Report on the Deliberation Results

August 14, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Setaneo Ophthalmic Solution 0.002%
Non-proprietary Name	Sepetaprost (JAN*)
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	September 26, 2024

Results of Deliberation

In its meeting held on July 31, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

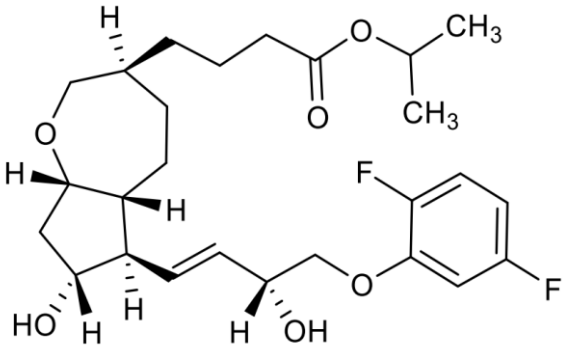
Review Report

July 11, 2025
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	Setaneo Ophthalmic Solution 0.002%
Non-proprietary Name	Sepetaprost
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	September 26, 2024
Dosage Form/Strength	Aqueous ophthalmic solution containing 0.02 mg of sepetaprost per mL
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula:	$C_{26}H_{36}F_2O_6$
Molecular weight:	482.56
Chemical name:	Propan-2-yl 4-{(3*S*,5a*R*,6*R*,7*R*,8a*S*)-6-[(1*E*,3*R*)-4-(2,5-difluorophenoxy)-3-hydroxybut-1-en-1-yl]-7-hydroxyoctahydro-2*H*-cyclopenta[*b*]oxepin-3-yl}butanoate

Items Warranting Special Mention None

Reviewing Office Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of glaucoma and ocular hypertension, 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 conditions. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Indications	Glaucoma and ocular hypertension
Dosage and Administration	Instill 1 drop into the eye once daily

Approval Conditions

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

Attachment

Review Report (1)

May 7, 2025

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	Setaneo Ophthalmic Solution 0.002%
Non-proprietary Name	Sepetaprost
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	September 26, 2024
Dosage Form/Strength	Aqueous ophthalmic solution containing 0.02 mg of sepetaprost per mL
Proposed Indications	Glaucoma and ocular hypertension
Proposed Dosage and Administration	Instill 1 drop into the eye once daily

Table of Contents

List of Abbreviations

See Appendix.

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

Setaneo Ophthalmic Solution 0.002% is an aqueous ophthalmic solution containing 0.002% of sepetaprost developed by Ono Pharmaceutical Co., Ltd. Sepetaprost is a prodrug of ONO-AG-367, a prostanoid receptor agonist that targets prostaglandin $F_{2\alpha}$ receptor (FP receptor) and prostaglandin E_2 receptor EP3 subtype (EP3 receptor).

In Japan, the clinical studies of sepetaprost began in [redacted] 20[redacted]. Recently, the applicant filed an application for the marketing approval of sepetaprost based on clinical study results that confirmed the efficacy and safety of sepetaprost in the treatment of glaucoma and ocular hypertension.

As of April 2025, sepetaprost has not been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance (sepetaprost) is registered in the master file (MF) by [redacted] (MF registration No. [redacted]).

2.1.1 Characterization

The drug substance is a white crystalline powder or white powder. Its description, solubility, hygroscopicity, melting point, [redacted], pH, partition coefficient, and specific optical rotation have been determined. While at least 3 crystalline forms ([redacted], [redacted], and [redacted]) have been identified for the drug substance, only [redacted] is produced in the commercial manufacturing process, and its stability at room temperature has been confirmed.

The chemical structure of the drug substance has been elucidated by elemental analysis, infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry (MS), ultraviolet spectroscopy (UV), and single-crystal X-ray crystallography.

2.1.2 Manufacturing process

See attached documents for data relating to the manufacturing process.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (ultraviolet-visible spectroscopy [UV/VIS], IR), purity (related substances [high performance liquid chromatography (HPLC)], diastereomer [HPLC], residual solvents [gas chromatography (GC)]), moisture, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows the main stability studies that have been conducted on the drug substance. The results showed that the drug substance is stable. The results of a photostability study also showed that the drug substance is photostable.

Table 1. Stability studies on the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Polyethylene bags	24 months
Accelerated	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above results, a retest period of 36 months was proposed for the drug substance when placed in polyethylene bags and stored at room temperature in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guideline. The long-term study will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an ophthalmic solution containing 0.02 mg of sepetaprost per mL. The drug product contains the following excipients: polysorbate 80, D-mannitol, sodium citrate hydrate, benzalkonium chloride, disodium edetate hydrate, [redacted], [redacted], and purified water.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising acceptance inspection, [redacted], [redacted], [redacted], and packaging/labeling/testing/storage steps. [redacted], [redacted], [redacted], and [redacted] are defined as critical steps, and process control items and values have been established.

The quality control strategy has been formulated based on the following evaluation, etc. (Table 2).

- Identification of critical quality attributes (CQAs)
- Quality risk assessment

Table 2. Outline of the control strategy for the drug product

CQA	Control method
Description	Specifications
Strength	Specifications
Related substances	Specifications
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Identification	Specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC), osmotic pressure ratio, pH, foreign insoluble matter, insoluble particulate matter, sterility, purity (related substances [HPLC]), sepetaprost assay (HPLC), and benzalkonium chloride assay (HPLC).

2.2.4 Stability of drug product

Table 3 shows the main stability studies that have been conducted on the drug product. The results showed that the drug product is stable. The results of a photostability study also showed that the drug product is photostable.

Table 3. Stability studies on the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	40% RH	Polypropylene container/shrink tack label package/paper box	24 months
Accelerated	3 commercial-scale batches	40°C	≤25% RH		6 months

Based on the above results, a shelf life of [redacted] months was proposed for the drug product when packaged in a polypropylene container, wrapped using shrink tack label, and placed in a paper box stored at room temperature in accordance with the ICH Q1E Guideline. The long-term study will be continued for up to 36 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 drug product is adequately controlled.

For the product, the data relating to the MF have been separately submitted by the MF registrant. See attached documents for the results of PMDA's review of the MF.

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

The applicant submitted the non-clinical pharmacology data on sepetaprost from the primary pharmacodynamic, secondary pharmacodynamic, and safety pharmacology studies. Some of the studies also evaluated ONO-AG-367, an active metabolite of sepetaprost. The main study results are summarized in the following sections. Unless otherwise specified, the values are expressed as mean or mean ± standard error.

3.1 Primary pharmacodynamics

3.1.1 Affinity for prostanoid receptors (CTD 4.2.1.1-1)

Using the membrane fraction of cells expressing prostanoid receptors (prostaglandin E_2 receptor EP1 subtype [EP1 receptor], prostaglandin E_2 receptor EP2 subtype [EP2 receptor], EP3 receptor, prostaglandin E_2 receptor EP4 subtype [EP4 receptor], FP receptor, prostaglandin D_2 receptor [DP receptor], prostacyclin receptor [IP], and thromboxane receptor [TP]), the binding affinity of sepetaprost or ONO-AG-367 for each receptor was evaluated by receptor binding assay. Table 4 shows the results.

Table 4. Inhibition of binding to prostanoid receptors

	Ki (nmol/L)							
	Human EP1	Human EP2	Human EP3	Mouse EP4	Human FP	Mouse DP	Mouse IP	Mouse TP
Sepetaprost	>10000 a)	>10000 a)	>10000 a)	>10000 a)	16.8	>10000 a)	>10000 a)	>10000 a)
ONO-AG-367	734	>10000 a)	25.0	>10000 a)	0.73	>10000 a)	>10000 a)	>10000 a)

Number of runs: 3

a) Inhibition at the maximum concentration (10000 nmol/L) used in the assay was <50%

3.1.2 Agonist activity against prostanoid receptors (CTD 4.2.1.1-2)

Using cells expressing prostanoid receptors (FP and EP3 receptors), the agonist activity of sepetaprost or ONO-AG-367 at each receptor was evaluated based on the changes in intracellular calcium concentration as an indicator. Table 5 shows the results.

Table 5. Agonist activity at prostanoid receptors

	EC_{50} (nmol/L)			
	Human FP	Human EP3	Mouse FP	Mouse EP3
Sepetaprost	3030	>10000 [a)]	1530	4510
ONO-AG-367	22.3	28.6	11.1	14.8

Number of runs: 3

a) Reaction at the maximum concentration (10000 nmol/L) used in the assay was <50%

3.1.3 Intraocular pressure-lowering effect of sepetaprost in normotensive dogs (CTD 4.2.1.1-3)

A single ocular dose of 30 μL of sepetaprost (0.0001%-0.001%) ophthalmic solution, latanoprost (LAT) 0.005% ophthalmic solution, timolol (TIM) 0.5% ophthalmic solution, the fixed-combination of LAT 0.005% and TIM 0.5% ophthalmic solution, or vehicle was administered to one eye of dogs. Intraocular pressure was measured at baseline, 2, 4, 6, 8, and 24 hours after instillation. Table 6 shows the maximum decrease in intraocular pressure (IOP) [1)] and decrease in IOP from baseline at 24 hours post-instillation.

Table 6. Maximum decrease in IOP and decrease in IOP from baseline at 24 hours post-instillation

	Maximum decrease in IOP (mmHg)	Decrease in IOP from baseline at 24 hours post-instillation (mmHg)
Sepetaprost 0.0001%	4.9 ± 0.73	2.4 ± 0.65
Sepetaprost 0.0003%	6.5 ± 0.49	4.1 ± 0.55
Sepetaprost 0.001%	7.0 ± 0.34	5.1 ± 0.49
LAT	5.4 ± 0.59	2.4 ± 0.52
TIM	3.2 ± 0.85	0.9 ± 0.87
LAT/TIM	6.0 ± 0.40	3.2 ± 0.36
Control (vehicle)	0.7 ± 0.61	0.1 ± 0.62

3.1.4 Intraocular pressure-lowering effect of sepetaprost in normotensive monkeys (CTD 4.2.1.1-4, CTD 4.2.1.1-5)

A single ocular dose of 30 μL of sepetaprost (0.00001%-0.003%), LAT 0.005%, or vehicle was administered to one eye of monkeys. Intraocular pressure was measured at baseline, 4, 8, 12, 24, 48, 72, and 96 hours post-instillation. The maximum decrease in IOP [2)] was 0.93, 1.63, 2.90, 4.31, 5.63, and 5.94 mmHg in the sepetaprost 0.00001%, 0.00003%, 0.0001%, 0.0003%, 0.001%, and 0.003% groups, respectively, and 2.98 mmHg in the LAT group. The change from baseline in mean IOP reached its maximum at 12 hours post-instillation in all sepetaprost groups except for the 0.00001% group, in which no change in IOP was observed, and at 4 hours post-instillation in the LAT group. The decrease in IOP from baseline at 24 hours post-instillation was 0.21, 1.04, 1.56, 2.63, 3.26, and 3.65 mmHg in the sepetaprost 0.00001%, 0.00003%, 0.0001%, 0.0003%, 0.001%, and 0.003% groups, respectively, and 0.66 mmHg in the LAT group.

A 30 μL ocular dose of sepetaprost (0.0001%-0.001%), LAT 0.005%, or vehicle was administered once daily to one eye of monkeys for 14 days. On Days 1, 4, 7, 11, and 14, IOP was measured immediately before instillation, and 4, 8, 12, and 24 hours after instillation (on Day 14, IOP was also measured at 48, 72, and 96 hours post-instillation). From Days 1 to 14, the maximum decrease in IOP [2)] from baseline (immediately before the first instillation) ranged from 3.16 to 3.60 mmHg (sepetaprost 0.0001%), 4.41 to 4.88 mmHg (sepetaprost

1) The greatest value among the means of decrease in IOP from baseline at measurement timepoints
2) The mean of the greatest decrease in IOP in each animal

0.0003%), 5.29 to 5.59 mmHg (sepetaprost 0.001%), and 2.54 to 3.08 mmHg (LAT). From Days 1 to 14, the decrease in IOP measured 24 hours after instillation, relative to the baseline IOP was 1.86 to 2.18 mmHg (0.0001%), 2.51 to 3.39 mmHg (0.0003%), 3.63 to 4.16 mmHg (0.001%), and 0.19 to 0.86 mmHg (LAT).

3.1.5 Effect of sepetaprost on aqueous humor dynamics (CTD 4.2.1.1-7, CTD 4.2.1.1-8)

In monkeys with elevated IOP induced by argon laser irradiation of the trabecular meshwork in one eye, 20 μL of sepetaprost 0.002% or vehicle was administered once daily to both eyes for 7 days. On the seventh day, the aqueous humor dynamics were measured following instillation using fluorophotometry. The aqueous humor flow rate in the treated eye was 3.08 ± 0.59 and 3.01 ± 0.46 μL/min in the sepetaprost and vehicle groups, respectively (2.5% increase in the sepetaprost group compared with the vehicle group [3)]), with no clear difference observed. Conversely, the aqueous humor outflow rate was 0.43 ± 0.13 and 0.25 ± 0.04 μL/min/mmHg in the sepetaprost and vehicle groups, respectively (68.4% increase in the sepetaprost group compared with the vehicle group[3)]), while the uveoscleral outflow rate was 3.68 ± 1.25 and 2.15 ± 0.56 μL/min, respectively (70.7% increase in the sepetaprost group compared with the vehicle group [3)]). In both cases, a tendency toward increased outflow was observed in the sepetaprost group.

3.2 Secondary pharmacodynamics

3.2.1 Analysis of off-target effects (CTD 4.2.1.2-1)

The binding affinity of sepetaprost or ONO-AG-367 to receptors, ion channels, and transporters was evaluated (66 proteins in total). At the tested concentration (10 μmol/L), neither sepetaprost nor ONO-AG-367 exhibited more than 50% inhibitory activity against any of the molecules examined.

3.3 Safety pharmacology

Table 7 summarizes the safety pharmacology studies on sepetaprost and ONO-AG-367.

3) (Mean in the sepetaprost group − mean in the vehicle group) / mean in the vehicle group × 100 (%)

Table 7. Summary of safety pharmacology study data

Organ system	Test system	Test parameter/ method	Dose or concentration	Route	Finding	CTD
Central nervous system	Monkeys (3/sex/group)	FOB	Sepetaprost: 0,[a] 2, 20, 200 μg/kg	IV	At 200 μg/kg, slow movement, motor discoordination, decreased response to contact, salivation, vomiting, soft feces, dilated or constricted pupils	4.2.3.2-11
Cardio-vascular system	HEK293 cells (5 specimens/group)	hERG current	Sepetaprost: 0,[b] 0.1, 0.3, 1, 3, 7 μmol/L	*In vitro*	At ≥1 μmol/L, hERG current inhibition, IC_{50} = 5.2 μmol/L	4.2.1.3-3
			ONO-AG-367: 0,[b] 0.1, 1, 10 μmol/L		No effects	4.2.1.3-4
	Guinea pigs Isolated papillary muscles		Sepetaprost: 0.1, 1, 7 μmol/L		At 7 μmol/L, shortening of action potential duration at 30%, 50%, 90%	4.2.1.3-5
			ONO-AG-367: 0.1, 1, 10, 1 μmol/L		No effects	4.2.1.3-6
	Monkeys (5 males)	Blood pressure, heart rate, electrocardiogram, body temperature	Sepetaprost: 0.02, 0.04,[c] 0.06,[c] 0.2, 2, 20 μg/kg	IV	At ≥2 μg/kg, increased blood pressure, increased heart rate, decreased body temperature At 20 μg/kg, QT interval shortening, lateral position or abdominal position	4.2.1.3-1
Respiratory system		Respiratory waveform, respiratory rate, tidal volume			At ≥0.06 μg/kg, increased respiratory rate, decreased tidal volume	4.2.1.3-1
Blood system	Human plasma (5 specimens/group)	Platelet aggregation	ONO-AG-367: 0.1, 1, 10, 100 μmol/L	*In vitro*	Effects on ADP-induced platelet aggregation At ≥1 μmol/L, increased platelet aggregation Effects on collagen-induced platelet aggregation At ≥10 μmol/L, increased platelet aggregation Effects on ONO-AG-367-induced platelet aggregation No effects	4.2.1.3-7
	Human plasma (5 specimens/group)	Blood coagulation, fibrinolysis systems	ONO-AG-367: 0.1, 1, 10, 100 μmol/L		No effects	4.2.1.3-8
	Rat plasma (5 specimens/group)	Platelet aggregation, coagulation, fibrinolysis systems	ONO-AG-367: 0.001, 0.01, 0.1, 1 μmol/L		No effects	4.2.1.3-9
Renal/ urinary system	Rats (8 females/group)	Urine volume, urinary pH, total urinary electrolyte excretion	Sepetaprost: 0.1, 1, 10, 100 μg/kg	IV	At ≥10 μg/kg, increased urine volume, decreased urinary pH, increased total urinary electrolyte excretion	4.2.1.3-10
Other organ systems	Monkeys (5 females)	Uterine contraction	Sepetaprost: 0,[a] 0.02, 0.06, 0.2, 2 μg/kg	IV	At ≥0.2 μg/kg, uterine contraction	4.2.1.3-11
	Monkeys (5 males/group)	Pupil diameter, refractive index of the eye	Sepetaprost: 0.01%	Ocular instillation	Pupil diameter: pupil dilation, pupil constriction Refractive index of the eye: no effects	4.2.1.3-12

a) [redacted] containing [redacted]
b) DMSO
c) N = 4

3.R Outline of the review conducted by PMDA

Based on the submitted data, and discussions in the following sections, PMDA concluded that sepetaprost can be expected to be effective in the treatment of glaucoma and ocular hypertension.

3.R.1 Mechanism of action of sepetaprost

PMDA asked the applicant to explain the mechanism of action of sepetaprost by comparing its pharmacological profile with those of prostanoid receptor agonists approved for the treatment of glaucoma.

The applicant's explanation:
After ocular instillation, sepetaprost is hydrolyzed immediately to ONO-AG-367, which exhibits agonist activity at FP and EP3 receptors [see Section 3.1.2]. The studies in monkeys suggested that sepetaprost tended to have a greater IOP-lowering effect with a longer duration of the IOP-lowering effect than LAT [see Section 3.1.4].

