The applicant explained that the results of investigations in accordance with the guideline for drug interaction studies showed that tenapanor is unlikely to cause drug interactions via inhibition of OATP1B1 and OATP1B3

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[11] In accordance with the guideline for drug interaction studies, the net ER was estimated based on efflux ratio of P-gp-expressing cells/efflux ratio of un-transfected cells.

[12] Cladribine was used as a substrate of BCRP for assessment.

[13] Rosuvastatin was used as a substrate of BCRP for assessment.

[14] [^{3}H]-digoxin and digoxin were used as substrates of P-gp for assessments of tenapanor and M1, respectively.

[15] Estradiol-17β-D-glucuronide was used as a substrate of OATP1B1 and OATP1B3 for assessment.

[16] The following substrates were used for assessment.
estradiol-17β-D-glucuronide for OATP1B1, atorvastatin for OATP1B3, p-aminohippuric acid for OAT1, furosemide for OAT3, metformin for OCT2, MATE1, and MATE2-K

[17] The OCT2 inhibition assessment was conducted twice, once in Batch 1 and once in Batch 2. M1 at high concentrations (100 μmol/L for Batch 1 and 30-100 μmol/L for Batch 2) inhibited OCT2.

and that M1 is unlikely to cause drug interactions via inhibition of BCRP, P-gp, OATP1B1, OATP1B3, OAT1, OCT2, MATE1, and MATE2-K.

Using HEK293 cells expressing OATP2B1 or Chinese hamster ovary (CHO) cells expressing peptide transporter 1 (PEPT1), the effects of tenapanor (0.003-2.5 μmol/L for OATP2B1, 0.007-5 μmol/L for PEPT1) on the transport of probe substrates of OATP2B1 and PEPT1[18)] were evaluated. Tenapanor inhibited OATP2B1 with an IC_{50} value of 0.01 μmol/L. Tenapanor caused no concentration-dependent inhibition of PEPT1-mediated transport over the concentration range tested. For the effect of tenapanor on OATP2B1, see Section 6.2.7.

4.5.5 Interactions with phosphate binders (CTD 4.2.2.6-16, Reference data 4.2.2.6-15)

Interactions of tenapanor (1-200 μmol/L) with different phosphate binders[19)] were evaluated in a buffer designed to simulate the intestinal environment. Tenapanor interacted with sevelamer carbonate and sodium polystyrene sulfonate, as demonstrated by 71% to 87% and 26% to 32%, respectively, of tenapanor being bound.

The percentages of tenapanor (1 μg/mL) bound to sevelamer carbonate, ferric citrate hydrate, sevelamer hydrochloride, sucroferric oxyhydroxide, bixalomer, and lanthanum carbonate hydrate in simulated gastrointestinal fluid were 37.9%, 42.3%, 50.3%, 8.61%, 4.46%, and 4.16%, respectively. The applicant explained that the differences in the percentage of tenapanor bound to sevelamer carbonate between the test systems (simulated intestinal fluid and simulated gastrointestinal fluid) may have been attributable to differences in matrix composition, the concentrations of matrix components (especially, the concentration of a bile acid component, taurocholic acid), and pH. For the effects of phosphate binders on tenapanor, see Section 6.2.9.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the non-clinical pharmacokinetics of tenapanor were adequately evaluated.

4.R.1 Pharmacokinetics following multiple oral dosing of tenapanor

Since repeated-dose studies in mice and rats [see Sections 4.1.3.1 to 4.1.3.3] showed a trend towards higher C_{max} and AUC values of tenapanor and M1 after multiple oral dosing, PMDA asked the applicant to explain the accumulation after multiple oral dosing of tenapanor.

The applicant's response:

The major cause for higher tenapanor exposure after multiple dosing may be increased intestinal absorption of tenapanor due to its pharmacological effects in the gastrointestinal tract. Tenapanor inhibits NHE3 in the

[18)] The following substrates were used for assessment.
estrone-3-sulfate for OATP2B1, glycylsarcosine for PEPT1

[19)] precipitated calcium carbonate, calcium acetate, sevelamer carbonate, and sodium polystyrene sulfonate

intestinal epithelial cells and increases the water volume in the intestinal lumen of rats [see Section 3.1.2]. Following oral administration of tenapanor 10, 50, and 200 mg/kg in mice, tenapanor concentrations in the intestinal lumen were estimated to be 0.204, 1.02, and 4.08 mg/mL,[20)] respectively. The tenapanor concentrations in the intestinal lumen at 50 and 200 mg/kg of tenapanor were 4.5- and 18-fold its solubility in simulated intestinal fluid in the fed state (0.226 mg/mL), indicating the possibility that tenapanor was not dissolved sufficiently in the intestinal lumen. Thus, tenapanor exposure increased after multiple dosing, possibly because inhibition of NHE3 by tenapanor increased the water volume in the intestinal lumen, thereby increasing the amount of tenapanor dissolved at the intestinal absorption site.

The cause for higher M1 exposure after multiple dosing of tenapanor may be an increase in the amount dissolved in the intestinal lumen due to the pharmacological effects of tenapanor, etc. However, the coefficients of variation for the C_{max} and $AUC_{0\text{-}t}$ were 18.8% to 90.9% and 13.7% to 56.4%, respectively, in the treatment groups of a 4-day repeated-dose study in rats, which markedly exceeded the acceptance criteria for precision for the analysis of M1 in plasma (within 15%). The variability in analysis of plasma M1 concentrations and the intra-individual variability in the pharmacokinetics of M1 were also considered large.

In a phase I study in Japanese and non-Japanese healthy volunteers (Study D5611C00005), the accumulation ratio of M1[21)] after 7-day oral administration of tenapanor 90 mg BID was 9.19 to 11.0. The major cause for these results may be the long $t_{1/2}$ of M1. In a clinical study that evaluated the effect of hepatic impairment on the pharmacokinetics of tenapanor [see Section 6.2.5], the $t_{1/2}$ of plasma M1 was 25.4 hours in subjects with normal hepatic function following a single oral dose of tenapanor. In a Japanese phase II study in patients with hyperphosphatemia on hemodialysis (HD), plasma M1 concentrations were assessed over a longer period (6 weeks after the start of treatment). The mean plasma M1 concentrations at Weeks 1, 4, and 6 were similar [see Section 6.2.4], indicating that a steady-state was reached. Based on the above, M1 is unlikely to accumulate beyond Week 1. In a clinical study, plasma concentrations of unchanged tenapanor were below the LLOQ in almost all samples,[22)] and there was no evident accumulation of unchanged tenapanor in humans.

PMDA's view:
The causes for higher tenapanor or M1 exposures after multiple dosing of tenapanor in non-clinical and clinical studies have been discussed appropriately, and the results of a Japanese phase II study indicate that following multiple dosing of tenapanor, the plasma M1 concentration reaches a steady state. Given these points etc., tenapanor and M1 are unlikely to accumulate in a treatment duration-dependent manner during long-term treatment with tenapanor.

[20)] Tenapanor concentrations in the intestinal lumen were estimated as follows: First, the water content in the gastrointestinal tract per body weight (49.0 mL/kg) was calculated from the water content in the gastrointestinal tract in the fed mouse (0.98 mL) (*J Pharm Pharmacol*. 2008; 60: 63-70) and mouse body weight (20 g) (*Pharm Res.* 1993; 10: 1093-5). Then, tenapanor concentrations in the intestinal lumen were calculated by dividing the dose of tenapanor (10, 50, and 200 mg/kg) by the water content in the gastrointestinal tract per body weight.

[21)] Ratio of $AUC_{0\text{-}8\,h}$ on Day 7 to $AUC_{0\text{-}8\,h}$ on Day 1

[22)] HD patients orally received tenapanor twice daily (the starting dose was 42 mg. The dose could be reduced in a stepwise manner [42→28→14→4.7 mg]). Plasma concentrations of unchanged tenapanor were below the LLOQ (0.5 ng/mL) at almost all time points (*Clin J Am Soc Nephrol*. 2016; 11: 1597-605).

4.R.2 Gender-related differences observed in rats

Given that the C_{max} and AUC of M1 were higher in females than in males in a 4-day repeated-dose study in rats [see Section 4.1.3.2], PMDA asked the applicant to explain gender-related differences in the pharmacokinetics of M1.

The applicant's response:

The possible reason for higher C_{max} and AUC of M1 in females than in males after 4-day oral dosing of tenapanor was gender-related differences in the formation of M1 from unchanged tenapanor and the metabolism of M1. CYP3A4 and CYP3A5 are considered to be primarily involved in the formation of M1 from unchanged tenapanor, and CYP2C8 and CYP2D6 are also considered to be involved [see Section 4.3.2]. In rat liver microsomes in the presence of NADPH, M1 was formed from unchanged tenapanor [see Section 4.3.1], and M1 was metabolized.[23)] The expression levels of the CYP2C and CYP3A subfamilies are different between male and female rats (*Toxicol Lett*. 1992; 64-65: 661-7, *Biochem Biophys Res Commun*. 1998; 242: 57-60). Thus, metabolizing enzymes that are expressed at higher levels in females are involved in the formation of M1, and metabolizing enzymes that show the sex-related differences in their expression levels are involved in the metabolism of M1, which may have resulted in gender-related differences in the pharmacokinetics of M1.

Among the isoforms involved in the formation of M1 from tenapanor [see Section 4.3.2], the primary metabolizing enzyme, CYP3A4 (a 1.73-fold higher expression level in women than in men) only has been reported as a gene that shows sex-related differences, in the literature on a comprehensive analysis of sex-related differences in the expression levels of drug metabolizing enzyme genes in human liver (*J Drug Metab Toxicol*. 2012; 3: 1-20). According to multiple papers, the expression of CYP3A4 (mRNA and protein) in human liver is higher in women than in men, and CYP3A4 exhibits higher activity in women than in men (*J Clin Pharm Ther*. 1999; 24: 339-46, *US Pharm*. 2014; 39: 40-3, etc.). Based on the above literature information, sex differences in the expression level or activity of the primary metabolizing enzyme, CYP3A4, in humans, may affect tenapanor and M1 exposures.

However, as shown below, clinical studies of tenapanor showed no clear gender-related differences in the plasma exposure of M1 after administration of tenapanor and the efficacy and safety of tenapanor. Thus, the gender-related differences observed in rats are of no human relevance, and there should be little gender-related differences in the pharmacokinetics, efficacy, and safety of tenapanor in humans.

● In a Japanese phase II study in patients with hyperphosphatemia on HD (Study 001), the plasma M1 concentrations at different time points after repeated oral administration of tenapanor were determined [see Section 6.2.4]. The female to male M1 concentration ratio (the mean) ranged from 0.75 to 1.38, except for the time points of study drug discontinuation, and there were no clear gender-related differences at any dose level or at any time point. Plasma concentrations of unchanged tenapanor were below the LLOQ in almost all samples from the clinical studies conducted.

[23)] When M1 (1 μmol/L) was incubated with mouse, rat, and human liver microsomes in the presence of NADPH, the CL_{int} values of M1 were 361, 68.2, and 16.3 μL/min/mg protein in mouse, rat, and human liver microsomes, respectively (CTD 4.2.2.4.-8).

● With respect to the primary endpoint of "the change from baseline in serum phosphorus at Week 8" for 3 Japanese phase III studies (Studies 004, 005, and 006), the results of a subgroup analysis according to sex were consistent with the results in the Modified Intention-to-Treat (mITT) population in all studies.
● In 4 Japanese phase III studies (Studies 004, 005, 006, and 007), the incidences of adverse events and adverse drug reactions were similar between male and female subjects.

PMDA's view:
Although a repeated-dose study in rats suggested gender-related differences in the pharmacokinetics of M1, given the pharmacokinetic, efficacy, and safety data from clinical studies of tenapanor by sex, the gender-related pharmacokinetic differences observed in rats are unlikely to become a clinically relevant problem.

5. Toxicity and Outline of the Review Conducted by PMDA

The following toxicity studies of tenapanor were conducted: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies, juvenile animal studies, and other toxicity studies (toxicity studies on its metabolite or impurities). Unless otherwise specified, 2% Tween 80 in deionized water was used as vehicle.

5.1 Single-dose toxicity

A single-dose toxicity study was conducted in female rats (Table 13). The acute toxicity of tenapanor was assessed based on the findings after the first dose in repeated-dose toxicity studies in mice, rats, and dogs (Table 14).

Table 13. Overview of single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Noteworthy findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female rat (SD)	Oral gavage	300[a)]	diarrhea, decreased food consumption, increased water consumption	>300	Reference data 4.2.3.1-1

a) Deionized water

Table 14. Overview of the findings after the first dose in repeated-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Noteworthy findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (CD-1)	Oral gavage	0, 30, 100, 300	No noteworthy findings	>300	Reference data 4.2.3.2-1
Male and female rats (SD)	Oral gavage	0,[a)] 100, 300, 1,000	No noteworthy findings	>1,000	Reference data 4.2.3.2-4
Male and female dogs (Beagle)	Oral	0,[b)] 100, 300, 1,000	No noteworthy findings	>1,000	Reference data 4.2.3.2-9

a) 10% propylene glycol
b) Capsule

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice (up to 28 days), rats (up to 6 months), and dogs (up to 9 months) (Table 15). As the noteworthy toxicological findings, gastrointestinal disorders such as diarrhea and soft feces related to the pharmacological effects of tenapanor and secondary changes associated with gastrointestinal disorders were observed. The no observed adverse effect levels (NOAELs) in mouse 28-day, rat 6-month, and dog 9-month repeated-dose toxicity studies (50 mg/kg/day in mice, 3 mg/kg/day (male) and

10 mg/kg/day (female) in rats, 1,000 mg/kg/day in dogs) were approximately 4-fold (mice), approximately 0.48-fold (male rats), approximately 1.6-fold (female rats), and approximately 540-fold (dogs) the maximum clinical dose of tenapanor (30 mg, twice daily).

Table 15. Overview of repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Male and female mice (CD-1)	Oral gavage	28 days (QD) + 14-day recovery period	0, 10, 50, 200	≥10: inflammatory cell infiltration of the rectal mucosa (male) ≥50: soft feces (male), perianal fur staining (male), decreased body weight gain, decreased food consumption, inflammatory cell infiltration of the rectal mucosa (female) 200: necrosis of crypt cells of the duodenum/jejunum/ileum/cecum, decreased goblet cells in the rectal mucosa (female) These findings were reversible.	50[a)]	4.2.3.2-2
Male and female rats (SD)	Oral gavage	14 days (QD) + 14-day recovery period	0, 0.1, 1, 10	≥0.1: decreased eosinophil count (female), decreased serum glucose (male), distended cecum and brown fluid contents in the cecum, decreased goblet cells/inflammatory cell infiltration in the cecum/colon/rectum ≥1: soft feces, diarrhea, perianal fur staining 10: decreases in body weight gain/food consumption (male), increased water consumption, decreases in white blood cell count/lymphocyte count (female), increases in blood total protein/phosphorus/potassium (male), decreases in spleen/thyroid/parathyroid weights (male) These findings were reversible.	10[b)]	4.2.3.2-5
Male and female rats (SD)	Oral gavage	14-18 days[c)] (QD) + 14-day recovery period	0, 30, 100, 300, 1,000	Mortality[d)]: 30 (1 of 21 females), 100 (3 of 21 females), 300 (1 of 21 males, 2 of 21 females), 1,000 (4 of 21 females) ≥30: soft feces, diarrhea, perianal fur staining, dermal atonia, thin appearance, decreases in body weight/food consumption, increased water consumption, increases in red blood cell count/hemoglobin concentration/hematocrit/mean corpuscular hemoglobin concentration/red cell distribution width/hemoglobin distribution width (female)/neutrophil count/monocyte count, decreased mean corpuscular volume (female), decreased blood sodium, increased blood urea nitrogen, increases in blood ALT/AST/creatinine (female)/A/G ratio, decreases in blood potassium (male)/albumin (female)/cholesterol (female)/chloride (female), decreased urine specific gravity, distended/brown fluid contents in the cecum/colon/duodenum/ileum/jejunum/stomach, small axillary lymph nodes/spleen/thymus, brown staining on the skin/tail/paws, decreased spleen weight, decreased goblet cells/inflammatory cell infiltration/mucosal atrophy/erosion/necrosis of glandular epithelial cells in the cecum/colon/duodenum/ileum/jejunum/rectum, hyaline casts/tubular degeneration/tubular regeneration in the kidney, atrophy of the ex-orbital lacrimal gland, lymphoid depletion in the mesenteric lymph nodes/axillary lymph nodes/spleen/thymus, lymphoid depletion in the bone marrow (femoral/sternal), decreased secretion in the coagulating glands/seminal vesicles These findings were reversible.	<30	4.2.3.2-6

Male and female rats (SD)	**Oral gavage**	**3 months (QD) + 28-day recovery period**	**0,[e] 0.1, 1, 5**	**≥1: soft feces/perianal fur staining, a trend towards decreased body weight, a transient decrease in food consumption** **These findings were reversible.**	**5[f]**	**4.2.3.2-7**
Male and female rats (SD)	**Oral gavage**	**6 months (QD)**	**0,[e] 1, 3, 10**	**Mortality: 10 (2 of 29 males)** **≥1: soft feces, diarrhea, perianal fur staining, increases in serum phosphorus/potassium, dark yellow/brown/red urine/bilirubin urine, minimal hypertrophy of the adrenal zona glomerulosa** **≥3: decreased body weight gain (male), a transient decrease in food consumption, decreased blood glucose (male), increased urine pH (female), turbid urine, urine protein positive (female)** **10: decreased body weight gain (female), decreased blood glucose (female), increased urine pH (male), urine nitrite positive (female), positive urine occult blood**	**3[g] (male)** **10[g] (female)**	**4.2.3.2-8**
Male and female dogs (Beagle)	**Oral**	**28 days (QD) + 14-day recovery period**	**0,[h] 50, 300, 1,000**	**≥50: abnormal excreta such as soft feces** **These findings were reversible.**	**1,000[i]**	**4.2.3.2-10**
Male and female dogs (Beagle)	**Oral**	**3 months (QD) + 28-day recovery period**	**0,[h] 50, 300, 1,000**	**≥50: diarrhea, diarrhea/feces containing red material, mucoid feces, red mucoid feces, yellow mucoid feces, soft feces** **These findings were reversible.**	**1,000[i]**	**4.2.3.2-11**
Male and female dogs (Beagle)	**Oral**	**9 months (QD)**	**0,[h] 50, 300, 1,000**	**≥50: soft feces, diarrhea, mucoid feces, red mucoid feces, feces containing red material**	**1,000[i]**	**4.2.3.2-12**

a) The findings observed at ≤50 mg/kg were related to the pharmacological effects of tenapanor and were reversible. Thus, these findings were considered of little toxicological significance.
b) The findings observed in this study were considered of little toxicological significance because these were not associated with deterioration in clinical observations etc. and were reversible, minimal or mild changes.
c) Although 28 days of dosing was planned, as mortality or deterioration in clinical observations were observed on Day 12 and thereafter in all tenapanor dose groups, dosing was terminated on Day 18 (males) or Day 15 (females). Recovery animals underwent a 14-day recovery period after dosing was terminated on Day 14.
d) While 1 male in the 300 mg/kg group died due to gastrointestinal disorder, the cause of death was unknown for all females. Marked reduction of body weight was observed before death in animals that were weighed.
e) 0.1% Tween 80 in deionized water
f) The findings observed in this study were not associated with deterioration in clinical observations etc. and were thus considered of little toxicological significance.
g) The findings in urinalysis were not associated with organic changes in the kidneys, and the findings observed in males at 1 and 3 mg/kg and females at 1, 3, and 10 mg/kg were minimal. Thus, these findings were considered of little toxicological significance.
h) Capsule
i) Abnormal excreta observed in dogs were related to the pharmacological effects of tenapanor, were not associated with deterioration in clinical observations etc., and were reversible. Thus, these findings were considered of little toxicological significance.

5.3 Genotoxicity

An *in vitro* bacterial reverse mutation assay, an *in vitro* mammalian chromosomal aberration assay, and *in vivo* bone marrow micronucleus assays in mice and rats were performed (Table 16). Tenapanor was considered to have little genotoxic potential.

Table 16. Overview of genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentrations (μg/plate or μg/mL) or doses (mg/kg/day)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A/pKM101	S9−/+	0,[a] 50, 150, 500, 1,500, 5,000	Negative	4.2.3.3.1-1
	In vitro chromosomal aberration assay in cultured mammalian cells	Human peripheral blood lymphocytes	S9− (4 hours)	0,[a] 500, 1,000, 3,000	Negative	4.2.3.3.1-2
			S9+ (4 hours)	0,[a] 250, 500, 2,000		
			S9− (20 hours)	0,[a] 250, 500, 2,000		
In vivo	Rodent micronucleus assays	Male and female mice (ICR) bone marrow		0, 500, 1,000, 2,000 Two oral doses, 24 hours apart	Negative	4.2.3.3.2-1
		Male rat (Wister Han) bone marrow		0, 1, 5, 10 Two IV doses, 24 hours apart	Negative	4.2.3.3.2-3

a) DMSO

5.4 Carcinogenicity

A carcinogenicity study in rats and a carcinogenicity study in Tg rasH2 mice were conducted (Table 17). There were no test article-related increases in tumor incidences. The no observed effect levels (NOELs) for carcinogenicity in the rat and Tg rasH2 mouse carcinogenicity studies (10/5 mg/kg/day in rats, 100 mg/kg/day (male) and 800 mg/kg/day (female) in Tg rasH2 mice) were approximately 1.6/0.8-fold (rats) and approximately 8-fold and approximately 64-fold (Tg rasH2 mice) the maximum clinical dose of tenapanor (30 mg, twice daily).

Table 17. Overview of carcinogenicity studies

Test system	Route of administration	Duration of dosing	Major lesions	Dose	(mg/kg/day)[a]								NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
					Male				Female					
					0[b]	1	3/2	10/5	0[b]	1	3/2	10/5		
				N	60	60	60	60	60	60	60	60		
Male and female rats (SD)	Oral gavage	83-96 weeks[c] (QD)	Neoplastic lesions		None								10/5	4.2.3.4.1-2
			Non-neoplastic lesions		None									
			Other non-neoplastic lesions		≥1: soft feces, diarrhea, decreased body weight (female), decreased food consumption (female) ≥3/2: perianal fur staining (male) 10/5: decreased body weight (male), decreased food consumption (male)									

Male and female mice (Tg rasH2)	Oral gavage	26 weeks (BID)	Major lesions	Dose	(mg/kg/day)										100 (male) 800 (female)	4.2.3.4.2-3
					Male					Female						
					0[d]	0[e]	10	30	100	0[d]	0[e]	100	300	800		
				N	25	25	25	25	25	25	25	25	25	25		
			Neoplastic lesions													
			Hemolymphoreticular system: Malignant lymphoma		0	0	0	0	0	0	0	0	0	0		
			Whole body: Hemangiosarcoma		3	1	0	0	1	0	2	1	0	0		
			Whole body: Hemangioma		0	0	0	0	0	0	0	0	0	0		
			Lung: Bronchoalveolar adenoma/carcinoma		4	1	2	2	1	1	3	2	1	1		
			Stomach: Squamous cell papilloma/carcinoma		0	0	0	0	0	1	0	0	0	0		
			Skin: Squamous cell papilloma/carcinoma		0	0	0	1	0	0	0	0	0	0		
			Non-neoplastic lesions		None											
			Other non-neoplastic lesions		100: decreased body weight (male)											

a) Due to marked body weight loss, animals in the 10 mg/kg group were placed on dosing holiday on Days 65-85, and then the dose was reduced to 5 mg/kg on Day 86. On Day 92, the 3 mg/kg dose level was reduced to 2 mg/kg.
b) 0.1% Tween 80 in Milli-Q water
c) Although 104 weeks of dosing was planned, as only 15 or 20 animals survived, dosing was terminated, and necropsy was performed at the following time points.
· Males in the 0, 1, and 3/2 mg/kg groups: Week 86
· Males in the 10/5 mg/kg group: Week 83
· All female groups: Weeks 95-96
d) Milli-Q water
e) 0.1% polysorbate and 1% DMSO in Milli-Q water. This solution was used also as vehicle for tenapanor dosing formulations.

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in mice, embryo-fetal development studies in rats and rabbits, and a mouse study for effects on pre- and postnatal development, including maternal function, were conducted (Table 18). There were no effects on embryo-fetal development. The NOAELs for embryo-fetal development in the embryo-fetal development studies in rats and rabbits (1 mg/kg/day in rats, 45 mg/kg/day in rabbits) were approximately 0.16-fold (rats) and approximately 14.4-fold (rabbits) the maximum clinical dose of tenapanor (30 mg, twice daily).

The applicant's explanation:

A dose range-finding embryo-fetal development study in rabbits showed decreased fetal weights that were considered related to maternal toxicity, and an embryo-fetal development study of M1 in rats showed fetal

external malformations and variations [see Section 5.7.1.4], etc. Thus, the package insert for tenapanor will advise that tenapanor may be used in pregnant women only if the expected therapeutic benefits outweigh the possible risks. As to the use of tenapanor in lactating women, there are no data available on milk excretion of tenapanor and M1, and the mouse study of effects on pre- and postnatal development, including maternal function, showed decreases in body weight/body weight gain, increased motor activity counts, effects on memory assessment, etc. Since these findings were caused by decreased phosphate delivery to the pups resulting from reduced phosphate absorption in the dams due to the pharmacological effects of tenapanor, these findings are unlikely to occur in clinical practice where blood phosphorus levels are managed. Although milk excretion of tenapanor was not studied, orally administered tenapanor is minimally absorbed, and the fetus and infant are minimally exposed to tenapanor via milk. Thus, the package insert will advise that whether to continue or discontinue breastfeeding should be determined, taking account of the therapeutic benefits, the effects of tenapanor on the infant, and the benefits of breastfeeding nutrition for the infant.

Table 18. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Female mouse (CD-1)	Oral gavage	From 14 days prior to mating until gestation day 6 (QD)	0,[a] 10, 50	Parental animals: No noteworthy findings	Female general toxicity: 50 Female fertility: 50	4.2.3.5.1-1
	Male rat (SD)	Oral gavage	10 weeks[b] (QD)	0,[c] 1, 3, 10	Parental animals: No noteworthy findings	Male reproductive performance: 10	4.2.3.2-8
Embryo-fetal development	Female rat (SD)	Oral gavage	Gestation days 6-17 (QD)	0,[c] 1, 3, 10, 30	Dams: ≥1: soft stool, diarrhea, a transient decrease in body weight associated with decreased food consumption ≥10: decreased body weight Fetuses: No noteworthy findings		4.2.3.5.2-1
	Female rat (SD)	Oral gavage	Gestation days 6-17 (QD)	0,[c] 1, 10, 30	Dams: Mortality[d]: 10 (25 of 25 animals), 30 (25 of 25 animals) 1: soft stool, diarrhea, decreases in body weight/food consumption Fetuses: No noteworthy findings	Maternal general toxicity: <1 Embryo-fetal development: 1	4.2.3.5.2-2
	Female rabbit (NZW)	Oral gavage	Gestation days 7-20 (QD)	0,[c] 3, 10, 30, 100, 300	Dams: ≥3: decreased defecation, small feces, soft stool, diarrhea ≥100: decreases in body weight/body weight gain/food consumption Fetuses: ≥30: decreased fetal weights		4.2.3.5.2-4
	Female rabbit (NZW)	Oral gavage	Gestation days 7-20 (QD)	0,[c] 5, 15, 45	Dams: ≥5: soft stool, diarrhea ≥15: slight decreases in body weight/food consumption 45: abortion Fetuses: No noteworthy findings	Maternal general toxicity: 5 Embryo-fetal development: 45	4.2.3.5.2-5
Pre- and postnatal development, including maternal function	Female mouse (CD-1)	Oral gavage	Dams: Gestation day 6 through lactation day 20 (QD)	0,[c] 20, 60, 200	Dams: No noteworthy findings F1 pups: ≥60: decreases in body weight/body weight gain 200: a transient increase in motor activity counts, increases in the number of errors and escape time in memory assessment (male)	Maternal general toxicity: 200 F1 developmental toxicity: 20	4.2.3.5.3-1

a) 0.1% Tween 80 in Milli-Q water

b) Male fertility was evaluated as part of a 6-month repeated oral dose toxicity study in rats. Males for fertility evaluation were dosed with tenapanor at 0, 1, 3, or 10 mg/kg/day for approximately 10 weeks and were then mated with naïve females that were not dosed.

c) 0.1% Tween 80 in deionized water

d) By gestation day 16, 2 females were found dead and 1 female was euthanized in extremis in the 30 mg/kg group. Due to marked body weight loss, reduced food consumption, and deterioration in clinical observations associated with these changes, all females in the 10 and 30 mg/kg groups were euthanized by gestation day 16. Embryo-fetal examination was precluded in the 10 and 30 mg/kg groups.

