Report on the Deliberation Results

December 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ryjusea Mini Ophthalmic Solution 0.025%
Non-proprietary Name	Atropine Sulfate Hydrate (JAN*)
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	February 28, 2024

Results of Deliberation

In its meeting held on December 2, 2024, 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 4 years. The drug product is classified as 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

November 11, 2024
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	Ryjusea Mini Ophthalmic Solution 0.025%
Non-proprietary Name	Atropine Sulfate Hydrate
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	February 28, 2024
Dosage Form/Strength	Ophthalmic solution containing 0.25 mg of atropine sulfate hydrate per mL
Application Classification	Prescription drug, (4) Drug with a new indication, (5) Drug in a new dosage form
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 slowing the progression of myopia with acceptable safety in view of its benefits (see Attachment).

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

Indication
Slowing the progression of myopia

Dosage and Administration
The usual dosage is 1 drop of the ophthalmic solution applied once daily at bedtime.

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

Attachment

Review Report (1)

September 20, 2024

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	Ryjusea Mini Ophthalmic Solution 0.025%
Non-proprietary Name	Atropine Sulfate Hydrate
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	February 28, 2024
Dosage Form/Strength	Ophthalmic solution containing 0.25 mg of atropine sulfate hydrate per mL
Proposed Indication	Slowing the progression of myopia
Proposed Dosage and Administration	The usual dosage is 1 drop of the ophthalmic solution applied once daily at bedtime.

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List of Abbreviations

See Appendix.

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

The product is an aqueous ophthalmic solution containing Atropine Sulfate Hydrate (hereinafter referred to as atropine), a muscarinic acetylcholine receptor antagonist, at 0.025%. In Japan, approved ophthalmologic products containing atropine as an active pharmaceutical ingredient are the ophthalmic ointments and ophthalmic solutions containing atropine at 1% with the indications of "mydriasis and cycloplegia for diagnosis or treatment."

By definition, myopia is a refractive error of the eye where parallel light rays entering the eye without any accommodation focus in front of the retina rather than on it or light rays emitted from a point at a finite distance in front of the eye converge at a point in front of the retina. Myopia with the objective spherical equivalent of ≥−0.5 D and <−3.0 D, ≥−3.0 D and <−6.0 D, and ≥−6.0 D is classified as low, moderate, and high severity, respectively (https://www.myopiasociety.jp/member/guideline/ [last accessed on September 12, 2024]). Myopia typically develops at the age of approximately 6 to 8 years and progresses through the age of 15 to 16 years (*Cochrane Database of Systematic Reviews.* 2011;7:CD004916). In Japan, the population with myopia has been increasing with lifestyle changes including decreased time outdoors and increased near work activities (*Ophthalmology.* 2016;123:1036-42). High myopia is considered a risk factor of severe complications with visual impairment such as retinal detachment, myopic maculopathy, and glaucoma (*Lancet.* 2012;379:1739-48). Slowing the progression of myopia is expected to prevent decreased quality of life (QOL) and severe ocular complications with visual impairment, but there are neither drugs nor medical devices approved for the indication of slowing the progression of myopia in Japan.

Reports on administration of an atropine ophthalmic solution for myopia showed that the 1% atropine ophthalmic solution slowed the progression of myopia but considerably affected the pupil size and accommodation, and its cessation led to rapid progression of myopia (*Ophthalmology.* 2006;113:2285-91, *Ophthalmology.* 2009;116:572-9). Later, ophthalmic solutions containing atropine at concentrations lower than 1% slowed the progression of myopia, indicating that atropine would be useful in myopia management at its concentrations lower than 1% (*Ophthalmology.* 2012;119:347-54, *Am J Ophthalmol.* 2014;157:451-7).

To develop the product as a drug slowing the progression of myopia, a clinical study was initiated in Japan in [redacted] 20[redacted]. Based on the data from Japanese and foreign clinical studies that demonstrated the efficacy of the product in slowing the progression of myopia and the safety, the applicant has submitted an application for marketing approval.