When activated in ocular tissue, FP receptors increase *MMP* gene expression, which contributes to degradation of the extracellular matrix in the ciliary muscle, thereby lowering IOP through promotion of aqueous humor outflow via the uveoscleral outflow pathway as a result of extracellular matrix remodeling (*Pharmacol Rev*. 2011;63:471-538, *J Ocul Pharmacol Ther*. 2020;36:208-28). Conversely, although it has been reported that activation of EP3 receptors alone did not produce an IOP-lowering effect (*Invest Ophthalmol Vis Sci*. 2009;50:2201-8), EP3 receptor activation has been reported to increase *MMP* gene expression, similarly to FP receptor activation (*J Biol Chem.* 1996;271:27744-50). Therefore, it is considered that ocular instillation of sepetaprost activates both FP and EP3 receptors, resulting in greater enhancement of *MMP* gene expression than that with activation of FP receptors alone, thereby contributing to promotion of aqueous humor outflow.

In a study that evaluated the effects of sepetaprost on aqueous humor dynamics [see Section 3.1.5], the aqueous humor outflow rate, a parameter considered to reflect the rate of aqueous humor outflow predominantly via the trabecular meshwork outflow pathway, tended to increase following administration of sepetaprost. These findings suggest that the instillation of sepetaprost may promote aqueous humor outflow not only via the uveoscleral outflow pathway but also through the trabecular meshwork outflow pathway.

Based on the above, sepetaprost is similar to existing FP receptor agonists in terms of the mechanism by which it lowers IOP by promoting aqueous humor outflow mainly via the uveoscleral outflow pathway. However, sepetaprost also activates EP3 receptors, leading to enhancement of aqueous humor outflow via the uveoscleral outflow pathway, which is expected to lead to a sustained IOP-lowering effect. Additionally, a sustained IOP-lowering effect by promoting aqueous humor outflow via the trabecular meshwork outflow pathway can also be expected with sepetaprost, unlike treatment with approved FP receptor agonists.

Furthermore, omidenepag isopropyl, an approved EP2 receptor agonist, is considered to lower IOP by inducing EP2 receptor activation-mediated smooth muscle relaxation, and thereby promoting aqueous humor outflow from the uveoscleral and trabecular meshwork outflow pathways (see Review Report of "Eybelis Ophthalmic Solution 0.002%," dated August 21, 2018). Although the receptors targeted differ, the mechanism by which omidenepag isopropyl lowers IOP is considered to be similar to that of sepetaprost.

PMDA's view:
The applicant explained that sepetaprost activates both FP and EP3 receptors to lower IOP in patients with glaucoma or ocular hypertension. Although the extent of the contribution of EP3 receptor activation to the therapeutic effect of sepetaprost remains unclear, given the submitted data, the applicant's explanation is

acceptable. Moreover, in terms of the impact of activating the EP3 receptors in addition to FP receptors on the safety of sepetaprost, no particular risks have been identified. However, the safety of sepetaprost will be further discussed in Sections 5.R and 7.R.2.

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

As part of the non-clinical pharmacokinetic studies of sepetaprost, study results on absorption, distribution, metabolism, and excretion in rats, dogs, and monkeys were submitted. The following sections outline the main study findings.

The concentrations of sepetaprost and its active metabolite ONO-AG-367 in biological samples were determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS) (lower limits of quantitation, 10 and 2 pg/mL, respectively). The radioactivity levels in biological samples using ^{3}H-labeled sepetaprost or ^{3}H-labeled ONO-AG-367 were measured by a liquid scintillation counter or high performance liquid chromatography-radioactivity detection (HPLC-RAD).

4.1 Absorption

4.1.1 Single-dose studies

Table 8 shows the plasma radioactivity pharmacokinetic parameters following a single bilateral ocular instillation of ^{3}H-labeled sepetaprost 0.008% ophthalmic solution (30 μL/eye [4.8 μg/body]) or a single intravenous administration of ^{3}H-labeled sepetaprost 10 μg/kg to male monkeys (N = 1/group). The absolute bioavailability following a single ocular instillation of ^{3}H-labeled sepetaprost was 72% [4)] (CTD 4.2.2.2-1).

Table 8. Plasma radioactivity pharmacokinetic parameters following ocular instillation or intravenous administration of ^{3}H-labeled sepetaprost

Route of administration	Dose	C_{max} (ng eq./mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{inf} (ng eq.·h/mL)
Ocular instillation	4.8 μg	1.95	0.08	8.7	1.88
IV	10 μg/kg	9.15	0.25	22	17.4

Individual values

4.1.2 Repeated-dose studies

Toxicokinetics was evaluated in a 39-week repeated instillation toxicity study in monkeys. The pharmacokinetic parameters of unchanged sepetaprost and its active metabolite ONO-AG-367 in plasma following ocular instillation of sepetaprost 0.003%, 0.005%, or 0.01% twice daily (every 6 hours) for 39 weeks into one eye are presented in Table 9 and Table 10, respectively. The plasma sepetaprost concentrations in the sepetaprost 0.003% group were below the lower limit of quantitation at all measurement timepoints except for 1 male (CTD 4.2.3.2-4).

4) (AUC_{inf} of plasma radioactivity following ocular instillation / ocular instillation dose) / (AUC_{inf} of plasma radioactivity following intravenous administration / intravenous dose) × 100 (%)

Table 9. Pharmacokinetic parameters of unchanged sepetaprost in plasma after repeated ocular instillation of sepetaprost

Time point	Dosing concentration (%)	Sex (N/group)	$C_{max0\text{-}6\ h}$ (pg/mL)	$t_{max\ 0\text{-}6\ h}$ [a] (h)	$AUC_{0\text{-}6\ h}$ (pg·h/mL)	$C_{max\ 6\text{-}24\ h}$ (pg/mL)	$t_{max\ 6\text{-}24h}$ [a] (h)	$AUC_{6\text{-}24\ h}$ (pg·h/mL)
Day 1	0.005	M (3/group)	0 (0, 48.8)	0.25 [b]	0 (0, 24.0)	11.1 (10.4, 16.1)	6.25 (6.08, 6.25)	4.77 (1.39, 9.09)
		F (3/group)	0 [c]	—	0 [c]	11.1 (0, 11.1)	6.08, 6.08 [d]	6.11 (0, 6.34)
	0.01	M (5/group)	21.7 (0, 27.0)	0.25(0.25, 0.25) [e]	12.5 (0, 21.1)	22.5 (0, 37.9)	6.25(6.25, 6.25) [f]	12.4 (0, 13.8)
		F (5/group)	10.7 (0, 21.1)	0.25 (0.25, 0.25) [e]	4.91 (0, 12.1)	14.9 (0, 32.5)	6.08 (6.08, 6.25) [e]	7.69 (0, 18.4)
Day 273	0.005	M (3/group)	0 (0, 12.8)	0.25 [c]	0 (0, 5.87)	0 (0, 14.9)	6.25 [c]	0 (0, 8.26)
		F (3/group)	0 [c]	—	0 [c]	0 [c]	—	0 [c]
	0.01	M (5/group)	14.5 (0, 31.0)	0.25 (0.08, 0.25) [f]	7.52 (0, 17.5)	13.7 (0, 18.6)	6.17 (6.08, 6.25) [f]	7.16 (0, 10.2)
		F (5/group)	0 (0, 24.6)	0.08, 0.25 [d]	0 (0, 10.4)	0 (0, 20.2)	6.08, 6.25 [d]	0 (0, 10.2)

Median (Min, Max) or individual values; a value of 0 was imputed for data below the lower limit of quantitation (10.0 pg/mL); —, not calculated
a) t_{max} for animals with values at or greater than the lower limit of quantitation; b) N = 1; c) measurements at all timepoints were below the lower limit of quantitation for all animals; d) N = 2; e) N = 3; f) N = 4

Table 10. Pharmacokinetic parameters of ONO-AG-367 in plasma after repeated ocular instillation of sepetaprost

Time point	Dosing concentration (%)	Sex (N/group)	$C_{max\ 0\text{-}6h}$ (pg/mL)	$t_{max\ 0\text{-}6h}$ [a] (h)	$AUC_{0\text{-}6h}$ (pg·h/mL)	$C_{max\ 6\text{-}24h}$ (pg/mL)	$t_{max\ 6\text{-}24h}$ [a] (h)	$AUC_{6\text{-}24h}$ (pg·h/mL)
Day 1	0.003	M (3/group)	401 ± 126	0.08 (0.08, 0.08)	207 ± 20	585 ± 209	6.08 (6.08, 6.08)	309 ± 26
		F (3/group)	446 ± 35	0.08 (0.08, 0.08)	246 ± 49	540 ± 30	6.08 (6.08, 6.08)	364 ± 90
	0.005	M (3/group)	703 ± 76	0.08 (0.08, 0.08)	403 ± 38	879 ± 102	6.08 (6.08, 6.08)	529 ± 78
		F (3/group)	734 ± 117	0.08 (0.08, 0.08)	389 ± 49	776 ± 156	6.08 (6.08, 6.08)	548 ± 76
	0.01	M (5/group)	1410 ± 340	0.08 (0.08, 0.08)	732 ± 120	1940 ± 400	6.08 (6.08, 6.08)	1090 ± 180
		F (5/group)	1060 ± 270	0.08 (0.08, 0.08)	623 ± 187	1300 ± 370	6.08 (6.08, 6.08)	890 ± 303
Day 273	0.003	M (3/group)	412 ± 90	0.08 (0.08, 0.08)	203 ± 35	290 ± 22	6.08 (6.08, 6.08)	236 ± 66
		F (3/group)	519 ± 30	0.08 (0.08, 0.08)	218 ± 22	466 ± 91	6.08 (6.08, 6.08)	301 ± 89
	0.005	M (3/group)	595 ± 70	0.08 (0.08, 0.08)	331 ± 18	458 ± 74	6.08 (6.08, 6.08)	422 ± 104
		F (3/group)	776 ± 71	0.08 (0.08, 0.08)	338 ± 24	858 ± 39	6.08 (6.08, 6.08)	466 ± 37
	0.01	M (5/group)	1400 ± 510	0.08 (0.08, 0.08)	673 ± 161	1310 ± 460	6.08 (6.08, 6.08)	870 ± 177
		F (5/group)	1480 ± 590	0.08 (0.08, 0.08)	627 ± 270	1270 ± 450	6.08 (6.08, 6.08)	778 ± 183

Mean ± standard deviation; a) median (Min, Max)

Toxicokinetics was evaluated in repeated intravenous administration studies in rats and monkeys. The pharmacokinetic parameters of ONO-AG-367 in plasma following repeated intravenous administration of sepetaprost once daily are presented in Table 11 (rats) and Table 12 (monkeys) (CTD 4.2.3.2-10, 4.2.3.2-11).

Table 11. Pharmacokinetic parameters of ONO-AG-367 in plasma after repeated intravenous administration of sepetaprost to rats for 26 weeks

Timepoint	Dose (μg/kg)	Sex (N/timepoint)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}4h}$ (pg·h/mL)	AUC_{inf} (pg·h/mL)
Day 1	0.4	M (4/timepoint)	509	0.02	—	99.4	—
		F (4/timepoint)	548	0.02	—	95.0	—
	2	M (4/timepoint)	2650	0.02	0.13	484	481
		F (4/timepoint)	2170	0.02	0.12	384	383
	10	M (4/timepoint)	10800	0.02	0.16	2530	2530
		F (4/timepoint)	10300	0.02	0.12	2190	2180
Day 181	0.4	M (4/timepoint)	725	0.02	0.19	227	224
		F (4/timepoint)	774	0.02	0.16	131	129
	2	M (4/timepoint)	4150	0.02	0.20	1130	1130
		F (4/timepoint)	3330	0.02	0.14	691	685
	10	M (4/timepoint)	21400	0.02	0.21	5860	5840
		F (4/timepoint)	19300	0.02	0.19	4130	4130

Mean values and parameters are calculated based on the mean plasma concentration at each timepoint; —, not calculated

Table 12. Pharmacokinetic parameters of ONO-AG-367 in plasma after repeated intravenous administration of sepetaprost to monkeys for 4 weeks

Timepoint	Dose (μg/kg)	Sex (N)	C_{max} (pg/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}24h}$ (pg·h/mL)
Day 1	2	M (N = 3)	1200 ± 370	0.08 (0.08, 0.25)	757 ± 137
		F (N = 3)	1420 ± 290	0.25 (0.08, 0.25)	949 ± 217
	20	M (N = 3)	12600 ± 1800	0.25 (0.08, 0.25)	9320 ± 660
		F (N = 3)	13100 ± 3400	0.08 (0.08, 0.25)	7440 ± 1470
	200	M (N = 5)	111000 ± 25000	0.08 (0.08, 0.25)	80800 ± 6800
		F (N = 5)	144000 ± 26000	0.08 (0.08, 0.25)	101000 ± 18000
Day 181	2	M (N = 3)	1260 ± 160	0.25 (0.08, 0.25)	832 ± 102
		F (N = 3)	1130 ± 100	0.08 (0.08, 0.08)	745 ± 150
	20	M (N = 3)	13000 ± 3100	0.08 (0.08, 0.25)	9560 ± 870
		F (N = 3)	11300 ± 3900	0.08 (0.08, 0.25)	7690 ± 2620
	200	M (N = 5)	96700 ± 23300	0.08 (0.08, 0.25)	70700 ± 20800
		F (N = 5)	83300 ± 11600	0.25 (0.08, 0.25)	72800 ± 11700

Mean ± standard deviation; a) median (Min, Max)

4.2 Distribution

4.2.1 Tissue distribution

A single ocular dose of ^{3}H-labeled sepetaprost 0.008% ophthalmic solution (30 μL/eye) was instilled into both eyes of monkeys (N = 2 males/timepoint), and radioactivity levels in eye and systemic tissues were evaluated for up to 48 hours after instillation. Of the eye tissues studied, [5)] tissue radioactivity levels peaked at 2 hours post-instillation in aqueous humor and at 0.5 hours post-instillation in other tissues. At 0.5 hours post-instillation, among eye tissues, radioactivity levels were highest in the cornea, followed by the iris, palpebral conjunctiva, sclera, ciliary body, bulbar conjunctiva, aqueous humor, choroid, retina, crystalline lens, and vitreous body. While radioactivity decreased over time, it was still quantifiable in all eye tissues studied except for the vitreous body and retina at 48 hours post-instillation. In melanin-containing eye tissues, the elimination half-life was 6.0, 5.7, and 7.3 hours in the iris, ciliary body, and choroid, respectively, and did not tend to be longer than those observed in non-melanin containing tissues (4.2 to 13 hours). Based on these findings, the applicant considers that sepetaprost and its metabolites are unlikely to bind to melanin. With respect to the systemic tissues studied, [6)] the radioactivity levels peaked at 2 hours post-instillation in the gallbladder, gallbladder bile, small intestine, and large intestine. In other tissues, the radioactivity levels peaked at 0.5 hours post-instillation. At each timepoint, tissue radioactivity levels in the gallbladder bile, large intestine, gallbladder, kidney, liver, small intestine, nasal mucosa, stomach, and urinary bladder were ≥2 times higher than plasma radioactivity levels (CTD 4.2.2.2-1).

A single intravenous dose of ^{3}H-labeled sepetaprost 10 μg/kg was administered to albino rats (N = 3 males/timepoint), and tissue radioactivity levels up to 72 hours post-dose were evaluated. After intravenous administration, radioactivity was widely distributed across tissues, with peak concentrations observed 0.25 hours post-dose in all tissues studied. [7)] Radioactivity levels in the liver, kidney, and urinary bladder were higher than those in plasma. Radioactivity levels decreased over time, and were below the lower limit of

5) Water, palpebral conjunctiva, bulbar conjunctiva, choroid, cornea, iris, ciliary body, crystalline lens, vitreous body, retina, sclera
6) Plasma, blood, submandibular gland, sublingual gland, parotid gland, nasal mucosa, thyroid gland, cerebrum, white adipose tissue, thymus gland, heart, lung, liver, gallbladder, gallbladder bile, kidney, adrenal gland, spleen, pancreas, skeletal muscle, skin, femur, testis, stomach, small intestine, large intestine, urinary bladder
7) Plasma, blood, cerebrum, cerebellum, pituitary gland, spinal cord, eyeball, thyroid gland, submandibular gland, thymus gland, heart, lung, liver, kidney, adrenal gland, spleen, pancreas, white adipose tissue, skeletal muscle, skin, femur, bone marrow, mesenteric lymph node, testis, epididymis, prostate, seminal vesicle, esophagus, stomach, small intestine, large intestine, urinary bladder

quantitation at 72 hours post-dose in all tissues except for the large intestine, liver, spleen, plasma, lung, kidney, blood, and skin (CTD 4.2.2.2-2).

4.2.2 Protein binding and distribution in blood cells

To rat and monkey sera, ^{3}H-labeled ONO-AG-367 0.3 to 30 ng/mL was added, and serum protein binding was evaluated by ultrafiltration. Serum protein binding of ONO-AG-367 was 78.3% to 79.0% in rats and 72.5% to 73.5% in monkeys (CTD 4.2.2.3-1).

To rat and monkey blood, ^{3}H-labeled ONO-AG-367 0.3 to 30 ng/mL was added, and distribution in blood cells was studied. The results showed that the percentage distribution of radioactivity in blood cells was 5.0% to 7.6% in rats and 10.7% to 14.1% in monkeys, and the blood-plasma concentration ratio in rats and monkeys ranged from 0.69 to 0.71 and 0.62 to 0.63, respectively, indicating that the distribution in blood cells was low.

A single intravenous dose of ^{3}H-labeled sepetaprost 10 μg/kg was administered to rats, and the percentage distribution of radioactivity in blood cells was evaluated using blood samples collected at each timepoint up to 72 hours post-dose. The percentage distribution of radioactivity in blood cells increased over time from 15 minutes to 72 hours post-dose (7.0%-76.9%) (CTD 4.2.2.3-1).

A single ocular dose of ^{3}H-labeled sepetaprost 0.008% ophthalmic solution was instilled into both eyes of monkeys and the percentage distribution of radioactivity in blood cells was evaluated using blood samples collected at each timepoint up to 48 hours post-instillation. The percentage distribution of radioactivity in blood cells increased over time from 30 minutes to 48 hours post-instillation (6.0%-40.4%) (CTD 4.2.2.2-1).