5.6 Juvenile animal studies

Repeated-dose toxicity studies of up to 60 days were conducted in juvenile rats (Table 19). The noteworthy toxicological findings were gastrointestinal disorders such as diarrhea and soft feces due to the pharmacological effects of tenapanor, and mortalities and moribundities etc. secondary to gastrointestinal disorders. The applicant explained that the package insert will advise that tenapanor is contraindicated in children aged <2 years and that the use of tenapanor is not recommended in children aged ≥2 years.

Table 19. Overview of juvenile animal studies

Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Juvenile male and female rats (SD)	Oral gavage	8 weeks (Postnatal days 5-61, QD) + 4-week recovery period	0,[a] 0.03, 0.1, 0.3	Mortality: 0.3 (6 of 64 males, 2 of 64 females) delayed growth (female), tremors during gait (female), frequent fall and closed eyes (female), rough haircoat (female), yellow material around the urogenital area and brown material around the anogenital area (female), decreased body weight 0.3: brown material around the anogenital area, decreases in body weight gain/food consumption, reductions in tibial length These findings were reversible.	0.1	4.2.3.5.4-3[b]
Juvenile male and female rats (SD)	Oral gavage	60 days (Postnatal days 21-80, QD) + 14-day recovery period	0, 0.1, 0.3, 0.7 (male), 1.0 (female)	≥0.3: soft feces/liquid feces, decreases in body weight and body weight gain, delayed mean age of vaginal opening, reductions in tibial length (male), decreased urine pH (male) 1.0: red anal area (female) These findings were reversible.	0.1	4.2.3.5.4-4[c]

a) 0.1% Tween 80 in deionized water
b) Animals were evaluated/examined for clinical signs, body weights, food consumption, tibial lengths, ophthalmology, developmental evaluations, neurobehavioral evaluations, estrous cycles, reproductive performance, parturition, litter viability and survival, hematology, clinical chemistry, urinalysis, necropsy findings, organ weights, neuropathology examinations, and histopathologic examinations.
c) Animals were evaluated for survival, clinical signs, body weights, food consumption, ophthalmology, sexual maturation, tibial lengths, hematology, clinical chemistry, urinalysis, femur lengths, necropsy findings, organ weights, and histopathologic examinations.

5.7 Other toxicity studies

5.7.1 Toxicity studies of metabolite M1

5.7.1.1 Repeated-dose toxicity studies of metabolite M1

Repeated oral dose toxicity studies in mice (up to 14 days) and a 28-day repeated oral dose toxicity study in Tg rasH2 mice were conducted with the M1 metabolite of tenapanor (Table 20). There were mortalities associated with deterioration in clinical observations in mice. The AUC_{last} values of M1 (201,000 ng·h/mL in males, 439,000 ng·h/mL in females) at the NOAEL in Tg rasH2 mice (250 mg/kg/day) were 1,026-fold and 2,240-fold the AUC of M1 at the maximum clinical dose of tenapanor (30 mg, twice daily), respectively. The M1 metabolite was evaluated also in a repeated-dose toxicity study in dogs, and the AUC_{0-t} values of M1 (334 ng·h/mL in males, 346 ng·h/mL in females) at the NOAEL in the 9-month repeated-dose toxicity study in dogs (1,000 mg/kg/day) were 1.70-fold and 1.77-fold the AUC of M1 at the maximum clinical dose of tenapanor (30 mg, twice daily), respectively.

Table 20. Overview of repeated-dose toxicity studies of M1

Test system	Route of administration	Duration of dosing	Doses (mg/kg)	Noteworthy findings	NOAEL (mg/kg)	Attached document CTD
Male and female mice (C57BL/6)	Oral gavage	4 days (QD)	M1: 0,[a] 30, 100, 300	≥100: hunched posture (male) 300: lethargy (male), labored/rapid breathing (male), increased locomotor activity (female)		Reference data 4.2.3.7.5-3
Male and female mice (CByB6Fl/j)	Oral gavage	14 days (QD)	M1: 0,[a] 500, 1,000	Mortality: 500 (3 of 6 males and 3 of 6 females), 1,000 (6 of 6 males and 6 of 6 females) lethargy, dyspnea, shaking, drooling, hunched posture, decreased body temperature, piloerection		Reference data 4.2.3.7.5-4
Male and female mice (Tg rasH2)	Oral gavage	28 days (QD)	M1: 0,[b] 75, 150, 250 Tenapanor: 400[a]	M1: No noteworthy findings Tenapanor: No noteworthy findings	M1: 250	4.2.3.7.5-5

a) 0.1% Tween 80 in deionized water was used as vehicle or negative control.
b) 0.1% Tween 80 and 280 mM hydrochloric acid in deionized water

5.7.1.2 Genotoxicity studies of metabolite M1

The M1 metabolite of tenapanor was tested in an *in vitro* bacterial reverse mutation assay and an *in vitro* micronucleus assay in mouse lymphoma cells (Table 21). M1 was considered to have little genotoxic potential.

Table 21. Overview of genotoxicity studies of M1

Type of study		Test system	Metabolic activation (Treatment)	Concentrations (μg/plate or μg/mL)	Test result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A/pKM101	S9−/+	M1: 0,[a] 5, 16, 50, 160, 500, 1,600, 5,000	Negative	4.2.3.7.5-6
	In vitro micronucleus assay in cultured mammalian cells	L5178Y mouse lymphoma cells	S9− (3 hours)	0,[a] 60, 80, 95, 100	Negative	4.2.3.7.5-7
			S9+ (3 hours)	0,[a] 60, 80, 90, 95		
			S9− (24 hours)	0,[a] 20, 30, 35, 40, 50		

a) DMSO

5.7.1.3 Carcinogenicity study of metabolite M1

A carcinogenicity study in Tg rasH2 mice was conducted with the M1 metabolite of tenapanor (Table 22). There were no test article-related increases in tumor incidences. The $AUC_{0\text{-}24}$ of M1 (89,500 ng·h/mL in males, 197,000 ng·h/mL in females) at the NOELs for carcinogenicity (165/110 mg/kg/day) in the carcinogenicity study of M1 in Tg rasH2 mice were 457-fold and 1,005-fold the AUC of M1 at the maximum clinical dose of tenapanor (30 mg, twice daily), respectively.

Table 22. Overview of carcinogenicity study of M1

Test system	Route of administration	Duration of dosing	Major lesions	Dose (mg/kg/day)								NOEL for carcinogenicity (mg/kg/day)	Attached document CTD
				Male				Female					
				0[a)]	0[b)]	55	165/110[c)]	0[a)]	0[b)]	55	165/110[c)]		
				N	25	25	25	25	25	25	25	25	
Male and female mice (Tg rasH2)	Oral gavage	26 weeks (QD)	**Neoplastic lesions**									165/110	4.2.3.4.2-3
			Hemolymphoreticular system: malignant lymphoma	0	1	0	0	0	0	0	1		
			Whole body: Hemangiosarcoma	3	0	3	0	0	1	1	2		
			Whole body: Hemangioma	0	0	0	0	0	0	0	0		
			Lung: Bronchoalveolar adenoma/carcinoma	4	2	2	2	1	0	2	1		
			Stomach: Squamous cell papilloma/carcinoma	0	0	1	1	1	0	0	0		
			Skin: Squamous cell papilloma/carcinoma	0	0	0	0	0	0	0	0		
			Non-neoplastic lesions	None									
			Other non-neoplastic lesions	165/110: decreased body weight									

a) Milli-Q Water
b) 0.1% Tween 80 in deionized water. This solution was used also as vehicle for tenapanor dosing formulations.
c) Due to marked weight loss, the dose level was reduced to 110 mg/kg/day on Day 99.

5.7.1.4 Reproductive and developmental toxicity study of metabolite M1

An embryo-fetal development study of the M1 metabolite of tenapanor was conducted in rats (Table 23). In rats, fetal external malformations (localized edema or anasarca and skeletal malformations) and variations (pale and small spleen, skeletal variations/reduced ossification) were observed. The AUC_{last} of M1 (897,000 ng·h/mL) at the NOAEL for embryo-fetal development (150 mg/kg/day) in the embryo-fetal development study of M1 in rats was 4,577-fold the AUC of M1 at the maximum clinical dose of tenapanor (30 mg, twice daily).

Table 23. Overview of reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of dosing	Doses (mg/kg/day)	Noteworthy findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development	Female rat (SD)	Oral gavage	Gestation days 6-17 (QD)	0,[a)] 30, 150, 400	**Dams:** **Mortality: 400 (1 of 33 animals)** **400: decreased defecation, pale feces, red vaginal discharge, rales, pale extremities, red material around the nose/on the forelimbs/around the mouth, decreased body weight gain, decreased food consumption** **Fetuses:** **400: reduced number of viable fetuses, reduced mean body weight, external malformations (localized edema or anasarca/skeletal malformations) and variations (pale/small spleen, skeletal variations/reduced ossification)**	**Maternal general toxicity: 150** **Embryo-fetal development: 150**	4.2.3.7.5-9

a) 0.1% Tween 80 and 280 mmol/L hydrochloric acid in deionized water

5.7.2 Toxicity studies on impurities

The drug substance contains 10 impurities (Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J) at a level exceeding the qualification threshold given in “Revision of the Guideline on Impurities in New Drug Substances (PFSB/ELD Notification No.1216001, dated December 16, 2002)." Since the amounts of these impurities administered in repeated-dose toxicity studies in dogs were higher than the levels of the impurities at the clinical dose of tenapanor in humans, it was concluded that these impurities had been evaluated based on the data from these toxicity studies. The genotoxic potential of these impurities was evaluated in accordance with “Revision of the Guideline on Impurities in New Drug Substances (PFSB/ELD Notification No.1216001, dated December 16, 2002)," etc., and the impurities were considered unlikely to have genotoxic potential.

5.R Outline of the review conducted by PMDA

PMDA's conclusion:

Based on the submitted data, a toxicological concern is unlikely to arise in the clinical use of tenapanor, provided that the package insert includes appropriate precautionary statements about the use of tenapanor in pregnant women, lactating women, and children.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted the main evaluation data, in the form of the results from Japanese phase II and phase III studies, in the present application. The proposed commercial formulation was used in Japanese phase III studies, and a formulation different from the proposed commercial formulation (film-coated tablets) was used in Japanese phase II studies. Dissolution testing demonstrated the bioequivalence between these two formulations.

Plasma and urine concentrations of tenapanor and plasma concentrations of its metabolite, M1, were determined by LC/MS/MS, and the LLOQ was 0.5 ng/mL for all. Sodium and phosphorus concentrations in stool were determined by inductively coupled plasma-optical emission spectrometry (ICP-OES). Doses are expressed in terms of tenapanor.

6.1.1 Food effect and gastric pH effect study (CTD 5.3.4.1.-1, Study D5611C00003 [Match to October 2013])

A randomized, open-label, crossover study (Part A, 3-treatment, 3-period; Part B, 2-treatment, 2-period) was conducted at 1 site overseas to evaluate the effects of food (Part A) and gastric pH (Part B) on the pharmacodynamics, safety, and pharmacokinetics of multiple oral doses of tenapanor in non-Japanese healthy volunteers (target sample size, 18 subjects/Part).

[Part A: Food effect]

Tenapanor 14 mg was to be administered orally twice daily, immediately prior to breakfast and dinner, after breakfast and dinner, or in a fasted state,[24] for 4 days. A washout period of 2 days was included between the periods.

All of 19 subjects who received tenapanor were included in the safety analysis set, and 18 subjects who completed the study were included in the pharmacodynamic analysis set.

Following 4-day administration of tenapanor, plasma concentrations of tenapanor were below the LLOQ in all subjects.

Table 24 shows daily stool sodium and phosphorus excretion and daily urinary sodium and phosphorus excretion[25] (pharmacodynamic measures) following 4-day administration of tenapanor immediately prior to meals, after meals, or in a fasted state. Urinary sodium and phosphorus excretion tended to be lower when tenapanor was given immediately prior to meals and after meals in comparison to when tenapanor was given in a fasted state, and stool sodium and phosphorus excretion was highest when tenapanor was given immediately prior to meals. Thus, tenapanor was to be given immediately prior to meals in Japanese phase II and phase III studies.

Table 24. Daily stool sodium and phosphorus excretion and daily urinary sodium and phosphorus excretion following administration of tenapanor

Analyte	Dosing condition of tenapanor	N	Stool excretion (mEq/day)	Urinary excretion (mmol/day)
Sodium	Immediately prior to meals	18	25.9 [19.5, 32.4]	127.1 [109.3, 144.9]
	Fed	18	17.2 [10.7, 23.6]	126.7 [108.9, 144.5]
	Fasted	18	14.1 [7.7, 20.6]	133.5 [115.7, 151.3]
Phosphorus	Immediately prior to meals	18	27.3 [24.0, 30.5]	21.4 [17.8, 25.0]
	Fed	18	25.6 [22.3, 28.9]	21.6 [18.0, 25.2]
	Fasted	18	22.3 [19.1, 25.6]	25.3 [21.7, 28.9]

Least squares mean [95% CI]

Regarding safety, the incidences of adverse events were 11.1% (2 of 18 subjects) after administration immediately prior to meals, 22.2% (4 of 18 subjects) after fed administration, and 21.1% (4 of 19 subjects) after fasted administration. The incidences of adverse drug reactions were 11.1% (2 of 18 subjects) after administration immediately prior to meals and 15.8% (3 of 19 subjects) after fasted administration. In any of the treatment groups, there were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

[Part B: Gastric pH effect]

Tenapanor 56 mg was to be administered orally twice daily, immediately prior to breakfast and dinner, for 4 days. A washout period of 5 days was included between the periods. Omeprazole 20 mg was to be administered

[24] In the morning, 1 hour before breakfast; At night, 3 hours after the start of intake of dinner and 1 hour before the next meal consumption (a late-night snack)

[25] Tenapanor inhibits NHE3 and reduces sodium and phosphate absorption from the gastrointestinal tract, resulting in increases in stool sodium and phosphate excretion and decreases in urinary sodium and phosphate excretion [see Sections 3.1.2.1 and 3.R.1]. Based on the above, as the pharmacodynamic measures of tenapanor, stool sodium and phosphorus excretion and urinary sodium and phosphorus excretion were assessed.

orally twice daily for 4 days, beginning from 5 days before the start of tenapanor. Omeprazole was to be administered immediately prior to breakfast and dinner before the start of tenapanor and 1 hour before administration of tenapanor after the start of tenapanor.

All of 17 subjects who received tenapanor were included in the safety and pharmacodynamic analysis sets.

Plasma concentrations of tenapanor following 4-day administration of tenapanor were all below the LLOQ, except for 1 time point in 1 subject.

Table 25 shows daily stool sodium and phosphorus excretion and daily urinary sodium and phosphorus excretion following 4-day administration of tenapanor with or without omeprazole. Stool sodium excretion was lower and urinary sodium excretion was higher when tenapanor was administered with omeprazole in comparison with when tenapanor was administered alone.

Table 25. Effects of omeprazole on daily stool sodium and phosphorus excretion and daily urinary sodium and phosphorus excretion after administration of tenapanor

Analyte	With or without omeprazole	N	Stool excretion (mEq/day)	Urinary excretion (mmol/day)
Sodium	Without omeprazole	17	39.3 [26.8, 51.9]	105.1 [85.0, 125.1]
	With omeprazole	16	25.3 [12.6, 38.1]	125.6 [105.3, 146.0]
Phosphorus	Without omeprazole	17	36.0 [27.6, 44.5]	19.2 [15.8, 22.6]
	With omeprazole	16	33.8 [25.2, 42.4]	19.9 [16.5, 23.4]

Least squares mean [95% CI]

Regarding safety, the incidences of adverse events were 82.4% (14 of 17 subjects) following administration of tenapanor alone and 56.3% (9 of 16 subjects) following administration of tenapanor with omeprazole, and the incidences of adverse drug reactions were 76.5% (13 of 17 subjects) following administration of tenapanor alone and 56.3% (9 of 16 subjects) following administration of tenapanor with omeprazole. In either period, there were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2 Clinical pharmacology

6.2.1 Phase I study in Japanese and non-Japanese healthy volunteers (CTD 5.3.3.1.-1, Study D5611C00005 [August to December 2013])

A placebo-controlled, randomized, double-blind study was conducted at 1 site overseas to assess the pharmacokinetics, pharmacodynamics, and safety of single and multiple doses of tenapanor in Japanese and non-Japanese healthy volunteers (target sample size, 83 subjects: 8 Japanese subjects in the single-dose cohort [2 in the placebo group and 6 in the tenapanor group], 15 Japanese subjects each in the multiple-dose cohorts [3 in the placebo group and 12 in the tenapanor group], 15 non-Japanese subjects in the multiple-dose cohort [3 in the placebo group and 12 in the tenapanor group]).

A single oral dose of placebo or tenapanor (168 mg) was to be administered immediately prior to breakfast, or placebo or tenapanor (14, 28, 56, or 84 mg)[26] was to be administered orally twice daily, immediately prior to breakfast and dinner, for 7 days.

All of 83 randomized subjects were included in the safety, pharmacokinetic, and pharmacodynamic analysis sets.

Plasma concentrations of tenapanor were all below the LLOQ, except for 3 samples. Table 26 shows the plasma pharmacokinetic parameters of M1. The C_{max} and $AUC_{0\text{-}t}$ of M1 generally increased dose-proportionally. The C_{max} and $AUC_{0\text{-}8\ h}$ of M1 tended to be higher on Day 7 than on Day 1 at all dose levels. The C_{max} and $AUC_{0\text{-}t}$ of M1 following 7-day oral administration of tenapanor 84 mg BID were comparable for Japanese and non-Japanese subjects.

Table 26. Pharmacokinetic parameters of M1 following single or multiple oral doses of tenapanor

Race	Regimen	Dose of tenapanor	Sampling time point (Day)	N	C_{max} (ng/mL)	t_{max} a) (h)	$AUC_{0\text{-}t}$ b) (ng·h/mL)
Japanese	Single dose	168 mg	－	6	21.4 ± 10.2	8.0 (8.0, 24.0)	335 ± 176
	Multiple doses	14 mg	1	12	1.88 ± 1.77	8.0 (4.0, 8.0)	9.75 ± 11.6 c)
			7	12	11.0 ± 4.04	4.0 (0, 8.0)	75.0 ± 26.1
		28 mg	1	12	2.73 ± 1.12	8.0 (8.0, 8.0)	10.7 ± 4.06
			7	12	13.8 ± 2.88	4.1 (0, 8.0)	98.0 ± 21.2
		56 mg	1	12	7.99 ± 2.82	8.0 (8.0, 8.1)	31.4 ± 14.1
			7	12	40.6 ± 22.9	4.0 (0, 8.0)	293 ± 167
		84 mg	1	12	11.2 ± 6.00	8.0 (8.0, 8.0)	47.1 ± 34.0
			7	12	52.7 ± 20.8	4.0 (0, 8.0)	364 ± 127
Non-Japanese		84 mg	1	12	9.48 ± 4.26	8.0 (8.0, 8.2)	36.8 ± 17.8
			7	12	52.1 ± 16.9	8.0 (0, 8.1)	340 ± 110

Mean ± SD; －, Not applicable
a) Median (Min., Max.)
b) $AUC_{0\text{-}24\ h}$ for single-dose cohort, $AUC_{0\text{-}8\ h}$ for multiple-dose cohorts
c) N = 9

Table 27 shows daily fecal sodium and phosphorus excretion and daily urinary sodium and phosphorus excretion during the tenapanor treatment period. After administration of tenapanor compared to placebo, fecal sodium and phosphorus excretion was higher, and urinary sodium and phosphorus excretion was lower. A clear dose-response relationship was not observed for any of the pharmacodynamic measures.

[26] Tenapanor 84 mg was administered to non-Japanese subjects.

Table 27. Fecal sodium and phosphorus excretion and urinary sodium and phosphorus excretion following administration of tenapanor

Analyte	Race	Treatment group	Dose of tenapanor	N	Fecal excretion (mEq/day)	Urinary excretion (mmol/day[a] or mg/day[b])
Sodium	Japanese	Placebo	－	14	4.1 ± 3.1 [c]	142.6 ± 41.2
		Tenapanor single dose	168 mg	6	41.9 ± 25.5	110.4 ± 49.3
		Tenapanor multiple doses	14 mg	12	21.3 ± 17.8	104.8 ± 17.9
			28 mg	12	32.2 ± 16.8	111.5 ± 30.7
			56 mg	12	28.4 ± 23.4	105.3 ± 33.1
			84 mg	12	30.8 ± 15.6	101.2 ± 32.0
	Non-Japanese	Placebo	－	3	3.1 ± 3.7	80.0 ± 22.3
		Tenapanor multiple doses	84 mg	12	17.2 ± 10.8	76.6 ± 35.6
Phosphorus	Japanese	Placebo	－	14	16.8 ± 7.9 [c]	790.1 ± 265.7
		Tenapanor single dose	168 mg	6	31.0 ± 11.5	577.9 ± 137.7
		Tenapanor multiple doses	14 mg	12	21.5 ± 6.5	543.2 ± 136.7
			28 mg	12	23.4 ± 7.0	599.7 ± 109.5
			56 mg	12	17.6 ± 7.5	480.3 ± 122.1
			84 mg	12	24.8 ± 8.6	473.1 ± 137.9
	Non-Japanese	Placebo	－	3	14.8 ± 5.3	677.8 ± 49.6
		Tenapanor multiple doses	84 mg	12	18.8 ± 9.5	500.1 ± 109.2

Mean ± SD, －, Not applicable
a) Sodium, b) Phosphorus
c) N = 13

Regarding safety, the incidences of adverse events among Japanese subjects were 21.4% (3 of 14 subjects) in the placebo group, 16.7% (1 of 6 subjects) in the 168 mg single-dose group, 16.7% (2 of 12 subjects) in the 14 mg multiple-dose group, 16.7% (2 of 12 subjects) in the 56 mg multiple-dose group, and 25.0% (3 of 12 subjects) in the 84 mg multiple-dose group. The incidences of adverse events among non-Japanese subjects were 33.3% (1 of 3 subjects) in the placebo group and 33.3% (4 of 12 subjects) in the 84 mg multiple-dose group. The incidences of adverse drug reactions among Japanese subjects were 14.3% (2 of 14 subjects) in the placebo group, 8.3% (1 of 12 subjects) in the 56 mg multiple-dose group, and 8.3% (1 of 12 subjects) in the 84 mg multiple-dose group. The incidences of adverse drug reactions among non-Japanese subjects were 33.3% (1 of 3 subjects) in the placebo group and 33.3% (4 of 12 subjects) in the 84 mg multiple-dose group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2 Phase I study (dose regimen study) (CTD 5.3.3.1.-2, Study RDX5791-102 [July to October 2011])

A placebo-controlled, randomized, double-blind study was conducted at 1 site overseas to evaluate the pharmacodynamics and safety of different multiple-dose regimens of tenapanor in non-Japanese healthy volunteers (target sample size, 15 subjects/cohort [3 in the placebo group and 12 in the tenapanor group]).

As shown in Table 28, placebo or tenapanor was to be administered orally immediately before meals, for 7 days.

All of 105 randomized subjects were included in the safety and pharmacodynamic analysis sets.

Table 28 shows the changes from baseline in daily stool and urinary sodium excretion on Day 8. Although twice-daily or thrice-daily dosing showed greater pharmacodynamic effects than once-daily dosing, pharmacodynamic differences between twice-daily and thrice-daily dosing appeared minimal.

Table 28. Dose regimens in different cohorts and changes from baseline in daily stool and urinary sodium excretion on Day 8

Cohort	Tenapanor dose regimen		Change in stool sodium excretion (mEq/day)	Change in urinary sodium excretion (mEq/day)
Placebo	—	N	11 [a)]	21 [b)]
		Change	0.4 ± 3.2	-29.8 ± 47.6
1	28 mg BID	N	8	12
		Change	25.2 ± 16.6	-81.3 ± 26.4
2	28 mg TID	N	10	12
		Change	32.2 ± 22.2	-104.5 ± 38.2
3	56 mg BID	N	6	10
		Change	46.6 ± 36.4	-53.2 ± 27.0
4	14 mg BID	N	8	12
		Change	29.8 ± 22.4	-43.3 ± 48.2
5	28 mg QD	N	8	12
		Change	7.2 ± 3.6	-5.4 ± 53.4
6	Escalating BID dose[c)]	N	9	12
		Change	31.7 ± 12.9	-48.7 ± 32.1
7	28 mg BID (with psyllium[d)])	N	9	12
		Change	27.6 ± 15.4	-3.2 ± 45.3

Mean ± SD; —, Not applicable

a) Including 2 subjects who received placebo and psyllium.

b) Including 3 subjects who received placebo and psyllium.

c) Subjects were to start with tenapanor 14 mg BID. The dose was to be escalated to tenapanor 28 mg BID on Day 3 and to 42 mg BID on Day 5 in subjects with a BSFS score of <6. The dose was escalated to 28 mg BID in 5 of 12 subjects.

d) Psyllium 6.8 g was administered in the evening on Day −3 (3 days before the first dose of tenapanor) and twice daily from Day −2 to Day 7.

Regarding safety, the incidences of adverse events were 38.1% (8 of 21 subjects) in the placebo group, 33.3% (4 of 12 subjects) in the tenapanor group of Cohort 2, 50.0% (6 of 12 subjects) in the tenapanor group of Cohort 3, 33.3% (4 of 12 subjects) in the tenapanor group of Cohort 4, 33.3% (4 of 12 subjects) in the tenapanor group of Cohort 5, 50.0% (6 of 12 subjects) in the tenapanor group of Cohort 6, and 50.0% (6 of 12 subjects) in the tenapanor group of Cohort 7. The incidences of adverse drug reactions were 28.6% (6 of 21 subjects) in the placebo group, 16.7% (2 of 12 subjects) in the tenapanor group of Cohort 2, 41.7% (5 of 12 subjects) in the tenapanor group of Cohort 3, 8.3% (1 of 12 subjects) in the tenapanor group of Cohort 4, 16.7% (2 of 12 subjects) in the tenapanor group of Cohort 5, 25.0% (3 of 12 subjects) in the tenapanor group of Cohort 6, and 50.0% (6 of 12 subjects) in the tenapanor group of Cohort 7. Adverse events leading to treatment discontinuation occurred in 16.7% (2 of 12) of subjects treated with tenapanor in Cohort 3 (abdominal pain [2 subjects]; and nausea; and proctalgia [1 subject each] [some patients had more than 1 event]), and all those events were classified as adverse drug reactions, with an outcome of "resolved." There were no deaths or serious adverse events.