Outside Japan, the product has not been approved in any countries or regions as of August 2024, while 0.01% atropine ophthalmic solution has been approved for the indication of "Slowing the progression of myopia in children" in Australia and China.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

Atropine sulfate hydrate, the drug substance, is listed in the Japanese Pharmacopoeia (JP). The drug substance (master file [MF] registration No., [redacted]) registered in the MF is used. The

specifications of the drug substance are as specified in the monograph of Atropine Sulfate Hydrate in the JP.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an ophthalmic solution containing 0.25 mg of atropine sulfate hydrate per mL. It contains concentrated glycerin, sodium dihydrogen phosphate, sodium citrate hydrate, hydroxyethylcellulose, [redacted], [redacted], and purified water as excipients.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of acceptance test of the drug substance, [redacted] and [redacted], [redacted] preparation, [redacted] and [redacted] preparation, filling, and packaging/labeling/testing/storage. Critical steps include [redacted] and [redacted] [redacted] and [redacted] as well as [redacted]. In-process control parameters and acceptance criteria are specified in [redacted] and [redacted], [redacted], [redacted] and [redacted], and [redacted] steps.

Based on the following investigations, the quality control strategy is constructed (Table 1):

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

Table 1. Overview of drug product control strategy

CQA	Control method
Strength	Specifications
Related substances	Specifications
pH	Manufacturing process, specifications
Osmolar ratio	Specifications
[redacted]	[redacted]
Foreign matters	Specifications
Sterility	Manufacturing process, specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (high performance liquid chromatography [HPLC]), osmolar ratio, pH, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], purity (related substances [HPLC]), and assay (HPLC).

2.2.4 Stability of drug product

The primary stability studies on the drug product are shown in Table 2, and the study results showed that the drug product is stable. Photostability data showed that the drug product packaged in an aluminum pillow bag is stable to light. The in-use stability study was conducted on the drug product after opening the aluminum pillow bag.[1)] The results showed that the drug product stored in the opened aluminum pillow bag or a lightproof dosing bag is stable for 3 months.

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1) [redacted] of the aluminum pillow bag or the drug product in a lightproof dosing bag was stored under [redacted] for 3 months (30°C ± 2°C/35% ± 5%RH).

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot /3 batches	30°C ± 2°C	35% ± 5%RH	Polyethylene container/polypropylene label/aluminum pillow bag	18 months
Accelerated		40°C ± 2°C	≤25%RH		6 months

Based on the above, a shelf life of 30 months was specified for the drug product when filled in a polyethylene container, given a polypropylene label, packaged in an aluminum-laminated film pillow bag, and stored protected from light at room temperature in accordance with the "Guideline on Evaluation of Stability Data" (ICH Q1E guideline). The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

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

The present application relates to a new indication and a new dosage form, and the applicant submitted published literature on the primary pharmacodynamics. Of the submitted published literature, the main literature is summarized below.

3.1 Primary pharmacodynamics

3.1.1 Effects on lens-induced myopia mouse model (*J Proteome Res.* 2014;13:4647-58)

A −15 D lens was placed over the eye of mice on Postnatal Day 10 to induce myopia. In this lens-induced myopia mouse model, a 1% atropine ophthalmic solution was applied from Postnatal Days 24 to 52, which suppressed the decrease in refraction and elongation of axial length.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the effect of atropine on slowing the progression of myopia:

Myopia is a refractive error of the eye where parallel light rays entering the eye without any accommodation focus in front of the retina rather than on it and are deemed to be mainly caused by elongation of axial length. Although the precise mechanism of elongation of axial length remains unknown, hypermetropic defocus where light rays entering the eye focus outside of the retina is considered to enhance remodeling of sclera and thereby extend axial length (*Eur J Ophthalmol.* 2021;31:853-83).