4.2.3 Placental transfer

A single intravenous dose of ^{3}H-labeled sepetaprost 10 μg/kg was administered to pregnant rats on gestational day 18 (N = 4/timepoint), and radioactivity levels in maternal and fetal tissues were evaluated. The results indicated that unchanged sepetaprost or metabolites can transfer across the placenta to the fetus. Results for maternal and fetal tissues showed that the radioactivity levels peaked at 15 minutes post-dose in the maternal blood, plasma, liver, and kidney, 1 hour post-dose in amniotic fluid, and 5 minutes post-dose in other maternal tissues and fetal tissues. The radioactivity levels were lower in fetal tissues than in maternal plasma at all timepoints except for radioactivity levels in fetal kidney at 6 hours post-dose (CTD 4.2.2.3-2).

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 4.2.2.4-1)

^{3}H-labeled sepetaprost 500 ng/mL was added to rat, dog, and monkey hepatocytes, and the specimens were incubated at 37°C for 4 hours. Unchanged sepetaprost detected was <1% in all the animal species studied, and the following metabolites were detected: glycine conjugate of ONO-AG-367 (monkeys only), glucuronide conjugate of ONO-AG-367, ONO-AG-450 (β-oxidation product of ONO-AG-367), reduced form of ONO-AG-450, dehydro form of ONO-AG-367 (dogs only), ONO-AG-367, reduced form of ONO-AG-367 (rats and dogs only), taurine conjugate of ONO-AG-450 (rats and dogs only), glucuronide conjugate of ONO-AG-450,

taurine conjugate of reduced form of ONO-AG-450 (rats only), taurine conjugate of ONO-AG-367, reduced form of hydroxylated form of ONO-AG-367 (rats only), taurine conjugate of reduced form of ONO-AG-367 (rats only), and hydroxylated form of ONO-AG-367.

4.3.2 *In vivo* metabolism (CTD 4.2.2.4-3)

A single ocular dose of ^{3}H-labeled sepetaprost 0.008% ophthalmic solution (30 μL/eye) was instilled into both eyes of monkeys (N = 1 to 2 males/group), and metabolites in aqueous humor, plasma, urine, feces, and bile were evaluated. In aqueous humor, no unchanged sepetaprost was detected at any timepoint, and ONO-AG-367, the predominant metabolite detected, accounted for 82.4%, 82.7%, 74.3%, and 41.7% of plasma radioactivity at 0.5, 2, 4, and 8 hours post-instillation, respectively. Another metabolite detected, ONO-AG-450, accounted for 5.2%, 8.7%, and 7.5% of plasma radioactivity at 2, 4, and 8 hours post-instillation, respectively. In plasma at 0.5 hours post-instillation, unchanged sepetaprost (2% of plasma radioactivity) was detected. The predominant metabolites detected were ONO-AG-367 (36.7% of plasma radioactivity) and ONO-AG-450 (20.9% of plasma radioactivity). In urine up to 24 hours post-instillation, the predominant metabolite detected was ONO-AG-450 (66.1% of radioactivity administered). Other metabolites detected included a glucuronide conjugate of ONO-AG-367 and a reduced form of ONO-AG-450 (15.0% and 3.9% of radioactivity administered, respectively). In feces up to 48 hours post-instillation, the predominant metabolite detected was ONO-AG-450 (63.4% of radioactivity administered). Other metabolites detected included ONO-AG-367, a reduced form of ONO-AG-450, and the hydroxylated form of ONO-AG-367 (7.7%, 2.9%, and 0.6% of radioactivity administered, respectively). In bile, at 2 hours post-instillation, no unchanged sepetaprost was detected, and the metabolites detected included ONO-AG-450 and ONO-AG-367 (14.5% and 8.4% of bile radioactivity, respectively).

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

Following instillation of a single ocular dose of ^{3}H-labeled sepetaprost 0.008% ophthalmic solution (30 μL/eye) into both eyes of a male monkey, the cumulative excretion of radioactivity in urine and feces up to 48 hours post-instillation accounted for 46.2% and 33.7% of the administered radioactivity, respectively (CTD 4.2.2.2-1).

Following single intravenous administration of ^{3}H-labeled sepetaprost 10 μg/kg to a monkey, the cumulative excretion of radioactivity in urine and feces up to 168 hours post-dose was 66.1% and 32.6% of the administered radioactivity, respectively (CTD 4.2.2.2-1).

A single intravenous dose of ^{3}H-labeled sepetaprost 10 μg/kg was administered to bile-duct non-cannulated and cannulated rats (4 males/group). In bile-duct non-cannulated rats, the cumulative excretion of radioactivity in urine and feces up to 120 hours post-dose was 26.7% and 70.7% of the administered radioactivity, respectively, while in bile-duct cannulated rats, the cumulative excretion of radioactivity in urine, feces and bile up to 48 hours post-dose was 22.7%, 0.4%, and 74.6% of the administered radioactivity, respectively (CTD 4.2.2.2-2).

4.4.2 Excretion into breast milk (CTD 4.2.2.3-2)

A single intravenous dose of ^{3}H-labeled sepetaprost 10 μg/kg was administered to lactating rats to investigate excretion into breast milk. Sepetaprost or its metabolites were excreted into milk. Plasma radioactivity peaked at 5 minutes post-dose, while radioactivity in breast milk peaked at 15 minutes post-dose. The elimination half-life of radioactivity was 0.99 in plasma and 1.67 hours in breast milk.

4.R Outline of the review conducted by PMDA

PMDA concluded that there were no particular problems with the submitted non-clinical pharmacokinetic study data.

5. Toxicology and Outline of the Review Conducted by PMDA

The results of the following toxicology studies of sepetaprost were submitted: repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, and sensitization studies.

5.1 Single-dose toxicity

In a 4-week repeated intravenous dose-toxicity study in rats, acute toxicity was evaluated based on the clinical signs following the initial dose. No changes in clinical signs were observed up to the maximum dose studied. The approximate lethal dose was determined to be >100 μg/kg in rats.

5.2 Repeated-dose toxicity

Ocular dose toxicity studies (4-, 13-, and 39-week) (Table 13) and intravenous dose toxicity studies (4-, 13-, and 26-week) (Table 14) were conducted in rats and monkeys.

The exposure to ONO-AG-367[8)] ($AUC_{0\text{-}4h}$, 174 pg·h/mL) at the no-observed adverse effect level (NOAEL) (0.4 μg/kg) in the 26-week repeated intravenous-dose toxicity study in rats and the exposure to ONO-AG-367[9)] ($AUC_{0\text{-}24h}$, 821 pg·h/mL) at the NOAEL (2 μg/kg) in the 4-week repeated intravenous-dose toxicity study in monkeys were 18 times and 87 times, respectively, the human exposure[10)] (AUC_{inf}, 9.41 pg·h/mL) following ocular administration of the recommended clinical dose (0.002%).

8) The mean of $AUC_{0\text{-}4h}$ on Day 1 (male, 99.4 pg·h/mL), Week 13 (male, 195 pg·h/mL), and Week 26 (male, 227 pg·h/mL).
9) The mean of $AUC_{0\text{-}24h}$ on Day 1 (male, 757 pg·h/mL; female, 949 pg·h/mL), and Week 4 (male, 832 pg·h/mL; female, 745 pg·h/mL).
10) The mean of AUC_{inf} on Day 1 (11.9 pg·h/mL) and Day 7 (6.91 pg·h/mL) following administration of repeated ocular doses of sepetaprost 0.002% ophthalmic solution once daily to both eyes for 7 days in a Japanese phase I study (Study 101260007LT).

Table 13. Summary of repeated ocular-dose toxicity studies

Test system	Route	Dosing duration	Dose	Major findings	NOAEL (%)	CTD
Male/ female rats (SD)	Ocular	4 weeks	0%,[a)] 0.001%, 0.003%, or 0.01%, 10 μL/eye	At ≥0.001%, vasoconstriction of the iris At 0.01%, vasoconstriction of the retinal vessels, iris color fading, retinal red spots, retinal hemorrhage,[c)] retinal atrophy with retinal folds/rosettes[c)]	0.003	4.2.3.2-5
Male/ female cynomolgus monkeys	Ocular	4 weeks + 4-week recovery period	0%,[a)] 0.0003%, 0.001%, 0.002%, 0.003%, 0.005%, or 0.01%, 30 μL/eye twice daily	At ≥0.001%, pupil dilation At ≥0.005%, pupil constriction, bulbar conjunctiva hemorrhage, hyperemia of the bulbar conjunctiva or palpebral conjunctiva Reversibility: reversible	0.0003	4.2.3.2-1 4.2.3.2-2
Male/ female cynomolgus monkeys	Ocular	13 weeks + 4-week recovery period	0%,[b)] 0.001%, 0.003%, 0.005%, or 0.01%, 30 μL/eye twice daily	At 0.01%, transient conjunctival hyperemia Reversibility: reversible	0.01	4.2.3.2-3
Male/ female cynomolgus monkeys	Ocular	39 weeks + 4-week recovery period	0%,[b)] 0.003%, 0.005%, or 0.01%, 30 μL/eye twice daily	At 0.003%, pupil constriction At ≥0.005%, deepening of upper eyelid sulcus, iris pigmentation, pupil dilation Reversibility: reversible	0.01	4.2.3.2-4

a) [redacted] containing [redacted], [redacted], [redacted], and [redacted], [redacted]

b) [redacted] containing [redacted], [redacted], [redacted], [redacted], and [redacted], [redacted]

c) The findings were noted in 1 of 20 animals. These events, which have been reported to occur spontaneously at low frequencies in SD rats (e.g., *Anim Eye Res.* 2008;27:31-7, *Biological Reference Data on CD(SD)IGS Rats.* 1999;60-2), were considered by the applicant to be naturally occurring changes.

Table 14. Summary of repeated intravenous dose toxicity studies

Test system	Route	Dosing duration	Dose (μg/kg/day)	Major findings	NOAEL (μg/kg/day)	CTD
Male/ female rats (SD)	IV	4 weeks + 4-week recovery period	0,[a] 0.03, 0.1, 0.3, 1, 10, 100	At ≥1 μg/kg/day, vitreous hemorrhage,[b] brown pigmentation of the retina,[b] dilation of retinal vessels[c] At ≥10 μg/kg/day, decreased concentrations of urinary sodium and chloride, decreased platelet count At 100 μg/kg/day, pale pinna, transient decrease in locomotor activity, bradypnea, deep respiration, decreased hematocrit/hemoglobin, increased reticulocyte percentage, shortened prothrombin time, increased ALT, increased γ-GTP, increased relative kidney weight Reversibility: reversible (except for eye changes[d])	0.3	4.2.3.2-6 4.2.3.2-7
Male/ female rats (SD)	IV	4 weeks + 4-week recovery period	100	At 100 μg/kg/day, death, pale pinna, decrease in locomotor activity, loss of righting reflex, bradypnea, deep respiration, dyspnea, dark red liver	Not calculated	4.2.3.2-8
Male/ female rats (SD)	IV	13 weeks + 4-week recovery period	0,[a] 0.1, 0.3, 1, 10	At 10 μg/kg/day, focal decrease in bone marrow cells in the femoral epiphysis and diaphyseal region of the sternum, extramedullary hematopoiesis of the spleen Reversibility: reversible	1	4.2.3.2-9
Male/ female rats (SD)	IV	26 weeks + 4-week recovery period	0,[a] 0.4, 2, 10	At ≥2 μg/kg/day, increased spleen weight, decreased local cell density in femoral and sternal bone marrow (males) At 10 μg/kg/day, increased reticulocyte count, decreased platelet count, increased trabeculae in femur and sternum, increased extramedullary hematopoiesis in the spleen, local decrease in cell density in femoral and sternal bone marrow (females) Reversibility: reversible	0.4 (male); 2 (female)	4.2.3.2-10
Male/ female cynomolgus monkeys	IV	4 weeks + 4-week recovery period	0,[a] 2, 20, 200	At ≥20 μg/kg/day, salivation, vomiting, abnormal stool consistency (muddy stool, soft stool, watery stool), decreased motility, decreased body weight, decreased thymus weight, atrophic changes in adipocytes, atrophy of the thymus At 200 μg/kg/day, decreased phosphorus/chloride/total cholesterol in blood, decreased urinary sodium/chloride, increased adrenal gland weight, atrophy of the spleen, FOB findings of central nervous system depression (e.g., slow movement, motor discoordination, decreased response to contact), dilated or constricted pupil Reversibility: reversible	2	4.2.3.2-11

a) [redacted] containing [redacted]
b) Vitreous hemorrhage was noted in 1 of 16 males and 1 of 16 females in the 1 μg/kg group and in 1 of 16 males in the 100 μg/kg group. One of the animals had brown pigmentation in the retina, and the applicant determined that bleeding from retinal vessels may have occurred.
c) Noted in 1 of 16 males in the 10 μg/kg group.
d) The applicant explained that reversibility for vitreous hemorrhage, brown pigmentation of the retina, dilation of retinal vessels could not be determined due to the low incidences although none of these events were reported after the recovery period.

5.3 Genotoxicity

Genotoxicity studies consisted of *in vitro* bacterial reverse mutation assays, an *in vitro* chromosome aberration study in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assays (Table 14). In the micronucleus study in rats, the ONO-AG-367 exposure ($AUC_{0\text{-}24h}$, 1150000 pg·h/mL) was higher than the clinical exposure[10] (AUC_{inf}, 9.41 pg·h/mL). Based on the negative results in both studies, it was concluded that sepetaprost and ONO-AG-367 are unlikely to be genotoxic.

Table 15. Summary of genotoxicity studies

Test type		Test system	Metabolic activation (treatment)	Concentration or dose	Test result	CTD
In vitro	Bacterial reverse mutation assay	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9−/+	S9−: 0,[a] 1.22, 2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 (μg/plate) S9+: 0,[a] 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000 (μg/plate)	Negative	4.2.3.3.1-1
	Chromosome aberration study in cultured mammalian cells	Human peripheral blood lymphocytes	S9+ (3 hours) S9− (3, 24 hours)	0,[a] 20, 40, 60, 80, 100, 140, 180 (μg/mL)	Negative	4.2.3.3.1-2
In vivo	Micronucleus study in rodents	Male rat (SD) bone marrow		0,[b] 1, 3, 10 (mg/kg/day) (intraperitoneal, for 3 days)	Negative	4.2.3.3.2-1

a) DMSO
b) [redacted] containing [redacted]

5.4 Carcinogenicity

No carcinogenicity studies were conducted because the dose of sepetaprost is 1 μg/day, less than the threshold of toxicological concern (1.5 μg/day), and the carcinogenicity studies of other FP receptor agonists (LAT, bimatoprost, travoprost, and tafluprost) have provided no evidence of carcinogenicity.

5.5 Reproductive and developmental toxicity

Studies were conducted to evaluate fertility and early embryonic development up to implantation in rats, embryo-fetal development in rats and rabbits, and the effects on pre- and postnatal development, including maternal function, in rats (Table 16).

Following intravenous administration of sepetaprost, embryonic death and teratogenicity (skeletal anomaly and deformity) were noted in rats while abortion and embryonic death were noted in rabbits. At the NOAEL for embryo-fetal development (3 μg/kg in rats and 0.04 μg/kg in rabbits) following intravenous administration of sepetaprost to rats and rabbits, the ONO-AG-367 exposure ($AUC_{0\text{-}4h}$) was 764 pg·h/mL [11] in rats and 18.7 pg·h/mL in rabbits,[12] which were 81 times and 2 times, respectively, the exposure[10] (AUC_{inf}: 9.41 pg·h/mL) in subjects who received ocular instillation of sepetaprost ophthalmic solution at the recommended clinical dose (0.002%).

Because of the sufficient safety margin given, the applicant considered that the findings reported in rats are unlikely to raise safety concerns for the clinical use of sepetaprost.

Findings reported in rabbits will be discussed in Section 5.R.

11) The mean of $AUC_{0\text{-}4h}$ on Day 6 (792 pg·h/mL) and Day 17 (736 pg·h/mL).
12) The mean of $AUC_{0\text{-}4h}$ on Day 6 (19.6 pg·h/mL) and Day 18 (17.8 pg·h/mL).

Table 16. Summary of reproductive and developmental toxicity studies

Test type	Test system	Route	Dosing duration	Dose (μg/kg)	Major findings	NOAEL (μg/kg)	CTD
Fertility and early embryonic development to implantation/ Embryo-fetal development	Male rats (SD)	IV	From 4 weeks prior to mating throughout the mating period	0,[a)] 3, 10, 30	At 30 μg/kg, death	Parents: 10 (general toxicity); 30 (male reproductive toxicity)	4.2.3.5.1-1
	Female rats (SD)		From 2 weeks prior to mating to gestational day 14		No findings	Parents: 30 (female reproductive toxicity)	
Embryo-fetal development	Pregnant rats (SD)	IV	From gestational days 6-17	0,[a)] 1, 3, 10	Dams: No findings Embryos/fetuses: At 10 μg/kg, increased number of embryo-fetal deaths, increased post-implantation loss, decreased fetal body weight, skeletal anomalies (vertebral body loss, morphological abnormality), skeletal mutation (asymmetric sternebrae, thoracic/lumbar spondylolysis), decreased number of ossified bones (sternebrae, sacrococcygeal vertebrae)	Dams: 10 Embryo-fetal toxicity: 3	4.2.3.5.2-2
	Pregnant rabbits (NZW)	IV	From gestational days 6-18	0,[a)] 0.02, 0.04, 0.1	Dams: At ≥0.04 μg/kg, abortion, vulva hemorrhage, decreased body weight gain, decreased food consumption At 0.1 μg/kg, corpus luteum regression Embryos/fetuses: At 0.1 μg/kg, increased number of embryo-fetal deaths, increased post-implantation loss, decreased fetal body weight	Dams: 0.02; Embryo-fetal toxicity: 0.04	4.2.3.5.2-4
Effects on pre-and postnatal development, including maternal function	Pregnant rats (SD)	IV	From gestational day 6 to lactating day 20	0,[a)] 0.3, 1, 3	No findings	Dams and F1 offspring development: 3	4.2.3.5.3-1

a) [redacted] containing [redacted]

5.6 Local tolerance

Local tolerance of sepetaprost was assessed by conducting ocular irritation studies in rabbits. No local irritability-related histopathological findings were noted. The risk of causing local irritation was considered to be low (Table 17).