6.2.3 Phase I study (mass balance study) (CTD 5.3.3.1.-3, Study D5611C00007 [April to May 2014])

An open-label study was conducted at 1 site overseas to characterize the mass balance etc. of a single oral dose of [^{14}C]-tenapanor in non-Japanese healthy male volunteers (target sample size, 8 subjects).

A single oral dose of [^{14}C]-tenapanor 15.2 mg was to be administered under fasting conditions.

All of 8 subjects enrolled in the study were included in the pharmacokinetic analysis set.

The $AUC_{0\text{-}t}$ values of radioactivity (geometric mean [geometric coefficient of variation (%)]) in plasma and whole blood were 1,040 nmol EQ·h/L (39.6) and 5,240 nmol EQ·h/L (47.7), respectively, and the C_{max} values of radioactivity in plasma and whole blood were 41.4 nmol EQ/L (45.6) and 74.5 nmol EQ/L (43.6), respectively. These values were higher in whole blood than in plasma.

In plasma samples collected up to 24 hours post-dose, M1, M2, M11, M12, and M15 were detected as metabolites and accounted for 16%, 7.6%, 5.0%, 5.1%, and 4.1% of the total radioactivity in plasma, respectively.

Over 240 hours, 8.99% and 79.3% of the administered radioactivity were recovered in urine and feces, respectively. In pooled urine collected through 144 hours post-dose, M1, M14, M11, M7, M12, M15, and M13 were detected as metabolites and accounted for 1.49%, 0.70%, 0.62%, 0.60%, 0.55%, 0.55%, and 0.3% of the administered radioactivity, respectively. In pooled feces collected through 144 hours post-dose, unchanged tenapanor was mainly detected (65.3% of the administered radioactivity), and M16 (2.4% of the administered radioactivity) was the most abundant metabolite.

6.2.4 Japanese phase II study in patients with hyperphosphatemia on HD (CTD 5.3.5.1-1, Study 7791-001 [March to December 2019])

Following multiple oral administration of tenapanor in patients with hyperphosphatemia on HD, plasma concentrations of M1 were determined.

Placebo or tenapanor 5, 10, or 30 mg was to be administered orally twice daily, immediately prior to meals (the placebo, 5 mg, 10 mg, and 30 mg groups). In the 30 mg down-titration group, subjects were to start at tenapanor 30 mg BID orally administered immediately prior to meals and could be down-titrated in a stepwise fashion up to 3 times to 20 mg, 10 mg, and 5 mg BID, at the investigator's discretion, if study drug-related gastrointestinal symptoms occurred. Once down-titrated, the dose could not be increased. The treatment period was 6 weeks.

For a brief description of the study and the efficacy and safety results, see Section 7.1.1.

Regarding pharmacokinetics, the mean plasma M1 concentrations at Weeks 1, 4, and 6[27)] are shown in Table 29. Plasma concentrations of M1 generally increased dose-proportionally. There was no evidence of clear accumulation after multiple dosing.

[27)] Predialysis plasma M1 concentrations

Table 29. Plasma M1 concentrations following multiple oral administration of tenapanor (ng/mL)

Dose of tenapanor	Week	1	4	6
5 mg[a)]	N	42	36	37
	M1 concentration	3.98 ± 2.62	4.01 ± 2.35	4.02 ± 2.42
10 mg	N	37	34	31
	M1 concentration	7.77 ± 4.08	8.92 ± 4.57	8.35 ± 4.48
30 mg	N	38	31	29
	M1 concentration	15.9 ± 6.6	15.4 ± 6.1	15.8 ± 5.6
30 mg down-titration[b)]	N	40	34	34
	M1 concentration	21.1 ± 8.5	18.5 ± 9.0	17.8 ± 9.1

Mean ± SD

a) Including 1 patient who received incorrect study drug for 7 days in Week 1.

b) The final doses of tenapanor were 30, 20, 10, and 5 mg in 25 subjects, 4 subjects, 5 subjects, and 1 subject, respectively.

6.2.5 Phase I study (effect of hepatic impairment) (CTD 5.3.3.3.-1, Study TEN-01-107 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 3 sites overseas to assess the effect of hepatic impairment on the pharmacokinetics of tenapanor in non-Japanese subjects with normal haptic function or moderate hepatic impairment (Child-Pugh class B) (target sample size, 20 in the normal hepatic function group, 10 in the moderate hepatic impairment group).[28)]

A single oral dose of tenapanor 100 mg was to be administered under fasting conditions.

All of 20 subjects who were enrolled in the study and received study drug (10 subjects with normal hepatic function and 10 subjects with moderate hepatic impairment) were included in the pharmacokinetic and safety analysis sets.

Plasma tenapanor was detected in 3 of 10 subjects with normal hepatic function (the concentrations were 0.52-1.09 ng/mL) and 6 of 10 subjects with moderate hepatic impairment (the concentrations were 0.51-3.41 ng/mL). With respect to the plasma pharmacokinetic parameters of M1, the geometric least squares mean ratios of the C_{max} and $AUC_{0\text{-}inf}$ for moderate hepatic impairment vs. normal hepatic function [90% CI] were 0.67 [0.44, 1.03] and 0.73 [0.45, 1.17], respectively. The applicant explained that due to the lack of pharmacological activity of M1 and its systemic exposure decreased by hepatic impairment, moderate hepatic impairment is unlikely to cause clinically relevant effects.

Regarding safety, the incidences of adverse events were 30.0% (3 of 10 subjects) in the normal hepatic function group and 30.0% (3 of 10 subjects) in the moderate hepatic impairment group. The incidences of adverse drug reactions were 20.0% (2 of 10 subjects) in the normal hepatic function group and 10.0% (1 of 10 subjects) in the moderate hepatic impairment group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

[28)] Subjects with mild hepatic impairment were not enrolled in the study because mild hepatic impairment was unlikely to cause clinically relevant effects based on the results from subjects with moderate hepatic impairment.

6.2.6 Phase I study (drug-drug interaction study with midazolam and cefadroxil) (CTD 5.3.3.4.-3, Study TEN-01-103 [[redacted] to [redacted] 20[redacted]])

In vitro studies suggested that M1 induces and inhibits CYP3A4 [see Sections 4.5.1 and 4.5.2]. Although tenapanor does not directly inhibit a proton-coupled intestinal transporter, PEPT1 [see Section 4.5.4], inhibition of NHE3 in the gastrointestinal tract can lead to indirect inhibition of PEPT1 by reducing the proton concentration in the lumen of the gastrointestinal tract. Thus, a study was conducted to evaluate the effect of tenapanor on the pharmacokinetics of midazolam (a CYP3A4 substrate) and cefadroxil (a PEPT1 substrate) in non-Japanese healthy volunteers (target sample size, 28 subjects).

Table 30 shows the geometric mean ratios of the C_{max} and $AUC_{0\text{-}inf}$ of midazolam and cefadroxil for with vs. without concomitant tenapanor. The applicant explained that tenapanor is unlikely to cause clinically relevant effects on the pharmacokinetics of a substrate of CYP3A4 or PEPT1.

Table 30. Geometric mean ratios of plasma pharmacokinetic parameters of midazolam or cefadroxil for with vs. without concomitant tenapanor[a)]

Tenapanor (oral administration)	Coadministered drug (oral administration)[b)]	N	C_{max}	$AUC_{0\text{-}inf}$
50 mg twice daily	Midazolam 7.5 mg	28	0.88 [0.76, 1.01]	1.17 [1.09, 1.25]
	Cefadroxil 500 mg	28	0.98 [0.92, 1.04]	0.91 [0.87, 0.95]

Geometric mean ratio [90% CI]

a) Midazolam or cefadroxil + tenapanor/midazolam or cefadroxil alone

b) Subjects received a single dose of cefadroxil 500 mg on Day 1, a single dose of midazolam 7.5 mg on Day 2, and tenapanor 50 mg BID on Days 3-16 with a single dose of cefadroxil 500 mg in the morning on Day 15 and a single dose of midazolam 7.5 mg in the morning on Day 16.

6.2.7 Phase I study (drug-drug interaction study with enalapril, digoxin, and warfarin) (CTD 5.3.3.4.-4, Study TEN-02-108 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A study was conducted to evaluate the effect of tenapanor on the pharmacokinetics of a substrate of OATP2B1, enalapril and a substrate of P-gp, digoxin (Cohort 1) and a substrate of CYP2C9, warfarin (Cohort 2) in non-Japanese healthy volunteers (target sample size, 38 subjects: 24 each in the enalapril and digoxin groups, 14 in the warfarin group).

Table 31 shows the geometric mean ratios of the C_{max} and AUC of enalapril and enalaprilat (its active metabolite) and digoxin for with vs. without concomitant tenapanor 30 mg. Tenapanor reduced the C_{max} and $AUC_{0\text{-}inf}$ of enalapril and enalaprilat. Concomitant administration of tenapanor did not affect the C_{max} and $AUC_{0\text{-}72\ h}$ of digoxin.

Table 31. Geometric mean ratios of plasma pharmacokinetic parameters of enalapril, enalaprilat, and digoxin for with vs. without concomitant tenapanor[a)]

Tenapanor (oral administration)	Coadministered drug (oral administration)[b)]	N	Analyte	C_{max}	$AUC_{0\text{-}inf}$
30 mg twice daily	Enalapril 20 mg	25	Enalapril	0.31 [0.27, 0.35]	0.39 [c)] [0.34, 0.44]
		25	Enalaprilat	0.32 [0.28, 0.37]	0.50 [0.46, 0.54]
	Digoxin 0.25 mg	25	Digoxin	0.87 [0.81, 0.94]	0.90 [d)] [0.85, 0.96]

Geometric mean ratio [90% CI]
a) Enalapril or digoxin + tenapanor/enalapril or digoxin alone
b) Subjects received a single dose of enalapril 20 mg on Day 1, a single dose of digoxin 0.25 mg on Day 5, and tenapanor 30 mg BID on Days 18-28 with a single dose of enalapril 20 mg in the morning on Day 22 and a single dose of digoxin 0.25 mg in the morning on Day 26.
c) Geometric mean ratio [90% CI] (N = 17)
d) Geometric mean ratio of $AUC_{0\text{-}72\,h}$ [90% CI] (N = 19)

Table 32 shows the geometric mean ratios of the C_{max} and $AUC_{0\text{-}inf}$ of *S*-warfarin for with vs. without concomitant tenapanor. Concomitant administration of tenapanor did not affect the C_{max} and $AUC_{0\text{-}inf}$ of *S*-warfarin.

Table 32. Geometric mean ratios of plasma pharmacokinetic parameters of *S*-warfarin for with vs. without concomitant tenapanor[a)]

Tenapanor (oral administration)	Coadministered drug (oral administration)	N	C_{max}	$AUC_{0\text{-}inf}$ [c)]
30 mg twice daily	Warfarin 10 mg [b)]	14	1.01 [0.88, 1.17]	1.11 [1.06, 1.17]

Geometric mean ratio [90% CI]
a) Warfarin + tenapanor/warfarin alone
b) Subjects received a single dose of warfarin 10 mg on Day 1 and tenapanor 30 mg BID on Days 18-28 with a single dose of warfarin 10 mg in the morning on Day 22.
c) Geometric mean ratio [90% CI] (N = 13)

6.2.8 Phase I study (drug-drug interaction study with itraconazole) (CTD 5.3.3.4.-5, Study TEN-01-104 [[redacted] to [redacted] 20[redacted]])

Since an *in vitro* study suggested that tenapanor is a substrate of CYP3A [see Section 4.3.2], a study was conducted to evaluate the effect of a CYP3A inhibitor, itraconazole, on the pharmacokinetics of tenapanor in non-Japanese healthy volunteers (target sample size, 14 subjects).

Following administration of tenapanor (50 mg) alone or with itraconazole (200 mg), plasma tenapanor was detected in 3 of 14 subjects (the concentrations were 0.52-0.66 ng/mL) or 7 of 14 subjects (the concentrations were 0.51-1.3 ng/mL), respectively.

Table 33 shows the geometric mean ratios of the C_{max} and $AUC_{0\text{-}inf}$ of M1 for tenapanor + itraconazole vs. tenapanor alone. Coadministration with itraconazole decreased the C_{max} and $AUC_{0\text{-}inf}$ of M1. The applicant explained that due to the lack of pharmacologic activity of M1 and its systemic exposure decreased by a CYP3A inhibitor, coadministration with a potent CYP3A inhibitor is unlikely to cause clinically relevant effects.

Table 33. Geometric mean ratios of plasma pharmacokinetic parameters of M1 for tenapanor + itraconazole vs. tenapanor alone[a)]

Tenapanor dose	Coadministered drug (oral administration)	N	C_{max}	$AUC_{0\text{-}inf}$
50 mg	Itraconazole[b)]	10	0.53 [0.44, 0.65]	0.58 [c)] [0.36, 0.94]

Geometric mean ratio [90% CI]

a) C_{max} or $AUC_{0\text{-}t}$ with itraconazole/C_{max} or $AUC_{0\text{-}t}$ without itraconazole

b) Subjects received a single dose of tenapanor 50 mg on Day 1, itraconazole 200 mg BID on Day 3, and itraconazole 200 mg QD on Days 4-7 with a single dose of tenapanor 50 mg on Day 6.

c) N = 3

6.2.9 Phase I study (drug-drug interaction study with sevelamer carbonate) (CTD 5.3.4.1.-2, Study D5611C00006 [March to May 2013])

Since an *in vitro* study suggested a binding interaction between tenapanor and sevelamer carbonate [see Section 4.5.5], a randomized, open-label, 2-treatment, 2-period, crossover study was conducted to evaluate the effect of sevelamer carbonate on the pharmacokinetics and pharmacodynamics of tenapanor in non-Japanese healthy volunteers (target sample size, 16 subjects).

Tenapanor 14 mg was to be administered orally twice daily, immediately prior to breakfast and dinner, on Days 1 to 4 or on Days 7 to 10. Sevelamer carbonate 800 mg was to be administered orally three times daily, before meals, on Days 1 to 4 or on Days 7 to 10.

Plasma tenapanor concentrations were below the LLOQ in all samples.

Table 34 shows daily stool sodium and phosphorus excretion following 4-day administration of tenapanor. Coadministration with sevelamer carbonate did not affect stool sodium and phosphorus excretion.

Table 34. Effect of sevelamer carbonate on daily stool sodium and phosphorus excretion after administration of tenapanor

Analyte	With or without sevelamer carbonate	N	Excretion (mEq/day)
Sodium	Without sevelamer carbonate	16	29.2 ± 19.3
	With sevelamer carbonate	16	25.7 ± 17.9
Phosphorus	Without sevelamer carbonate	16	37.4 ± 11.4
	With sevelamer carbonate	16	37.7 ± 7.5

Mean ± SD

6.2.10 Concentration-response analysis for QT/QTc interval (CTD 5.3.3.1.-1)

Based on the data from a phase I study in Japanese and non-Japanese healthy volunteers (Study D5611C00005), a concentration-response analysis was performed using a linear mixed-effects model. Although ΔΔQTcF tended to increase with increasing plasma concentration of M1, the major metabolite of tenapanor, the upper bound of the 90% confidence interval for the model-based ΔΔQTcF (7.68 ms in Japanese subjects, 7.34 ms in non-Japanese subjects) at the geometric mean C_{max} of M1 (51.4 ng/mL in Japanese subjects, 49.7 ng/mL in non-Japanese subjects) following oral administration of tenapanor 84 mg BID, which is higher than the maximum clinical dose (30 mg BID), was below 10 ms.

Based on the above, the applicant explained that the risk of QT/QTc interval prolongation is low at the proposed dosing regimen of tenapanor.

6.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that enalapril should be coadministered with caution, and that evaluation from a clinical pharmacology standpoint is appropriate for the clinical use of tenapanor.

6.R.1 Interactions with drugs that increase gastric pH

The applicant's explanation:

Daily stool sodium excretion was lower and daily urinary sodium excretion was higher when the tenapanor free base tablets were administered with omeprazole in comparison with when the tenapanor free base tablets were administered alone [see Section 6.1.1], suggesting that coadministration with omeprazole reduces the pharmacodynamic effects of tenapanor. The reason for this result may be the influence of a change in gastric pH on the dissolution of tenapanor from the tablet. In Part B of this study, the tenapanor free base tablets were used. While tenapanor was rapidly dissolved from the tablet in an acidic medium (0.1 mol/L hydrochloric acid), the dissolution rate tended to be slower in a fed state simulated intestinal fluid with a higher pH (FeSSIF, pH 5.0). On the other hand, tenapanor was rapidly dissolved from the proposed commercial formulation also in a pH 4.0 medium (a citrate buffer), and this formulation is unlikely to be influenced by drugs that increase gastric pH. In the tenapanor groups of Japanese phase III studies (Studies 004 and 005), the efficacy of tenapanor with concomitant anti-peptic ulcer drugs including proton pump inhibitors was compared with the efficacy of tenapanor without concomitant anti-peptic ulcer drugs. There were no marked differences in the change from baseline in serum phosphorus, and similar reductions in serum phosphorus were achieved. In the tenapanor groups of Japanese phase III studies (Studies 004 and 005), there were no marked differences in the incidences of all adverse events including diarrhea, the most commonly reported adverse event associated with tenapanor, between subjects with and without concomitant anti-peptic ulcer drugs. Thus, drugs that increase gastric pH are unlikely to affect the efficacy and safety of tenapanor. Based on the above, there is no particular problem with coadministration with drugs that increase gastric pH, and there is no need to include a relevant precautionary statement in the package insert.

PMDA's view:

Tenapanor dissolution from the proposed commercial formulation is unlikely to be influenced by gastric pH. There were no major differences in the change from baseline in serum phosphorus and the incidence of adverse events between subjects with and without concomitant anti-peptic ulcer drugs in Japanese phase III studies. Given these findings etc., the applicant's decision not to include a precautionary statement about coadministration with drugs that increase gastric pH in the package insert, is appropriate.

6.R.2 Coadministration with CYP3A inducers

The applicant's explanation:

Tenapanor is metabolized primarily by CYP3A to form the major metabolite M1. A positive relationship between the plasma M1 concentration and ΔΔQTcF has been found [see Section 6.2.10]. Effects on the pharmacokinetics of tenapanor and M1 were assessed to address the potential for drug-drug interaction.

Coadministration with a potent CYP3A inhibitor did not significantly affect the plasma concentration of unchanged tenapanor, but decreased M1 exposure [see Section 6.2.8]. Thus, coadministration with CYP3A inducers may increase M1 exposure. The effect of a CYP3A inducer on the pharmacokinetics of tenapanor and M1 was not evaluated. However, for the following reasons, coadministration with CYP3A inducers is unlikely to cause clinically relevant effects on the pharmacokinetics of tenapanor and M1, and there is no need to include a precautionary statement about coadministration with CYP3A inducers in the package insert.

● There are pathways to metabolize tenapanor to not only M1 but also other metabolites, and a pathway to further metabolize and eliminate M1 has been suggested.[23)]

● Table 35 shows plasma M1 concentrations[29)] at Weeks 1, 4, and 6 in patients receiving tenapanor with potent CYP3A inducers[30)] in a Japanese phase II study (Study 001). M1 concentrations in 2 patients receiving concomitant carbamazepine were lower than the mean M1 concentrations in patients without concomitant carbamazepine in their respective dose groups, and M1 concentration in 1 patient receiving concomitant phenytoin was similar to the mean M1 concentration in patients without concomitant phenytoin in the tenapanor 10 mg group.

Table 35. Plasma M1 concentrations following multiple dose administration of tenapanor (ng/mL)

Dose of tenapanor	Concomitant drug	Week 1	Week 4	Week 6
5 mg	None[a)]	4.03 ± 2.63 (N = 41)	4.09 ± 2.34 (N = 35)	4.08 ± 2.43 (N = 36)
	Carbamazepine	2.00	1.16	1.81
10 mg	None[a)]	7.89 ± 4.13 (N = 35)	9.04 ± 4.68 (N = 32)	8.54 ± 4.55 (N = 29)
	Carbamazepine	3.70	5.70	3.64
	Phenytoin	7.85	8.13	7.49

Individual value for N = 1
a) Mean ± SD (N)

● All of patients receiving tenapanor with potent CYP3A inducers[30)] in Japanese phase II studies (Studies 001 and 003) had been taking potent CYP3A inducers from before enrollment in the clinical study until the end of the clinical study, but no adverse drug reaction of QT/QTc interval prolongation was reported. In Japanese phase III studies (Studies 004, 005, 006, and 007), 43 of 82 subjects, 50 of 84 subjects, 31 of 54 subjects, and 136 of 212 subjects received tenapanor with CYP3A inducers,[31)] respectively, and there were no marked differences in the incidence of adverse events including diarrhea and cardiac adverse events between subjects with and without concomitant CYP3A inducers.

● Tenapanor 50 mg BID has been approved for the treatment of irritable bowel syndrome with constipation in the US and Canada (brand name: Ibsrela). According to the post-marketing surveillance programs of Ibsrela, among 404 patients with adverse events reported by [redacted], 20[redacted], 17 were using concomitant CYP3A inducers,[31)] but no cardiac adverse events including QT/QTc interval prolongation and proarrhythmia were reported.

[29)] Predialysis plasma M1 concentrations

[30)] Patients receiving tenapanor with potent CYP3A inducers (apalutamide, carbamazepine, enzalutamide, phenytoin, mitotane, rifampicin) in clinical studies in patients with hyperphosphatemia were identified. Three patients with hyperphosphatemia (1 in the 5 mg group, 2 in the 10 mg group) in Study 7791-001 (a Japanese phase II study) and 1 patient with hyperphosphatemia (the 30 mg down-titration group) in Study 7791-003 (a Japanese phase II study) used concomitant potent CYP3A inducers.

[31)] CYP3A inducers contained in DRUGBANK Online (Drug Categories, https://go.drugbank.com/categories)

PMDA's view:

Despite the fact that tenapanor is metabolized primarily by CYP3A to form the major metabolite M1, no drug interaction study of tenapanor with CYP3A inducers was conducted. Though evaluation has limitations due to the limited number of subjects with concomitant CYP3A inducers in Japanese phase II studies (Studies 001 and 003), the plasma M1 concentrations were similar between subjects with and without concomitant CYP3A inducers. There were no major differences in adverse events between subjects with and without concomitant CYP3A inducers in Japanese clinical studies. Outside Japan, though for a different indication (irritable bowel syndrome with constipation), tenapanor has been approved for a higher dosing regimen (50 mg twice daily) than proposed in Japan. At present, post-marketing safety information has raised no concern warranting a labeling change to include a precautionary statement about coadministration with CYP inducers. Given these points etc., the applicant's decision not to include a precautionary statement about coadministration with CYP3A inducers in the package insert, is appropriate.

6.R.3 Coadministration with P-gp inhibitors

The applicant's explanation:

A positive relationship between the plasma M1 concentration and ΔΔQTcF has been found [see Section 6.2.10]. Effects on the pharmacokinetics of tenapanor and M1 were assessed to address the potential for drug-drug interaction. Since the major metabolite, M1 is considered a substrate of P-gp [see Section 4.5.3], coadministration with P-gp inhibitors may increase M1 exposure by inhibiting P-gp-mediated efflux of M1 from the gastrointestinal epithelial cells or from the tubular epithelial cells. The effect of a P-gp inhibitor on the pharmacokinetics of tenapanor and M1 was not evaluated. However, for the following reasons, coadministration with P-gp inhibitors is unlikely to cause clinically relevant effects on the pharmacokinetics of tenapanor and M1, and there is no need to include a precautionary statement about coadministration with P-gp inhibitors in the package insert.

● Multiple pathways for the clearance of M1 have been suggested: renal excretion and metabolism in the body.[23)]

● In Japanese phase III studies (Studies 004, 005, 006, and 007), 58 of 82 subjects, 61 of 84 subjects, 42 of 54 subjects, and 158 of 212 subjects received tenapanor with P-gp inhibitors,[32)] respectively, and there were no marked differences in the incidences of adverse events including diarrhea and cardiac adverse events between subjects with and without concomitant P-gp inhibitors.

● Tenapanor 50 mg BID has been approved for the treatment of irritable bowel syndrome with constipation in the US and Canada. Among 404 patients with adverse events reported between the approval in 2019 and [redacted], 20[redacted], 40 were using concomitant P-gp inhibitors,[32)] but no cardiac adverse events including QT/QTc interval prolongation and proarrhythmia were reported.

PMDA's view:

Despite the fact that the major metabolite of tenapanor, M1 was considered a substrate of P-gp, no drug interaction study of tenapanor with P-gp inhibitors was conducted. Multiple pathways for the clearance of M1

[32)] P-gp inhibitors contained in DRUGBANK Online (Drug Categories, https://go.drugbank.com/categories)

have been suggested. There were no major differences in adverse events between subjects with and without concomitant P-gp inhibitors in Japanese clinical studies. Outside Japan, though for a different indication, tenapanor has been approved for a higher dosing regimen (50 mg twice daily) than proposed in Japan. At present, post-marketing safety information has raised no concern warranting a labeling change to include a precautionary statement about coadministration with P-gp inhibitors. Given these points etc., the applicant's decision not to include a precautionary statement about coadministration with P-gp inhibitors in the package insert, is appropriate.

6.R.4 Interactions with enalapril

The applicant's explanation:

An *in vitro* study suggested that tenapanor inhibits OATP2B1 activity [see Section 4.5.4]. In a foreign phase I study (Study TEN-02-108), concomitant administration of tenapanor reduced the exposure of enalapril and its active metabolite, enalaprilat [see Section 6.2.7]. An *in vitro* study using HEK293 cells expressing OATP2B1 showed that enalapril is transported by OATP2B1, and tenapanor is unlikely to impact the pharmacokinetics of enalapril and enalaprilat via transporters other than OATP2B1 or metabolizing enzymes. Thus, tenapanor may inhibit OATP2B1-mediated gastrointestinal absorption of drugs. Although there are no substrate drugs that have clearly been demonstrated to be absorbed via OATP2B1 into the gastrointestinal tract in clinical use at present, the possibility that tenapanor decreases enalapril exposure by inhibiting OATP2B1 and reduces its therapeutic effect cannot be ruled out.

Based on the above, the package insert should advise that enalapril should be coadministered with caution.

PMDA's view:

The effect of tenapanor on the pharmacokinetics of enalapril and enalaprilat has been discussed appropriately, and a relevant precautionary statement has been included in the package insert accordingly.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from 3 Japanese phase II studies and 4 Japanese phase III studies (Table 36). Doses are expressed in terms of tenapanor.

Table 36. Overview of efficacy and safety evaluation data

Study Number	Study design	Study population	Group: Number of subjects	Treatment duration	Primary efficacy endpoint
7791-001	Phase II placebo-controlled double-blind randomized parallel-group	HD patients (Monotherapy)	5 mg/day: 42 10 mg/day: 41 30 mg/day: 42 30 mg down-titration: 41 Placebo: 41	6 weeks	Change from baseline in serum phosphorus at Week 6
7791-002	Phase II placebo-controlled double-blind randomized parallel-group	HD patients (Add-on therapy to phosphate binders)	Tenapanor: 23 (30 mg down-titration) Placebo: 24	6 weeks	Change from baseline in serum phosphorus at Week 6
7791-003	Phase II open-label uncontrolled	HD patients (Switching from phosphate binders)	Tenapanor: 67 (30 mg down-titration, the dose could be up-titrated within 5-30 mg/day from Week 9 onward)	26 weeks	Proportion of subjects who achieved a ≥30% reduction in the total number of phosphate binder and tenapanor tablets prescribed daily based on an average calculated for the 3 most recent time points after Week 9 compared with the number of prescribed phosphate binder tablets per day at baseline
7791-004	Phase III placebo-controlled double-blind randomized parallel-group	HD patients (Monotherapy)	Tenapanor: 82 (Starting dose of 5 mg/day, titrated within 5-30 mg/day) Placebo: 82	8 weeks	Change from baseline in serum phosphorus at Week 8
7791-005	Phase III placebo-controlled double-blind randomized parallel-group	HD patients (Add-on therapy to phosphate binders)	Tenapanor: 84 (Starting dose of 5 mg/day, titrated within 5-30 mg/day) Placebo: 85	8 weeks	Change from baseline in serum phosphorus at Week 8
7791-006	Phase III open-label uncontrolled	PD patients	Tenapanor: 54 (Starting dose of 5 mg/day, titrated within 5-30 mg/day)	16 weeks	Change from baseline in serum phosphorus at Week 8
7791-007	Phase III open-label uncontrolled	HD patients (Switching from phosphate binders)	Tenapanor: 212 (Starting dose of 5 mg/day, titrated within 5-30 mg/day)	52 weeks	None[a)]

a) The primary endpoint was safety.