Atropine is a reversible muscarinic acetylcholine receptor antagonist and has affinity to all of the 5 receptor subtypes of M_1 to M_5 (*Life Sci.*1999;64:2351-8). The muscarinic acetylcholine receptor is found in various ocular tissues such as cornea, iris, ciliary body, lens epithelium, retina, retinal pigment epithelium, choroid, and sclera (*Eye Contact Lens.* 2020;46:129-35). In a lens-induced myopia mouse model, the application of the 1% atropine ophthalmic solution was shown to slow the progression of myopia [see Section 3.1.1]. In form-deprivation myopia[2)] chick and rhesus monkey models, the application of 0.25% atropine ophthalmic solution or intravitreal administration of 0.1%

2) Model of experimental myopia induced by blocking light from reaching the retina

atropine ophthalmic solution slowed the progression of myopia (*Invest Ophthalmol Vis Sci.* 1993;34:205-15, *Optom Vis Sci.* 1999;76:397-407). Although the precise mechanism of atropine slowing the progression of myopia remains unknown, its direct or indirect involvement in remodeling of the sclera through the muscarinic acetylcholine receptor present in the retina or sclera is considered to suppress the elongation of axial length and thereby slow the progression of myopia (*Eye Contact Lens.* 2020;46:129-35).

PMDA concluded that atropine applied in the eye is expected to slow the progression of myopia because atropine has been reported to slow the progression of myopia in multiple animal models, although the precise mechanism of atropine slowing the progression of myopia remains unknown.

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

The present application pertains to a new indication and a new dosage form, and the applicant submitted the toxicokinetic study data in a repeated-dose toxicity study in rabbits. In this study, atropine concentrations in biological samples were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 0.008 ng/mL). The applicant also submitted published literature on the distribution and metabolism in rats, dogs, monkeys, and rabbits.

4.1 Absorption

In the 39-week repeated-dose toxicity study of atropine in rabbits, the toxicokinetics was investigated, and pharmacokinetic parameters of atropine in plasma are shown in Table 3 (CTD 4.2.3.2-1).

Table 3. Pharmacokinetic parameters of atropine in plasma after repeated doses

Measurement point	Atropine concentrations (%)	Sex n/group	C_{max} (ng/mL)	t_{max} (h)[a)]	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$[b)] (ng•h/mL)	$AUC_{0\text{-}\infty}$[b)] (ng•h/mL)
Day 1	0.05	Male 6	0.45 ± 0.11	0.08 (0.08, 0.08)	0.57 ± 0.17	0.47 ± 0.06	0.37 ± 0.06
		Female 6	0.48 ± 0.14	0.08 (0.08, 0.25)	0.62 ± 0.12[c)]	0.52 ± 0.18	0.48 ± 0.16[c)]
	0.18	Male 6	1.63 ± 0.41	0.17 (0.08, 0.25)	1.32 ± 1.33	2.23 ± 0.56	1.97 ± 0.61
		Female 6	1.36 ± 0.24	0.17 (0.08, 0.50)	0.67 ± 0.03[c)]	1.87 ± 0.63	1.55 ± 0.52[c)]
	1	Male 8	8.45 ± 2.55	0.25 (0.08, 0.50)	3.18 ± 1.06	17.3 ± 6.9	17.2 ± 7.0
		Female 8	8.40 ± 2.82	0.38 (0.08, 1.00)	3.02 ± 1.13[d)]	22.7 ± 10.4	22.1 ± 11.7[d)]
Week 12	0.05	Male 6	0.70 ± 0.16	0.08 (0.08, 0.08)	0.85 ± 0.10	0.65 ± 0.06	0.53 ± 0.07
		Female 6	0.62 ± 0.18	0.17 (0.08, 0.25)	0.81 ± 0.04	0.83 ± 0.26	0.68 ± 0.22
	0.18	Male 6	2.39 ± 0.63	0.08 (0.08, 0.25)	2.25 ± 3.56	4.72 ± 4.92	4.99 ± 6.68
		Female 6	1.93 ± 0.33	0.08 (0.08, 0.25)	1.76 ± 1.46	2.65 ± 0.90	2.40 ± 1.03
	1	Male 8	13.9 ± 2.4	0.08 (0.08, 0.50)	2.76 ± 0.21	35.3 ± 7.0	35.3 ± 7.0
		Female 8	12.0 ± 2.2	0.38 (0.08, 0.50)	3.08 ± 0.42	34.7 ± 12.4	34.9 ± 12.4
Week 36	0.05	Male 6	1.13 ± 0.66	0.08 (0.08, 0.08)	0.90 ± 0.11	0.81 ± 0.17	0.65 ± 0.12
		Female 6	0.88 ± 0.16	0.08 (0.08, 0.08)	0.94 ± 0.08	1.09 ± 0.36	0.84 ± 0.25
	0.18	Male 6	2.84 ± 0.35	0.08 (0.08, 0.08)	0.91 ± 0.07	2.74 ± 0.49	2.17 ± 0.39
		Female 6	2.04 ± 0.41	0.08 (0.08, 0.08)	1.38 ± 1.20	2.82 ± 0.43	2.33 ± 0.40
	1	Male 7	14.2 ± 1.1	0.25 (0.08, 0.25)	2.92 ± 0.23	37.4 ± 7.9	37.5 ± 7.9
		Female 8	12.8 ± 2.3	0.50 (0.08, 0.50)	2.93 ± 0.28	40.6 ± 10.4	40.7 ± 10.4