Table 17. Summary of local tolerance studies

Test system	Application site	Test method	Major findings	CTD
Male rabbits (NZW)	Ocular	0%,[a)] 0.0003%, 0.001%, 0.005%, or 0.01% 30 μL/eye, 10 times daily	At ≥0.0003%, increasing trend in blink rate, transient conjunctival hyperemia	4.2.3.6-1
	Ocular	0%,[a)] 0.0003%, 0.001%, 0.005%, or 0.01%, 30 μL/eye, twice daily for 28 days	At ≥0.003%, transient conjunctival hyperemia	4.2.3.6-3

a) [redacted] containing [redacted], [redacted], [redacted], and [redacted], [redacted]

5.7 Other toxicity studies

5.7.1 Sensitization

A skin sensitization study of sepetaprost was conducted in guinea pigs. Sepetaprost was not considered to be a skin sensitizer (Table 18).

Table 18. Summary of skin sensitization study

Test type	Test system	Test method	Major findings	CTD
Maximization test	Male guinea pigs (Hartley)	0.1 mL at 0.01% was intradermally administered to induce sensitization; subsequently, a challenge dose at 0.01% was applied to elicit a reaction	None No sensitization was observed	4.2.3.7.1-1

5.7.2 Photosafety

No photosafety studies were conducted. Since sepetaprost does not have an absorption band within the wavelength of sunlight (290 to 700 nm), it was concluded that there are no phototoxicity concerns.

5.7.3 Impurity safety evaluation

For Impurity A (originating from both the drug substance and drug product), Impurity B (originating from the drug substance), and Impurity C (ONO-AG-367, originating from the drug product), the proposed specifications exceed the qualification thresholds requiring safety evaluations in accordance with the ICH Q3A and ICH Q3B Guidelines.

The following studies were conducted to evaluate the safety of Impurity A and Impurity B: a 39-week ocular toxicity study in monkeys using test substances containing concentrations of the impurity exceeding the specification limit (CTD 4.2.3.2-4), bacterial reverse mutation assays (CTD 4.2.3.3.1-1), and rat micronucleus assays (CTD 4.2.3.3.2-1). For Impurity C (ONO-AG-367), safety was evaluated in the rat micronucleus study (CTD 4.2.3.3.2-1) at levels exceeding both the clinical dose and amount calculated from the upper limits of specifications of Impurity C (ONO-AG-367) in the drug substance and drug product. In addition, the safety of Impurity C (ONO-AG-367) as a metabolite was evaluated in the 39-week monkey ocular toxicity study (CTD 4.2.3.2-4) and bacterial reverse mutation assays (CTD 4.2.3.3.1-1). Based on these evaluations, it was concluded that there are no safety concerns associated with any of these impurities.

5.R Outline of the review conducted by PMDA

5.R.1 Reproductive and developmental toxicity

The exposure at the NOAEL for embryo-fetal developmental toxicity in the embryo-fetal development study in rats [see Section 5.5] was 81 times the human exposure, while the exposure at the NOAEL for embryo-fetal developmental toxicity in the embryo-fetal development study in rabbits [see Section 5.5] was 2 times the human exposure, indicating a smaller safety margin in the rabbit study. PMDA asked the applicant to explain the mechanism of occurrence of embryo-fetal toxicities in rabbits as well as safety in humans.

The applicant's explanation:

- Cesarean section findings in the embryo-fetal development study in rabbits were recorded by classifying events into implantation sites, retained placenta, and dead fetuses. An increase in implantation sites, which

suggests early embryonic death, was noted only in the maximum dose group. From gestational day 17, abortions were noted in the intermediate to higher dose groups. FP receptor activation contributes not only to contraction of uterine smooth muscle but also to promoting luteal regression specifically in rabbits and rodents, adversely impacting maintenance of pregnancy (*Endocrinology*. 2004;145:2551-60). These findings suggest that embryonic deaths and abortions observed in rabbits are attributable to luteal regression resulting from FP receptor activation by ONO-AG-367.

- Compared to rats, rabbits are more prone to reduction in ovarian venous blood flow caused by FP receptor activation (*Reprod Fertil Suppl.* 1970;10:97-103), suggesting that rabbits are susceptible to abortion caused by luteal regression. In tafluprost, another FP receptor agonist, the dose level (6.7 times the clinical dose) at which increased abortion and post-implantation loss were observed in an embryo-fetal development study in rabbits was lower than that at which increased post-implantation loss was observed in an embryo-fetal development study in rats (2000 times the clinical dose) (see the package inserts for Tapros Ophthalmic Solution 0.0015%, Tapros Mini Ophthalmic Solution 0.0015%).
- The effective concentration, 50% (EC_{50} = 22.3 nmol/L) [see Section 3.1.2] of ONO-AG-367 for the human FP receptor is comparable to the EC_{50} of LAT (EC_{50} = 23 nmol/L) and prostaglandin $F_{2\alpha}$ (endogenous ligand; EC_{50} = 9.42 nmol/L) for the human FP receptor (CTD 4.2.1.1-2). Given that the unbound plasma concentration of ONO-AG-367 (5.04 pmol/L)[13)] in human subjects receiving ocular instillation of sepetaprost at the clinical dose (0.002%, 1 drop, instilled once daily) is approximately 1/5000 of the EC_{50} of ONO-AG-367 for the human FP receptor (EC_{50} = 22.3 nmol/L) [see Section 3.1.2], it is unlikely that sepetaprost 0.002% ophthalmic solution would exhibit FP receptor-mediated systemic effects when administered to humans.

PMDA accepted the applicant's explanation.

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

6.1 Biopharmaceutic studies and associated analytical methods

No biopharmaceutic study data were submitted.

Concentrations of unchanged sepetaprost and its metabolite ONO-AG-367 in biological samples were determined by LC-MS/MS (lower limits of quantitation, 5 pg/mL for unchanged sepetaprost; 1 pg/mL for ONO-AG-367).

The 0.02% formulation used in Japanese clinical studies (Studies 101260005LT, 101260006LT, and 101260007LT) and a global study (Study 012601IN) is identical in composition to the to-be-marketed formulation.

13) Calculated based on the mean (13.8 pg/mL [0.0313 nmol/L]) of C_{max} values of ONO-AG-367 on Day 1 (16.0 pg/mL) and Day 7 (11.5 pg/mL) and protein binding (83.9%; CTD 6.2.1) in a Japanese phase I study (Study 101260007LT), in which subjects received ocular instillation of sepetaprost 0.002% ophthalmic solution into both eyes for 7 days.

6.2 Clinical pharmacology

The applicant submitted evaluation data in the form of results from a phase I study (Study 101260007LT) in healthy Japanese adults. Results from the following studies were also submitted as reference data: a phase I study (Study ONO-9054IOU001) in healthy non-Japanese adults and a phase I study (Study ONO-9054IOU002) in non-Japanese patients with open-angle glaucoma or ocular hypertension. Data from *in vitro* studies of human biological samples were also submitted. The following sections provide a summary of the main pharmacokinetic studies.

6.2.1 Studies using human biological samples

(1) Protein binding and distribution in blood cells

Serum protein binding was investigated by the ultrafiltration method after adding the sepetaprost metabolite, ^{3}H-labeled ONO-AG-367 (0.3-30 ng/mL), to human serum. Serum protein binding was 83.9% to 85.4% in ONO-AG-367 (0.3-30 ng/mL). Protein binding of ONO-AG-367 (0.3-30 ng/mL) to human serum albumin and human α1-acid glycoprotein was also investigated by adding ^{3}H-labeled ONO-AG-367 (0.3-30 ng/mL) to these proteins. Protein binding of ONO-AG-367 (0.3-30 ng/mL) was 77.8% and 55.1% to 56.7% for human serum albumin and human α1-acid glycoprotein, respectively (CTD 4.2.2.3-1).

When ^{3}H-labeled ONO-AG-367 (0.3-30 ng/mL) was added to human blood, the blood/plasma ONO-AG-367 concentration ratio was 0.47 to 0.55, and 0% to 0.4% of ONO-AG-367 was distributed in blood cells (CTD 4.2.2.3-1).[14)]

(2) Metabolites in humans

When ^{3}H-labeled sepetaprost (500 ng/mL) was added to human hepatocytes and incubated for 4 hours, the active metabolites ONO-AG-367 (36.2%) and ONO-AG-450 (34.9%; a β-oxidation product of ONO-AG-367) were detected as the predominant metabolites. Unchanged sepetaprost accounted for <1% (CTD 4.2.2.4-1).

(3) Enzymes involved in metabolism

Recombinant human carboxylesterases 1 and 2, human red blood cell acetylcholinesterase, and human serum butyrylcholinesterase were incubated with ^{3}H-labeled sepetaprost (0.1 μmol/L) for 30 minutes to investigate esterase species involved in the metabolism of sepetaprost. The results showed that ONO-AG-367 was quantifiable only when incubated with human carboxylesterase 1, suggesting that the conversion of sepetaprost to ONO-AG-367 is mediated by carboxylesterase 1, and the other esterases studied are not involved (CTD 4.2.2.4-5).

When ONO-AG-367 was added to human liver microsomes and incubated for 2 hours in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), ONO-AG-367 was not metabolized. The results

14) To calculate the distribution of ONO-AG-367 in blood cells, hematocrit levels measured in each sample (36%-47%) were used.

suggest that cytochrome P450 (CYP) isoforms are not involved in the metabolism of ONO-AG-367 (CTD 4.2.2.4-4).

(4) Enzyme inhibition

Using specific substrates[15] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, the inhibitory effects of ONO-AG-367 (0.001-1 μmol/L) on CYP isoforms in human liver microsomes were evaluated. No clear inhibitory effects on any CYP isoforms were noted within the concentration range studied (CTD 4.2.2.4-6).

(5) Transport by drug transporters (CTD 4.2.2.6-1)

Membrane permeability of sepetaprost (0.2-20 μmol/L) was evaluated using monolayers of Madin-Darby canine kidney II (MDCK II) cells expressing human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP). The net efflux ratio (efflux ratio[16] of P-gp or BCRP-expressing cells / efflux ratio of non-expressing cells) was 0.34 to 1.36 for P-gp and 0.30 to 2.74 for BCRP. Sepetaprost 0.2 μmol/L was added in the presence of a BCRP inhibitor (Ko143, 1 μmol/L) and BCRP-mediated transport was evaluated. The net efflux ratio was 3.18 and 0.47 in the absence and presence of the BCRP inhibitor, respectively. These results suggest that sepetaprost can be a substrate for BCRP.

The transporter-mediated intracellular uptake of sepetaprost (1 and 10 μmol/L) was investigated in human embryonic kidney (HEK) 293 cells expressing human organic anion transporter (OAT)1, OAT3, organic anion transporting polypeptide (OATP)1B1, or OATP1B3, Chinese hamster ovary (CHO) cells expressing organic cation transporter (OCT)1 or OCT2, and MDCK II cells expressing multidrug and toxin extrusion protein (MATE)1 or MATE2-K. There were no clear differences in the uptake activity of sepetaprost between transporter-expressing and non-expressing cells. These results suggest that sepetaprost is not a substrate for any of the transporters studied (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K).

Bile salt export pump (BSEP)-mediated transport of sepetaprost (1 and 10 μmol/L) was investigated using membrane vesicles of HEK293 cells expressing human BSEP. There were no clear differences in the transport of sepetaprost between conditions in the presence of adenosine triphosphate (ATP) and in its absence (presence of adenosine monophosphate [AMP]). These results suggest that sepetaprost is not a substrate for BSEP.

The membrane permeability of ONO-AG-367 (0.2-20 μmol/L) was investigated using monolayers of MDCK II cells expressing human P-gp or BCRP. The net efflux ratio was 0.56 to 0.68 for P-gp and 0.11 to 1.70 for BCRP, suggesting that ONO-AG-367 is not a substrate of P-gp or BCRP.

The transporter-mediated intracellular uptake of ONO-AG-367 (1 and 10 μmol/L) was investigated in HEK-

15) The following compounds were used as substrates: phenacetin (CYP1A2); efavirenz (CYP2B6); amodiaquine (CYP2C8); diclofenac (CYP2C9); *S*-mephenytoin (CYP2C19); dextromethorphan (CYP2D6); midazolam and testosterone (CYP3A)

16) The ratio of the apparent permeability in the basal to apical direction (Papp $_{B\rightarrow A}$) to the apparent permeability in the apical to the basal direction (Papp $_{A\rightarrow B}$)

293 cells expressing human OAT1, OAT3, OATP1B1, or OATP1B3, CHO cells expressing OCT1 or OCT2, MDCK II cells expressing MATE1 or MATE2-K. Intracellular uptake activity of ONO-AG-367 increased in cells expressing OAT3, OATP1B1, OATP1B3, or MATE2-K compared with the corresponding non-expressing cell lines. Furthermore, when the intracellular uptake of ONO-AG-367 (1 μmol/L) was assessed in the presence of OAT3, OATP1B1, OATP1B3, or MATE2-K inhibitors, intracellular uptake of ONO-AG-367 was inhibited by each transporter inhibitor.[17)] The above results suggest that ONO-AG-367 can be a substrate for OAT3, OATP1B1, OATP1B3, or MATE2-K.

Bile salt export pump-mediated transport of ONO-AG-367 (1 and 10 μmol/L) was investigated using membrane vesicles of HEK293 cells expressing human BSEP. As no clear differences in the transport of ONO-AG-367 was observed between conditions in the presence of ATP and its absence (presence of AMP), these results suggest that ONO-AG-367 is not a substrate for BSEP.

(6) Inhibition on drug transporters (CTD 4.2.2.6-1)

The inhibitory effects of sepetaprost[18)] on the transport of substrates[19)] for each transporter were evaluated using monolayers of MDCK II cells expressing human P-gp or BCRP. While sepetaprost inhibited BCRP (IC_{50} = 0.64 μmol/L), it did not show inhibitory effects on P-gp within the concentration range studied.

The inhibitory effects of sepetaprost[20)] on the transport of substrates[21)] for various transporters were investigated in HEK293 cells expressing human OAT1, OAT3, OATP1B1, or OATP1B3, CHO cells expressing OCT1 or OCT2, MDCK II cells expressing MATE1 or MATE2-K. Sepetaprost inhibited OATP1B1, OATP1B3, OCT1, OCT2, and MATE1, with a maximum inhibition of 42%, 59%, 79%, 98%, and 33%, respectively. The IC_{50} values for OATP1B3, OCT1, and OCT2 were 14.5, 7.34, and 0.35 μmol/L, respectively. Conversely, sepetaprost did not show inhibitory effects on OAT1, OAT3, or MATE2-K within the concentration range studied.

The inhibitory effects of sepetaprost (2 and 20 μmol/L) on the substrate for BSEP (taurocholic acid, 0.2 μmol/L) were evaluated in membrane vesicles of HEK293 cells expressing human BSEP. Sepetaprost did not inhibit the transport of BSEP substrates within the concentration range studied.

The inhibitory effects of ONO-AG-367[22)] on the transport of substrates[23)] for various transporters were investigated using monolayers of MDCK II cells expressing human P-gp or BCRP. The results showed that

17) The following compounds were used as transporter inhibitors: probenecid 500 μmol/L (OAT3); rifampicin 50 μmol/L (OATP1B1/OATP1B3); pyrimethamine 10 μmol/L (MATE2-K)
18) 20 μmol/L. In the evaluation of IC_{50} values against BCRP, 0.25 to 20 μmol/L was evaluated.
19) The following compounds were used as substrates for the transporters: ^{3}H-labeled digoxin 5 μmol/L (P-gp); ^{3}H-labeled prazosin 1 μmol/L (BCRP).
20) 2 and 20 μmol/L. In the evaluation of IC_{50} values against OATP1B3, OCT1, and OCT2, 0.03 to 20 μmol/L was evaluated.
21) The following compounds were used as substrates for the transporters: ^{3}H-labeled *p*-aminohippuric acid 5 μmol/L (OAT1); ^{3}H-labeled estrone-3-sulfate 1 μmol/L (OAT3); ^{3}H-labeled estradiol-17-β-glucuronide 1 μmol/L (OATP1B1); ^{3}H-labeled cholecystokinin octapeptide 0.11 μmol/L (OATP1B3); ^{14}C-labeled metformin hydrochloride 10 μmol/L (OCT1, OCT2, MATE1, and MATE2-K)
22) 20 μmol/L. In the evaluation of IC_{50} values against BCRP, 3.7 to 300 μmol/L was evaluated.
23) The following compounds were used as substrates for the transporters: ^{3}H-labeled digoxin 5 μmol/L (P-gp); ^{3}H-labeled prazosin 1 μmol/L (BCRP)

ONO-AG-367 inhibited the transport of BCRP substrates, with a maximum inhibition of 28%, while ONO-AG-367 did not show inhibitory effects on P-gp substrates within the concentration range studied.

The inhibitory effects of ONO-AG-367[24)] on the transport of substrates[25)] for various transporters were investigated in HEK293 cells expressing human OAT1, OAT3, OATP1B1, or OATP1B3, CHO cells expressing OCT1 or OCT2, MDCK II cells expressing MATE1 or MATE2-K. The results showed that ONO-AG-367 inhibited uptake of substrates for OAT3 (IC_{50} = 11.6 μmol/L), OATP1B1 (IC_{50} = 29.9 μmol/L), OATP1B3 (IC_{50} = 36.2 μmol/L), and OCT2 (IC_{50} = 122 μmol/L), while ONO-AG-367 did not show inhibitory effects on OAT1, OCT1, MATE1, or MATE2-K within the concentration range studied.

The inhibitory effects of ONO-AG-367 (2 and 20 μmol/L) on the substrate for BSEP (taurocholic acid, 0.2 μmol/L) were investigated using membrane vesicles of HEK293 cells expressing human BSEP. Sepetaprost inhibited the transport of the BSEP substrate with a maximum inhibition of 26%.[26)]

Given the findings described in Subsections (3) through (6) above and other data including the C_{max} of sepetaprost (below the lower limit of quantitation [5 pg/mL]) and C_{max} of ONO-AG-367 (13.8 pg/mL [0.03 nmol/L][27)]) in patients with glaucoma and ocular hypertension who received multiple ocular instillations of sepetaprost 0.002% ophthalmic solution into both eyes once daily, the applicant considers that it is unlikely that drug interactions mediated by metabolic enzymes and transporters investigated above will cause problems in clinical use.