7.1 Phase II studies

7.1.1 Japanese phase II study in HD patients (CTD 5.3.5.1-1, Study 7791-001 [March 2019 to December 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 31 sites in Japan to evaluate the efficacy and safety of tenapanor in patients with hyperphosphatemia on HD (Table 37) (target sample size, 200 subjects [40 per group][33)]).

[33)] The target sample size was determined based on data from a foreign study [redacted]. Assuming a ≥1.5 mg/dL difference between the tenapanor 30 mg and placebo groups in the change in serum phosphorus level from baseline to Week 6 with a standard deviation of 2.0 mg/dL, 40 subjects per group were required to provide a 90% power to detect at least a treatment difference between the tenapanor 30 mg and placebo groups using a 4-arm Williams test (placebo group, tenapanor 5 mg group, tenapanor 10 mg group, tenapanor 30 mg group) with a 1-sided significance level of 2.5%. A target sample size of 200 subjects (including subjects in the 30-mg down-titration group) was selected.

Table 37. Key inclusion/exclusion criteria

Key inclusion criteria
● ≥20 and <80 years of age
● Patients with stable CKD on HD 3 times per week for ≥12 weeks
● Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening
● Taking phosphate binders 3 times per day with the dosing regimen unchanged from 4 weeks before screening through the start of the 1st washout period
● Serum phosphorus levels of ≥3.5 mg/dL and ≤6.0 mg/dL at screening
● Following phosphate binder washout after pre-enrollment. serum phosphorus levels of ≥6.1 mg/dL and <10.0 mg/dL at 1 or 2 weeks after the start of the 1st washout period, and an increase of ≥1.0 mg/dL vs. screening value
● If on any vitamin D or calcimimetics regimen, the prescribed dosing regimen unchanged from 4 weeks before screening through the start of the 1st washout period
● Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening
Key exclusion criteria
● Intact PTH >600 pg/mL
● Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome
● History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery between 3 months before screening and 1st washout period
● Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment
***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a 1st washout period (up to 3 weeks from pre-enrollment until enrollment), an evaluation period (6-week study treatment), and a 2nd washout period (3 weeks after completion of study treatment).

Placebo or tenapanor 5, 10, or 30 mg was to be administered orally twice daily, immediately prior to meals[34] (the placebo, 5 mg, 10 mg, and 30 mg groups). In the 30 mg down-titration group, subjects were to start at tenapanor 30 mg BID orally administered immediately prior to meals and could be down-titrated in a stepwise fashion up to 3 times to 20 mg, 10 mg, and 5 mg BID, at the investigator's discretion, if study drug-related gastrointestinal symptoms occurred. Once down-titrated, the dose could not be increased. The duration of treatment was 6 weeks.

All of 207 randomized subjects (41 in the placebo group, 42 in the 5 mg group, 41 in the 10 mg group, 42 in the 30 mg group, 41 in the 30 mg down-titration group) received study drug and were included in the mITT population and in the safety analysis set. The mITT population was used as the primary efficacy population. There were 66 discontinuations (15 in the placebo group, 10 in the 5 mg group, 14 in the 10 mg group, 17 in the 30 mg group, 10 in the 30 mg down-titration group). When analyzed by period, 47 subjects discontinued during the evaluation period (12 in the placebo group, 5 in the 5 mg group, 10 in the 10 mg group, 13 in the 30 mg group, 7 in the 30 mg down-titration group), and 19 subjects discontinued during the 2nd washout period (3 in the placebo group, 5 in the 5 mg group, 4 in the 10 mg group, 4 in the 30 mg group, 3 in the 30 mg down-titration group). The reasons for discontinuations (some subjects had more than 1 reason) during the evaluation period were "withdrawal by subject" (18 subjects) (1 in the placebo group, 2 in the 5 mg group, 5 in the 10 mg group, 6 in the 30 mg group, 4 in the 30 mg down-titration group), "elevated serum phosphorus levels (≥10.0 mg/dL)" (16 subjects) (11 in the placebo group, 2 in the 5 mg group, 2 in the 10 mg group, 1 in the 30 mg group), "adverse events" (8 subjects) (1 in the 5 mg group, 3 in the 10 mg group, 3 in the 30 mg group, 1 in the

[34] As a rule, study drug was to be taken immediately prior to breakfast and dinner. If a subject could not eat breakfast or dinner, study drug was to be taken immediately prior to another meal such as lunch, or at the usual time of meal intake. On the day of dialysis, as a rule, study drug was not to be taken immediately before or during a dialysis session, and study drug was to be taken immediately prior to another meal such as lunch. Note that if the investigator etc. considered that there was no problem with subject safety, study drug could be taken immediately before or during a dialysis session.

30 mg down-titration group), "decreased serum phosphorus levels (≤2.5 mg/dL)" (3 subjects) (2 in the 30 mg group, 1 in the 30 mg down-titration group), and "lost to follow-up" (2 subjects) (1 in the 30 mg group, 1 in the 30 mg down-titration group). The reasons for discontinuations during the 2nd washout period were "elevated serum phosphorus levels (≥10.0 mg/dL)" (17 subjects) (3 in the placebo group, 4 in the 5 mg group, 4 in the 10 mg group, 4 in the 30 mg group, 2 in the 30 mg down-titration group), "protocol deviation" (1 subject) (1 in the 5 mg group), and "physician decision" (1 subject) (1 in the 30 mg down-titration group).

Table 38 shows the primary efficacy endpoint of "the change from baseline in serum phosphorus at Week 6." There were statistically significant differences between each of the tenapanor fixed dose groups and the placebo group (for all groups, $P < 0.001$, Williams test with a one-sided significance level of 2.5%), and tenapanor reduced serum phosphorus in a dose-dependent manner.

Table 38. Change from baseline in serum phosphorus at Week 6 (mg/dL) (mITT)

	Placebo (N = 41)	5 mg (N = 42)	10 mg (N = 41)	30 mg (N = 42)	30 mg down-titration (N = 41)
Baseline serum phosphorus level (Mean ± SD)	7.55 ± 1.32	7.46 ± 1.09	8.06 ± 1.13	7.65 ± 1.40	7.39 ± 1.13
Serum phosphorus level at Week 6[a] (Mean ± SD)	8.19 ± 1.82	6.52 ± 1.55	6.70 ± 1.74	5.73 ± 1.74	5.40 ± 1.34
Change in serum phosphorus (Mean ± SD)	0.64 ± 1.55	-0.93 ± 1.74	-1.36 ± 1.52	-1.92 ± 1.17	-1.99 ± 1.12
Treatment difference (Tenapanor group − placebo group) (Mean [95% CI][b])	—	-1.57 [-2.29, -0.85]	-2.00 [-2.67, -1.33]	-2.56 [-3.16, -1.96]	-2.62 [-3.22, -2.03]
P-value[c]		<0.001	<0.001	<0.001	—

a) LOCF was used to impute missing data.
b) Calculated using Student's t test.
c) A 4-arm Williams test (the placebo, tenapanor 5 mg, tenapanor 10 mg, and tenapanor 30 mg groups) with a one-sided significance level of 2.5%

Regarding safety, the incidences of adverse events were 51.2% (21 of 41 subjects) in the placebo group, 78.6% (33 of 42 subjects) in the 5 mg group, 78.0% (32 of 41 subjects) in the 10 mg group, 85.7% (36 of 42 subjects) in the 30 mg group, and 80.5% (33 of 41 subjects) in the 30 mg down-titration group, and adverse events reported by ≥2 subjects in any group are shown in Table 39. The incidences of adverse drug reactions were 17.1% (7 of 41 subjects) in the placebo group, 52.4% (22 of 42 subjects) in the 5 mg group, 68.3% (28 of 41 subjects) in the 10 mg group, 76.2% (32 of 42 subjects) in the 30 mg group, and 68.3% (28 of 41 subjects) in the 30 mg down-titration group, and adverse drug reactions reported by ≥2 subjects in any group were diarrhea (9.8% [4 of 41 subjects] in the placebo group, 50.0% [21 of 42 subjects] in the 5 mg group, 65.9% [27 of 41 subjects] in the 10 mg group, 76.2% [32 of 42 subjects] in the 30 mg group, 65.9% [2 of 41 subjects] in the 30 mg down-titration group).

Table 39. Adverse events reported by ≥2 subjects in any group (Safety analysis set)

	Placebo (N = 41)	5 mg (N = 42)	10 mg (N = 41)	30 mg (N = 42)	30 mg down-titration (N = 41)
Any adverse event	**51.2 (21)**	**78.6 (33)**	**78.0 (32)**	**85.7 (36)**	**80.5 (33)**
Diarrhea	**22.0 (9)**	**57.1 (24)**	**65.9 (27)**	**76.2 (32)**	**70.7 (29)**
Nasopharyngitis	**7.3 (3)**	**7.1 (3)**	**9.8 (4)**	**9.5 (4)**	**14.6 (6)**
Skin abrasion	**0**	**0**	**2.4 (1)**	**0**	**4.9 (2)**
Soft faeces	**0**	**2.4 (1)**	**4.9 (2)**	**0**	**2.4 (1)**
Contusion	**0**	**0**	**0**	**4.8 (2)**	**0**
Back pain	**0**	**0**	**4.9 (2)**	**2.4 (1)**	**0**
Arthralgia	**7.3 (3)**	**0**	**0**	**2.4 (1)**	**0**
Constipation	**0**	**4.8 (2)**	**0**	**0**	**0**
Eczema	**0**	**4.8 (2)**	**0**	**0**	**0**

Incidence % (n)
MedDRA/J ver.22.1

No deaths were reported. Serious adverse events occurred in 2.4% (1 of 42) of subjects in the 5 mg group (shunt stenosis [1 subject]), 4.9% (2 of 41) of subjects in the 10 mg group (angina pectoris; and diverticulitis [1 subject each]), 2.4% (1 of 42) of subjects in the 30 mg group (arthritis [1 subject]), and 4.9% (2 of 41) of subjects in the 30 mg down-titration group (shunt occlusion; and gastric cancer [1 subject each]), and the event of diverticulitis reported by 1 subject in the 10 mg group was classified as a serious adverse drug reaction and led to study drug discontinuation. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 2.4% (1 of 42) of subjects in the 5 mg group (diarrhea [1 subject]), 4.9% (2 of 41) of subjects in the 10 mg group (diarrhea; and hyperkalaemia [1 subject each]), 7.1% (3 of 42) of subjects in the 30 mg group (diarrhea [3 subjects]), and 2.4% (1 of 41) of subjects in the 30 mg down-titration group (diarrhea [1 subject]), all of which were classified as adverse drug reactions.

7.1.2 Japanese phase II study of tenapanor in combination with phosphate binders in HD patients inadequately controlled on existing treatment (CTD 5.3.5.1-2, Study 7791-002 [March 2019 to December 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 9 sites in Japan to evaluate the efficacy and safety of tenapanor in combination with phosphate binders in HD patients inadequately controlled on existing phosphate binders (Table 40) (target sample size, 40 subjects [20 per group][35)]).

[35)] A sample size of 40 subjects (20 per group) was selected for this exploratory study. Based on the data from foreign studies [redacted] and TEN-02-201, assuming mean changes in serum phosphorus level from baseline to Week 6 of −0.5 mg/dL (placebo group) and −1.5 mg/dL (tenapanor group) with a common standard deviation of 2.0 mg/dL and a sample size of 40 subjects (20 per group), there was a 78.5% probability of finding a difference of ≥0.5 mg/dL in the mean change between the tenapanor and placebo groups.

Table 40. Key inclusion/exclusion criteria

Key inclusion criteria ● **≥20 and <80 years of age** ● **Patients with stable CKD on HD 3 times per week for ≥12 weeks** ● **Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening** ● **Taking phosphate binders 3 times per day with the dosing regimen unchanged from 2 weeks before screening through enrollment** ● **Serum phosphorus levels of ≥6.1 mg/dL and <10.0 mg/dL at screening and at 1 or 2 weeks after the start of the run-in period** ● **If on any vitamin D or calcimimetics regimen, the prescribed dosing regimen unchanged from 2 weeks before screening through enrollment** ● **Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening** **Key exclusion criteria** ● **Intact PTH >600 pg/mL** ● **Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome** ● **History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery between 3 months before screening and enrollment** ● **Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment** ***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a run-in period (up to 3 weeks from pre-enrollment until enrollment), and a treatment period (6-week study treatment).

Placebo or tenapanor 30 mg was to be administered orally twice daily, immediately prior to meals,[34)] for 6 weeks. The dose of tenapanor could be down-titrated in a stepwise fashion up to 3 times to 20 mg, 10 mg, and 5 mg BID, at the investigator's discretion, if study drug-related gastrointestinal symptoms occurred. Once down-titrated, the dose could not be increased.

All of 47 randomized subjects (24 in the placebo group, 23 in the tenapanor group) received study drug and were included in the mITT population and in the safety analysis set. The mITT population was used as the primary efficacy population. There were 9 discontinuations (2 in the placebo group, 7 in the tenapanor group), and the reasons for discontinuations were "adverse events" (3 subjects in the tenapanor group), "withdrawal by subject" (2 subjects in the tenapanor group), "elevated serum phosphorus levels (≥10.0 mg/dL)" (2 subjects in the placebo group), "decreased serum phosphorus levels (≤2.5 mg/dL)" (1 subject in the tenapanor group), and "physician decision" (1 subject in the tenapanor group).

Table 41 shows the primary efficacy endpoint of "the change from baseline in serum phosphorus at Week 6." There was a statistically significant difference between the tenapanor and placebo groups ($P < 0.001$, Student's t-test with a two-sided significance level of 5%).

Table 41. Change from baseline in serum phosphorus at Week 6 (mg/dL) (mITT)

	Placebo (N = 24)	**Tenapanor (N = 23)**
Baseline serum phosphorus level (Mean ± SD)	**7.01 ± 1.25**	**6.77 ± 0.88**
Serum phosphorus level at Week 6 (Mean ± SD)[a)]	**7.10 ± 1.91**	**4.78 ± 1.28**
Change in serum phosphorus (Mean ± SD)	**0.08 ± 1.52**	**-1.99 ± 1.24**
Treatment difference (Tenapanor group − placebo group) (Mean [95% CI][b)])	—	**-2.07 [-2.89, -1.26]**
***P*-value[b)]**		**<0.001**

a) LOCF was used to impute missing data.
b) Calculated using Student's t test with a two-sided significance level of 5%

Regarding safety, the incidences of adverse events were 37.5% (9 of 24 subjects) in the placebo group and 78.3% (18 of 23 subjects) in the tenapanor group, and adverse events reported by ≥2 subjects in either group were diarrhea (16.7% [4 of 24 subjects] in the placebo group, 65.2% [15 of 23 subjects] in the tenapanor group) and nasopharyngitis (4.2% [1 of 24 subjects] in the placebo group, 8.7% [2 of 23 subjects] in the tenapanor group). The incidences of adverse drug reactions were 8.3% (2 of 24 subjects) in the placebo group and 69.6% (16 of 23 subjects) in the tenapanor group, and adverse drug reactions reported by ≥2 subjects in either group were diarrhea (8.3% [2 of 24 subjects] in the placebo group, 65.2% [15 of 23 subjects] in the tenapanor group).

No deaths were reported. A serious adverse event occurred in 4.3% (1 of 23) of subjects in the tenapanor group (ankle fracture [1 subject]) and led to study drug discontinuation, but the event was considered unrelated to study drug. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 13.0% (3 of 23) of subjects in the tenapanor group (diarrhea [3 subjects]), all of which were classified as adverse drug reactions.

7.1.3 Japanese phase II study of switching to tenapanor in HD patients (CTD 5.3.5.2-1, Study 7791-003 [December 2018 to November 2019])

An open-label, uncontrolled study was conducted at 8 sites in Japan to evaluate the efficacy and safety of switching from phosphate binders to tenapanor in patients with hyperphosphatemia on HD (Table 42) (target sample size, 60 subjects[36)]).

Table 42. Key inclusion/exclusion criteria

Key inclusion criteria
● ≥20 and <80 years of age
● Patients with stable CKD on HD 3 times per week for ≥12 weeks
● Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening
● Taking ≥2 tablets of phosphate binder 3 times per day with the dosing regimen unchanged from 2 weeks before screening through enrollment
● Serum phosphorus levels of ≥3.5 mg/dL and ≤7.0 mg/dL at screening and at 1 or 2 weeks after the start of the run-in period
● If on any vitamin D or calcimimetics regimen, the prescribed dosing regimen unchanged from 2 weeks before screening through enrollment
● Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening
Key exclusion criteria
● Intact PTH >600 pg/mL
● Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome
● History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery between 3 months before screening and enrollment
● Diarrhea or loose stool, defined as BSFS ≥6＊ and ≥3 bowel movements on 2 or more days during the week before enrollment
＊BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a run-in period (3 weeks from pre-enrollment until enrollment), and an evaluation period (26-week study treatment).

Tenapanor 30 mg was to be administered orally twice daily, immediately prior to meals,[34)] for 26 weeks. The dose of tenapanor could be down-titrated in a stepwise fashion to 20 mg, 10 mg, and 5 mg BID at the investigator's discretion, if gastrointestinal symptoms for which a causal relationship to study drug could not

[36)] Based on the data from foreign Study TEN-02-201, the proportion of subjects achieving a 30% reduction in pill burden was assumed to be 40%, and ≥59 subjects were required to provide at least 90% power, using a binomial test with a threshold level of 20% and a 1-sided significance level of 2.5%. Thus, a target sample size of 60 subjects was selected. In a foreign study [redacted], serum phosphorus levels at Week 4/discontinuation were in the range of screening value + 0.5 mg/dL in 15.4% (4 of 26) of subjects receiving placebo, indicating that these subjects could maintain serum phosphorus with placebo only. Therefore a threshold level of 20% was selected.

be ruled out (up to Week 8) or adverse events (from Week 9 onward) occurred. The dose of phosphate binders subjects had been taking before enrollment was to be adjusted, with the aim of maintaining serum phosphorus in the range of baseline value ± 0.5 mg/dL. The dose of tenapanor could be reduced by 1 level if serum phosphorus dropped below 2.5 mg/dL after subjects completely switched from phosphate binders. From Week 9 onward, the reduced dose of tenapanor could be up-titrated in a stepwise fashion if considered necessary by the investigator, based on serum phosphorus concentrations and the occurrence of adverse events. Up-titration of tenapanor was permitted if a subject had been on a stable dose for ≥2 weeks. If the dose of phosphate binders was adjusted, a minimum interval of 2 weeks was required to allow up-titration.

All of 67 subjects who received study drug were included in the mITT population and in the safety analysis set, and the mITT population was used as the primary efficacy population. There were 24 discontinuations, and the reasons for discontinuations were "withdrawal by subject" (14 subjects), "adverse events" (6 subjects), "decreased serum phosphorus levels (≤2.5 mg/dL for 2 consecutive weeks)" (3 subjects), and "physician decision" (1 subject).

The primary efficacy endpoint of "the proportion of subjects who achieved a ≥30% reduction in the total number of phosphate binder and tenapanor tablets prescribed daily based on an average calculated for the 3 most recent time points after Week 9 compared with the number of prescribed phosphate binder tablets per day at baseline [95% CI][37)] (the number of subjects who achieved the primary endpoint/the number of subjects evaluated)" was 71.6% [53.9%, 82.0%] (48 of 67 subjects), and the lower bound of the 95% confidence interval was above the pre-specified threshold of 20%.

Regarding safety, the incidence of adverse events was 92.5% (62 of 67 subjects), and adverse events reported by ≥2 subjects are shown in Table 43. The incidence of adverse drug reactions was 76.1% (51 of 67 subjects), and adverse drug reactions reported by ≥2 subjects were diarrhea (74.6% [50 of 67 subjects]) and soft faeces (3.0% [2 of 67 subjects]).

[37)] The 95% confidence interval was calculated by Clopper-Pearson method.

Table 43. Adverse events reported by ≥2 subjects (Safety analysis set)

	Tenapanor (N = 67)		Tenapanor (N = 67)
Any adverse event	92.5 (62)	Otitis externa	3.0 (2)
Diarrhea	76.1 (51)	Pharyngitis	3.0 (2)
Nasopharyngitis	13.4 (9)	Arthropod sting	3.0 (2)
Nausea	4.5 (3)	Contusion	3.0 (2)
Pyrexia	4.5 (3)	Back pain	3.0 (2)
Shunt stenosis	4.5 (3)	Carpal tunnel syndrome	3.0 (2)
Melaena	3.0 (2)	Cerebral infarction	3.0 (2)
Soft faeces	3.0 (2)		

Incidence % (n)
MedDRA/J ver.22.1

No deaths were reported. Serious adverse events occurred in 7.5% (5 of 67) of subjects (diarrhea; acute myocardial infarction; vessel puncture site pain; diverticulitis; and cerebral infarction [1 subject each]), and the event of cerebral infarction led to study drug discontinuation. The events of diarrhea and acute myocardial infarction were classified as adverse drug reactions. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 7.5% (5 of 67) of subjects (diarrhea [4 subjects]; and coronary artery stenosis; and melaena [1 subject each] [some patients had more than 1 event]), all of which were classified as adverse drug reactions.

7.2 Phase III studies

7.2.1 Japanese phase III study in HD patients (CTD 5.3.5.1-3, Study 7791-004 [March 2021 to August 2021])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 34 sites in Japan to evaluate the efficacy and safety of tenapanor in patients with hyperphosphatemia on HD (Table 44) (target sample size, 140 subjects [70 per group][38)]).

Table 44. Key inclusion/exclusion criteria

Key inclusion criteria
- **≥20 years of age**
- **Patients with stable CKD on HD 3 times per week for ≥12 weeks**
- **Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening**
- **Taking phosphate binders 3 times per day with the dosing regimen unchanged from 4 weeks before screening through the start of the washout period**
- **Serum phosphorus levels of ≥3.5 mg/dL and ≤6.0 mg/dL at screening**
- **Following phosphate binder washout, serum phosphorus levels of ≥6.1 mg/dL and <10.0 mg/dL at 1 or 2 weeks after the start of washout, and an increase of ≥1.0 mg/dL vs. screening value**
- **If on treatment with vitamin D supplementation, calcimimetics, bisphosphonates, calcitonin, selective estrogen receptor modulators, or teriparatide, the prescribed dosing regimen unchanged during the last 4 weeks before screening**
- **Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening**

Key exclusion criteria
- **Intact PTH >600 pg/mL**
- **Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome**
- **History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery (excluding endoscopic resection and cecectomy) between 3 months before screening and enrollment**
- **Use of anti-RANKL antibody preparations between 6 weeks before screening and enrollment**
- **Use of anti-sclerostin antibody preparations between 12 weeks before screening and enrollment**
- **Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment**

***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

[38)] The change in serum phosphorus level from baseline to Week 8 in the placebo group of Study 7791-004 was assumed to be 0 mg/dL, based on the results in the placebo groups of Studies 7791-001 and [redacted]. In Study 7791-004, the starting dose of tenapanor was to be 5 mg and then up-titrated. Therefore the change in serum phosphorus level from baseline to Week 8 in the tenapanor group of Study 7791-004 was assumed to be −1.0 mg/dL based on the results in the tenapanor 5 mg group of Study 7791-001. Assuming the above and a common standard deviation of 1.8 mg/dL, 52 subjects per group (104 in total) were required to provide 80% power at a two-sided significance level of 5%. Assuming a 30% dropout rate, a target sample size of 70 subjects per group (140 in total) was selected.

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a washout period (up to 3 weeks from pre-enrollment until enrollment), and a treatment period (8-week study treatment).

Subjects initially received placebo or tenapanor 5 mg orally twice daily, immediately prior to meals.[34)] Then, the dose was titrated in a stepwise fashion (5, 10, 20, and 30 mg) according to the guidance on dose adjustments (Table 45). The duration of treatment was 8 weeks.

Table 45. Guidance on tenapanor dose adjustments

Criteria for dose increase	**Both of the following criteria were met. Following dose reduction according to the dose reduction criterion 2), even if the dose increase criterion 1) was not met, the dose could be increased back to the previous dose immediately prior to a meal after the end of dialysis following the longest dialysis interval, provided that the investigator considered that there was no problem with subject safety.** **1) A subject on a stable dose for ≥1 week had serum phosphorus ≥6.1 mg/dL after the latest longest dialysis interval, or had serum phosphorus ≤6.0 mg/dL but the investigator considered that the dose could be increased to achieve a target serum phosphorus level of 4.5 mg/dL.** **2) The investigator considered that there was no problem with subject safety and that the dose could be increased.**
Criteria for dose reduction	**The dose was ≥10 mg, and either of the following criteria was met.** **1) A subject on a stable dose for ≥1 week had serum phosphorus <3.5 mg/dL after the latest longest dialysis interval.** **2) Study drug-related gastrointestinal symptoms occurred, and the investigator considered that the dose should be reduced.**
Interruption criteria	**Either of the following criteria was met.** **1) A subject on the 5 mg dose for ≥1 week had serum phosphorus <3.5 mg/dL at the scheduled visits after the 2 latest longest dialysis intervals.** **2) Study drug-related gastrointestinal symptoms occurred, and the investigator considered that the drug should be interrupted.**
Resumption criteria	**If either of the following criteria was met, study drug was to be resumed immediately prior to a meal after the end of dialysis following the longest dialysis interval. After interruption, study drug was to be resumed at the same dose level or at 1 dose level lower. If on the 5 mg dose, study drug was to be resumed at a dose of 5 mg.** **1) Following interruption according to the interruption criterion 1), a confirmed serum phosphorus level of ≥3.5 mg/dL after the longest dialysis interval** **2) Following interruption according to the interruption criterion 2), the investigator considered that there was no problem with subject safety.**

Among 165 randomized subjects (82 in the placebo group, 83 in the tenapanor group), 164 subjects (82 in the placebo group, 82 in the tenapanor group) after excluding 1 subject in the tenapanor group who discontinued before receiving study drug, received study drug and were included in the safety analysis set. After excluding subjects who had no post-baseline serum phosphorus measurement, 157 subjects (76 in the placebo group, 81 in the tenapanor group) were included in the mITT population, which was used as the primary efficacy population. There were 41 discontinuations after the start of study treatment (24 in the placebo group, 17 in the tenapanor group). The reasons for discontinuations were "elevated serum phosphorus levels (≥10.0 mg/dL)" (27 subjects) (20 in the placebo group, 7 in the tenapanor group), "adverse events" (6 subjects) (2 in the placebo group, 4 in the tenapanor group), "withdrawal by subject" (5 subjects) (1 in the placebo group, 4 in the tenapanor group), "protocol deviation" (1 subject in the tenapanor group), "physician decision" (1 subject in the placebo group), and "study drug not resumed" (1 subject in the tenapanor group).