Mean ± standard deviation (SD)
a) Median (minimum, maximum), b) Values below the lower limit of quantification were handled as 0 ng/mL in the calculation, c) n = 5, d) n = 7

4.2 Distribution

4.2.1 Tissue distribution

A single dose of 2% ^{3}H-atropine ophthalmic solution was applied in both eyes of albino rabbits, and radioactivity concentrations in ocular tissues were determined at up to 4 hours post-dose. In any of the

tissues,[3] the concentration peaked at 1 hour post-dose. The highest tissue radioactivity concentration was found in the cornea followed by sclera, iris and ciliary body, aqueous humor, choroid, retina, and vitreous humor in this order (*Optom Vis Sci.* 1999;76:397-407).

A single dose of 2% ^{3}H-atropine ophthalmic solution was applied in both eyes of albino rabbits and pigmented rabbits, and radioactivity concentrations in the iris were determined. The iris radioactivity concentrations in pigmented rabbits at 96 hours post-dose were approximately 8 times higher than those in albino rabbits, suggesting that atropine bound to melanin in the iris (*Invest Ophthalmol.* 1976;15:671-3).

To albino rats, ^{3}H-atropine was intraperitoneally administered at 1.25 to 10 mg/kg, and tissue radioactivity concentrations were determined at up to 4 hours post-dose. In any of the tissues investigated,[4] the radioactivity concentration peaked at 0.05 hours post-dose. At 0.05 hours post-dose, the radioactivity concentrations in the liver and kidney were approximately 10 times higher than that in plasma, and the radioactivity concentrations in the other tissues (fat, heart, brain) were higher than that in plasma. The elimination half-life of radioactivity was the shortest in plasma (40-46 minutes) and the longest in fat (97-106 minutes) (*Pharmacol Biochem Behav.* 1974;2:843-5).

4.3 Metabolism

4.3.1 *In vitro* metabolism (*Naunyn Schmiedebergs Arch Pharmacol.* 2006;373:230-6)

Plasma specimens from rabbits (n = 3 positive and n = 6 negative for atropine esterase), dogs (n = 3), and monkeys (n = 3) were incubated with atropine at 4.43 mmol/L at 35°C for 24 hours. In the plasma specimens from rabbits positive for atropine esterase, atropine was mostly metabolized into tropic acid, but in those from rabbits negative for atropine esterase, dogs, and monkeys, atropine mostly remained unchanged. The tropic acid concentrations in the plasma specimens from rabbits positive for atropine esterase at 24 hours of incubation were ≥40 times higher than those in the plasma specimens from rabbits negative for atropine esterase, dogs, and monkeys.

4.3.2 *In vivo* metabolism (*Invest Ophthalmol.* 1976;15:671-3)

A single dose of 2% ^{3}H-atropine ophthalmic solution was applied in both eyes of rabbits, and in the iris at 96 hours post-dose, only atropine was detected.

4.R Outline of the review conducted by PMDA

PMDA concluded that the submitted non-clinical pharmacokinetic study data have no particular problems.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application relates to a new indication and a new dosage form, the data related to toxicity has been evaluated during the review process of the existing indications of atropine. The applicant submitted data from repeated-dose toxicity and ocular local tolerance studies to evaluate the safety of

[3] Cornea, aqueous humor, iris and ciliary body, vitreous humor, sclera, choroid, and retina
[4] Plasma, brain, fat, heart, liver, and kidney

atropine applied in the eye. Because no differences were observed in major findings after application of atropine between these 2 studies, data only from the repeated-dose toxicity study are presented.