6.2.2 Studies in healthy adults

6.2.2.1 Japanese phase I study (CTD 5.3.3.1-1, Study 101260007LT)

In healthy Japanese adults (8 subjects for pharmacokinetic evaluation), 1 drop of sepetaprost 0.002% ophthalmic solution was instilled into both eyes, once daily for 7 days to evaluate the pharmacokinetics of sepetaprost and ONO-AG-367 in plasma. Plasma sepetaprost concentrations were below the lower limit of quantitation (5 pg/mL) in all subjects. Table 19 shows the pharmacokinetic parameters of ONO-AG-367 in plasma.

Table 19. Pharmacokinetic parameters of ONO-AG-367 following ocular instillation of sepetaprost 0.002% ophthalmic solution

Timepoint	N	C_{max} (pg/mL)	t_{max} (h) [a)]	$t_{1/2}$ (h)	$AUC_{0\text{-}2h}$ (pg·h/mL)	AUC_{inf} (pg·h/mL)
Day 1	8	16.0 ± 4.58 15.9 (10.4, 22.3)	0.17 (0.17, 0.33)	0.51 ± 0.12 0.53 (0.30, 0.70)	10.8 ± 3.06 10.6 (5.22, 15.3)	11.9 ± 3.29 11.6 (5.89, 17.2)
Day 7	8	11.5 ± 3.38 11.8 (6.17, 15.8)	0.17 (0.08, 0.33)	0.40 ± 0.17 0.34 (0.24, 0.71)	6.04 ± 1.97 5.96 (3.17, 9.46)	6.91 ± 2.17 6.66 (3.87, 10.9)

Upper row, mean ± standard deviation; lower row, median (Min, Max); data below the lower limit of quantitation were imputed as 0
a) Median (Min, Max)

24) 2 and 20 μmol/L. In the evaluation of IC_{50} values against OAT3, OATP1B1, OATP1B3, and OCT2, 0.41 to 300 μmol/L was evaluated.
25) The following compounds were used as substrates for the transporters: ^{3}H-labeled *p*-aminohippuric acid 5 μmol/L (OAT1); ^{3}H-labeled estrone-3-sulfate 1 μmol/L (OAT3); ^{3}H-labeled estradiol-17-β-glucuronide 1 μmol/L (OATP1B1); ^{3}H-labeled cholecystokinin octapeptide 0.11 μmol/L (OATP1B3); ^{14}C-labeled metformin hydrochloride 10 μmol/L (OCT1, OCT2, MATE1, and MATE2-K)
26) To evaluate the IC_{50} value for BSEP, the inhibitory effect of ONO-AG-367 was assessed at 0.21 to 150 μmol/L. No clear inhibitory effects were shown (maximum inhibition of 9%).
27) In the Japanese phase I study (Study 101260007LT), 1 drop of sepetaprost 0.002% ophthalmic solution was instilled into both eyes once daily for 7 days. The mean was calculated from the C_{max} on Day 1 (16.0 pg/mL) and Day 7 (11.5 pg/mL).

6.2.2.2 Foreign phase I study (CTD 5.3.3.1-3, Study ONO-9054IOU001)

In healthy non-Japanese adults (36 subjects for pharmacokinetic evaluation), a single ocular dose of sepetaprost ophthalmic solution at 0.00003% to 0.003% was instilled into both eyes, and the pharmacokinetics of sepetaprost and ONO-AG-367 in plasma was evaluated. Plasma sepetaprost concentrations were below the lower limit of quantitation (5 pg/mL) at all timepoints except for 1 timepoint in 1 subject in the 0.003% group (9.74 pg/mL at 5 minutes post-instillation). Plasma concentrations of ONO-AG-367 were below the lower limit of quantitation (1 pg/mL) in all subjects in the 0.00003% group, and at all timepoints in the 0.0001% group except for 1 timepoint in 1 subject (1.02 pg/mL at 10 minutes post-instillation). Table 20 shows the pharmacokinetic parameters in the 0.0003% to 0.003% groups.

Table 20. Pharmacokinetic parameters of ONO-AG-367 following a single ocular instillation of sepetaprost

Sepetaprost ophthalmic solution concentration (%)	N	C_{max} (pg/mL)	t_{max} (h) [a]	$t_{1/2}$ (h)	AUC_{last} (pg·h/mL)	AUC_{inf} (pg·h/mL)
0.0003	6	2.02 ± 1.10 2.23 (0, 3.28)	0.17 (0.17, 0.33)[b]	—	0.70 ± 0.40 0.71 (0, 1.12)	—
0.001	6	5.54 ± 2.71 5.96 (1.58, 8.74)	0.25 (0.17, 0.33)	0.48 ± 0.20 0.42 (0.32, 0.76)[c]	3.88 ± 2.21 3.98 (0.87, 6.84)	6.09 ± 2.17 6.48 (3.76, 8.05)[d]
0.002	6	16.5 ± 6.93 14.7 (10.6, 29.5)	0.17 (0.17, 0.17)	0.69 ± 0.12 0.67 (0.55, 0.90)	9.34 ± 1.96 9.85 (6.78, 12.1)	10.6 ± 2.03 11.2 (7.91, 13.2)
0.003	6	29.1 ± 9.63 27.4 (14.6, 43.4)	0.17 (0.08, 0.33)	0.83 ± 0.31 0.74 (0.54, 1.4)[b]	18.1 ± 6.61 19.6 (8.72, 25.9)	21.4 ± 6.82 24.2 (10.4, 27.9)[b]

Upper row, mean ± standard deviation; lower row, median (Min, Max); data below the lower limit of quantitation were imputed as 0; —, not calculated

a) Median (Min, Max); b) N = 5; c) N = 4; d) N = 3

In Study ONO-9054IOU001, in all subjects in the sepetaprost 0.003% group (N = 6), urinary excretion of ONO-AG-367 was <10% up to 24 hours post-instillation (CTD 5.3.3.1-6).

6.2.3 Studies in patients

6.2.3.1 Foreign phase I study (CTD 5.3.3.2-1, Study ONO-9054IOU002)

In non-Japanese patients with open-angle glaucoma or ocular hypertension (36 subjects for pharmacokinetic evaluation), the pharmacokinetics of sepetaprost and ONO-AG-367 in plasma were evaluated following either a single bilateral instillation or once-daily bilateral instillation (1 drop per eye for 14 days) of sepetaprost ophthalmic solution at 0.0003% to 0.003%. At all the studied concentrations of sepetaprost ophthalmic solution, plasma sepetaprost concentrations were below the lower limit of quantitation (5 pg/mL) in all subjects at all timepoints. The pharmacokinetic parameters of ONO-AG-367 in plasma are presented in Table 21 and Table 22.

Table 21. Pharmacokinetic parameters of ONO-AG-367 following a single ocular instillation of sepetaprost

Sepetaprost ophthalmic solution concentration (%)	N	C_{max} (pg/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	AUC_{last} (pg·h/mL)	AUC_{inf} (pg·h/mL)
0.0003	9	3.42 ± 1.42 2.93 (1.27, 5.71)	0.17 (0.08, 0.50) [b]	0.41 ± 0.18 0.38 (0.21, 0.70) [c]	1.97 ± 1.00 2.00 (0.53, 3.46)	3.50 [d]
0.001	9	8.50 ± 4.47 7.86 (3.02, 17.7)	0.17 (0.08, 0.33)	0.46 ± 0.13 0.50 (0.22, 0.61) [e]	4.22 ±1.97 3.93 (1.63, 6.76)	5.38 ± 1.93 4.89 (3.45, 7.65) [c]
0.002	9	14.9 ± 4.58 12.7 (10.1, 22.2)	0.17 (0.17, 0.33) [b]	0.52 ± 0.15 0.48 (0.40, 0.89)	11.0 ± 3.65 9.55 (7.46, 17.4)	12.1 ± 3.62 11.2 (8.47, 18.2)
0.003	9	28.1 ± 12.9 28.9 (11.3, 49.0)	0.17 (0.08, 0.33) [b]	0.67 ± 0.19 0.62 (0.49, 1.1)	19.6 ± 7.63 20.4 (7.09, 29.3)	21.5 ± 7.94 22.9 (8.29, 31.2)

Upper row, mean ± standard deviation; lower row, median (Min, Max) or individual values; data below the lower limit of quantitation were imputed as 0
a) Median (Min, Max); b) N = 8; c) N = 5; d) N = 1; e) N = 7

Table 22. Pharmacokinetic parameters of ONO-AG-367 following ocular instillation of sepetaprost once daily for 14 days

Sepetaprost ophthalmic solution concentration (%)	N	C_{max} (pg/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	AUC_{last} (pg·h/mL)
0.0003	9	3.98 ± 2.07 3.35 (1.62, 8.03)	0.17 (0.08, 0.50)	0.49 ± 0.19 [b] 0.40 (0.39, 0.78)	2.09 ± 1.24 1.64 (0.82, 4.02)
0.001	9	8.65 ± 6.01 7.55 (2.27, 18.7)	0.17 (0.17, 0.33)	0.44 ± 0.15 [c] 0.38 (0.24, 0.69)	4.04 ± 2.29 4.91 (0.53, 7.06)
0.002	9	15.2 ± 7.99 14.6 (6.46, 27.5)	0.17 (0.08, 0.33) [c]	0.46 ± 0.09 0.43 (0.32, 0.60)	9.01 ± 4.43 8.10 (4.52, 15.1)
0.003	8	24.5 ± 14.0 21.6 (11.0, 46.6)	0.17 (0.08, 0.17)	0.57 ± 0.10 0.58 (0.45, 0.72)	15.4 ± 8.92 12.5 (6.27, 31.7)

Upper row, mean ± standard deviation; lower row, median (Min, Max); data below the lower limit of quantitation were imputed as 0
a) Median (Min, Max); b) N = 4; c) N = 8

In non-Japanese patients with open-angle glaucoma or ocular hypertension (12 subjects for pharmacokinetic evaluation), the effects of dosing timing (morning 7 a.m. or evening 7 p.m.) on the pharmacokinetics of sepetaprost were investigated by instilling 1 drop of sepetaprost 0.003% ophthalmic solution once daily in the morning or evening for 14 days into both eyes. At all the studied concentrations of sepetaprost ophthalmic solution, plasma sepetaprost concentrations were below the lower limit of quantitation (5 pg/mL) in all subjects at all timepoints. Table 23 shows the ONO-AG-367 pharmacokinetic parameters in plasma. There were no clear differences between administration in the morning and evening.

Table 23. Pharmacokinetic parameters of ONO-AG-367 following ocular instillation of sepetaprost once daily in the morning or evening for 14 days

Instillation time	Measurement timepoint	N	C_{max} (pg/mL)	t_{max} [a] (h)	$t_{1/2}$ (h)	AUC_{last} (pg·h/mL)	AUC_{inf} (pg·h/mL)
7 a.m.	Day 1	12	23.4 ± 10.7 22.6 (8.06, 40.5)	0.17 (0.08, 0.33)	0.84 ± 0.36 0.80 (0.40, 1.5)	16.4 ± 7.87 13.9 (7.36, 28.6)	18.2 ± 8.44 16.0 (8.75, 29.9)
	Day 14	12	20.6 ± 7.23 19.0 (10.0, 35.5) [b]	0.17 (0.08, 0.33)	0.80 ± 0.29 0.73 (0.40, 1.3)	15.3 ± 6.39 12.8 (8.61, 26.7) [b]	—
7 p.m.	Day 1	12	20.4 ± 6.86 19.5 (11.4, 35.3)	0.17 (0.08, 0.33)	0.96 ± 0.35 0.95 (0.37, 1.7)	15.1 ± 5.06 15.4 (5.30, 22.3)	17.2 ± 5.49 17.4 (6.25, 25.8)
	Day 14	12	23.4 ± 11.1 22.7 (5.73, 46.1)	0.17 (0.08, 0.33) [b]	1.00 ± 0.34 0.98 (0.58, 1.6) [c]	16.4 ± 7.82 16.1 (4.25, 29.7)	—

Upper row, mean ± standard deviation; lower row, median (Min, Max); data below the lower limit of quantitation were imputed as 0
a) Median (Min, Max); b) N = 11; c) N = 10

6.R Outline of the review conducted by PMDA

PMDA concluded that the results indicated no particular issues in the pharmacokinetics of sepetaprost.

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 results data from 3 Japanese clinical studies and 1 global clinical study (Table 24). Other reference data submitted were results from 5 foreign clinical studies. The following sections present the main study results.

Table 24. List of main clinical studies on efficacy and safety

Data category	Location	Study ID CTD	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japan	101260007LT 5.3.3.1-1	I	Healthy adults	8	Instillation of 1 drop of sepetaprost 0.002% ophthalmic solution into both eyes once daily for 7 days	Safety Pharmacokinetics
	Global	012601IN 5.3.5.1-1	II	Patients with primary open-angle glaucoma or ocular hypertension	241 (114 Japanese)	Instillation of 1 drop of sepetaprost ophthalmic solution (0.0005%, 0.001%, 0.002%, or 0.003%), LAT 0.005% ophthalmic solution, or placebo into both eyes once daily for 3 months	Efficacy Safety
	Japan	101260005LT 5.3.5.1-2	III	Patients with primary open-angle glaucoma or ocular hypertension	325	Instillation of 1 drop of sepetaprost 0.002% ophthalmic solution or LAT 0.005% ophthalmic solution into both eyes once daily (at 9 p.m.) for 3 months	Efficacy Safety
	Japan	101260006LT 5.3.5.2-1	III	Patients with primary open-angle glaucoma (broad definition), pseudoexfoliation glaucoma, pigmentary glaucoma, or ocular hypertension	131	Instillation of 1 drop of sepetaprost 0.002% ophthalmic solution into both eyes once daily; or instillation of 1 drop of TIM 0.5% ophthalmic solution into both eyes twice daily for 52 weeks	Efficacy Safety

7.1 Evaluation data

7.1.1 Japanese phase I study (CTD5.3.3.1-1, Study 101260007LT [May to June 2023])

An unmasked, uncontrolled study was conducted in Japan to evaluate safety and pharmacokinetics following administration of multiple doses of the sepetaprost 0.002% ophthalmic solution to healthy Japanese adults (target sample size, 8 subjects) [see Section 6.2.2.1 for pharmacokinetic data].

The dosage regimen was instillation of 1 drop of sepetaprost 0.002% ophthalmic solution once daily (at 9 a.m.) to both eyes for 7 days.

All 8 subjects who were enrolled in this study and received the study drug were included in the safety analysis set. No subjects discontinued the study.

Adverse events occurred in 8 of 8 subjects (100%; conjunctival hyperaemia [8 subjects], punctate keratitis [1 subject]). All of these events were considered to be related to the study drug. There were no serious adverse events, including death, or no adverse events leading to treatment discontinuation.

There were no clinically significant changes in vital signs (blood pressure and pulse rate), electrocardiograms, or ophthalmologic assessments (IOP, slit-lamp microscopy, fundoscopy, and visual acuity).

7.1.2 Global phase II study (CTD5.3.5.1-1, Study 012601IN [August 2017 to February 2018])

A randomized, observer-masked, placebo-controlled, parallel-group study was conducted in Japan and the US to evaluate the efficacy and safety of sepetaprost in Japanese and non-Japanese patients with primary open-angle glaucoma or ocular hypertension [28] (target sample size, 220 subjects [29]).

This study consisted of a screening phase (including a washout period of 1 to 35 days) and a treatment phase (3 months). After the screening phase, subjects were randomized in a 2:2:2:2:2:1 ratio to the sepetaprost 0.0005%, 0.001%, 0.002%, or 0.003% group, LAT group, or placebo-sepetaprost 0.003% group. [30]

The dosage regimen was bilateral instillation of 1 drop of sepetaprost 0.0005%, 0.001%, 0.002%, or 0.003% ophthalmic solution, or LAT 0.005% ophthalmic solution, once daily (at 9 p.m.) for 3 months. Subjects in the placebo group were to receive bilateral instillation of 1 drop of placebo once daily for 6 weeks followed by bilateral instillation of 1 drop of sepetaprost 0.003% once daily up to the end of treatment.

Of the 301 subjects enrolled in this study, 241 subjects were randomized and received the study drug (43 subjects [sepetaprost 0.0005%], 43 subjects [sepetaprost 0.001%], 44 subjects [sepetaprost 0.002%], 45 subjects [sepetaprost 0.003%], 44 subjects [LAT], and 22 subjects [placebo-sepetaprost 0.003%]; the same applies hereinafter for the order of treatment groups). All subjects were included in the safety analysis set and the full analysis set (FAS), which was defined as the primary efficacy analysis set. Eight subjects (1, 0, 1, 3, 1, and 2 subjects, respectively) discontinued the study. Common reasons for discontinuation were “adverse events” in 3 subjects (0, 0, 1, 1, 1, and 0 subjects, respectively), “lack of efficacy” in 2 subjects (2 subjects in the placebo-sepetaprost group only), and “protocol deviation” in 3 subjects (1, 0, 0, 2, 0, and 0 subjects, respectively).

Table 25 shows the results for the primary endpoint, IOP in the study eye for efficacy evaluation [31] at each measurement timepoint (9 a.m., 1 p.m., and 5 p.m.) at Month 3. At all timepoints at Month 3, IOP values in the sepetaprost 0.002% ophthalmic solution group were lower than those in other sepetaprost ophthalmic solution groups, and were comparable to those in the LAT group. Changes from baseline in mean diurnal IOP in the sepetaprost and LAT ophthalmic solution groups were generally consistent from Week 1 through Month 3.

28) Patients who were diagnosed as having primary open-angle glaucoma (excluding pseudoexfoliation syndrome) or ocular hypertension in both eyes and had an anterior chamber angle grade ≥2 (Shaffer scale) in each eye, and whose IOP was ≥22 mmHg in at least one eye at all measurement timepoints (9 a.m., 1 p.m., and 5 p.m.) at baseline (Day 1) and ≤34 mmHg in both eyes.