Table 46 shows the primary efficacy endpoint of "the change from baseline in serum phosphorus at Week 8." There was a statistically significant difference between the tenapanor and placebo groups, and the superiority of tenapanor to placebo was demonstrated ($P < 0.0001$, mixed-effects model for repeated measures [MMRM], a two-sided significance level of 5%).

Table 46. Change from baseline in serum phosphorus at Week 8 (mg/dL) (mITT)

	Placebo (N = 76)	Tenapanor (N = 81)
Baseline serum phosphorus level (Mean ± SD)	7.64 ± 1.27 (N = 76)	7.83 ± 1.42 (N = 81)
Serum phosphorus level at Week 8 (Mean ± SD)	7.32 ± 1.29 (N = 58)	5.61 ± 1.10 (N = 65)
Change in serum phosphorus (Least squares mean [95% CI][a)])	0.05 [-0.25, 0.36]	-1.89 [-2.19, -1.60]
Treatment difference (Tenapanor group − placebo group) (Least squares mean [95% CI][a)])	—	-1.95 [-2.37, -1.53]
P-value[a) b)]		<0.0001

a) Calculated from an MMRM model with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline serum phosphorus level as a covariate under the assumption of an unstructured variance-covariance matrix for within-subject correlation.
b) Two-sided significance level of 5%

Regarding safety, the incidences of adverse events were 65.9% (54 of 82 subjects) in the placebo group and 92.7% (76 of 82 subjects) in the tenapanor group, and adverse events reported by ≥2 subjects in either group are shown in Table 47. The incidences of adverse drug reactions were 15.9% (13 of 82 subjects) in the placebo group and 75.6% (62 of 82 subjects) in the tenapanor group, and adverse drug reactions reported by ≥2 subjects in either group were diarrhea (9.8% [8 of 82 subjects] in the placebo group, 70.7% [58 of 82 subjects] in the tenapanor group) and soft faeces (4.9% [4 of 82 subjects] in the placebo group, 4.9% [4 of 82 subjects] in the tenapanor group).

Table 47. Adverse events reported by ≥2 subjects in either group (Safety analysis set)

	Placebo (N = 82)	Tenapanor (N = 82)		Placebo (N = 82)	Tenapanor (N = 82)
Any adverse event	65.9 (54)	92.7 (76)	Hypertension	0 (0)	2.4 (2)
Diarrhea	19.5 (16)	74.4 (61)	Hypotension	0 (0)	2.4 (2)
Pyrexia	7.3 (6)	6.1 (5)	Fall	0 (0)	2.4 (2)
Soft faeces	4.9 (4)	6.1 (5)	Pain in extremity	4.9 (4)	1.2 (1)
Shunt stenosis	3.7 (3)	6.1 (5)	Iron deficiency anaemia	2.4 (2)	1.2 (1)
Nasopharyngitis	3.7 (3)	3.7 (3)	Oropharyngeal pain	2.4 (2)	1.2 (1)
Muscle spasms	1.2 (1)	3.7 (3)	Vaccination complication	3.7 (3)	0 (0)
Vaccination site pain	1.2 (1)	3.7 (3)	Headache	3.7 (3)	0 (0)
Injection site pain	0 (0)	3.7 (3)	Nausea	2.4 (2)	0 (0)
Arthralgia	3.7 (3)	2.4 (2)	Myalgia	2.4 (2)	0 (0)
Skin abrasion	2.4 (2)	2.4 (2)	Pruritus	2.4 (2)	0 (0)
Neck pain	1.2 (1)	2.4 (2)			

Incidence % (n)
MedDRA/J ver.24.1

Death occurred in 2.4% (2 of 82) of subjects in the placebo group (cardiac failure[39)]; and pneumonia[40)] [1 subject each]). The incidences of serious adverse events were 3.7% (3 of 82 subjects) (renal cyst infection; urinary tract infection; and shunt infection [1 subject each]) in the placebo group and 4.9% (4 of 82 subjects) (coronary artery stenosis; renal cyst infection; fracture; and hand fracture [1 subject each]) in the tenapanor group. The 1 case of fracture in the tenapanor group led to study drug discontinuation, but all those events were considered unrelated to study drug. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 3.7% (3 of 82) of subjects in the tenapanor group (diarrhea [2 subjects]; and sudden hearing loss [1 subject]), and the 2 cases of diarrhea were classified as adverse drug reactions.

[39)] A 71-year-old man. The subject had cardiac failure on Day 51 and died on Day 52. This was worsened cardiac failure due to inadequate fluid removal and was considered unrelated to study drug.
[40)] A 68-year-old man. The subject had pneumonia on Day 24 and died on Day 24. This was considered unrelated to study drug.

7.2.2 Japanese phase III study of tenapanor in combination with phosphate binders in HD patients inadequately controlled on existing treatment (CTD 5.3.5.1-4, Study 7791-005 [March 2021 to September 2021])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 40 sites in Japan to evaluate the efficacy and safety of tenapanor in combination with phosphate binders in HD patients inadequately controlled on existing phosphate binders (Table 48) (target sample size, 140 subjects [70 per group][41]).

Table 48. Key inclusion/exclusion criteria

Key inclusion criteria
● **≥20 years of age**
● **Patients with stable CKD on HD 3 times per week for ≥12 weeks**
● **Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening**
● **Taking phosphate binders with the dosing regimen unchanged from 2 weeks before screening through enrollment**
● **Serum phosphorus levels of ≥6.1 mg/dL and <10.0 mg/dL at screening and at 1 or 2 weeks after the start of the run-in period**
● **If on treatment with vitamin D supplementation, calcimimetics, bisphosphonates, calcitonin, selective estrogen receptor modulators, or teriparatide, the prescribed dosing regimen unchanged during the last 2 weeks before screening**
● **Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening**
Key exclusion criteria
● **Intact PTH >600 pg/mL**
● **Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome**
● **History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery (excluding endoscopic resection and cecectomy) between 3 months before screening and enrollment**
● **Use of anti-RANKL antibody preparations between 6 weeks before screening and enrollment**
● **Use of anti-sclerostin antibody preparations between 12 weeks before screening and enrollment**
● **Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment**
***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a run-in period (up to 3 weeks from pre-enrollment until enrollment), and a treatment period (8-week study treatment).

Subjects initially received placebo or tenapanor 5 mg orally twice daily, immediately prior to meals.[34] Then, the dose was titrated in a stepwise fashion (5, 10, 20, and 30 mg) according to the guidance on dose adjustments (Table 49). The duration of treatment was 8 weeks.

All of 169 randomized subjects (85 in the placebo group, 84 in the tenapanor group) received study drug and were included in the safety analysis set. After excluding subjects who had no post-baseline serum phosphorus measurement, 164 subjects (83 in the placebo group, 81 in the tenapanor group) were included in the mITT population, which was used as the primary efficacy population. There were 22 discontinuations (11 in the placebo group, 11 in the tenapanor group). The reasons for discontinuations were "withdrawal by subject" (8 subjects) (3 in the placebo group, 5 in the tenapanor group), "elevated serum phosphorus levels (≥10.0 mg/dL)" (7 subjects) (4 in the placebo group, 3 in the tenapanor group), "physician decision" (3 subjects) (2 in the placebo group, 1 in the tenapanor group), "adverse events" (2 subjects in the tenapanor group), "protocol deviation" (1 subject in the placebo group), and "lost to follow-up" (1 subject in the placebo group).

[41] The change from baseline in serum phosphorus at Week 8 in the placebo group of this study was assumed to be 0 mg/dL, based on the results in the placebo groups of Studies 7791-001 and TEN-02-202. In this study, the starting dose was 5 mg and then titrated. Based on the results in the tenapanor 5 mg group of Study 7791-001, the change from baseline in serum phosphorus at Week 8 in the tenapanor group of this study was assumed to be −1.0 mg/dL. Assuming the above and a common standard deviation of 1.8 mg/dL, 52 subjects per group, a total of 104 subjects, were required to provide 80% power at a two-sided significance level of 5%. Assuming a 30% dropout rate, a target sample size of 70 subjects per group, a total of 140 subjects, was chosen.

Table 49 shows the primary efficacy endpoint of "the change from baseline in serum phosphorus at Week 8." There was a statistically significant difference between the tenapanor and placebo groups, and the superiority of tenapanor to placebo was demonstrated ($P < 0.0001$, MMRM, a two-sided significance level of 5%).

Table 49. Change from baseline in serum phosphorus at Week 8 (mg/dL) (mITT)

	Placebo (N = 83)	Tenapanor (N = 81)
Baseline serum phosphorus level (Mean ± SD)	6.92 ± 1.07 (N = 83)	6.76 ± 1.08 (N = 81)
Serum phosphorus level at Week 8 (Mean ± SD)	6.51 ± 1.20 (N = 74)	4.62 ± 1.07 (N = 73)
Change in serum phosphorus (Least squares mean [95% CI][a)])	-0.24 [-0.52, 0.04]	-2.00 [-2.28, -1.72]
Treatment difference (Tenapanor group − placebo group) (Least squares mean [95% CI][a)])	—	-1.76 [-2.16, -1.37]
P-value[a) b)]		<0.0001

a) Calculated from an MMRM model with treatment, visit, and treatment-by-visit interaction as fixed effects and baseline serum phosphorus level as a covariate under the assumption of an unstructured variance-covariance matrix for within-subject correlation.
b) Two-sided significance level of 5%

Regarding safety, the incidences of adverse events were 62.4% (53 of 85 subjects) in the placebo group and 85.7% (72 of 84 subjects) in the tenapanor group, and adverse events reported by ≥2 subjects in either group are shown in Table 50. The incidences of adverse drug reactions were 14.1% (12 of 84 subjects) in the placebo group and 64.3% (54 of 84 subjects) in the tenapanor group, and adverse drug reactions reported by ≥2 subjects in either group were diarrhea (9.4% [8 of 85 subjects] in the placebo group, 58.3% [49 of 84 subjects] in the tenapanor group), soft faeces (4.8% [4 of 84 subjects] in the tenapanor group), nausea (2.4% [2 of 84 subjects] in the tenapanor group), and abdominal discomfort (2.4% [2 of 85 subjects] in the placebo group).

Table 50. Adverse events reported by ≥2 subjects in either group (Safety analysis set)

	Placebo (N = 85)	Tenapanor (N = 84)		Placebo (N = 85)	Tenapanor (N = 84)
Any adverse event	**62.4 (53)**	**85.7 (72)**	**Contusion**	**1.2 (1)**	**2.4 (2)**
Diarrhea	**14.1 (12)**	**63.1 (53)**	**Wound**	**0 (0)**	**2.4 (2)**
Pyrexia	**8.2 (7)**	**13.1 (11)**	**Abdominal discomfort**	**2.4 (2)**	**1.2 (1)**
Pain in extremity	**5.9 (5)**	**4.8 (4)**	**Post vaccination syndrome**	**2.4 (2)**	**1.2 (1)**
Soft faeces	**0 (0)**	**4.8 (4)**	**Muscle spasms**	**2.4 (2)**	**1.2 (1)**
Vomiting	**2.4 (2)**	**3.6 (3)**	**Headache**	**2.4 (2)**	**1.2 (1)**
Nasopharyngitis	**2.4 (2)**	**3.6 (3)**	**Shunt stenosis**	**4.7 (4)**	**0 (0)**
Vaccination site pain	**1.2 (1)**	**3.6 (3)**	**Arthralgia**	**2.4 (2)**	**0 (0)**
Skin abrasion	**0 (0)**	**3.6 (3)**	**Back pain**	**2.4 (2)**	**0 (0)**
Blood pressure decreased	**2.4 (2)**	**2.4 (2)**	**Restless legs syndrome**	**2.4 (2)**	**0 (0)**
Nausea	**1.2 (1)**	**2.4 (2)**	**Peripheral arterial occlusive disease**	**2.4 (2)**	**0 (0)**
Injection site pain	**1.2 (1)**	**2.4 (2)**	**Ligament sprain**	**2.4 (2)**	**0 (0)**
Vaccination complication	**1.2 (1)**	**2.4 (2)**	**Shunt infection**	**2.4 (2)**	**0 (0)**
Hyperkalaemia	**1.2 (1)**	**2.4 (2)**			

Incidence % (n)
MedDRA/J ver.24.1

No deaths were reported. The incidences of serious adverse events were 3.5% (3 of 85 subjects) (shunt stenosis [2 subjects]; and limb injury; and peripheral arterial occlusive disease [1 subject each] [some patients had more than 1 event]) in the placebo group and 2.4% (2 of 84 subjects) (large intestine polyp; and cerebral thrombosis [1 subject each]) in the tenapanor group. Although the 1 case of cerebral thrombosis in the tenapanor group led to study drug discontinuation, all those events were considered unrelated to study drug. An adverse event leading to study drug discontinuation other than serious adverse events occurred in 1.2% (1 of 84) of subjects in the tenapanor group (hyperkalaemia [1 subject]) and was considered unrelated to study drug.

7.2.3 Japanese phase III study in peritoneal dialysis (PD) patients (CTD 5.3.5.2.2, Study 7791-006 [March 2021 to December 2021])

An open-label, uncontrolled study was conducted at 20 sites in Japan to evaluate the efficacy and safety of tenapanor in patients with hyperphosphatemia on PD (Table 51) (target sample size, 40 subjects[42)]).

[42)] For the primary endpoint of the change from baseline in serum phosphorus at Week 8, assuming a mean change in serum phosphorus of −1.0 mg/dL with a standard deviation of 2.0 mg/dL, a sample size of 40 subjects would allow for a 95% confidence interval with a precision of − 1.6 to − 0.4 mg/dL.

Table 51. Key inclusion/exclusion criteria

Key inclusion criteria ● **≥20 years of age** ● **Patients with stable CKD on PD for ≥12 weeks** ● **Unchanged dialysis conditions during the last 2 weeks before screening** ● **Taking phosphate binders with the dosing regimen unchanged from 4 weeks before screening through the start of the washout period** ● **Serum phosphorus levels of ≥3.5 mg/dL and ≤7.0 mg/dL at screening** ● **Following phosphate binder washout, serum phosphorus levels of ≥6.1 mg/dL and <10.0 mg/dL after the start of washout and an increase vs. screening value** ● **If on treatment with vitamin D supplementation, calcimimetics, bisphosphonates, calcitonin, selective estrogen receptor modulators, or teriparatide, the prescribed dosing regimen unchanged during the last 4 weeks before screening** **Key exclusion criteria** ● **Had received concomitant HD or HD filtration between 12 weeks before screening and enrollment** ● **Confirmed to have peritonitis, catheter-related infection, or catheter malfunction, etc., between 4 weeks before screening and enrollment and considered to have difficulty in continuing PD** ● **Had undergone parathyroid intervention between 24 weeks before screening and enrollment** ● **Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome** ● **History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery (excluding endoscopic resection and cecectomy) between 3 months before screening and enrollment** ● **Use of anti-RANKL antibody preparations between 6 weeks before screening and enrollment** ● **Use of anti-sclerostin antibody preparations between 12 weeks before screening and enrollment** ● **Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment** ***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

The study consisted of a screening period (from the date of obtaining consent until pre-enrollment), a washout period (up to 4 weeks from pre-enrollment until enrollment), and a treatment period (16-week study treatment).

Subjects initially received tenapanor 5 mg orally twice daily, immediately prior to meals.[34)] Then, the dose was titrated in a stepwise fashion (5, 10, 20, and 30 mg) according to the guidance on dose adjustments (Table 52). The duration of treatment was 16 weeks. If the investigator etc. considered that the tolerable dose of tenapanor was insufficient to reduce serum phosphorus levels after completing the week 8 evaluation, rescue treatment with a phosphate binder was allowed.

Table 52. Guidance on tenapanor dose adjustments

Criteria for dose increase	**Both of the following criteria were met. Following dose reduction according to the dose reduction criterion 2), even if the dose increase criterion 1) was not met, the dose could be increased back to the previous dose, provided that the investigator considered that there was no problem with subject safety.** **If a phosphate binder was initiated after the Week 8 evaluation, dose increase of tenapanor was to be considered before dose increase of the phosphate binder.** **1) A subject on a stable dose for ≥1 week had serum phosphorus ≥6.1 mg/dL at the scheduled visit, or had serum phosphorus ≤6.0 mg/dL but the investigator considered that the dose could be increased to achieve a target serum phosphorus level of 4.5 mg/dL.** **2) The investigator considered that there was no concern about subject safety and that the dose could be increased.**
Criteria for dose reduction	**The dose was ≥10 mg, and either of the following criteria was met.** **If a phosphate binder was initiated after the Week 8 evaluation, dose reduction of the phosphate binder was to be considered before dose reduction of tenapanor.** **1) A subject on a stable dose for ≥1 week had serum phosphorus <3.5 mg/dL at the scheduled visit.** **2) Tenapanor-related adverse events occurred, and the investigator considered that the dose should be reduced.**
Interruption criteria	**Either of the following criteria was met.** **1) A subject on the 5 mg dose had serum phosphorus <3.5 mg/dL at the 2 consecutive scheduled visits.** **2) Tenapanor-related adverse events occurred, and the investigator considered that the drug should be interrupted.**
Resumption criteria	**Either of the following criteria was met.** **Tenapanor was to be resumed at the same dose level or at 1 dose level lower. If on the 5 mg dose, tenapanor was to be resumed at a dose of 5 mg.** **1) Following interruption according to the interruption criterion 1), a confirmed serum phosphorus level of ≥3.5 mg/dL** **2) Following interruption according to the interruption criterion 2), the investigator considered that there was no problem with subject safety.**

All of 54 subjects who received study drug were included in the safety analysis set. After excluding subjects who had no post-baseline serum phosphorus measurement, 52 subjects were included in the mITT population, which was used as the primary efficacy population. There were 20 discontinuations, and the reasons for

discontinuations were "withdrawal by subject" (12 subjects), "adverse events" (5 subjects), "elevated serum phosphorus levels (≥10.0 mg/dL)" (2 subjects), and "physician decision" (1 subject).

Table 53 shows the primary efficacy endpoint of "the change from baseline in serum phosphorus at Week 8."

Table 53. Change from baseline in serum phosphorus at Week 8 (mg/dL) (mITT)

	Tenapanor (N = 52)
Baseline serum phosphorus level (Mean ± SD)	7.65 ± 1.07
Serum phosphorus level at Week 8 (Mean ± SD)[a)]	6.47 ± 1.67
Change in serum phosphorus [95% CI][b)]	-1.18 [-1.54, -0.81]

a) LOCF was used to impute missing data.
b) Calculated using t-distribution.

Regarding safety, the incidence of adverse events was 88.9% (48 of 54 subjects), and adverse events reported by ≥2 subjects are shown in Table 54. Adverse drug reactions occurred in 74.1% (40 of 54) of subjects, and those reported by ≥2 subjects were diarrhea (70.4% [38 of 54 subjects]) and soft faeces (5.6% [3 of 54 subjects]).

Table 54. Adverse events reported by ≥2 subjects (Safety analysis set)

	Tenapanor (N = 54)		Tenapanor (N = 54)
Any adverse event	88.9 (48)	Catheter site infection	3.7 (2)
Diarrhea	74.1 (40)	Decreased appetite	3.7 (2)
Pyrexia	9.3 (5)	Arthralgia	3.7 (2)
Soft faeces	5.6 (3)	Myalgia	3.7 (2)
Peritonitis	5.6 (3)	Insomnia	3.7 (2)

Incidence % (n)
MedDRA/J ver.24.1

No deaths were reported. The incidence of serious adverse events was 13.0% (7 of 54 subjects) (peritonitis [3 subjects]; and coronary artery arteriosclerosis; clavicle fracture; cerebral infarction; and acquired hydrocele [1 subject each]). Although the event of peritonitis (2 subjects) led to study drug discontinuation, all those events were considered unrelated to study drug. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 5.6% (3 of 54) of subjects (diarrhea [3 subjects]; and decreased appetite [1 subject] [some patients had more than 1 event]), all of which were classified as adverse drug reactions.

7.2.4 Japanese long-term treatment study in HD patients (CTD 5.3.5.2.3, Study 7791-007 [March 2021 to June 2022])

An open-label, uncontrolled study was conducted at 30 sites in Japan to evaluate the long-term safety and efficacy of tenapanor in patients with hyperphosphatemia on HD (Table 55) (target sample size, 200 subjects[43)]).

Table 55. Key inclusion/exclusion criteria

Key inclusion criteria
● ≥20 years of age
● Patients with stable CKD on HD 3 times per week for ≥12 weeks
● Unchanged dialysis conditions excluding dry weight during the last 2 weeks before screening
● Taking phosphate binders with the dosing regimen unchanged during the last 4 weeks before screening
● Serum phosphorus levels of ≥3.5 mg/dL and ≤7.0 mg/dL at screening
● If on treatment with vitamin D supplementation, calcimimetics, bisphosphonates, calcitonin, selective estrogen receptor modulators, or teriparatide, the prescribed dosing regimen unchanged during the last 4 weeks before screening
● Kt/Vurea ≥1.2 at most recent measurement during routine clinical monitoring before screening
Key exclusion criteria
● Had received concomitant PD within 12 weeks before screening
● Intact PTH >600 pg/mL
● Current or history of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome
● History of gastrectomy or enterectomy (excluding endoscopic resection and cecectomy) or had undergone gastrointestinal tract surgery (excluding endoscopic resection and cecectomy) within 3 months before screening
● Use of anti-RANKL antibody preparations within 6 weeks before screening
● Use of anti-sclerostin antibody preparations within 12 weeks before screening
● Diarrhea or loose stool, defined as BSFS ≥6* and ≥3 bowel movements on 2 or more days during the week before enrollment
***BSFS 6 (mushy consistency with ragged edges) or BSFS 7 (entirely liquid)**

The study consisted of a screening period (from the date of obtaining consent until enrollment) and a treatment period (52-week study treatment).

Subjects initially received tenapanor 5 mg orally twice daily, immediately prior to meals.[34)] Then, as shown in Table 56, the doses of tenapanor and phosphate binders were to be adjusted with the goal of maintaining serum phosphorus in the range of baseline value ± 0.5 mg/dL (≤6.0 mg/dL) for subjects with baseline serum phosphorus levels of ≤6.0 mg/dL or in the range of 5.5 mg/dL to 6.0 mg/dL for subjects with baseline serum phosphorus levels of ≥6.1 mg/dL. The dose of tenapanor was to be titrated in a stepwise fashion (5, 10, 20, and 30 mg). When the dose was adjusted, switching from phosphate binders to tenapanor was considered wherever possible. The doses of tenapanor and phosphate binders were not to be adjusted simultaneously. If an adverse event for which a causal relationship to both tenapanor and phosphate binders could not be ruled out occurred, and dose reductions of these drugs were considered necessary, the dose of the more likely causative drug was to be reduced first. The duration of treatment was 52 weeks.

[43)] In accordance with "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (PAB/ELD Notification No. 592 of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated May 24, 1995), 100 subjects exposed for a minimum of one-year in this study were needed to include as part of the safety data base. On the basis of Study 7791-003 (35.8% [24 of 67] of subjects withdrew from the study before completing the 26-week treatment period) and Study TEN-02-301 (39.5% [167 of 423] of subjects withdrew from the study before completing the 26-week treatment period), given the 52-week treatment period in this study, the total dropout rate was assumed to be 50%, and a target sample size of 200 subjects was chosen.

Table 56. Guidance on dose adjustments of tenapanor and phosphate binders

	Tenapanor	Phosphate binders
Criteria for dose increase	**Both of the following criteria 1) and 2) were met. Following dose reduction according to the dose reduction criterion 2), even if the dose increase criterion 1) was not met, the dose could be increased back to the previous dose immediately prior to a meal after the end of dialysis following the longest dialysis interval, provided that the investigator considered that there was no problem with subject safety.** **1) A subject on stable doses of tenapanor and phosphate binders for ≥1 week had serum phosphorus of i), ii), or iii) at the scheduled visit after the latest longest dialysis interval.** **i) ≥6.1 mg/dL** **ii) ≤6.0 mg/dL, but above baseline value** **iii) ≤6.0 mg/dL and lower than baseline value, but ≥3.5 mg/dL, and the investigator considered that the dose should be increased.** **2) The investigator considered that there was no problem with subject safety etc. and that the dose could be increased.**	**All of the following criteria were met.** **1) The dose of tenapanor could not be increased.** **2) A subject on stable doses of tenapanor and phosphate binders for ≥1 week had serum phosphorus of ≥6.1 mg/dL at the scheduled visit after the latest longest dialysis interval, or ≤6.0 mg/dL but above baseline value + 0.5 mg/dL, and the investigator considered that dose increase of phosphate binders was needed.** **3) The investigator considered that there was no problem with subject safety following dose increase of phosphate binders.**
Criteria for dose reduction	**The dose was ≥10 mg, and either of the following criteria was met.** **1) A subject on a stable dose of tenapanor without phosphate binders for ≥1 week had serum phosphorus <3.5 mg/dL after the latest longest dialysis interval.** **2) Adverse events occurred, and the investigator considered that dose reduction was needed.**	**Either of the following criteria was met.** **1) Based on the serum phosphorus level at the scheduled visit after the latest longest dialysis interval in a subject on stable doses of tenapanor and phosphate binders for ≥1 week, the investigator considered that the dose of phosphate binders could be reduced.** **2) Adverse events occurred, and the investigator considered that dose reduction of phosphate binders was needed.**
Interruption criteria	**Either of the following criteria was met.** **1) A subject on the 5 mg dose of tenapanor without phosphate binders for ≥1 week had serum phosphorus <3.5 mg/dL at the scheduled visits after the 2 latest longest dialysis intervals.** **2) Adverse events occurred, and the investigator considered that the drug should be interrupted.**	**Phosphate binders were to be interrupted if the dose was reduced to 0 mg according to the dose reduction criteria for phosphate binders.**
Resumption criteria	**If either of the following criteria was met, tenapanor was to be resumed immediately prior to a meal after the end of dialysis following the longest dialysis interval. After interruption, tenapanor was to be resumed at the same dose level or at 1 dose level lower. If on the 5 mg dose, tenapanor was to be resumed at a dose of 5 mg.** **1) Following interruption according to the interruption criterion 1), a confirmed serum phosphorus level of ≥3.5 mg/dL after the longest dialysis interval. If the investigator was concerned about hypophosphataemia following treatment resumption, tenapanor could be resumed immediately prior to a meal after the end of dialysis following the longest dialysis interval after next or later, instead of the next longest dialysis interval. When tenapanor was resumed, a serum phosphorus level of ≥3.5 mg/dL after the latest longest dialysis interval was confirmed.** **2) Following interruption according to the interruption criterion 2), the investigator considered that there was no problem with subject safety.**	**After interruption, phosphate binders were resumed according to the dose increase criteria for phosphate binders.**

Among 213 enrolled subjects, after excluding 1 subject who had arrhythmia and was withdrawn by the investigator before receiving study drug, 212 subjects received study drug and were included in the safety analysis set. After excluding subjects who had no post-baseline serum phosphorus measurement, 204 subjects were included in the mITT population, which was used as the primary efficacy population. There were 58 discontinuations, and the reasons for discontinuations were "withdrawal by subject" (27 subjects), "adverse events" (17 subjects), "protocol deviation" (7 subjects), "lost to follow-up" (4 subjects), "study drug not resumed" (2 subjects), and "physician decision" (1 subject).

Regarding efficacy, the proportion of subjects who achieved a ≥30% reduction in the total number of phosphate binder and tenapanor tablets prescribed daily based on an average calculated for the most recent 3 weeks

compared with the number of prescribed phosphate binder tablets per day at baseline [95% CI][44] (the number of subjects who achieved/the number of subjects evaluated) was 77.5% [71.1%, 83.0%] (158 of 204 subjects), and the lower bound of the confidence interval was above the pre-specified threshold of 20%.