5.1 Repeated-dose toxicity

To evaluate the safety of atropine when applied in the eye for a long period of time, the 39-week repeated-dose toxicity study in rabbits was conducted, and no clear toxicity changes were observed (Table 4).

Table 4. Summary of repeated-dose toxicity study

Test system	Route of administration	Dosing period	Atropine concentrations (%)	Major findings	NOAEL (%)	CTD
Female and male Juvenile (7 weeks of age) Pigmented rabbit (Dutch)	Instillation	39 weeks (once daily) + 4 weeks of recovery	0,[a] 0.05, 0.18, 1	≥0.05: Mydriasis[b] Reversible	1	4.2.3.2-1

a) Vehicle
b) It was attributable to the pharmacological action of atropine and thus considered of little toxicological significance.

5.2 Evaluation of impurities

Tropic acid, an impurity of which the amount in the drug product exceeds the qualification threshold defined in the "Revision of Guideline on Impurities in New Drug Products" (ICH Q3B guideline), was subjected to evaluation for general toxicity and genotoxicity.

5.2.1 General toxicity of tropic acid

In the 39-week repeated-dose toxicity study in rabbits, a 0.18% atropine ophthalmic solution containing tropic acid at a concentration 13.9 times higher than that ([redacted] μg/mL) in Ryjusea Mini was used for general toxicity evaluation No clear toxicity changes were observed.

5.2.2 Genotoxicity of tropic acid

The daily exposure to tropic acid through administration of Ryjusea Mini is less than 1 mg. Genotoxicity evaluation was performed by an *in silico* (quantitative) structure-activity relationship ([Q]SAR) and raised no concerns about genotoxicity.

5.R Outline of the review conducted by PMDA

From a toxicological viewpoint, PMDA concluded that the submitted data indicate no particular problems with clinical use of atropine applied.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant did not submit data related to biopharmaceutic studies.

Atropine concentrations in biological samples were measured by LC-MS/MS (lower limit of quantification, 2 pg/mL).

In clinical studies of atropine, 0.0025%, 0.005%, 0.01%, and 0.025% ophthalmic solutions were used. The formulation used in a foreign phase II study (Study 012701LT) is different from that used in a Japanese phase I study (Study 012703LT) and a Japanese phase II/III study (Study 012702LT) in terms of [redacted]. The 0.025% ophthalmic solution used in the Japanese clinical studies (Studies 012703LT and 012702LT) had the same formulation as the proposed commercial one.

6.2 Clinical pharmacology

The applicant submitted the data relating to clinical pharmacology in the form of results from a phase I clinical study in Japanese pediatric patients with low to moderate myopia. The applicant also submitted published literature relating to *in vitro* studies using human biological samples and a mass balance study.

6.2.1 Studies using human biological samples

(a) Plasma protein binding

Mixtures of human plasma and atropine (2-20 ng/mL) were subjected to ultrafiltration and equilibrium dialysis to determine the plasma protein binding rate. At the atropine concentrations of 2, 5, 10, and 20 ng/mL, the plasma protein binding rates were 44%, 39%, 35%, and 29%, respectively; the rate decreased with increasing atropine concentration. The binding rates of atropine to human serum albumin and alpha 1-acid glycoprotein were 2% and 42%, respectively (*J Pharmacol Exp Ther*. 1990;255:1133-9).

(b) Investigation of metabolites in humans

In mixtures of human plasma and atropine at 4.43 mmol/L incubated at 35°C for 24 hours, unchanged atropine was mainly detected (4.03 mmol/L), and a trace of tropic acid was detected (0.13 mmol/L) (*Naunyn Schmiedebergs Arch Pharmacol.* 2006;373:230-6).

(c) Transport through drug transporters

Membrane permeability of atropine at 1 μmol/L was investigated using Lewis lung cancer porcine kidney 1 epithelial (LLC-PK1) cell line expressing human P-glycoprotein (P-gp). The efflux ratio of atropine (ratio of the apparent permeability in basolateral to apical direction [Papp $_{B\rightarrow A}$] to that in apical to basal direction [Papp $_{A\rightarrow B}$]) was 3.4, which was decreased to 1.2 in the presence of a P-gp inhibitor (elacridar 1 μmol/L), suggesting that atropine might act as a substrate of P-gp (*Drug Metab Dispos.* 2014; 42:1411-22).