29) As a secondary endpoint, assuming a minimal expected treatment difference at each timepoint (9 a.m., 1 p.m., and 5 p.m.) of −5.1 mmHg between the sepetaprost and placebo groups at Week 6, and a standard deviation of 3.9 mmHg for each group, with a two-sided significance level of 1.25% (adjusted by Bonferroni correction), with a 2:1 ratio (each sepetaprost group: placebo), a sample size of 36 subjects for each sepetaprost group and 18 subjects for the placebo group would provide 92% power to detect a difference at all 3 timepoints. For the entire study, assuming the same sample size for LAT (active control), with a 10% dropout rate, a target sample size of 220 subjects (40 subjects in each sepetaprost group, 20 subjects in the placebo group, and 40 subjects in the LAT group) was determined.

30) The stratifying factor was country (Japan or the US).

31) The study eye for efficacy evaluation was defined as the eye that met the inclusion criteria at baseline. If both eyes met the inclusion criteria, the eye with a higher mean diurnal IOP at baseline would be designated as the study eye. If both eyes met the inclusion criteria and had the same mean diurnal IOP, then the right eye would be designated as the study eye.

Table 25. Intraocular pressure values (mmHg) in the study eye for the efficacy evaluation at each measurement timepoint (9 a.m., 1 p.m., and 5 p.m.) at Month 3

Timepoint		Sepetaprost 0.0005%	Sepetaprost 0.001%	Sepetaprost 0.002%	Sepetaprost 0.003%	LAT	Placebo-sepetaprost 0.003%
Baseline	9 a.m.	24.9 ± 2.58 (43)	24.9 ± 2.50 (43)	24.8 ± 2.88 (44)	24.7 ± 2.31 (45)	25.0 ± 2.90 (44)	25.0 ± 2.72 (22)
	1 p.m.	24.5± 2.64 (43)	24.2 ± 2.42 (43)	24.1 ± 2.59 (44)	24.3 ± 2.21 (45)	24.2 ± 2.21 (44)	24.0 ± 1.91 (22)
	5 p.m.	23.8 ± 2.39 (43)	23.6 ± 2.03 (43)	23.6 ± 2.25 (44)	23.6 ± 1.93 (45)	23.5 ± 1.79 (44)	24.5 ± 2.93 (22)
Study treatment Month 3	9 a.m.	19.7 ± 3.27 (42)	19.2 ± 3.37 (43)	17.6 ± 3.13 (44)	19.3 ± 2.92 (42)	18.1 ± 3.73 (43)	18.8 ± 4.11 (20)
	1 p.m.	18.5 ± 2.98 (42)	18.1 ± 2.99 (43)	17.4 ± 2.39 (44)	18.7 ± 3.17 (42)	17.3 ± 3.01 (43)	17.6 ± 3.18 (20)
	5 p.m.	18.3 ± 2.55 (42)	17.8 ± 2.93 (43)	16.7 ± 2.74 (44)	17.9 ± 2.82 (42)	17.2 ± 3.10 (43)	17.8 ± 2.87 (20)

Mean ± standard deviation (N)

The incidence of adverse events was 48.8% (21 of 43 subjects) in the sepetaprost 0.0005% group, 44.2% (19 of 43 subjects) in the sepetaprost 0.001% group, 34.1% (15 of 44 subjects) in the sepetaprost 0.002% group, 51.1% (23 of 45 subjects) in the sepetaprost 0.003% group, and 50.0% (22 of 44 subjects) in the LAT group. In the placebo-sepetaprost 0.003% group, the incidence of adverse events was 22.7% (5 of 22 subjects) in the placebo period (up to Week 6) and 50.0% (10 of 20 subjects) in the sepetaprost period (after Week 6). There were no deaths. A serious adverse event excluding death occurred in 1 subject (muscular weakness) in the placebo period in the placebo-sepetaprost 0.003% group, for which a causal relationship to the study drug was ruled out. Adverse events that led to study drug discontinuation occurred in 1 subject in the sepetaprost 0.002% group (conjunctival hyperaemia and conjunctival oedema), 1 subject in the sepetaprost 0.003% group (conjunctivitis allergic), and 1 subject in the LAT group (sudden hearing loss). Among these events, conjunctivitis allergic was considered to be related to the study drug. The incidence of adverse events (including laboratory test abnormality) determined to be related to the study drug was 20.9% (9 of 43 subjects) in the sepetaprost 0.0005% group, 25.6% (11 of 43 subjects) in the sepetaprost 0.001% group, 20.5% (9 of 44 subjects) in the sepetaprost 0.002% group, 24.4% (11 of 45 subjects) in the sepetaprost 0.003% group, 29.5% (13 of 44 subjects) in the LAT group, 4.5% (1 of 22 subjects) in the placebo-sepetaprost 0.003% group (placebo period), and 20.0% (4 of 20 subjects) in the placebo-sepetaprost 0.003% group (sepetaprost treatment period). Adverse events occurring in ≥2 subjects in any group were conjunctival hyperaemia (5 subjects [sepetaprost 0.0005%], 4 subjects [sepetaprost 0.001%], 8 subjects [sepetaprost 0.002%], 5 subjects [sepetaprost 0.003%], 9 subjects [LAT], 0 subjects [placebo-sepetaprost 0.003%, placebo period], and 2 subjects [placebo-sepetaprost 0.003%, sepetaprost 0.003% treatment]; the same applies hereinafter for the order of treatment groups), growth of eyelashes (3, 2, 0, 0, 2, 0, and 1 subjects, respectively), eye pruritus (2, 1, 0, 3, 2, 0, and 0 subjects, respectively), eye irritation (0, 2, 0, 0, 1, 1, and 0 subjects, respectively), instillation site pain (0, 1, 3, 1, 0, 0, and 0 subjects, respectively), lacrimation increased (0, 0, 0, 0, 3, 0, and 1 subjects, respectively).

There were no clinically significant changes in vital signs (blood pressure and pulse rate) or ophthalmologic assessments (e.g., refraction, corrected visual acuity, slit-lamp microscopy, visual field, fundoscopy).

7.1.3 Japanese phase III study (CTD:5.3.5.1-2, Study 101260005LT [August 2022 to April 2023])

A randomized, observer-masked, active-controlled, parallel-group study was conducted in patients with primary open-angle glaucoma or ocular hypertension [32)] (target sample size, 300 subjects, 150 subjects/group) [33)] to evaluate the non-inferiority of sepetaprost 0.002% ophthalmic solution to LAT.

This study consisted of a washout period (1 to 35 days) and a treatment period (3 months). After completing the washout period, subjects were randomized in a 1:1 ratio to sepetaprost or LAT. The dosage regimen was bilateral instillation of 1 drop of sepetaprost 0.002% ophthalmic solution, or LAT 0.005% ophthalmic solution, once daily (at 9 p.m.) for 3 months.

Of the 383 subjects enrolled in this study, 325 subjects were randomized and received the study drug (162 subjects [sepetaprost] and 163 subjects [LAT]) and were included in the safety analysis set and the FAS, which was defined as the primary efficacy analysis set. Fifteen subjects discontinued the study (6 and 9 subjects in the sepetaprost and LAT groups, respectively; the same applies hereinafter for the order of treatment groups). Common reasons for discontinuation were “adverse events” in 8 subjects (2 and 6 subjects, respectively), “discontinuation related to COVID-19” in 3 subjects (1 and 2 subjects, respectively), “death” in 2 subjects (1 subject each), and “protocol deviation” in 1 subject (1 and 0 subjects, respectively).

Table 26 shows the results for the primary endpoint, the change from baseline in mean diurnal IOP (mean of IOP at 3 timepoints, at 9 a.m., 1 p.m., and 5 p.m.) in the study eye for efficacy evaluation [34)] at Week 4. The upper bound for the 95% confidence interval (CI) for the difference between the sepetaprost and LAT groups (0.77 mmHg) was lower than the prespecified non-inferiority margin (1.5 mmHg), demonstrating the non-inferiority of sepetaprost to LAT. Figure 1 shows the change from baseline in mean diurnal IOP over time.

Table 26. Change from baseline in mean diurnal IOP (mmHg) at Week 4
(Study 101260005LT; FAS)

Treatment group	IOP[a)]		Change from baseline in IOP[b), c)]	Between-group difference[c), d)]
	Baseline	Week 4		
Sepetaprost	23.32 ± 1.47 (162)	17.51 ± 2.18 (158)	-5.77 ± 0.16	0.32 [-0.12, 0.77]
LAT	23.12 ± 1.22 (163)	17.06 ± 2.21 (160)	-6.10 ± 0.16	

a) Mean ± standard deviation (N)
b) Least squares mean ± standard error
c) Calculated using a mixed model for repeated measures (MMRM) using treatment, visit, treatment by visit interaction, and baseline IOP as covariates, assuming an unstructured covariance structure.
d) Least squares mean [95% CI]; sepetaprost group − LAT group

32) Patients who were diagnosed as having primary open-angle glaucoma or ocular hypertension in both eyes, or having primary open-angle glaucoma in one eye and ocular hypertension in the other eye, an anterior chamber angle grade ≥2 (Shaffer scale) in each eye, whose IOP was ≥22 mmHg in at least one eye at all measurement timepoints (9 a.m., 1 p.m., and 5 p.m.) at baseline (Day 1) and ≤34 mmHg in both eyes.

33) For the primary endpoint, assuming an expected difference of 0 mmHg in the change from baseline in mean diurnal IOP (mean of IOP at 3 timepoints, at 9 a.m., 1 p.m., and 5 p.m.) between the sepetaprost and LAT groups at Week 4, and a standard deviation of 3.8 mmHg, with a non-inferiority margin of 1.5 mmHg, with a two-sided significance level of 5%, a sample size of 272 subjects (136 subjects per group) would provide at least 90% power to detect a difference. For the entire study, with a 10% dropout rate, a target sample size of 300 subjects (150 subjects per group) was determined.

34) The study eye for efficacy evaluation was defined as the eye that met the inclusion criteria at baseline. If both eyes met the inclusion criteria, the eye with a higher mean diurnal IOP at baseline would be designated as the study eye. If both eyes met the inclusion criteria and had the same mean diurnal IOP, then the right eye would be designated as the study eye.

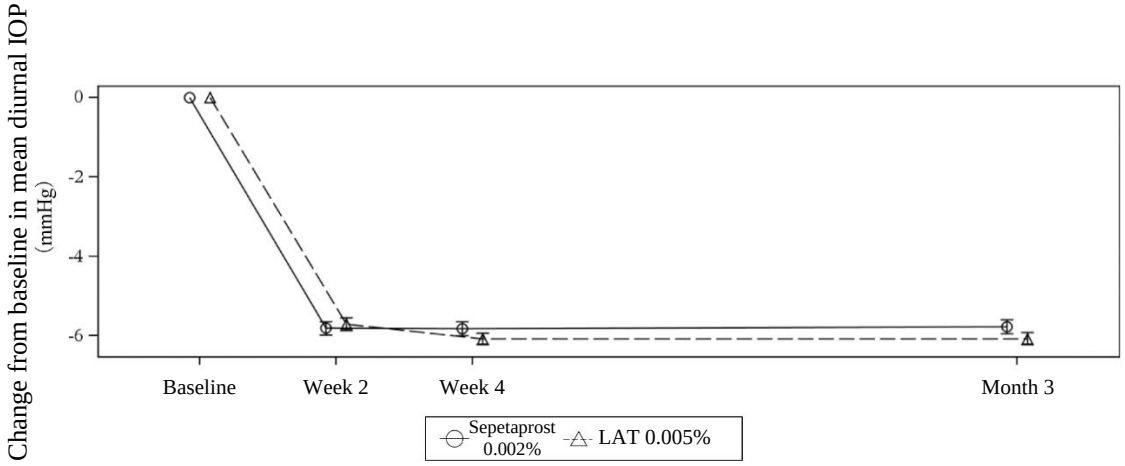


Figure 1. Change from baseline in mean diurnal IOP over time (mmHg) (Study 101260005LT; FAS; mean ± standard error)

The incidence of adverse events was 53.1% (86 of 162 subjects) in the sepetaprost 0.002% group and 41.7% (68 of 163 subjects) in the LAT group. Two subjects died (myocardial ischaemia [1 subject in the sepetaprost group] and myocardial infarction [1 subject in the LAT group]), and a causal relationship to the study drug was ruled out for both cases. Serious adverse events excluding deaths occurred in 2 subjects in the LAT group (spinal compression fracture and bile duct stone, 1 subject each), and a causal relationship to the study drug was ruled out for both cases.

Adverse events leading to treatment discontinuation of the study drug occurred in 2 subjects in the sepetaprost0.002% group (conjunctival hyperaemia/foreign body sensation in eyes/headache/nausea/eye discharge [1 subject], conjunctival oedema/palpitations [1 subject]) and 6 subjects in the LAT group (spinal compression fracture, conjunctival hyperaemia, corneal infection, conjunctivitis bacterial, breast cancer, and eye pain [1 subject each]). Conjunctival hyperaemia, foreign body sensation in eyes, eye discharge, conjunctival oedema, palpitations, corneal infection, and eye pain were considered to be related to the study drug. Adverse events (including laboratory test abnormality) that were considered to be related to the study drug occurred in 36.4% (59 of 162) of subjects in the sepetaprost group and 20.2% (33 of 163) of subjects in the LAT group. Among these events, those that occurred in ≥2 subjects in either group were conjunctival hyperaemia (48 and 14 subjects in the sepetaprost and LAT groups, respectively; the same applies hereinafter for the order of treatment groups), erythema of eyelid (4 subjects, 0 subjects), eye irritation (3 subjects, 7 subjects), dry eye (3 subjects, 1 subject), eye pruritus (3 subjects, 0 subjects), punctate keratitis (2 subjects, 6 subjects), abnormal sensation in eye (2 subjects, 1 subject), ocular hyperaemia (2 subjects, 0 subjects), conjunctival oedema (2 subjects, 0 subjects), eye discharge (2 subjects, 0 subjects), and blepharitis (0 subjects, 2 subjects).

There were no clinically significant changes in vital signs (blood pressure and pulse rate) or ophthalmologic assessments (visual acuity and slit-lamp microscopy).

7.1.4 Japanese long-term study (CTD5.3.5.2-1, Study 101260006LT [August 2022 to January 2024])

An unmasked, uncontrolled study was conducted in patients with primary open-angle glaucoma, normal

tension glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma, or ocular hypertension [35] (target sample size, 138 subjects, 46 subjects per group) to evaluate the long-term efficacy and safety of sepetaprost 0.002% ophthalmic solution administered alone or in combination with TIM 0.5%.

After completion of a washout period, subjects were divided into the following 2 cohorts based on diurnal IOP [36] at the start of the treatment phase (baseline): Cohort 1 (≥16 mmHg and <22 mmHg) and Cohort 2 (≥22 mmHg and <34 mmHg). Subjects in Cohort 1 were assigned to sepetaprost monotherapy (Group 1). In Cohort 2, subjects were randomized in a 1:1: ratio to sepetaprost monotherapy (Group 2) or sepetaprost in combination with TIM (Group 3).

The dosage regimen in Groups 1 and 2 was instillation of 1 drop of sepetaprost once daily (at 9 p.m.). In Group 3, the dosage regimen was instillation of 1 drop of sepetaprost once daily (at 9 p.m.) and instillation of 1 drop of TIM 0.5% ophthalmic solution twice daily (at 9 a.m. and 9 p.m.). In all groups, the ophthalmic solution was to be instilled into both eyes for 52 weeks.

Of the 172 subjects enrolled in the study, 131 subjects received the study drug (49 subjects, 42 subjects, and 40 subjects in Groups 1, 2, and 3, respectively; the same applies hereinafter for the order of treatment groups) and were included in the safety analysis set and the FAS, which was defined as the primary efficacy analysis set. Eleven subjects (6, 3, and 2 subjects, respectively) discontinued the study. Common reasons for discontinuation were “adverse events” in 8 subjects (3, 3, and 2 subjects, respectively) and “withdrawal of consent unrelated to COVID-19” in 2 subjects (2, 0, and 0 subjects, respectively).

Table 26 shows the change from baseline in mean diurnal IOP of the study eye for efficacy evaluation [37] by group in each evaluation timepoint and Figure 2 shows the change from baseline in mean diurnal IOP over time. The IOP-lowering effect was maintained throughout the treatment period.

Table 27. Change from baseline in mean diurnal IOP (mmHg) in each evaluation timepoint (Study 101260006LT, FAS)

Timepoint	Cohort 1	Cohort 2	
	Group 1 (sepetaprost monotherapy)	Group 2 (sepetaprost monotherapy)	Group 3 (sepetaprost/TIM combination)
Baseline	18.83 ± 1.39 (49)	23.21 ± 1.46 (42)	24.00 ± 1.83 (40)
Week 4	-4.52 ± 1.49 (47)	-6.03 ± 1.94 (42)	-7.69 ± 2.14 (40)
Week 8	-4.20 ± 1.43 (47)	-6.14 ± 1.96 (42)	-7.93 ± 2.40 (39)
Week 26	-3.99 ± 1.74 (47)	-6.28 ± 1.96 (40)	-7.73 ± 2.23 (39)
Week 52	-4.40 ± 1.56 (43)	-6.38 ± 2.00 (38)	-7.51 ± 1.80 (38)

Mean ± standard deviation (N)

35) Patients who were diagnosed as having primary open-angle glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma, or ocular hypertension in both eyes and had an anterior chamber angle grade ≥2 (Shaffer scale) in each eye, and whose IOP was ≥16 mmHg in at least one eye at all measurement timepoints (9 a.m., 1 p.m., and 5 p.m.) at baseline (Day 1) and ≤34 mmHg in both eyes.
36) The mean of IOP at 9 a.m., 1 p.m., and 5 p.m.
37) The study eye for efficacy evaluation was defined as the eye with a higher mean diurnal IOP at baseline. If both eyes had the same mean diurnal IOP, then the right eye would be designated as the study eye.