Regarding safety, the incidence of adverse events was 96.2% (204 of 212 subjects), and adverse events reported by ≥3% of subjects are shown in Table 57. Adverse drug reactions occurred in 63.2% (134 of 212) of subjects, and those reported by ≥3% of subjects were diarrhea (56.6% [120 of 212 subjects]) and soft faeces (4.2% [9 of 212 subjects]).

Table 57. Adverse events reported by ≥3% of subjects (Safety analysis set)

	Tenapanor (N = 212)		Tenapanor (N = 212)
Any adverse event	96.2 (204)	Muscle spasms	5.2 (11)
Diarrhea	63.7 (135)	Headache	5.2 (11)
Vaccination complication	19.8 (42)	Vaccination site pain	4.7 (10)
Pyrexia	17.5 (37)	Eczema	4.7 (10)
Contusion	13.2 (28)	Vomiting	4.7 (10)
Back pain	9.4 (20)	Soft faeces	4.2 (9)
Nasopharyngitis	9.4 (20)	Abdominal pain	3.8 (8)
Shunt stenosis	8.5 (18)	Wound	3.8 (8)
Hyperkalaemia	7.1 (15)	Hypocalcaemia	3.8 (8)
Arthralgia	6.1 (13)	Hyperkeratosis	3.8 (8)
Pain in extremity	5.7 (12)	Iron deficiency anaemia	3.8 (8)
COVID-19	5.7 (12)	Vaccination site reaction	3.3 (7)
Nausea	5.2 (11)	Subcutaneous haemorrhage	3.3 (7)
Ligament sprain	5.2 (11)	Hypertension	3.3 (7)
Shunt occlusion	5.2 (11)	Vertigo	3.3 (7)

Incidence % (n)
MedDRA/J ver.24.1

Death occurred in 0.5% (1 of 212) of subjects [COVID-19[45] (1 subject)]) and was considered unrelated to study drug. The incidence of serious adverse events was 20.3% (43 of 212 subjects) (COVID-19; and shunt occlusion [7 subjects each]; angina pectoris [5 subjects]; cellulitis; and peripheral arterial occlusive disease [3 subjects each]; colon cancer; and cerebral infarction [2 subjects each]; and unstable angina; atrial fibrillation; congestive cardiac failure; coronary artery stenosis; Prinzmetal angina; colitis; duodenal perforation; gastric ulcer haemorrhage; large intestine polyp; diverticular perforation; acute cholecystitis; bacteraemia; shunt infection; bacterial infection; rib fracture; spinal compression fracture; shunt stenosis; costochondritis; lumbar spinal stenosis; amyloid arthropathy; breast cancer; transient ischaemic attack; partial seizures; thrombotic cerebral infarction; ureterolithiasis; asthma; drug eruption; aortic aneurysm; and haemorrhagic shock [1 subject each] [some patients had more than 1 event]). The events of gastric ulcer haemorrhage, spinal compression fracture, and Prinzmetal angina (1 subject each) led to study drug discontinuation. The events of colitis, gastric ulcer haemorrhage, and diverticular perforation (1 subject each) were classified as adverse drug reactions. Adverse events leading to study drug discontinuation other than serious adverse events occurred in 6.1% (13 of 212) of subjects (diarrhea [9 subjects]; and anaemia; haematochezia; acidosis; and abdominal pain [1 subject each]), all of which were classified as adverse drug reactions, except for anaemia and abdominal pain.

[44] The 95% confidence interval was calculated by Clopper-Pearson method.
[45] A 84-year-old man. The subject had COVID-19 on Day 294 and died on Day 295. This was considered unrelated to study drug.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

Based on the considerations in Sections 7.R.1.1 to 7.R.1.2, the submitted data have demonstrated the efficacy of tenapanor in HD patients, and the efficacy of tenapanor is expected also in PD patients.

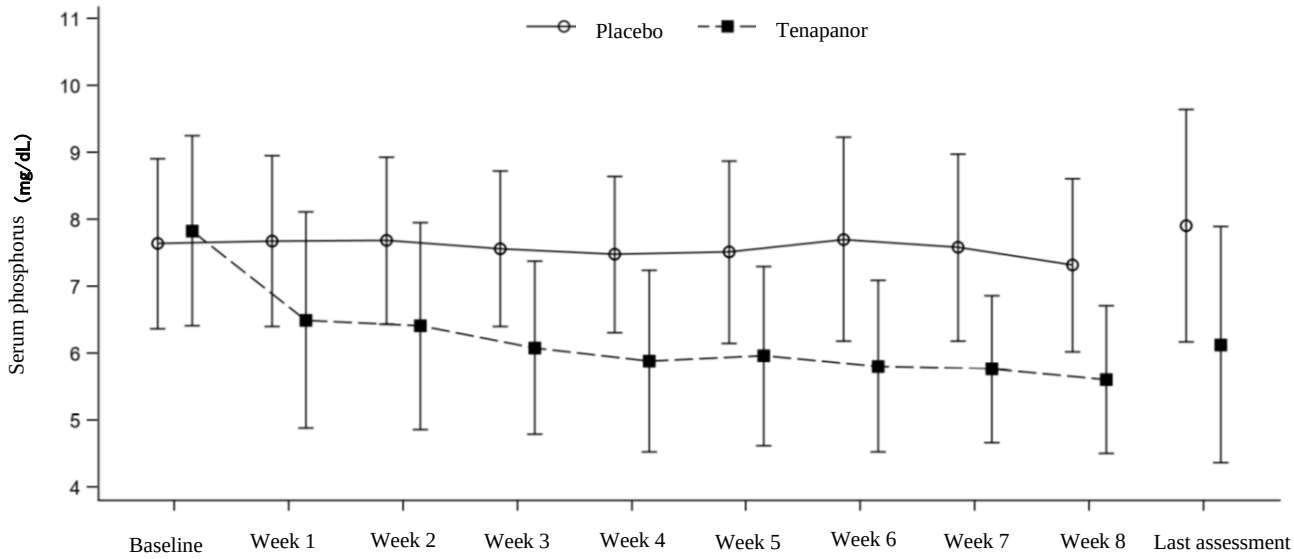
7.R.1.1 HD patients

7.R.1.1.1 Results of primary endpoint etc.

The applicant's explanation about the efficacy of tenapanor in patients with hyperphosphatemia on HD:

Both a Japanese phase III study of tenapanor monotherapy in HD patients (Study 004) and a Japanese phase III study of tenapanor as add-on therapy to phosphate binders in HD patients inadequately controlled on existing phosphate binders (Study 005) demonstrated the superiority of tenapanor to placebo in the primary endpoint of "the change from baseline in serum phosphorus at Week 8" (Table 46 and Table 49).

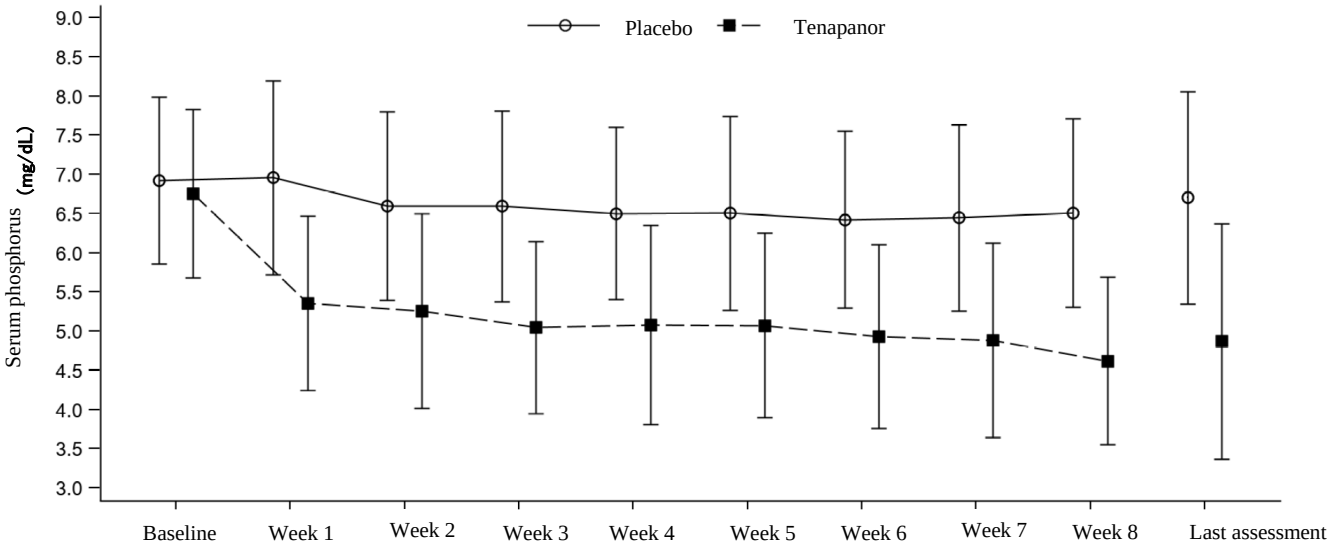
Figure 1 shows change in serum phosphorus over time in Study 004. While there were no reductions from baseline in the placebo group, serum phosphorus levels in the tenapanor group decreased markedly from baseline to Week 1 and then decreased gradually until Week 8. The proportions of subjects who achieved the target serum phosphorus levels (≥3.5 mg/dL and ≤6.0 mg/dL) at each subject's last assessment were 11.8% (9 of 76 subjects) in the placebo group and 60.5% (49 of 81 subjects) in the tenapanor group. In the tenapanor group, the time to the first achievement of the target serum phosphorus levels was 14.0 ± 11.7 days.



Time point	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Last assessment
Placebo (N)	76	76	73	69	67	67	67	63	58	76
Tenapanor (N)	81	81	76	72	69	68	66	65	65	81

Figure 1. Change in serum phosphorus from baseline over time (Study 004, mITT population, Mean ± SD)

Figure 2 shows change in serum phosphorus over time in Study 005. Serum phosphorus levels in the placebo group decreased slightly from baseline to Week 2, but there were no changes thereafter. Serum phosphorus levels in the tenapanor group decreased markedly from baseline to Week 1 and then decreased gradually until Week 8. The proportions of subjects who achieved the target serum phosphorus levels (≥3.5 mg/dL and ≤6.0 mg/dL) at each subject's last assessment were 28.9% (24 of 83 subjects) in the placebo group and 70.4% (57 of 81 subjects) in the tenapanor group. In the tenapanor group, the time to the first achievement of the target serum phosphorus levels was 10.7 ± 8.2 days.



Time point	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Last assessment
Placebo (N)	83	83	80	80	78	76	75	74	74	83
Tenapanor (N)	81	81	79	76	75	74	74	74	73	81

Figure 2. Change in serum phosphorus from baseline over time (Study 005, mITT population, Mean ± SD)

PMDA's view:

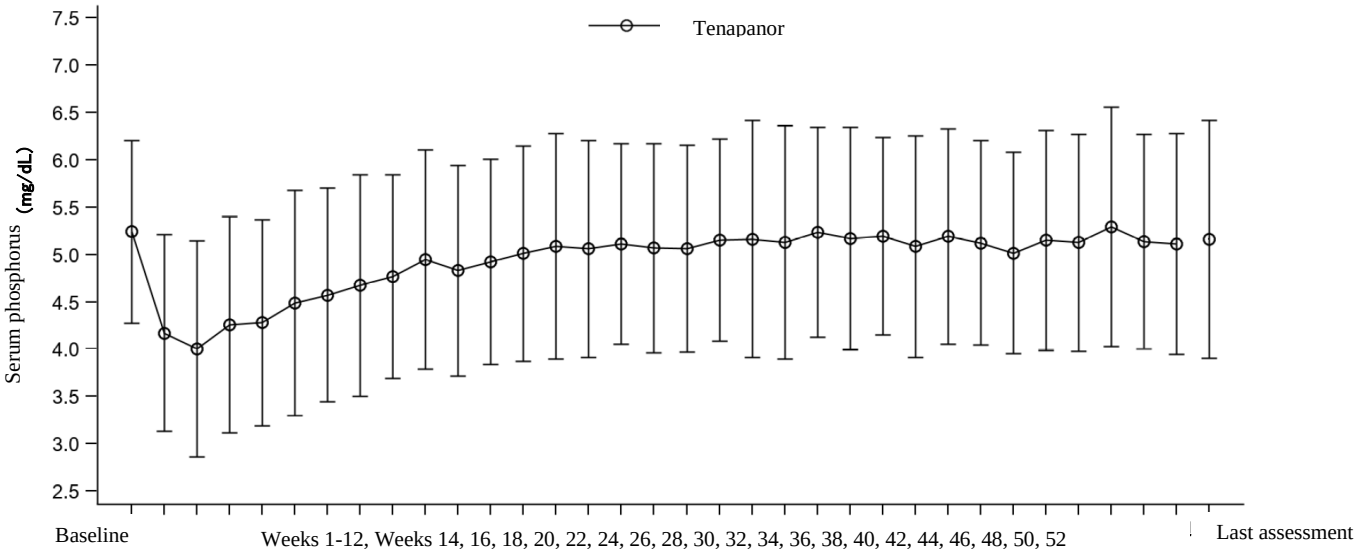
Studies 004 and 005 demonstrated the superiority of tenapanor to placebo. In the tenapanor group, 60.5% to 70.4% of subjects achieved the target serum phosphorus levels at the last assessment, and serum phosphorus levels could be managed with dose adjustments based on serum phosphorus levels. Thus, the efficacy of tenapanor, both as monotherapy and as add-on therapy to phosphate binders, was demonstrated in patients with hyperphosphatemia on HD.

7.R.1.1.2 Long-term efficacy

The applicant's explanation about the long-term efficacy of tenapanor:

In a Japanese long-term treatment study in patients with hyperphosphatemia on HD (Study 007), patients on phosphate binders with serum phosphorus levels of ≥3.5 mg/dL and ≤7.0 mg/dL were included. After the initiation of tenapanor, switching from phosphate binders to tenapanor was considered wherever possible, while managing serum phosphorus levels. Figure 3 shows change in serum phosphorus over time. A reduction from baseline in serum phosphorus occurred at 1 to 2 weeks after the initiation of tenapanor, and then serum phosphorus levels gradually returned towards baseline and remained stable thereafter. The proportions of

subjects who achieved the target serum phosphorus levels (≥3.5 mg/dL and ≤6.0 mg/dL) were 77.9% (159 of 204 subjects) at baseline, 73.3% (126 of 172 subjects) at Week 26, 77.6% (118 of 152 subjects) at Week 52, and 72.1% (147 of 204 subjects) at each subject's last assessment. The proportion of subjects who achieved the target serum phosphorus levels at time points through Week 52 ranged from 62.6% to 80.4%. As phosphate binders were to be switched to tenapanor wherever possible after the initiation of tenapanor, the number of prescribed phosphate binder tablets was reduced from baseline (Table 58).



Time point	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
N	204	204	198	198	196	190	189	187	186	185	185	184
Time point	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 26	Week 28	Week 30	Week 32	Week 34
N	183	180	175	174	171	172	172	172	172	167	167	163
Time point	Week 36	Week 38	Week 40	Week 42	Week 44	Week 46	Week 48	Week 50	Week 52	Last assessment		
N	162	165	163	158	158	157	154	152	152	204		

Figure 3. Change in serum phosphorus from baseline over time (Study 007, mITT population, Mean ± SD)

Table 58. Summary of total number of phosphate binder and tenapanor tablets prescribed daily (mITT)

Number of prescribed phosphate binder tablets per day at baseline (Mean ± SD)	**11.4 ± 7.6 tablets (N = 204)**
Total number of phosphate binder and tenapanor tablets prescribed daily at Week 50 (at last prescription) (Mean ± SD)	**5.1 ± 5.5 tablets (N = 154)**
% (Number) of subjects who achieved a ≥30% reduction in the total number of phosphate binder and tenapanor tablets prescribed daily based on an average calculated for the most recent 3 weeks compared with the number of prescribed phosphate binder tablets per day at baseline	**77.5% (158 of 204 subjects)**
% (Number) of subjects who achieved a ≥50% reduction in the total number of phosphate binder and tenapanor tablets prescribed daily based on an average calculated for the most recent 3 weeks compared with the number of prescribed phosphate binder tablets per day at baseline	**56.4% (115 of 204 subjects)**
% (Number) of subjects who completely switched from phosphate binders to tenapanor (a 100% reduction in the number of prescribed phosphate binder tablets per day based on an average calculated for the most recent 3 weeks compared with the number of prescribed phosphate binder tablets per day at baseline)	**45.6% (93 of 204 subjects)**

If taking phosphate binder formulations other than tablets, e.g., granules and fine granules, the number of prescribed tablets per day was calculated by estimating the dose in terms of tablets.

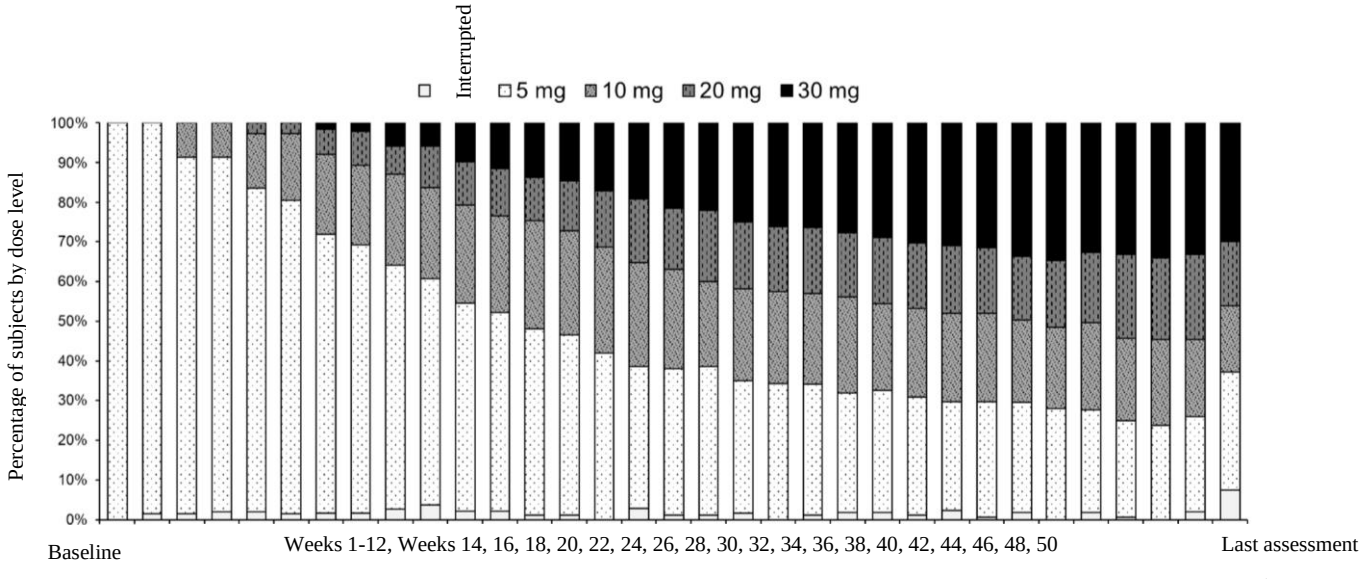


Figure 4. Change in dose level of tenapanor through Week 52 (Study 007, mITT population)

PMDA's view:

In Study 007, even though phosphate binders were switched to tenapanor wherever possible, the long-term control of serum phosphorus was maintained. Thus, the long-term efficacy of tenapanor is also expected.

7.R.1.1.3 Efficacy by subject characteristics

The applicant's explanation about the efficacy of tenapanor by subject characteristics in Studies 004 and 005:

Tables 59 and 60 show the primary endpoint of the change from baseline in serum phosphorus at Week 8 by major subject characteristics in Studies 004 and 005, respectively. Although evaluation has limitations due to the limited number of subjects in some subgroups, the results in all subgroups were consistent with the results in the entire mITT population.

Table 59. Change from baseline in serum phosphorus at Week 8 by major subject characteristics (mg/dL) (Study 004, mITT population)

		Placebo (N = 76)		Tenapanor (N = 81)		Treatment difference
		Number of subjects at baseline	Change from baseline at Week 8	Number of subjects at baseline	Change from baseline at Week 8	
Sex	**Female**	**25**	**0.13 [-0.40, 0.67] (21)**	**28**	**-1.76 [-2.29, -1.24] (22)**	**-1.90 [-2.65, -1.14]**
	Male	**51**	**-0.05 [-0.42, 0.32] (37)**	**53**	**-1.92 [-2.28, -1.56] (43)**	**-1.87 [-2.38, -1.35]**
Age (years)	**<65**	**31**	**-0.02 [-0.50, 0.47] (22)**	**36**	**-2.07 [-2.51, -1.64] (30)**	**-2.05 [-2.71, -1.40]**
	≥65	**45**	**0.08 [-0.32, 0.48] (36)**	**45**	**-1.75 [-2.16, -1.34] (35)**	**-1.83 [-2.40, -1.26]**
Body weight (kg)	**<60**	**38**	**0.19 [-0.26, 0.64] (31)**	**35**	**-1.61 [-2.09, -1.12] (28)**	**-1.79 [-2.46, -1.13]**
	≥60	**38**	**-0.07 [-0.49, 0.35] (27)**	**46**	**-2.11 [-2.48, -1.74] (37)**	**-2.04 [-2.60, -1.48]**
Baseline serum phosphorus level (mg/dL)	**≤7.0**	**33**	**0.73 [0.23, 1.23] (29)**	**24**	**-1.05 [-1.64, -0.46] (21)**	**-1.78 [-2.55, -1.01]**
	≥7.1 and ≤8.0	**15**	**-0.44 [-0.99, 0.12] (12)**	**24**	**-2.04 [-2.46, -1.61] (21)**	**-1.60 [-2.30, -0.90]**
	≥8.1	**28**	**-0.50 [-1.01, 0.01] (17)**	**33**	**-2.69 [-3.15, -2.24] (23)**	**-2.20 [-2.28, -1.51]**

Least squares means from an MMRM model [95% CI] (Number of subjects at Week 8)

Table 60. Change from baseline in serum phosphorus at Week 8 by major subject characteristics (mg/dL) (Study 005, mITT population)

		Placebo (N = 83)		Tenapanor (N = 81)		Treatment difference
		Number of subjects at baseline	Change from baseline at Week 8	Number of subjects at baseline	Change from baseline at Week 8	
Sex	Female	28	-0.51 [-1.01, 0.00] (25)	30	-2.10 [-2.58, -1.63] (29)	-1.60 [-2.29, -0.90]
	Male	55	-0.10 [-0.43, 0.24] (49)	51	-1.94 [-2.29, -1.59] (44)	-1.84 [-2.33, -1.36]
Age (years)	<65	50	-0.24 [-0.61, 0.13] (46)	46	-1.94 [-2.32, -1.55] (43)	-1.69 [-2.23, -1.16]
	≥65	33	-0.24 [-0.65, 0.18] (28)	35	-2.11 [-2.51, -1.71] (30)	-1.87 [-2.45, -1.29]
Body weight (kg)	<60	30	-0.51 [-0.95, -0.06] (26)	30	-2.14 [-2.57, -1.70] (29)	-1.63 [-2.25, -1.01]
	≥60	53	-0.08 [-0.44, 0.27] (48)	51	-1.93 [-2.29, -1.56] (44)	-1.84 [-2.36, -1.33]
Baseline serum phosphorus level (mg/dL)	≤7.0	50	0.12 [-0.18, 0.41] (46)	55	-1.58 [-1.86, -1.31] (52)	-1.70 [-2.10, -1.29]
	≥7.1 and ≤8.0	20	-0.89 [-1.63, -0.14] (19)	15	-2.39 [-3.25, -1.52] (13)	-1.50 [-2.64, -0.36]
	≥8.1	13	-0.90 [-1.70, -0.10] (9)	11	-3.77 [-4.63, -2.91] (8)	-2.87 [-4.05, -1.69]
Number of concomitant phosphate binders	1	38	-0.12 [-0.51, 0.26] (32)	32	-2.05 [-2.46, -1.65] (29)	-1.93 [-2.49, -1.37]
	≥2	45	-0.37 [-0.76, 0.03] (42)	49	-1.94 [-2.33, -1.56] (44)	-1.58 [-2.13, -1.02]

Least squares means from an MMRM model [95% CI] (Number of subjects at Week 8)

Since the incidence of diarrhea was high, and diarrhea leading to dose reduction or discontinuation occurred frequently in the tenapanor group, a subgroup analysis was performed according to the occurrence of diarrhea within the first 2 weeks of treatment. The changes from baseline in serum phosphorus at Week 8 in the subgroups with or without diarrhea within the first 2 weeks of treatment were similar to that in the entire mITT population in both Studies 004 and 005 (Table 61 and Table 62).

Table 61. Change from baseline in serum phosphorus at Week 8 by occurrence of diarrhea within the first 2 weeks of treatment (mg/dL) (Study 004, mITT population)

		Placebo (N = 76)		Tenapanor (N = 81)		Treatment difference
		Number of subjects at baseline	Change from baseline at Week 8	Number of subjects at baseline	Change from baseline at Week 8	
Diarrhea within the first 2 weeks of treatment	Yes	12	-0.25 [-1.13, 0.62] (9)	45	-1.67 [-2.14, -1.20] (32)	-1.42 [-2.41, -0.42]
	No	64	0.13 [-0.19, 0.46] (49)	36	-2.08 [-2.49, -1.67] (33)	-2.22 [-2.74, -1.70]

Least squares means from an MMRM model [95% CI] (Number of subjects at Week 8)

Table 62. Change from baseline in serum phosphorus at Week 8 by occurrence of diarrhea within the first 2 weeks of treatment (mg/dL) (Study 005, mITT population)

		Placebo (N = 83)		Tenapanor (N = 81)		Treatment difference
		Number of subjects at baseline	Change from baseline at Week 8	Number of subjects at baseline	Change from baseline at Week 8	
Diarrhea within the first 2 weeks of treatment	Yes	7	-0.72 [-1.94, 0.49] (5)	32	-2.21 [-2.74, -1.68] (29)	-1.49 [-2.81, -0.16]
	No	76	-0.18 [-0.45, 0.10] (69)	49	-1.89 [-2.23, -1.55] (44)	-1.71 [-2.15, -1.27]

Least squares means from an MMRM model [95% CI] (Number of subjects at Week 8)

PMDA's view:

Regarding the efficacy of tenapanor by subject characteristics and by the occurrence of diarrhea in the early phase of treatment, the change from baseline in serum phosphorus at Week 8 tended to be greater in the

tenapanor group than in the placebo group across all subgroups, and those subject characteristics or the occurrence of diarrhea in the early phase of treatment do not significantly affect the efficacy of tenapanor.

7.R.1.1.4 Efficacy by concomitant phosphate binder

The applicant's explanation about efficacy by concomitant phosphate binder:

Table 63 shows the change from baseline in serum phosphorus at Week 8 by concomitant phosphate binder in Study 005. Subjects taking more than 1 type of phosphate binder were counted once for each type of phosphate binder. When used in combination with any type of phosphate binder, the reduction from baseline in serum phosphorus was greater in the tenapanor group than in the placebo group, which was consistent with the analysis results in the entire mITT population.

Table 63. Change from baseline in serum phosphorus at Week 8 by concomitant phosphate binder (mg/dL) (Study 005, mITT population)

	Placebo (N = 83)		Tenapanor (N = 81)		Treatment difference
	Number of subjects on Day 1	Change from baseline at Week 8	Number of subjects on Day 1	Change from baseline at Week 8	
Precipitated calcium carbonate	37	-0.28 [-0.69, 0.12] (35)	40	-1.86 [-2.26, -1.45] (34)	-1.57 [-2.15, -0.99]
Sevelamer hydrochloride	11	-0.65 [-1.33, 0.03] (11)	10	-1.94 [-2.65, -1.23] (10)	-1.29 [-2.27, -0.31]
Lanthanum carbonate hydrate	41	-0.52 [-0.93, -0.11] (37)	46	-2.15 [-2.54, -1.76] (41)	-1.63 [-2.19, -1.07]
Bixalomer	14	-0.20 [-0.85, 0.45] (14)	9	-2.22 [-3.07, -1.38] (8)	-2.02 [-3.08, -0.95]
Sucroferric oxyhydroxide	12	0.56 [-0.19, 1.31] (11)	13	-2.06 [-2.80, -1.33] (12)	-2.63 [-3.68, -1.58]
Ferric citrate hydrate	23	-0.67 [-1.32, -0.02] (18)	22	-1.69 [-2.33, -1.04] (19)	-1.01 [-1.93, -0.10]

Least squares means from an MMRM model [95% CI] (Number of subjects at Week 8)

PMDA's view:

Based on the results of subgroup analysis, the efficacy of tenapanor in combination with any type of existing phosphate binder is expected.

7.R.1.2 PD patients

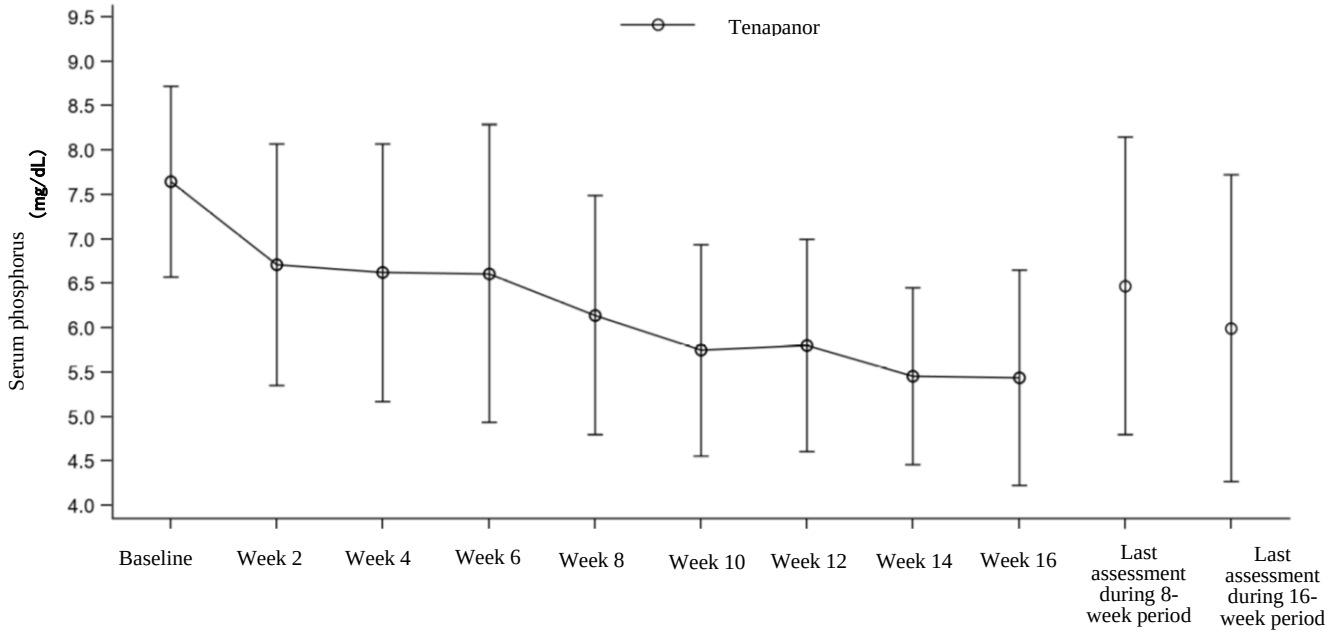
7.R.1.2.1 Results of primary endpoint etc.

The applicant's explanation about the efficacy of tenapanor in patients with hyperphosphatemia on PD:

The primary endpoint of Study 006, i.e., "the change from baseline in serum phosphorus at Week 8" (the mean [95% CI]) was −1.18 [−1.54, −0.81] mg/dL.

The change from baseline in serum phosphorus was smaller in PD patients than in HD patients. Since PD removes less phosphorus than HD (*Journal of Japanese Society for Dialysis Therapy.* 2012; 45: 301-56) etc., the phosphorus load that should be removed by anti-hyperphosphatemia drugs is greater in PD patients, and as with tenapanor, the serum phosphorus lowering effect of other phosphate binders also differed between HD and PD patients (*Perit Dial International.* 2008; 28: 673-5, *Nephron Clin Pract.* 2014; 128: 135-40). Tenapanor reduces intestinal phosphate absorption, resulting in a decreased phosphorus load delivered to the kidney with residual function. This may have affected urinary phosphorus excretion.

In Study 006, tenapanor was to be administered for 16 weeks following phosphate binder washout. If the investigator considered that the tolerable dose of tenapanor was insufficient to reduce serum phosphorus levels after completing the week 8 evaluation, rescue treatment with a phosphate binder was allowed. Figure 5 shows serum phosphorus over time in Study 006. Serum phosphorus levels decreased from baseline to Week 2 and then decreased gradually until Week 16. The mean change from baseline in serum phosphorus at Week 16 (at each subject's last assessment) [95% CI] was −1.65 [−2.08, −1.22] mg/dL. The mean changes from baseline in serum phosphorus at Week 16 were −2.65 [−3.48, −1.81] mg/dL (N = 13) in subjects who received rescue treatment with a phosphate binder after Week 8 and −1.32 [−1.79, −0.85] mg/dL (N = 39) in subjects who did not receive rescue treatment after Week 8. The proportions of subjects who achieved the target serum phosphorus levels (≥3.5 mg/dL and ≤6.0 mg/dL) at each subject's last assessment during the 8-week period and at each subject's last assessment during the 16-week period were 40.4% (21 of 52 subjects) and 59.6% (31 of 52 subjects), respectively. The proportion of subjects who achieved the target levels at time points through Week 16 ranged from 39.6% to 76.5%. The time to the first achievement of the target serum phosphorus levels was 38.5 ± 33.2 days.



Time point	Baseline	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Last assessment during 8-week period	Last assessment during 16-week period
N	52	52	49	48	41	38	38	35	34	52	52

Figure 5. Change in serum phosphorus from baseline over time (Study 006, mITT population, Mean ± SD)

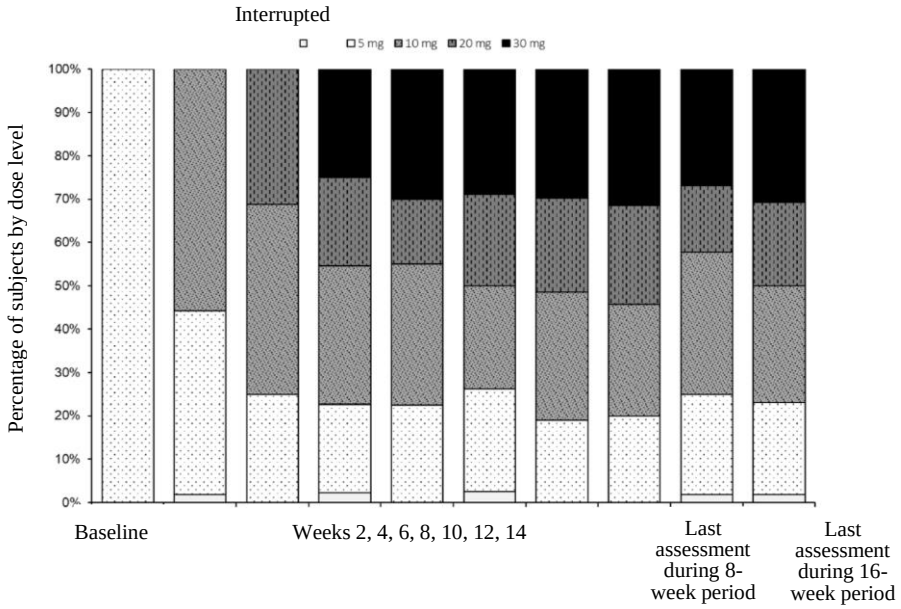


Figure 6. Change in dose level of tenapanor through Week 16 (Study 006, mITT population)

PMDA's view:

In Study 006 in patients with hyperphosphatemia on PD, reductions in serum phosphorus occurred, and a certain proportion of subjects achieved the target serum phosphorus levels. Serum phosphorus could be managed with dose adjustments based on serum phosphorus levels. Thus, the efficacy of tenapanor is expected also in patients with hyperphosphatemia on PD.

7.R.1.2.3 Efficacy by subject characteristics

The applicant's explanation about efficacy by subject characteristics in Study 006:

Table 64 shows the change from baseline in serum phosphorus at Week 8 by major subject characteristics. Serum phosphorus levels tended to decrease across all subgroups. When analyzed by the occurrence of diarrhea within the first 2 weeks of treatment, the changes from baseline in serum phosphorus at Week 8 were −1.24 [−1.72, −0.75] mg/dL (N = 25) in the subgroup with diarrhea and −1.12 [−1.69, −0.55] mg/dL (N = 27) in the subgroup without diarrhea, showing that serum phosphorus levels tended to decrease in the subgroups with or without diarrhea within the first 2 weeks of treatment.

Table 64. Change from baseline in serum phosphorus at Week 8 by major subject characteristics (mg/dL) (Study 006, mITT population)

		Tenapanor (N = 52)
Sex	**Female**	**-1.21 [-2.20, -0.22] (16)**
	Male	**-1.16 [-1.50, -0.82] (36)**
Age (years)	**<65**	**-1.26 [-1.68, -0.83] (21)**
	≥65	**-1.12 [-1.68, -0.56] (31)**
Body weight (kg)	**<60**	**-1.01 [-1.73, -0.28] (21)**
	≥60	**-1.29 [-1.69, -0.89] (31)**
Baseline serum phosphorus level (mg/dL)	**≤7.0**	**-1.16 [-1.53, -0.80] (18)**
	≥7.1 and ≤8.0	**-1.12 [-2.11, -0.13] (15)**
	≥8.1	**-1.23 [-1.89, -0.57] (19)**

Mean [95% CI] (Number of subjects)

PMDA's view:

Regarding the efficacy of tenapanor by subject characteristics and by the occurrence of diarrhea in the early phase of treatment, serum phosphorus levels tended to decrease across all subgroups, and those subject characteristics or the occurrence of diarrhea in the early phase of treatment do not significantly affect the efficacy of tenapanor.

7.R.2 Effects on serum calcium levels and serum intact parathyroid hormone (iPTH) levels

According to the Japanese clinical practice guideline, it is important to regularly monitor and control serum calcium and iPTH as well as serum phosphorus for the management of chronic kidney disease-mineral and bone disorder (CKD-MBD) and secondary hyperparathyroidism (*Journal of Japanese Society for Dialysis Therapy*. 2012; 45: 301-56).

PMDA's conclusion:

Based on the following considerations in Sections 7.R.2.1 and 7.R.2.2, there were no meaningful changes in serum calcium or iPTH following administration of tenapanor. During treatment with tenapanor, it is necessary to regularly monitor serum calcium and iPTH in accordance with the current guideline etc. used in clinical practice.

7.R.2.1 Serum calcium levels

The applicant's explanation about the effect of tenapanor on serum calcium:

As to corrected calcium levels in Japanese phase III studies, though there were slight increases from baseline in the tenapanor groups of Studies 004, 005, and 006, the mean value at the last assessment was within the target range (8.4-10.0 mg/dL) in all studies, and there were no clinically relevant, major changes (Table 65).

Table 65. Corrected serum calcium levels in Japanese phase III studies (mg/dL)

Study	Study population	Treatment duration	Group	Baseline	Last assessment	Change
004	HD patients	8 weeks	Tenapanor	8.73 ± 0.62 (81)	8.93 ± 0.71 (81)	0.20 ± 0.43
			Placebo	8.86 ± 0.62 (76)	8.93 ± 0.64 (76)	0.07 ± 0.36
005	HD patients	8 weeks	Tenapanor	9.03 ± 0.67 (81)	9.19 ± 0.67 (81)	0.16 ± 0.44
			Placebo	9.22 ± 0.70 (83)	9.24 ± 0.64 (83)	0.02 ± 0.39
007	HD patients	52 weeks	Tenapanor (at Week 26)	9.02 ± 0.51 (204)	9.01 ± 0.53 (172)	0.00 ± 0.51
			Tenapanor (at last assessment)		8.93 ± 0.60 (204)	-0.09 ± 0.61
006	PD patients	16 weeks	Tenapanor (at Week 8)	8.87 ± 0.70 (52)	8.90 ± 0.61 (41)	0.08 ± 0.53
			Tenapanor (at last assessment)		9.00 ± 0.56 (52)	0.12 ± 0.59

Mean ± SD (Number of subjects)

7.R.2.2 Serum iPTH levels

The applicant's explanation about the effect of tenapanor on serum iPTH:

In the Japanese phase III Studies 004 and 005, serum iPTH levels after the start of study treatment in the placebo group remained unchanged from baseline, but those in the tenapanor group decreased from baseline. The tenapanor group of Study 006 also showed decreased serum iPTH from baseline. In Study 007, serum iPTH levels increased from baseline after the initiation of tenapanor. The mean value at the last assessment was within the target range (60-240 pg/dL) in all studies, and there were no clinically relevant, major changes (Table 66).

Table 66. Serum iPTH levels in Japanese phase III studies (mg/dL)

Study	Study population	Treatment duration	Group	Baseline	Last assessment	Change
004	HD patients	8 weeks	Tenapanor	228.9 ± 125.0 (81)	186.1 ± 119.3 (77)	-46.3 ± 70.8
			Placebo	226.1 ± 141.0 (76)	222.7 ± 134.4 (73)	2.1 ± 73.1
005	HD patients	8 weeks	Tenapanor	184.0 ± 109.9 (81)	157.5 ± 102.2 (79)	-27.5 ± 52.5
			Placebo	191.0 ± 120.6 (83)	195.5 ± 140.6 (81)	2.1 ± 64.7
007	HD patients	52 weeks	Tenapanor	147.4 ± 87.4 (204)	166.9 ± 118.1 (198)	19.1 ± 107.4
006	PD patients	16 weeks	Tenapanor (at Week 8)	245.0 ± 147.5 (52)	222.6 ± 152.9 (41)	-36.7 ± 69.7
			Tenapanor (at last assessment)		205.4 ± 131.8 (49)	-44.9 ± 76.2

Mean ± SD (Number of subjects)

7.R.3 Safety

PMDA's conclusion:

Based on the considerations in Sections 7.R.3.1 to 7.R.3.3, the submitted data indicate that attention should be paid to the possible occurrence of gastrointestinal disorders, mainly diarrhea, during treatment with tenapanor. Meanwhile, the safety of tenapanor in dialysis patients can be managed by taking appropriate measures such as dose reduction and interruption.

7.R.3.1 Overview of adverse events

Table 67 and Table 68 show an overview of adverse events in Japanese phase II and III studies, respectively. In all of the controlled studies in HD patients (tenapanor monotherapy in Studies 001 and 004; tenapanor in combination with phosphate binders in Studies 002 and 005), the incidences of adverse events and adverse drug reactions were higher in the tenapanor group than in the placebo group, and the most commonly reported event was diarrhea [see Section 7.R.3.3.1]. There were no relevant differences in the trend of occurrence of other adverse events, and no serious adverse drug reactions occurred in any treatment group.

Regarding adverse events reported in Study 006 in PD patients (Table 54), "catheter site infection," "peritonitis," etc., which were considered related to PD procedure, occurred, but there were no clinically relevant differences in the occurrence of other adverse events between PD and HD patients.

Table 67. Overview of adverse events and adverse drug reactions in Japanese phase II studies (Safety analysis set)

	Study 001					Study 002		Study 003
	Placebo (N = 41)	5 mg (N = 42)	10 mg (N = 41)	30 mg (N = 42)	30 mg down-titration (N = 41)	Placebo (N = 24)	Tenapanor (N = 23)	Tenapanor (N = 67)
All adverse events	51.2 (21)	78.6 (33)	78.0 (32)	85.7 (36)	80.5 (33)	37.5 (9)	78.3 (18)	92.5 (62)
All adverse drug reactions	17.1 (7)	52.4 (22)	68.3 (28)	76.2 (32)	68.3 (28)	8.3 (2)	69.6 (16)	76.1 (51)
Serious adverse events[a)]	0	2.4 (1)	4.9 (2)	2.4 (1)	4.9 (2)	0	4.3 (1)	7.5 (5)
Adverse events leading to treatment discontinuation[b)]	0	2.4 (1)	4.9 (2)	7.1 (3)	2.4 (1)	0	13.0 (3)	7.5 (5)
Death	0	0	0	0	0	0	0	0

Incidence % (n)
a) Excluding adverse events leading to death
b) Excluding adverse events leading to death and serious adverse events

Table 68. Overview of adverse events and adverse drug reactions in Japanese phase III studies (Safety analysis set)

	Study 004		Study 005		Study 006	Study 007
	Placebo (N = 82)	Tenapanor (N = 82)	Placebo (N = 85)	Tenapanor (N = 84)	Tenapanor (N = 54)	Tenapanor (N = 212)
All adverse events	65.9 (54)	92.7 (76)	62.4 (53)	85.7 (72)	88.9 (48)	96.2 (204)
All adverse drug reactions	15.9 (13)	75.6 (62)	14.1 (12)	64.3 (54)	74.1 (40)	63.2 (134)
Serious adverse events[a)]	3.7 (3)	4.9 (4)	3.5 (3)	2.4 (2)	13.0 (7)	20.3 (43)
Adverse events leading to treatment discontinuation[b)]	0	3.7 (3)	0	1.2 (1)	5.6 (3)	6.1 (13)
Death	2.4 (2)	0	0	0	0	0.5 (1)

Incidence % (n)
a) Excluding adverse events leading to death
b) Excluding adverse events leading to death and serious adverse events

PMDA's conclusion:

The most commonly reported adverse event or adverse drug reaction was diarrhea in HD and PD patients, and no other clinically relevant specific events were identified with tenapanor. Diarrhea will be reviewed separately in Section "7.R.3.3.1 Diarrhea."

7.R.3.2 Safety by time from onset of therapy

The applicant's explanation about safety by time from the onset of therapy:

Table 69 shows the incidence of adverse events through Week 52 by time from the onset of therapy in a Japanese long-term treatment study in HD patients (Study 007). There was no clinically relevant trend in the incidence of adverse events by time from the onset of therapy, e.g., the incidence of overall adverse events increased with longer tenapanor exposure, or the incidence of a specific adverse event increased with longer tenapanor exposure.

Table 69. Incidence of adverse events by time from onset of tenapanor therapy (Study 007, Safety analysis set)

	0-12 weeks (N = 212)	12-24 weeks (N = 183)	24-36 weeks (N = 172)	36-52 weeks (N = 165)	Entire study period (N = 212)
All adverse events	82.1 (174)	64.5 (118)	65.7 (113)	83.6 (138)	96.2 (204)
All adverse drug reactions	52.8 (112)	12.6 (23)	10.5 (18)	10.9 (18)	63.2 (134)
Serious adverse events	21.2 (45)	12.0 (22)	10.5 (18)	15.8 (26)	42.0 (89)
Serious adverse drug reactions	13.2 (28)	1.6 (3)	2.3 (4)	1.8 (3)	17.9 (38)
Adverse events leading to treatment discontinuation	5.2 (11)	0 (0)	1.7 (3)	1.8 (3)	8.0 (17)
Adverse drug reactions leading to treatment discontinuation	4.2 (9)	0 (0)	1.7 (3)	0 (0)	5.7 (12)
Adverse events reported by ≥5% of subjects in the overall population during the entire study period					
Diarrhea	50.9 (108)	11.5 (21)	13.4 (23)	13.9 (23)	63.7 (135)
Vaccination complication	12.3 (26)	4.4 (8)	1.2 (2)	11.5 (19)	19.8 (42)
Pyrexia	8.5 (18)	6.0 (11)	2.9 (5)	7.9 (13)	17.5 (37)
Contusion	2.4 (5)	4.9 (9)	2.9 (5)	9.1 (15)	13.2 (28)
Nasopharyngitis	3.3 (7)	2.2 (4)	5.8 (10)	3.6 (6)	9.4 (20)
Back pain	2.4 (5)	1.6 (3)	2.9 (5)	5.5 (9)	9.4 (20)
Shunt stenosis	2.8 (6)	5.5 (10)	2.3 (4)	5.5 (9)	8.5 (18)
Hyperkalaemia	2.4 (5)	1.1 (2)	1.7 (3)	3.0 (5)	7.1 (15)
Arthralgia	0.5 (1)	1.1 (2)	2.3 (4)	4.2 (7)	6.1 (13)
Pain in extremity	2.8 (6)	1.1 (2)	1.2 (1)	2.4 (4)	5.7 (12)
COVID-19	0 (0)	0 (0)	1.2 (2)	6.1 (10)	5.7 (12)
Shunt occlusion	2.4 (5)	2.2 (4)	0.6 (1)	3.0 (5)	5.2 (11)
Nausea	3.3 (7)	1.1 (2)	0.6 (1)	0.6 (1)	5.2 (11)
Muscle spasms	0.5 (1)	2.2 (4)	1.2 (2)	2.4 (4)	5.2 (11)
Ligament sprain	1.4 (3)	1.6 (3)	0.6 (1)	3.0 (5)	5.2 (11)
Headache	1.9 (4)	0.5 (1)	2.9 (5)	1.8 (3)	5.2 (11)
Adverse drug reactions reported by ≥2 subjects in the overall population during the entire study period					
Diarrhea	47.2 (100)	7.7 (14)	8.7 (15)	9.1 (15)	56.6 (120)
Soft faeces	3.3 (7)	0.5 (1)	0 (0)	0.6 (1)	4.2 (9)
Hypocalcaemia	1.4 (3)	0.5 (1)	0 (0)	0.6 (1)	1.9 (4)
Abdominal pain	0.9 (2)	0 (0)	0 (0)	0 (0)	0.9 (2)
Metabolic acidosis	0.5 (1)	0 (0)	0.6 (1)	0 (0)	0.9 (2)
Hypophosphataemia	1.4 (3)	0.5 (1)	0 (0)	0 (0)	1.4 (3)
Weight decreased	0.5 (1)	0 (0)	0 (0)	0.6 (1)	0.9 (2)
Frequent bowel movements	0 (0)	1.1 (2)	0 (0)	0 (0)	0.9 (2)
Abdominal distension	0.5 (1)	0.5 (1)	0 (0)	0 (0)	0.9 (2)

Incidence % (n)
MedDRA/J ver.24.1

PMDA's conclusion:

Based on the results of Study 007, there was no trend towards increasing incidence of adverse events with longer tenapanor exposure, etc., and no particular clinical problem associated with long-term treatment was identified. In Study 006 in PD patients, the duration of treatment was 16 weeks, and only 34 subjects completed the clinical study. Thus, information on the long-term safety of tenapanor in PD patients should be collected via post-marketing surveillance, etc.

7.R.3.3 Adverse events of special interest

The applicant's explanation about adverse events of special interest associated with tenapanor:

According to the safety information from non-clinical and clinical studies, the risks of special interest associated with tenapanor were considered non-infectious diarrhea-related events,[46)] dehydration-related

[46)] As non-infectious diarrhea-related events, the following PTs were counted: "defaecation urgency," "diarrhoea," " haemorrhagic diarrhoea," "frequent bowel movements," "gastrointestinal hypermotility," "abnormal faeces," "anal incontinence," "antidiarrhoeal supportive care," "bowel movement irregularity," "change of bowel habit," "faecal volume increased," "gastrointestinal motility disorder," "gastrointestinal tract irritation," "intestinal transit time abnormal," "intestinal transit time decreased," "overflow diarrhoea," "soft faeces"

events,[47] and hyponatremia-related events.[48]

7.R.3.3.1 Non-infectious diarrhea-related events

The applicant's explanation about non-infectious diarrhea-related events:

Table 70 and Table 71 show the incidence of non-infectious diarrhea-related events in Japanese phase II and III studies, respectively. Diarrhea occurred frequently in the tenapanor group. In 4 Japanese phase III studies (Studies 004, 005, 006, and 007), no serious events were reported. The majority of diarrhea events were mild or moderate in severity. Severe diarrhea occurred in 2 subjects, and the both events resolved following discontinuation of tenapanor. In the tenapanor group, diarrhea leading to study drug discontinuation, interruption, or dose reduction occurred in 11 subjects in Study 004, 11 subjects in Study 005, 10 subjects in Study 006, and 35 subjects in Study 007, but all those events had an outcome of "resolved."

The events of diarrhea were counted by time to first onset in the 4 Japanese phase III studies (Studies 004, 005, 006, and 007). In all studies, the majority started to experience diarrhea at a dose of 5 mg within the first week of treatment (47.6% [39 of 82 subjects] in Study 004, 35.7% [30 of 84 subjects] in Study 005, 38.9 [21 of 54 subjects] in Study 006, 31.6% [67 of 212 subjects] in Study 007). On the other hand, as some subjects started to experience diarrhea beyond the first week of treatment, it is necessary to closely monitor patients during treatment with tenapanor and consider taking appropriate measures such as dose reduction, interruption, and discontinuation, as needed.

Table 70. Summary of incidence of non-infectious diarrhea-related events in Japanese phase II studies (Safety analysis set)

	Study 001					Study 002		Study 003
	Placebo (N = 41)	5 mg (N = 42)	10 mg (N = 41)	30 mg (N = 42)	30 mg down-titration (N = 41)	Placebo (N = 24)	Tenapanor (N = 23)	Tenapanor (N = 67)
Diarrhea	22.0 (9)	57.1 (24)	65.9 (27)	76.2 (32)	70.7 (29)	16.7 (4)	65.2 (15)	76.1 (51)
Soft faeces	0	2.4 (1)	4.9 (2)	0	2.4 (1)	0	4.3 (1)	3.0 (2)
Frequent bowel movements	0	0	0	0	0	0	0	0

Incidence % (n)
MedDRA/J ver.22.1

Table 71. Summary of incidence of non-infectious diarrhea-related events in Japanese phase III studies (Safety analysis set)

	Study 004		Study 005		Study 006	Study 007
	Placebo (N = 82)	Tenapanor (N = 82)	Placebo (N = 85)	Tenapanor (N = 84)	Tenapanor (N = 54)	Tenapanor (N = 212)
Diarrhea	19.5 (16)	74.4 (61)	14.1 (12)	63.1 (53)	74.1 (40)	63.7 (135)
Soft faeces	4.9 (4)	6.1 (5)	0	4.8 (4)	5.6 (3)	4.2 (9)
Frequent bowel movements	0	1.2 (1)	0	1.2 (1)	0	0.9 (2)

Incidence % (n)
MedDRA/J ver.24.1

Table 72 shows the details of subjects with serious diarrhea associated with tenapanor in all clinical studies including foreign clinical studies in dialysis patients with hyperphosphatemia (submitted as reference data). Four cases of serious diarrhea were reported in foreign clinical studies and a Japanese phase II study in dialysis

[47] As dehydration-related events, the following PTs were counted: "dehydration," "hypovolaemia," "hypovolaemic shock"
[48] Events in the MedDRA SMQ "hyponatraemia/SIADH"

patients with hyperphosphatemia in which tenapanor was administered with a dosing regimen different from that proposed in Japan. The 2 cases led to study drug discontinuation and the 1 case led to dose reduction of study drug. All those events had an outcome of "resolved." Since diarrhea resolved following dose reduction or discontinuation of study drug, diarrhea is a reversible adverse event and can be managed by taking appropriate measures such as dose reduction, interruption, and discontinuation, as needed.