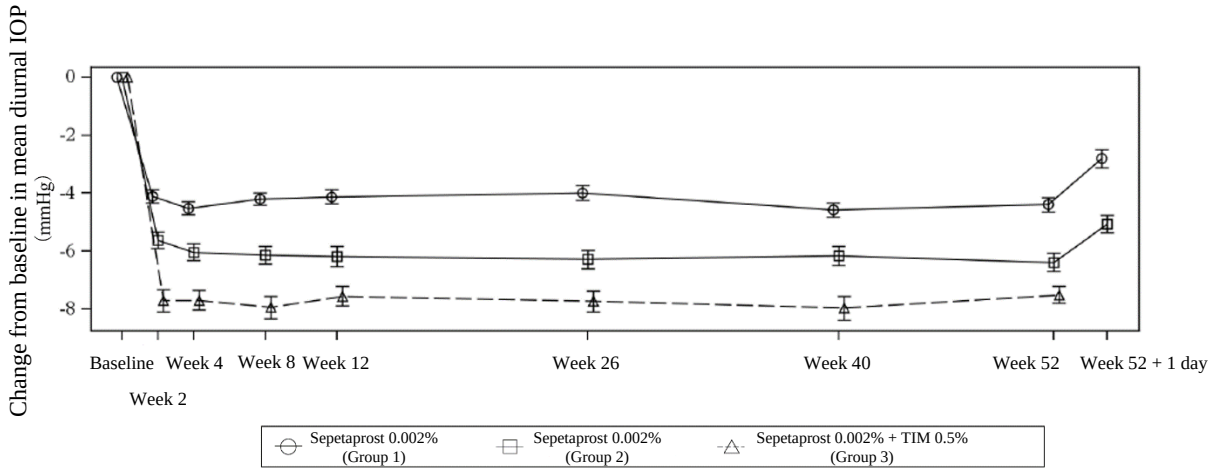


Figure 2. Change from baseline in mean diurnal IOP (mmHg) over time (Study 101260006LT, FAS; mean ± standard error)

The incidence of adverse events was 87.8% (43 of 49 subjects) in Group 1, 76.2% (32 of 42 subjects) in Group 2, and 95.0% (38 of 40 subjects) in Group 3. There were no deaths. Serious adverse events were angina unstable, cholesteatoma, and large intestine polyp (1 subject each) in Group 1; colon cancer and large intestine polyp (1 subject each) in Group 2; and pneumonia, cellulitis, large intestine polyp (1 subject each) in Group 3. A causal relationship to the study drug was ruled out for all these cases. The incidence of adverse events leading to treatment discontinuation of the study drug was 6.1% (3 of 49 subjects) in Group 1, 7.1% (3 of 42 subjects) in Group 2, and 5.0% (2 of 40 subjects) in Group 3. These events were abdominal discomfort, intraocular pressure increased, keratitis (1 subject each) in Group 1, supraventricular tachycardia, growth of eyelashes, photopsia/blepharal pigmentation (1 subject each) in Group 2, and pneumonia, bladder cancer (1 subject each) in Group 3. Keratitis, growth of eyelashes, photopsia, and blepharal pigmentation were considered to be related to the study drug.

Adverse events (including laboratory test abnormality) that were considered to be related to the study drug occurred in 59.2% (29 of 49) of subjects in Group 1, 59.5% (25 of 42) of subjects in Group 2, and 65.0% (26 of 40) of subjects in Group 3. Adverse events occurring in ≥2 subjects in any group were growth of eyelashes (11, 15, and 17 subjects in Groups 1, 2, and 3, respectively; the same applies hereinafter for the order of treatment groups), conjunctival hyperaemia (15, 12, and 12 subjects, respectively), eyelid vellus hair changes (4, 9, and 6 subjects, respectively), eyelash changes (9, 6, and 3 subjects, respectively), eyelash thickening (6, 5, and 2 subjects, respectively), blepharal pigmentation (4, 4, and 3 subjects, respectively), eyelash hyperpigmentation (1, 3, and 2 subjects, respectively), eye irritation (0, 0, and 3 subjects, respectively), erythema of eyelid (0, 0, and 2 subjects, respectively), hypertrichosis (3, 1, and 0 subjects, respectively).

There were no clinically significant changes in vital signs (blood pressure and pulse rate) or ophthalmologic assessments (visual acuity, slit-lamp microscopy, central corneal thickness, iris, eyelashes, and change in eyelids).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the rationale for the design of the Japanese phase III study (Study 101260005LT):

The Japanese phase III study (Study 101260005LT) was designed to assess the non-inferiority of sepetaprost (0.002% ophthalmic solution) to LAT, which is widely used in Japan as the first-line treatment of glaucoma and ocular hypertension.

Based on the following factors, change from baseline in mean diurnal IOP at Week 4 was selected as the primary endpoint.

- The true endpoint in glaucoma treatment is to slow the progression of visual field defects. Given that the only reliable evidence-based treatment to slow the progression of visual field defects is reduction of IOP (Japanese Glaucoma Guideline), change from baseline in IOP was selected as the primary endpoint.
- It is known that there are daily fluctuations in IOP and that control of IOP throughout the day is important in the treatment of glaucoma (e.g., *Glaucoma* [in Japanese]. Igaku Shoin; 2004;93-116; *Curr Opin Ophthalmol.* 2004;15:90-2); therefore, it was considered appropriate to evaluate the change in IOP based on the mean IOP measurements at multiple timepoints. Accordingly, timepoints at which the peak, trough, and intermediate diurnal IOP can be measured, i.e., 12 hours post-dose (9 a.m.), 16 hours post-dose (1 p.m.), and 20 hours post-dose (5 p.m.) were selected, taking into account the feasibility of measurements at medical institutions.
- In the global phase II study (Study 012601IN), the changes from baseline in mean diurnal IOP for sepetaprost and LAT remained generally constant at Week 1 to Month 3 [see Section 7.1.2], indicating that the IOP-lowering effect would reach a plateau at Week 1 or later. Therefore, the primary timepoint for analysis was set at Week 4 in Study 101260005LT.

In the meta-analysis on IOP-lowering effects of glaucoma medications (*Ophthalmology.* 2005;112:1177-85), the estimated changes from baseline [95% CI] in IOP at Month 1 were −6.8 [−7.6, −6.1] mmHg and −7.9 [−8.3, −7.4] mmHg at trough and peak timepoints, respectively, in the LAT group; and −1.3 [−2.4, −0.3] mmHg and −1.6 [−2.7, −0.5] mmHg at trough and peak timepoints, respectively, in the placebo group. Based on the above and other data, a non-inferiority margin of 1.5 mmHg was selected, which is sufficiently small compared to the difference in IOP change between LAT (active control) and placebo.

The applicant's explanation about the efficacy of sepetaprost in the treatment of glaucoma and ocular hypertension based on the results of Study 101260005LT:

The non-inferiority of sepetaprost to LAT in terms of change from baseline in mean diurnal IOP at Week 4, the primary endpoint in Study 101260005LT, was assessed (Table 26). The least squares mean [95% CI] [38)] difference between groups (sepetaprost − LAT) in change from baseline in mean diurnal IOP at Week 2 and

38) Calculated using an MMRM using treatment, visit, treatment by visit interaction, and baseline IOP as covariates, assuming an unstructured covariance structure.

Month 3 was −0.05 [−0.51, 0.40] and 0.32 [−0.14, 0.77], respectively. The results did not reveal any significant difference in the IOP-lowering effect between the sepetaprost and LAT groups at Week 2 or Month 3.

Table 28 shows the change in mean IOP from baseline to each measurement timepoint at Week 2, Week 4, and Month 3, the key secondary endpoint. The results did not reveal any significant difference in the IOP-lowering effect between the sepetaprost and LAT groups at any timepoint.

Table 28. Change from baseline in IOP at each timepoint (Study 101260005LT, FAS)

Time	Evaluation timepoint	IOP[a)]		Change from baseline		
		Sepetaprost	LAT	Sepetaprost[b), c)]	LAT[b), c)]	Between-group difference[c), d)]
9 a.m.	Baseline	23.56 ± 1.77 (162)	23.27 ± 1.52 (163)			
	Week 2	17.89 ± 2.56 (160)	17.75 ± 2.48 (162)	-5.62 ± 0.18	-5.58 ± 0.18	-0.04 [-0.53, 0.45]
	Week 4	17.77 ± 2.46 (158)	17.29 ± 2.23 (160)	-5.73 ± 0.17	-6.05 ± 0.17	0.32 [-0.16, 0.80]
	Month 3	17.90 ± 2.54 (156)	17.28 ± 2.41 (154)	-5.62 ± 0.18	-6.03 ± 0.18	0.41 [-0.09, 0.92]
1 p.m.	Baseline	23.29 ± 1.60 (162)	23.11 ± 1.36 (163)			
	Week 2	17.54 ± 2.49 (159)	17.27 ± 2.56 (162)	-5.73 ± 0.19	-5.87 ± 0.19	0.15 [-0.37, 0.67]
	Week 4	17.50 ± 2.40 (158)	16.94 ± 2.42 (160)	-5.74 ± 0.18	-6.21 ± 0.18	0.47 [-0.02, 0.97]
	Month 3	17.55 ± 2.55 (156)	16.96 ± 2.39 (153)	-5.70 ± 0.18	-6.16 ± 0.18	0.46 [-0.04, 0.96]
5 p.m.	Baseline	23.12 ± 1.52 (162)	22.98 ± 1.34 (163)			
	Week 2	17.14 ± 2.40 (159)	17.24 ± 2.46 (162)	-5.95 ± 0.18	-5.75 ± 0.17	-0.20 [-0.69, 0.28]
	Week 4	17.25 ± 2.23 (158)	16.94 ± 2.49 (160)	-5.83 ± 0.17	-6.06 ± 0.17	0.23 [-0.25, 0.71]
	Month 3	17.15 ± 2.44 (156)	16.86 ± 2.37 (154)	-5.93 ± 0.18	-6.07 ± 0.18	0.13 [-0.36, 0.63]

Unit, mmHg
a) Mean ± standard deviation (N)
b) Least squares mean ± standard error
c) Calculated using an MMRM using treatment, visit, treatment by visit interaction, and baseline IOP as covariates, assuming an unstructured covariance structure.
d) Least squares mean [95% CI], sepetaprost − LAT

In the Japanese long-term study (Study 101260006LT), the IOP-lowering effects were maintained throughout the treatment period up to Week 52 following administration of sepetaprost alone or in combination with TIM (Table 27 and Figure 2).

The above-mentioned data have demonstrated the efficacy of sepetaprost in the treatment of glaucoma and ocular hypertension.

PMDA's view:
There are no particular problems with the design of Study 101260005LT (i.e., control, primary endpoint, non-inferiority margin).

Based on the results of Studies 101260005LT and 101260006LT such as those shown below, PMDA concluded that the efficacy of sepetaprost in the treatment of glaucoma and ocular hypertension has been demonstrated.

- The non-inferiority of sepetaprost to LAT was demonstrated in terms of change from baseline in mean diurnal IOP at Week 4, the primary endpoint for Study 101260005LT.
- While it is known that there are circadian fluctuations in IOP, in Study 101260005LT, at all evaluation/measurement timepoints, no clear differences were detected in the change from baseline in IOP or in the IOP-lowering effect between the sepetaprost and LAT groups; in addition, the data demonstrated

that the IOP-lowering effect of sepetaprost was sustained throughout the day.

- In Study 101260006LT, there was no clear trend towards waning of the IOP-lowering effect over the course of long-term treatment with sepetaprost.

7.R.2 Safety

PMDA's view:

Based on the submitted clinical data and discussions in Section 7.R.2.1 below, patients treated with sepetaprost should be closely monitored for the development of known events associated with approved FP receptor agonists, namely, conjunctival hyperaemia, thick eyelashes/eyelid hair (growth of eyelashes, eyelid vellus hair changes, eyelash changes, eyelash thickening, and eyelash hyperpigmentation), blepharal pigmentation, and iris pigmentation. However, provided that precautions similar to those for other FP receptor agonists are implemented, the safety profile of sepetaprost is acceptable.

7.R.2.1 Safety profile of sepetaprost

The applicant's explanation about the safety profile of sepetaprost (0.002% ophthalmic solution):

Table 29 summarizes the incidence of adverse events in the Japanese phase III study (Study 101260005LT) and Japanese long-term study (Study 101260006LT).

In Study 101260005LT, myocardial ischaemia resulted in death in 1 subject in the sepetaprost group, although its causal relationship to sepetaprost was ruled out. Among the adverse events leading to treatment discontinuation reported in the sepetaprost group (conjunctival hyperaemia, foreign body sensation in eyes, eye discharge, headache, nausea, palpitations, conjunctival oedema), conjunctival hyperaemia, foreign body sensation in eyes, eye discharge, conjunctival oedema, and palpitations were considered to be related to sepetaprost. However, these events were mild in severity except for palpitations, a moderate event, and all were non-serious and their outcomes were reported as resolved. The incidence of conjunctival hyperaemia in the sepetaprost group tended to increase compared to the LAT group. However, all conjunctival hyperaemia events were mild or moderate, and non-serious, and their outcomes were reported as resolved, with the exception of 1 case. [39)] There were no marked differences in the incidence of other events between the sepetaprost and LAT groups.

In Study 101260006LT, there were no marked differences in the incidence of adverse events between cohorts or treatment groups. No adverse events led to death. A causal relationship to sepetaprost was ruled out for the serious adverse events excluding deaths: angina unstable, cholesteatoma, and large intestine polyp (1 subject each) in Group 1 (sepetaprost monotherapy); large intestine polyp and colon cancer (1 subject each) in Group 2 (sepetaprost monotherapy); large intestine polyp, pneumonia, and cellulitis (1 subject each) in Group 3 (sepetaprost/TIM combination). No adverse events leading to treatment discontinuation occurred in ≥2 subjects, and the following events were considered to be related to sepetaprost: keratitis (1 subject), growth of eyelashes (1 subject), photopsia and blepharal pigmentation (1 subject). Compared to Study 101260005LT, the incidence

39) This was a mild, non-serious event, for which a causal relationship to sepetaprost was ruled out, and the study was continued.

of growth of eyelashes, blepharal pigmentation, eyelid vellus hair changes, eyelash changes, eyelash thickening, and eyelash hyperpigmentation tended to be higher in Study 101260006LT; however, these events, which were mild and non-serious, were also known to occur in association with FP receptor agonists, in addition to conjunctival hyperaemia mentioned above. In Study 101260006LT Cohort 2, the incidence of all adverse events tended to be higher in Group 3 (sepetaprost/TIM combination) than that in Group 2 (sepetaprost monotherapy); however, there were no clear differences between treatment groups in the incidence of adverse events that were determined to be related to the study drug.

Table 29. Incidence of adverse events (Studies 101260005LT and 101260006LT, safety analysis set)

	101260005LT		101260006LT		
			Cohort 1	Cohort 2	
	Sepetaprost	LAT	Group 1 (sepetaprost monotherapy)	Group 2 (sepetaprost monotherapy)	Group 3 (sepetaprost/TIM combination)
Number of subjects evaluated	162	163	49	42	40
All adverse events	86 (53.1)	68 (41.7)	43 (87.8)	32 (76.2)	38 (95.0)
Deaths	1 (0.6)	1 (0.6)	0	0	0
Serious adverse events	0	1 (0.6)	3 (6.1)	2 (4.8)	3 (7.5)
Adverse events leading to treatment discontinuation	2 (1.2)	6 (3.7)	3 (6.1)	3 (7.1)	2 (5.0)
Adverse events determined to be related to the study drug	59 (36.4)	33 (20.2)	29 (59.2)	25 (59.5)	26 (65.0)
Common adverse events (individual adverse events occurring in ≥3% of subjects in any group)					
Ocular adverse events	68 (42.0)	53 (32.5)	36 (73.5)	27 (64.3)	28 (70.0)
Conjunctival hyperaemia	51 (31.5)	21 (12.9)	15 (30.6)	12 (28.6)	13 (32.5)
Punctate keratitis	5 (3.1)	11 (6.7)	4 (8.2)	1 (2.4)	2 (5.0)
Eye irritation	3 (1.9)	7 (4.3)	0	0	3 (7.5)
Dry eye	3 (1.9)	1 (0.6)	3 (6.1)	0	1 (2.5)
Growth of eyelashes	1 (0.6)	0	11 (22.4)	15 (35.7)	17 (42.5)
Blepharal pigmentation	1 (0.6)	0	4 (8.2)	4 (9.5)	3 (7.5)
Conjunctivitis allergic	1 (0.6)	2 (1.2)	3 (6.1)	2 (4.8)	2 (5.0)
Eyelid vellus hair changes	0	1 (0.6)	4 (8.2)	9 (21.4)	6 (15.0)
Eyelash changes	0	0	9 (18.4)	6 (14.3)	3 (7.5)
Eyelash thickening	0	0	6 (12.2)	5 (11.9)	2 (5.0)
Meibomian gland dysfunction	0	0	2 (4.1)	0	0
Eyelash hyperpigmentation	0	0	1 (2.0)	3 (7.1)	2 (5.0)
Erythema of eyelid	0	0	0	0	2 (5.0)
Non-ocular adverse events	27 (16.7)	23 (14.1)	30 (61.2)	18 (42.9)	19 (47.5)
COVID-19	5 (3.1)	5 (3.1)	2 (4.1)	0	2 (5.0)
Nasopharyngitis	4 (2.5)	1 (0.6)	7 (14.3)	2 (4.8)	1 (2.5)
Pyrexia	1 (0.6)	2 (1.2)	1 (2.0)	2 (4.8)	0
Eczema	1 (0.6)	1 (0.6)	2 (4.1)	1 (2.4)	3 (7.5)
Cough	0	2 (1.2)	2 (4.1)	0	0
Dental caries	0	0	3 (6.1)	1 (2.4)	0
Hypertrichosis	0	0	3 (6.1)	1 (2.4)	0
Coronavirus infection	0	1 (0.6)	2 (4.1)	2 (4.8)	2 (5.0)
Abdominal discomfort	0	0	2 (4.1)	2 (4.8)	0
Seasonal allergy	0	0	2 (4.1)	1 (2.4)	1 (2.5)
Rhinitis allergic	0	0	2 (4.1)	0	0
Periodontitis	0	0	2 (4.1)	0	0
Constipation	0	0	2 (4.1)	0	0
Diarrhoea	0	0	2 (4.1)	0	0
Oropharyngeal pain	1 (0.6)	0	1 (2.0)	2 (4.8)	0
Gastroenteritis	0	0	0	2 (4.8)	3 (7.5)
Gingivitis	0	0	0	2 (4.8)	1 (2.5)
Pharyngitis	0	0	0	0	2 (5.0)

n (incidence, %)

Table 30 shows the incidence of adverse events by time to initial onset in Study 101260006LT. The most

common time to initial onset of growth of eyelashes and conjunctival hyperaemia ranged from Days 31 to 90, and Days 1 to 30, respectively. There were no trends towards an increase in the incidence of these and other events with increasing treatment duration.

Table 30. Incidence of adverse events by time to initial onset (Study 101260006LT, safety analysis set)

Period	Overall	Day 1-30	Day 31-90	Day 91-180	Day 181-270	Day 271-360	Day 361-
Number of subjects evaluated	131	131	130	127	125	122	96
All adverse events	113 (86.3)	61 (46.6)	51 (39.2)	43 (33.9)	35 (28.0)	24 (19.7)	10 (10.4)
Serious adverse events	8 (6.1)	2 (1.5)	2 (1.5)	2 (1.6)	1 (0.8)	1 (0.8)	0
Common adverse events (adverse events occurring in ≥3% of overall subjects)							
Growth of eyelashes	43 (32.8)	7 (5.3)	21 (16.2)	7 (5.5)	4 (3.2)	3 (2.5)	1 (1.0)
Conjunctival hyperaemia	40 (30.5)	32 (24.4)	3 (2.3)	1 (0.8)	4 (3.2)	0	0
Eyelid vellus hair changes	19 (14.5)	1 (0.8)	7 (5.4)	3 (2.4)	3 (2.4)	2 (1.6)	3 (3.1)
Eyelash changes	18 (13.7)	2 (1.5)	6 (4.6)	3 (2.4)	3 (2.4)	2 (1.6)	2 (2.1)
Eyelash thickening	13 (9.9)	3 (2.3)	5 (3.8)	3 (2.4)	1 (0.8)	0	1 (1.0)
Blepharal pigmentation	11 (8.4)	1 (0.8)	2 (1.5)	4 (3.1)	3 (2.4)	1 (0.8)	0
Nasopharyngitis	10 (7.6)	0	2 (1.5)	4 (3.1)	1 (0.8)	3 (2.5)	0
Conjunctivitis allergic	7 (5.3)	1 (0.8)	3 (2.3)	3 (2.4)	0	0	0
Punctate keratitis	7 (5.3)	6 (4.6)	1 (0.8)	0	0	0	0
Eyelash hyperpigmentation	6 (4.6)	2 (1.5)	0	2 (1.6)	0	1 (0.8)	1 (1.0)
Coronavirus infection	6 (4.6)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.6)	0
Eczema	6 (4.6)	0	2 (1.5)	1 (0.8)	0	2 (1.6)	1 (1.0)
Gastroenteritis	5 (3.8)	2 (1.5)	1 (0.8)	1 (0.8)	1 (0.8)	0	0
Dry eye	4 (3.1)	2 (1.5)	0	2 (1.6)	0	0	0
Abdominal discomfort	4 (3.1)	1 (0.8)	2 (1.5)	0	1 (0.8)	0	0
Dental caries	4 (3.1)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	0	0
Hypertrichosis	4 (3.1)	1 (0.8)	0	3(2.4)	0	0	0
Seasonal allergy	4 (3.1)	0	2 (1.5)	2 (1.6)	0	0	0
COVID-19	4 (3.1)	0	2 (1.5)	0	2 (1.6)	0	0

n (incidence, %)

Based on the above, the most common adverse events associated with sepetaprost in Studies 101260005LT and 101260006LT are known adverse events of FP receptor agonists, namely, conjunctival hyperaemia, thick eyelashes/eyelid hair (growth of eyelashes, eyelid vellus hair changes, eyelash changes, eyelash thickening, eyelash hyperpigmentation), and blepharal pigmentation. Eyelash abnormalities and blepharal pigmentation were more frequent in Study 101260006LT than in Study 101260005LT, suggesting that the cumulative incidence may increase with prolonged treatment time. However, given that the majority of these events in Study 101260006LT were mild in severity, and all of the adverse events leading to treatment discontinuation resolved, no new safety risks unique to sepetaprost have been identified. Therefore, the applicant considers that the risks can be adequately managed by including cautionary statements equivalent to those for already-approved FP receptor agonists.

It is considered that iris pigmentation, one of the adverse events characteristic of already-approved FP receptor agonists, is caused by FP receptor activation, which increases melanin pigments in the iris. No adverse events related to iris pigmentation occurred following instillation of sepetaprost in Study 101260005LT. In Study 101260006LT, iris hyperpigmentation occurred in 1 subject in Group 1 (sepetaprost monotherapy), and the event was determined to be related to sepetaprost. Although this was mild and non-serious, and it was determined that the treatment could be continued, the outcome was reported as not resolved. The incidence of iris pigmentation-related events following instillation of sepetaprost in clinical studies was low, and there was no trend towards an increase in the incidence of events associated with sepetaprost compared to already-

approved FP receptor agonists. Nevertheless, iris pigmentation is an event of concern based on the pharmacological action of sepetaprost, and once it develops, the outcome may be irreversible. Therefore, as with already-approved FP receptor agonists, a cautionary statement regarding iris pigmentation will be included in the package insert.

PMDA's view:
Based on the submitted clinical data and the applicant's explanation, although the incidence of conjunctival hyperaemia was higher with sepetaprost than with LAT, none of the events were classified as severe; therefore, it is unlikely that conjunctival hyperaemia will pose clinically significant problems. In addition, the findings suggest that there are no new safety-related concerns unique to sepetaprost, such as adverse events that have not been reported with already-approved FP receptor agonists. Therefore, PMDA concluded that sepetaprost has acceptable safety provided that a cautionary statement similar to that for the already-approved FP receptor agonists will be included.

7.R.3 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of sepetaprost:
The only reliable evidence-based treatment to slow the progression of visual field defects is reduction of IOP (Japanese Glaucoma Guideline) and IOP-lowering ophthalmic solutions are primarily used in the treatment of glaucoma. A general pharmacotherapy plan recommended in the Japanese Glaucoma Guideline is to start treatment as a monotherapy, and in cases where the target IOP cannot be achieved by monotherapy, to switch the drug to another one or add a drug with a different mechanism of action. In clinical practice, FP receptor agonists, EP2 receptor agonists, and β-blockers have been used as first-line therapy for glaucoma. However, because monotherapy often fails to achieve the target IOP, there remains a need for new treatment options for glaucoma, such as drugs with a more potent IOP-lowering effect or a novel mechanism of action.

Sepetaprost exhibits agonist activity at EP3 receptors as well as at FP receptors, and is expected to lower IOP by promoting aqueous humor outflow from the uveoscleral and trabecular meshwork outflow pathways [see Section 3.R.1]. Given that the Japanese phase III study (Study 101260005LT) demonstrated the non-inferiority of sepetaprost to LAT [see Section 7.R.1] and sepetaprost has acceptable safety [see Section 7.R.2], sepetaprost is expected to provide a new first-line treatment option for glaucoma and ocular hypertension.

Based on the above, the proposed indication for sepetaprost, "glaucoma and ocular hypertension" is appropriate.

In clinical practice, it is considered that the selection between sepetaprost and other first-line drugs will be determined based on their safety profiles. Furthermore, the response to glaucoma drugs varies from person to person, and the use of combination therapy requires careful consideration as it may result in poor medication adherence (Japanese Glaucoma Guideline). Accordingly, sepetaprost can be considered as a treatment option not only when switching from first-line drugs other than prostanoid receptor agonists but also when switching from other prostanoid receptor agonists.

Since no particular safety-related problems have been reported for sepetaprost in combination with TIM 0.5% compared with sepetaprost monotherapy, it is considered possible to use sepetaprost in combination with TIM 0.5% or other β-blockers in the treatment of glaucoma. The safety of sepetaprost in combination with non-β blocker glaucoma drugs has not been studied, and thus no data on whether their concomitant use is allowed are currently available. However, given that the Japanese Glaucoma Guideline states that drugs that have the same pharmacologically active sites should not be selected together, FP receptor agonists, which have pharmacologically active sites identical to those of sepetaprost, will not be used in combination.

PMDA's view:
Studies 101260005LT and 101260006LT demonstrated the efficacy of sepetaprost [see Section 7.R.1] and sepetaprost has acceptable safety provided that appropriate precautions are implemented [see Section 7.R.2]. Based on these factors and the applicant's explanation about the clinical positioning of sepetaprost, PMDA concluded that sepetaprost can be positioned as a treatment option for glaucoma and ocular hypertension, with "glaucoma and ocular hypertension" as the indication. Currently, knowledge is limited regarding the appropriate selection between sepetaprost and other approved glaucoma drugs, as well as the efficacy and safety of concomitant use of sepetaprost with other glaucoma drugs. Therefore, it is desirable for these issues to be discussed by the relevant academic societies and other professional forums taking into account both the currently available clinical data and post-marketing data collected in the future.

7.R.4 Dosage and administration

The applicant's explanation about the rationale for the dosage regimens of sepetaprost ophthalmic solutions in the Japanese phase III study (Study 101260005LT) and long-term study (Study 101260006LT) as well as the appropriateness of the proposed regimen:
Regarding the dosage regimen, the foreign phase I study (Study ONO-9054IOU002) demonstrated that 1 drop once daily had an IOP-lowering effect.[40)] Based on this and other factors, the dosage regimen of instillation of 1 drop once daily was adopted in subsequent studies. In Study 101260005LT, a sepetaprost concentration of 0.002% was selected based on the following: in the global phase II study (Study 012601IN), sepetaprost 0.0005% to 0.003% ophthalmic solution was administered as 1 drop once daily. The IOP values in the sepetaprost 0.002% group were lower than those in the other sepetaprost groups at all measurement timepoints (9 a.m., 1 p.m., and 5 p.m.) at Month 3, and it was suggested that the IOP-lowering effect of sepetaprost 0.002% was comparable to that of LAT 0.005%. In addition, there was no safety concerns at any of the sepetaprost concentrations studied.

In Studies 101260005LT and 101260006LT, which were conducted using the above regimen, the efficacy and safety of sepetaprost were confirmed [see Section 7.R.1 and 7.R.2]. Accordingly, a concentration of 0.002% and the proposed dosage regimen of 1 drop once daily were selected.

40) In the study,1 drop of sepetaprost ophthalmic solution at different concentrations was instilled into both eyes, once daily for 14 days in non-Japanese patients with open-angle glaucoma or ocular hypertension (9 subjects per group). The changes from baseline in mean diurnal IOP (mean of measurements at 8 a.m., 12 a.m., 4 p.m., and 7 p.m.) were −4.46, −7.82, −5.46, and −7.67 mmHg at sepetaprost 0.0003%, 0.001%, 0.002%, and 0.003%, respectively, with an IOP-lowering effect being observed at all concentrations.

PMDA considers that the applicant's explanation is acceptable and there are no particular problems with the proposed sepetaprost regimen of "instill 1 drop into the eye once daily."

7.R.5 Post-marketing investigations

The applicant's explanation:

The non-clinical and clinical study results indicate that all the adverse events requiring particular attention when administering sepetaprost [see Section 7.R.2] are known events associated with already-approved FP receptor agonists, and no new safety-related concerns unique to sepetaprost have been identified [see Section 7.R.2]. Therefore, early post-marketing phase vigilance and routine pharmacovigilance activities will be conducted, instead of implementing post-marketing surveillance of sepetaprost at this time.

PMDA's view:

Based on the discussions from Sections 7.R.1 and 7.R.2, as well as the applicant's explanation, there are currently no particular concerns that need to be addressed on the use of sepetaprost in patients with glaucoma or ocular hypertension after the product launch. Therefore, implementation of post-marketing surveillance immediately after approval is of low priority. However, if any new issues warranting further investigation emerge after the product launch, additional pharmacovigilance activities including post-marketing surveillance should be considered promptly.

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 5.3.5.1-2, CTD 5.3.5.2-1) 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 sepetaprost (0.002% ophthalmic solution) has efficacy in the treatment of glaucoma and ocular hypertension, and that sepetaprost has acceptable safety in view of its benefits. The drug substance is classified as a powerful drug and the drug product is not classified

as a poisonous drug or a powerful drug. Sepetaprost is clinically meaningful because it offers a new treatment option for patients with glaucoma or ocular hypertension.

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

Review Report (2)

July 11, 2025

Product Submitted for Approval

Brand Name	Setaneo Ophthalmic Solution 0.002%
Non-proprietary Name	Sepetaprost
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	September 26, 2024

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

In view of the discussions presented in Section "7.R.1 Efficacy" in Review Report (1), PMDA concluded that the efficacy of sepetaprost (0.002% ophthalmic solution; the same applies hereinafter) in the treatment of glaucoma and ocular hypertension has been demonstrated.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

1.2 Safety

In view of the discussions presented in Section "7.R. 2 Safety" in Review Report (1), when administering sepetaprost, increased vigilance is needed for the known adverse events associated with the already-approved FP receptor agonists, namely, conjunctival hyperaemia, thick eyelashes/eyelid hair (growth of eyelashes, eyelid vellus hair changes, eyelash changes, eyelash thickening, and eyelash hyperpigmentation), blepharal pigmentation, and iris pigmentation. However, PMDA concluded that sepetaprost has acceptable safety provided that a cautionary statement similar to that for the FP receptor agonists will be included in the package insert.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above. The following comments were made by the expert advisors:

- It has been reported that lid sulcus deepened occurred in patients treated with the already-approved FP receptor agonists; and patients with aphakia or pseudophakia who were treated with the already-approved prostanoid receptor agonists (EP or FP receptor agonists) had macular oedema including cystoid macular oedema. Although lid sulcus deepened and macular oedema were not reported in the clinical studies of sepetaprost, the possibility that lid sulcus deepened may occur, and that macular oedema including cystoid macular oedema may occur in patients with aphakia or pseudophakia, cannot be ruled out.

Based on the above, PMDA asked the applicant to include a cautionary statement regarding these events in the package insert, equivalent to that provided for the already-approved FP receptor agonists. The applicant took actions accordingly.

1.3 Clinical positioning and indication

In view of the discussions presented in Section "7.R.3 Clinical positioning and indication" in Review Report (1), PMDA concluded that sepetaprost can be positioned as a treatment option for glaucoma and ocular hypertension, and the indication can be established as "glaucoma and ocular hypertension."

Currently, knowledge is limited regarding the appropriate selection between sepetaprost and other approved glaucoma drug, as well as the efficacy and safety of concomitant use of sepetaprost with other glaucoma drugs. Therefore, PMDA concluded that it is desirable for these issues to be discussed by the relevant academic societies and other professional forums taking into account both the currently available clinical data and post-marketing data collected in the future.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

1.4 Dosage and administration

In view of the discussions presented in Section "7.R.4 Dosage and administration" in Review Report (1), PMDA concluded that there are no particular problems with establishing the dosage and administration as "instill 1 drop into the eye once daily."

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.5 Post-marketing investigations" in Review Report (1), PMDA has concluded that there are currently no particular concerns that need to be addressed on the use of sepetaprost in patients with glaucoma or ocular hypertension after the product launch. Therefore, implementation of post-marketing surveillance immediately after approval is of low priority.

However, if any new issues warranting further investigation emerge after the product launch, additional pharmacovigilance activities including post-marketing surveillance should be considered promptly.

As the expert advisors supported the PMDA's conclusion above at the Expert Discussion, PMDA has concluded that the current draft risk management plan (draft) for sepetaprost, should include the safety specification presented in Table 31, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 32.

Table 31. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Iris pigmentation	• Macular oedema	• None
Efficacy specification		
• None		

Table 32. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Disseminate data gathered during early post-marketing phase vigilance

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 approval conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years.

Indications

Glaucoma and ocular hypertension

Dosage and Administration

Instill 1 drop into the eye once daily

Approval Conditions

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

Appendix

List of Abbreviations

ADP	Adenosine diphosphate
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
$AUC_{0\text{-}xh}$	Area under the concentration-time curve from zero to x h after administration
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time curve from zero to the last measurable concentration
BCRP	Breast cancer resistance protein
BMI	Body mass index
BSEP	Bile salt export pump
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
C_{max}	Maximum Concentration
CQA	Critical quality attribute
CTD	Common technical document
DMSO	Dimethyl sulfoxide
DP receptor	Prostaglandin D_2 receptor
EC_{50}	Effective concentration, 50%
EP1 receptor	Prostaglandin E_2 receptor EP1 subtype
EP2 receptor	Prostaglandin E_2 receptor EP2 subtype
EP3 receptor	Prostaglandin E_2 receptor EP3 subtype
EP4 receptor	Prostaglandin E_2 receptor EP4 subtype
FAS	Full analysis set
FOB	Functional observational battery
FP receptor	Prostaglandin $F_{2\alpha}$ receptor
GC	Gas chromatography
HEK293 cells	Human embryonic kidney 293 cell
hERG	Human enter-a-go-go related gene
HPLC	High performance liquid chromatography
HPLC-RAD	High performance liquid chromatography-radioactivity detection
ICH Q1E Guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
ICH Q3A Guideline	"Partial Revision of 'Revision of Guidelines on Impurities in New Drug Substances'" (PFSB/ELD Notification No. 1204001, dated December 4, 2006)
ICH Q3B Guideline	"Revision of 'Revision of Guidelines on Impurities in New Drug Products'" (PFSB/ELD Notification No. 0703004 dated July 3, 2006)
IP	Prostacyclin receptor
IR	Infrared absorption spectroscopy
Japanese Glaucoma Guidelines	Glaucoma Guidelines (*Journal of Japanese Ophthalmological Society*. 2022;126:85-177 [in Japanese])
Ki	Inhibitory constant
LAT	Latanoprost
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
MATE	Multidrug and toxin extrusion protein

MDCK cells	Madin-Darby canine kidney cells
MF	Master file
MMP	Matrix metalloproteinase
MMRM	Mixed model for repeated measures
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand white
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
RH	Relative humidity
SD	Sprague Dawley
Sepetaprost	Sepetaprost
Setaneo Ophthalmic Solution 0.002%	Sepetaprost 0.002% ophthalmic solution
$t_{1/2}$	Elimination half-life
TIM	Timolol
t_{max}	Time of maximum concentration
TP	Thromboxane receptor
UV	Ultraviolet spectroscopy
UV/VIS	Ultraviolet-visible spectroscopy
γ-GTP	Gamma-glutamyltransferase