Table 72. Listing of subjects with serious diarrhea associated with tenapanor

Study ID	Age	Sex	Non-Japanese/ Japanese	Dose of study drug	Severity	Time to onset (days)	Duration (days)	Action taken with tenapanor	Outcome
TEN-02-201	54	Female	Non-Japanese	3 mg twice daily	Severe	36	4	Discontinued	Resolved
TEN-02-301	58	Female	Non-Japanese	30 mg twice daily	Severe	10	49	Not applicable	Resolved
	68	Male	Non-Japanese	30 mg twice daily	Severe	6	22	Discontinued	Resolved
7791-003	65	Female	Japanese	30 mg twice daily	Moderate	6	89	Dose reduced	Resolved

7.R.3.3.2 Dehydration-related events and hyponatremia-related events

The applicant's explanation about dehydration-related events and hyponatremia-related events:
In Japanese phase III studies, dehydration-related events and hyponatremia-related events were collected as adverse events of special interest. In Study 007, as a dehydration-related adverse event, dehydration occurred in 1 subject (0.5%), but this event was considered unrelated to study drug.

In a foreign clinical study in dialysis patients with hyperphosphatemia (TEN-02-301) (tenapanor 30 mg BID with dose titration permitted), dehydration occurred in 1.0% (4 of 419) of subjects during the 26-week treatment period and 0.5% (1 of 220) of subjects during the 14-week safety extension period following the up to 12-week placebo-controlled randomized withdrawal period. Three cases of dehydration during the treatment period were classified as adverse drug reactions, including 1 case of a severe event and 1 case of a serious event. Hypovolaemia occurred in 0.2% (1 of 419) of subjects during the treatment period. Since dehydration-related events are secondary events following diarrhea, the risk can be minimized by appropriately treating diarrhea.

Although hyponatremia-related events were designated as adverse events of special interest based on the mechanism of action of tenapanor, as no hyponatremia-related events were reported in any of Japanese or foreign clinical studies in dialysis patients with hyperphosphatemia, there should be little concern about the occurrence of hyponatremia-related events in the clinical use of tenapanor.

Based on the applicant's explanation in Sections 7.R.3.3.1 and 7.R.3.3.2, PMDA's view on the safety of tenapanor relating to adverse drug reactions of special interest:
Severe diarrhea was reported in Japanese phase III studies, and serious diarrhea also occurred within the dose range proposed in Japan in Japanese and foreign clinical studies in dialysis patients. Severe diarrhea is also expected to be associated with dehydration. The majority of diarrhea events tended to occur in the early phase of treatment, and a certain proportion of patients experienced diarrhea thereafter. Thus, it is necessary to closely monitor patients during treatment with tenapanor and take appropriate measures such as symptomatic treatment,

dose reduction, interruption, and discontinuation, as needed. Though not reported in Japanese clinical studies, serious dehydration associated with diarrhea has also been reported in a foreign clinical study. Thus, the package insert should list severe diarrhea as a clinically significant adverse reaction and include a relevant precautionary statement.

7.R.3.4 Safety by subject characteristics

The applicant's explanation about safety by subject characteristics:

The effects of sex, age, and body weight on the safety of tenapanor were evaluated based on the incidences of adverse events and adverse drug reactions in 4 Japanese phase III studies (Studies 004, 005, 006, and 007) (Table 73, Table 74, Table 75).

Table 73. Incidence of adverse event by sex in Japanese phase III studies (Safety analysis set)

	Study 004				Study 005				Study 006		Study 007	
	Placebo (N = 82)		Tenapanor (N = 82)		Placebo (N = 85)		Tenapanor (N = 84)		Tenapanor (N = 54)		Tenapanor (N = 212)	
	Female (27)	Male (55)	Female (29)	Male (53)	Female (30)	Male (55)	Female (26)	Male (54)	Female (16)	Male (38)	Female (84)	Male (128)
All adverse events	81.5 (22)	58.2 (32)	100.0 (29)	88.7 (47)	63.3 (19)	61.8 (34)	86.7 (26)	85.2 (46)	93.8 (15)	86.8 (33)	95.2 (80)	96.9 (124)
All adverse drug reactions	18.5 (5)	14.5 (8)	86.2 (25)	69.8 (37)	13.3 (4)	14.5 (8)	63.3 (19)	64.8 (35)	62.5 (10)	78.9 (30)	60.7 (51)	64.8 (83)
Adverse event of special interest												
Diarrhea	22.2 (6)	18.2 (10)	82.8 (24)	69.8 (37)	10.0 (3)	16.4 (9)	66.7 (20)	61.1 (33)	68.8 (11)	76.3 (29)	61.9 (52)	64.8 (83)

Incidence % (n)
MedDRA/J ver.24.1

Table 74. Incidence of adverse events by age group in Japanese phase III studies (Safety analysis set)

	Study 004				Study 005				Study 006		Study 007	
	Placebo (N = 82)		Tenapanor (N = 82)		Placebo (N = 85)		Tenapanor (N = 84)		Tenapanor (N = 54)		Tenapanor (N = 212)	
	<65 years (36)	≥65 years (46)	<65 years (36)	≥65 years (46)	<65 years (51)	≥65 years (34)	<65 years (48)	≥65 years (36)	<65 years (22)	≥65 years (32)	<65 years (100)	≥65 years (112)
All adverse events	55.6 (20)	73.9 (34)	91.7 (33)	93.5 (43)	62.7 (32)	61.8 (21)	85.4 (41)	86.1 (31)	90.9 (20)	87.5 (28)	97.0 (97)	95.5 (107)
All adverse drug reactions	16.7 (6)	15.2 (7)	72.2 (26)	78.3 (36)	13.7 (7)	14.7 (5)	60.4 (29)	69.4 (25)	72.7 (16)	75.0 (24)	58.0 (58)	67.9 (76)
Adverse event of special interest												
Diarrhea	13.9 (5)	23.9 (11)	69.4 (25)	78.3 (36)	11.8 (6)	17.6 (6)	60.4 (29)	66.7 (24)	68.2 (15)	78.1 (25)	61.0 (61)	66.1 (74)

Incidence % (n)
MedDRA/J ver.24.1

Table 75. Incidence of adverse events by body weight category in Japanese phase III studies (Safety analysis set)

	Study 004				Study 005				Study 006		Study 007	
	Placebo (N = 82)		Tenapanor (N = 82)		Placebo (N = 85)		Tenapanor (N = 84)		Tenapanor (N = 54)		Tenapanor (N = 212)	
	<60kg (41)	≥60kg (41)	<60kg (36)	≥60kg (46)	<60kg (31)	≥60kg (54)	<60kg (30)	≥60kg (54)	<60kg (21)	≥60kg (33)	<60kg (107)	≥60kg (105)
All adverse events	73.2 (30)	58.5 (24)	97.2 (35)	89.1 (41)	64.5 (20)	61.1 (33)	86.7 (26)	85.2 (46)	90.5 (19)	87.9 (29)	95.3 (102)	97.1 (102)
All adverse drug reactions	19.5 (8)	12.2 (5)	77.8 (28)	73.9 (34)	16.1 (5)	13.0 (7)	66.7 (20)	63.0 (34)	71.4 (15)	75.8 (25)	64.5 (69)	61.9 (65)
Adverse event of special interest												
Diarrhea	19.5 (8)	19.5 (8)	83.3 (30)	67.4 (31)	12.9 (4)	14.8 (8)	70.0 (21)	59.3 (32)	76.2 (16)	72.7 (24)	63.6 (68)	63.8 (67)

Incidence % (n)
MedDRA/J ver.24.1

PMDA's view:

There were no major differences in the incidences of adverse events and adverse drug reactions according to sex, age, or body weight. These subject characteristics do not affect the safety profile of tenapanor.

7.R.3.5 Safety by concomitant phosphate binder

The applicant's explanation about safety by concomitant phosphate binder:

Table 76 shows the incidence of adverse events by type of baseline phosphate binder (precipitated calcium carbonate, sevelamer hydrochloride, lanthanum carbonate hydrate, bixalomer, sucroferric oxyhydroxide, ferric citrate hydrate). Subjects taking more than 1 type of phosphate binder were counted once for each type of phosphate binder.

Table 76. Incidence of adverse events by concomitant phosphate binder (Study 005, Safety analysis set)

	Placebo (N = 85)						Tenapanor (N = 84)					
	Precipitated calcium carbonate (N = 38)	Sevelamer hydrochloride (N = 11)	Lanthanum carbonate hydrate (N = 42)	Bixalomer (N = 14)	Sucroferric oxyhydroxide (N = 12)	Ferric citrate hydrate (N = 24)	Precipitated calcium carbonate (N = 40)	Sevelamer hydrochloride (N = 11)	Lanthanum carbonate hydrate (N = 49)	Bixalomer (N = 10)	Sucroferric oxyhydroxide (N = 13)	Ferric citrate hydrate (N = 22)
All adverse events	57.9 (22)	72.7 (8)	71.4 (30)	71.4 (10)	58.3 (7)	50.0 (12)	85.0 (34)	81.8 (9)	85.7 (42)	90.0 (9)	76.9 (10)	86.4 (19)
All adverse drug reactions	10.5 (4)	18.2 (2)	21.4 (9)	0	8.3 (1)	16.7 (4)	67.5 (27)	54.5 (6)	67.3 (33)	70.0 (7)	46.2 (6)	72.7 (16)
Adverse event of special interest												
Diarrhea	7.9 (3)	0	23.8 (10)	7.1 (1)	16.7 (2)	12.5 (3)	67.5 (27)	45.5 (5)	63.3 (31)	70.0 (7)	46.2 (6)	77.3 (17)

Incidence % (n)
MedDRA/J ver.24.1

PMDA's view:

Although evaluation has limitations due to the limited number of subjects analyzed, as there were no major differences in the incidences of adverse events and adverse drug reactions according to type of concomitant phosphate binder, tenapanor may be used in combination with any type of phosphate binder.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of tenapanor:

The Japanese clinical practice guideline mentions the importance of treatment of hyperphosphatemia in terms of improving patient prognosis, and the target range for serum phosphorus concentrations in dialysis patients is 3.5 to 6.0 mg/dL (*Journal of Japanese Society for Dialysis Therapy.* 2012; 45: 301-56).

Currently in Japan, phosphate binders are used as drug therapy for hyperphosphatemia in dialysis patients. All of existing phosphate binders have a similar mechanism of action. They physically bind to phosphorus in the intestinal tract, resulting in increased phosphorus excretion in feces thereby limiting its intestinal absorption. Different types of phosphate binders cause their characteristic adverse reactions or risks, which pose a problem

for the management of serum phosphorus concentrations. A calcium-containing phosphate binder, precipitated calcium carbonate can promote vascular calcification by increasing the calcium burden or inducing hypercalcemia. In addition, its therapeutic effects are reduced when used with an inhibitor of gastric acid secretion. The major adverse reactions to calcium-free phosphate binding polymers, sevelamer hydrochloride and bixalomer, include gastrointestinal disorders such as constipation and serious symptoms such as intestinal obstruction. A calcium-free metal-based phosphate binder, lanthanum carbonate hydrate, possesses superior phosphate binding capacity. However, gastrointestinal symptoms such as nausea and vomiting are a problem, and there is a concern about the consequences of lanthanum (a non-essential metallic element) deposition in bone tissue etc. following chronic administration. Other metal-based phosphate binders, ferric citrate hydrate and sucroferric oxyhydroxide, are associated with the risks of gastrointestinal symptoms such as diarrhea, iron excess, worsening of hepatitis due to iron accumulation in the liver, etc.

Associations between higher prescribed phosphate binder pill burden and lower phosphate binder adherence have been reported (*Hemodial Int*. 2016; 20: 38-49, *Journal of Japanese Society for Dialysis Therapy.* 2016; 49: 475-82, etc.). Existing phosphate binders must be taken 3 times daily, before or after every meal. The number of tablets or capsules taken for a required dosage is high, and especially, high pill burden is posed by phosphate binding polymers to obtain therapeutic effects. Furthermore, patients on dialysis therapy often have comorbid conditions in addition to hyperphosphatemia, and high dosing frequency and a high total pill burden are a problem (*Journal of Japanese Society for Dialysis Therapy.* 2011; 44: 337-425).

Since tenapanor is taken twice daily, and the pill burden was reduced after switching from existing phosphate binders to tenapanor in Study 007 (Table 58), it is expected that serum phosphorus levels can be managed with a lower pill burden. Moreover, tenapanor has a safety profile different from those of existing phosphate binders. Thus, tenapanor can become a new treatment measure for patients with hyperphosphatemia.

PMDA's view:
Tenapanor has a different mechanism of action from existing phosphate binders. Studies 004 and 005 demonstrated the efficacy of tenapanor, both as monotherapy and as add-on therapy to phosphate binders. In Study 007, the control of serum phosphorus was maintained also after switching from existing phosphate binders to tenapanor [see Section 7.R.1]. Thus, serum phosphorus can be controlled with tenapanor. Regarding safety, the risks observed with existing phosphate binders (hypercalcaemia, intestinal obstruction, the consequences of lanthanum deposition in bone tissues etc., iron excess, etc.) were not found with tenapanor, but attention should be paid to the possible occurrence of diarrhea and dehydration [see Section 7.R.3].

Drugs for the treatment of hyperphosphatemia in dialysis patients are selected according to individual patients' conditions. As with existing phosphate binders, tenapanor will be selected as a new treatment option for patients with hyperphosphatemia on HD or PD, taking account of patient characteristics and the safety profiles of the drugs.

7.R.5 Indication

PMDA's view on the indication for tenapanor:

The results of Japanese phase III studies (Studies 004 and 005) demonstrated the efficacy of tenapanor in patients with hyperphosphatemia on HD, and the results of a Japanese phase III study (Study 006) indicated that the efficacy of tenapanor is expected also in patients with hyperphosphatemia on PD [see Section 7.R.1]. Given the efficacy results from these studies, the safety of tenapanor [see Section 7.R.3] is clinically acceptable. Based on the above, the proposed indication of "Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis" is appropriate. Tenapanor does not facilitate the excretion of blood phosphorus. Thus, as with the currently approved phosphate binders, the following statement should be included in the Precautions Concerning Indication section of the package insert: "Dietary phosphate restrictions should be considered."

7.R.6 Dosage and administration

7.R.6.1 Starting dose in Japanese phase III studies

The applicant's explanation about the starting dose of tenapanor:

A Japanese phase II study in HD patients (Study 001) demonstrated statistically significant differences between each of the tenapanor groups (5 mg group, 10 mg group, 30 mg group, 30 mg down-titration group) and the placebo group in the primary endpoint of "the change from baseline in serum phosphorus at Week 6," and tenapanor tended to reduce serum phosphorus in a dose-dependent manner (Table 38). On the other hand, the incidence of an adverse drug reaction of diarrhea increased dose-dependently (Table 39). Based on the above results, a starting dose of 5 mg was chosen for Japanese phase III studies because tenapanor 5 mg BID significantly reduced serum phosphorus compared with placebo, with the least safety concern.

7.R.6.2 Dose adjustments in Japanese phase III studies

The applicant's explanation about dose adjustments of tenapanor:

In Study 001, tenapanor (5 to 30 mg) reduced serum phosphorus in a dose-dependent manner. Although the incidence of diarrhea increased dose-dependently, as diarrhea leading to treatment discontinuation occurred in 7.1% (3 of 42) of subjects in the 30 mg group, the 30 mg dose was also considered tolerable. Based on the above, dose titration up to a maximum of 30 mg, which had been demonstrated to be tolerable in Study 001, was permitted in Japanese phase III studies. In the Japanese phase III studies, after initiation of treatment, the dose was to be titrated in a stepwise fashion (5, 10, 20, and 30 mg), and a minimum interval of 1 week before dose adjustment was required to assess the effect of an increased dose. In the Japanese phase III studies, after interruption, tenapanor was to be resumed at the same dose level or at 1 dose level lower.

7.R.6.3 Dosing frequency and dosing timing relative to a meal in Japanese phase III studies

The applicant's explanation about the dosing frequency and dosing timing relative to a meal:

As to the dosing frequency of tenapanor, a phase I study in healthy volunteers showed minimal pharmacodynamic differences between the BID and TID regimens. Thus, tenapanor BID was also expected to exert full pharmacodynamic effects [see Section 6.2.2].

As to dosing timing relative to a meal, in a food effect study in healthy volunteers [see Section 6.1.1], urinary sodium and phosphorus excretion tended to be lower when tenapanor was given immediately prior to meals and after meals in comparison to when tenapanor was given in a fasted state, but stool sodium and phosphorus excretion was highest when tenapanor was given immediately prior to meals. Thus, it was considered that tenapanor should be taken immediately prior to meals.

Based on the above, tenapanor was to be administered twice daily immediately prior to meals in Japanese phase III studies.

7.R.6.4 Tenapanor in combination with existing phosphate binders in Japanese phase III studies

The applicant's explanation about tenapanor in combination with existing phosphate binders:

As to dose selection of tenapanor when used in combination with phosphate binders, the results in the tenapanor 30 mg down-titration group from Study 001 of tenapanor monotherapy in patients with hyperphosphatemia on HD were compared with those from Study 002 of tenapanor in combination with phosphate binders in patients with hyperphosphatemia on HD. The efficacy and safety of tenapanor in the 30 mg down-titration group were similar between Studies 001 and 002, showing no differences with or without phosphate binders. Thus, it was considered that the same doses of tenapanor should be used with or without phosphate binders in Japanese phase III studies.

The dosing regimen of tenapanor for Japanese phase III studies was chosen as described in Sections 7.R.6.1 to 7.R.6.4, and these studies demonstrated the efficacy and safety of tenapanor. In Study 007 (52 weeks of treatment) and Study 006 (16 weeks of treatment), the dose of tenapanor taken ranged widely from 5 to 30 mg (Figure 4 and Figure 6). Thus, based on the Japanese phase III studies, the proposed dosage and administration statement should be "The usual adult starting dose is 5 mg of tenapanor orally twice daily, immediately prior to meals. Then, the dose should be adjusted according to the symptoms and serum phosphorus levels. The maximum dose is 30 mg twice daily." The following information should be included in the Precautions Concerning Dosage and Administration section of the package insert: "The dose may be up-titrated in a stepwise fashion at intervals of ≥1 week." and "the recommended dose levels when tenapanor is resumed after interruption."

PMDA's view:

Given that tenapanor is intended to maintain serum phosphorus within the target range, and that dose adjustments are needed according to serum phosphorus levels, tolerability, etc., a starting dose of 5 mg with dose titration up to a maximum of 30 mg in Japanese phase III studies is appropriate because 5 mg was the minimum effective dose and the 30 mg dose was demonstrated to be tolerable in a Japanese phase II study (Study 001).

Japanese phase III studies in HD patients (Studies 004 and 005) demonstrated the clinically meaningful efficacy of tenapanor, both as monotherapy and as add-on therapy to phosphate binders. The results of a Japanese phase III study in PD patients (Study 006) suggested the efficacy of tenapanor. No safety concerns that would become

a particular problem with the clinical use of tenapanor were identified in any of the studies. Given these findings etc., the dosing regimen of tenapanor and guidance on dose adjustments (provided in the Precautions Concerning Dosage and Administration section of the package insert) based on the Japanese phase III studies are appropriate.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing investigations:

Diarrhea occurred frequently in Japanese clinical studies of tenapanor in patients with hyperphosphatemia on HD or PD. Although no dehydration classified as an adverse drug reaction was reported in Japanese clinical studies, severe diarrhea can be associated with dehydration in clinical practice [see Section 7.R.3.3]. Thus, post-marketing specified use-results surveys in HD or PD patients (Table 77 and Table 78) will be conducted to investigate the incidences of diarrhea and dehydration associated with diarrhea. Many of HD and PD patients have been taking drugs for the treatment of hyperphosphatemia over a long period of time, and tenapanor is also intended for long-term treatment. Thus, an observation period of 52 weeks was chosen to evaluate the long-term safety and efficacy of tenapanor in clinical practice.

Table 77. Specified use-results survey (Long-term use in HD patients) (draft)

Objective	**To assess the long-term safety and efficacy of tenapanor in clinical practice.**
Survey method	**Central registry system**
Population	**Patients with hyperphosphatemia on HD**
Planned sample size	**1,000 patients**
Observation period	**52 weeks from the start of treatment with tenapanor**
Main survey items	**● Diarrhea, dehydration associated with diarrhea**

Table 78. Specified use-results survey (Long-term use in PD patients) (draft)

Objective	**To assess the long-term safety and efficacy of tenapanor in clinical practice.**
Survey method	**Central registry system**
Population	**Patients with hyperphosphatemia on PD**
Planned sample size	**100 patients**
Observation period	**52 weeks from the start of treatment with tenapanor**
Main survey items	**● Diarrhea, dehydration associated with diarrhea**

PMDA's view:

An investigation of the incidences of diarrhea and dehydration associated with diarrhea in post-marketing surveillance is appropriate. The details of the survey plan, including the observation period, need to be further discussed.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-3, CTD 5.3.5.1-4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tenapanor has efficacy in the treatment of hyperphosphatemia in patients with chronic kidney disease on dialysis, and that tenapanor has acceptable safety in view of its benefits. Tenapanor is clinically meaningful because it offers a new treatment option for hyperphosphatemia in patients with chronic kidney disease on dialysis.

PMDA has concluded that tenapanor may be approved if tenapanor is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 8, 2023

Product Submitted for Approval

Brand Name	Phozevel Tablets 5 mg
	Phozevel Tablets 10 mg
	Phozevel Tablets 20 mg
	Phozevel Tablets 30 mg
Non-proprietary Name	Tenapanor Hydrochloride
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	October 28, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported PMDA’s conclusions regarding Sections "7.R.1 Efficacy" and "7.R.3 Safety" presented in the Review Report (1).

1.2 Indication

At the Expert Discussion, the expert advisors supported PMDA’s conclusion regarding Section "7.R.5 Indication" presented in the Review Report (1).

PMDA concluded that the indication statement should be as shown below, and that the following statement should be included in the Precautions Concerning Indication section. The applicant responded appropriately.

Indication

Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis

Precautions Concerning Indication

Since tenapanor does not facilitate the excretion of blood phosphorus, dietary phosphate restrictions should be considered.

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.6 Dosage and administration" of the Review Report (1).

PMDA concluded that the dosage and administration statement should be as shown below, and that the following statements should be included in the Precautions Concerning Dosage and Administration section. The applicant responded appropriately.

Dosage and Administration

The usual adult starting dose is 5 mg of tenapanor orally twice daily, immediately prior to the morning and evening meals. Then, the dose should be adjusted according to the symptoms and serum phosphorus levels. The maximum dose is 30 mg.

Precautions Concerning Dosage and Administration

- It is advisable to monitor serum phosphorus at 1 to 2 weeks after the initiation or dose adjustment of tenapanor.
- The dose of tenapanor may be up-titrated in a stepwise fashion (5→10→20→30 mg) at intervals of ≥1 week.
- After interruption, tenapanor should be resumed at the same dose level or at 1 dose level lower.
- Some patients may feel the need for a bowel movement during a hemodialysis session. Such patients are allowed not to take tenapanor immediately before a hemodialysis session, and are allowed to take tenapanor immediately before another a meal other than the morning and evening meals.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.7 Post-marketing investigations" of the Review Report (1).

PMDA has concluded that the risk management plan (draft) for tenapanor should include the safety and efficacy specifications presented in Table 79, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 80, 81, and 82.

Table 79. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
● Severe diarrhea	**● None**	**● None**
Efficacy specification		
● None		

Table 80. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
● Early post-marketing phase vigilance ● Specified use-results survey (Long-term use in HD patients) ● Specified use-results survey (Long-term use in PD patients)	● Disseminate data gathered during early post-marketing phase vigilance

Table 81. Specified use-results survey (long-term use in HD patients) (draft)

Objective	To assess the long-term safety and efficacy of tenapanor in clinical practice.
Survey method	Central registry system
Population	Patients with hyperphosphatemia on HD
Planned sample size	1,000 patients
Observation period	52 weeks from the start of treatment with tenapanor
Main survey items	Patient characteristics (disease that led to dialysis, dialysis status, medical history, complications, prior treatment, etc.), use of tenapanor, concomitant medications, clinical laboratory values, occurrence of adverse events, occurrence of severe diarrhea

Table 82. Specified use-results survey (long-term use in PD patients) (draft)

Objective	To assess the long-term safety and efficacy of tenapanor in clinical practice.
Survey method	Central registry system
Population	Patients with hyperphosphatemia on PD
Planned sample size	100 patients
Observation period	52 weeks from the start of treatment with tenapanor
Main survey items	Patient characteristics (disease that led to dialysis, dialysis status, medical history, complications, prior treatment, etc.), use of tenapanor, concomitant medications, clinical laboratory values, occurrence of adverse events, occurrence of severe diarrhea

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. As the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Improvement of hyperphosphatemia in patients with chronic kidney disease on dialysis

Dosage and Administration

The usual adult starting dose is 5 mg of tenapanor orally twice daily, immediately prior to the morning and evening meals. Then, the dose should be adjusted according to the symptoms and serum phosphorus levels. The maximum dose is 30 mg.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
Adverse drug reaction	Adverse event for which a causal relationship to study drug cannot be ruled out
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
BCRP	Breast cancer resistance protein
BSFS	Bristol stool form scale
Caco-2 cells	Human colon adenocarcinoma cell line
CKD	Chronic kidney disease
CHO cells	Chinese hamster ovary cells
C_{max}	Maximum concentration
CQA	Critical quality attribute
CTD	Common technical document
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
Drug interaction guideline	Drug interaction guideline for drug development and labeling recommendations (PSEHB/PED Notification No. 0723-4 dated July 23, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
EC_{50}	50% effective concentration
Efflux ratio	The ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
E_{max}	Maximum effect
FMO	Flavin-containing monooxygenase
GC	Gas chromatography
HD	Hemodialysis
HEK293 cells	Human embryonic kidney 293 cells
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
5-HT	5-hydroxytryptamine
IC_{50}	50% inhibit concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared absorption spectroscopy
Japanese clinical practice guideline	"Clinical Practice Guideline for the Management of Chronic Kidney Disease-Mineral and Bone Disorder" (*Journal of Japanese Society for Dialysis Therapy*. 2012; 45: 301-56)
Kt/Vurea	Normalized dialysis dose
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
MATE	Multidrug and toxic compound extrusion
MDCK cells	Madin-Darby canine kidney cells
MDR	Multidrug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mITT	Modified Intention-to-Treat
MMRM	Mixed-effects model for repeated measures

MS	Mass spectrometry
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NaPi2b	Sodium-dependent phosphate co-transporter type 2b
NHE	Na^+/H^+ exchanger
NK1	Neurokinin 1
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app} A→B	Apparent permeability coefficient in the apical to basolateral direction
P_{app} B→A	Apparent permeability coefficient in the basolateral to apical direction
PD	Peritoneal dialysis
PEPT1	Peptide transporter 1
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PTH	Parathyroid hormone
QOL	Quality of life
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
R_b	Blood to plasma partition ratio
SD	Sprague Dawley
Study 7791-001	Study 001
Study 7791-002	Study 002
Study 7791-003	Study 003
Study 7791-004	Study 004
Study 7791-005	Study 005
Study 7791-006	Study 006
Study 7791-007	Study 007
$t_{1/2}$	Elimination half-life
The product	Phozevel Tablets 5 mg, Phozevel Tablets 10 mg, Phozevel Tablets 20 mg, Phozevel Tablets 30 mg
T_{max}	Time to reach maximum concentration
UV/VIS	Ultraviolet-visible spectroscopy