Using human embryonic kidney 293 (HEK293) cell line which expressed human organic cation transporter (OCT)1, OCT2, OCT3, multidrug and toxin extrusion protein (MATE)1, or MATE2-K, cellular uptake of atropine (1 and 5 μmol/L) through each of the drug transporters was investigated in the presence or absence of an inhibitor against the corresponding transporter.[5)] The uptake of atropine through OCT1, OCT2, and OCT3 was decreased in the presence of the inhibitor, suggesting that atropine might act as a substrate of OCT1, OCT2, and OCT3. On the other hand, the uptake of atropine through MATE1 and MATE2-K did not change irrespective of presence or absence of the

[5)] OCT, 1-methyl-4-phenylpyridinium at 1 mmol/L; MATE, cimetidine at 1 mmol/L

inhibitor, suggesting that atropine might not be a substrate of MATE1 or MATE2-K (*Biol Chem*. 2017;398:237-49).

(d) Inhibition of drug transporters

Using HEK293 cell line which expressed OCT1, OCT2, OCT3, MATE1, or MATE-2K, the inhibitory effect of atropine (0.1-1000 μmol/L) against cellular uptake of a representative substrate of each of the transporters was investigated. Atropine inhibited OCT1, OCT2, OCT3, MATE1, and MATE-2K with the 50% inhibitory concentration (IC_{50}) values of 3.1, 37.9, 42.9, 17.7, and 69.0 μmol/L, respectively (*Biol Chem.* 2017;398:237-49).

The applicant, however, explained that the drug interactions through each of the drug transporters investigated above were considered unlikely to cause problems in clinical use in view of C_{max} of atropine in patients with myopia for whom a 0.025% atropine ophthalmic solution was applied in both eyes once daily (16.5 pg/mL [see Section 6.2.2]) and the unbound fraction of atropine in plasma (0.6-0.7 [see Section 6.2.1 (a)]) in addition to the above study results.

6.2.2 Japanese phase I study (CTD 5.3.3.2-2, Study 012703LT)

In Japanese patients with low to moderate myopia aged 5 to 15 years (10 patients included in pharmacokinetic evaluation), the 0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose in the evening (19:00) once daily for 7 days. The pharmacokinetic parameters are shown in Table 5.

Table 5. Pharmacokinetic parameters of atropine after application

Day of measurement	n	C_{max} (pg/mL)	t_{max} (min)	$AUC_{0\text{-}60min}$ (pg·min/mL)
Day 1	10	19.7 ± 7.0 17.2 (12.4, 33.3)	46 ± 20 60 (5.0, 60)	939 ± 370 817 (515, 1580)
Day 7	10	16.5 ± 3.6 17.9 (11.3, 20.4)	54 ± 13 60 (30, 60)	798 ± 188 833 (545, 1020)

Top, Mean ± SD; Bottom, Median (minimum, maximum)

6.2.3 Mass balance study in non-Japanese healthy adults (*Clin Pharmacol Ther.* 1960;1:597-603)

To non-Japanese healthy adults (2 adults included in pharmacokinetic evaluation), ^{14}C-atropine 2 mg was intramuscularly administered to investigate the mass balance of atropine. Of the radioactivity administered, 85% to 88% was excreted into urine up to 48 hours post-dose, and in the urine, unchanged atropine and tropic acid, a metabolite, accounted for approximately 50% and <2%, respectively. Of the radioactivity administered, <0.5% was excreted into feces up to 72 hours post-dose, and no radioactivity was detected in expired air up to 6 hours post-dose.

6.R Outline of the review conducted by PMDA

PMDA concluded that the pharmacokinetics of atropine after application of the 0.025% atropine ophthalmic solution in both eyes presents no particular problems.

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 from 2 Japanese clinical studies and reference data in the form of results from 1 foreign clinical study (Table 6).

Table 6. List of clinical studies for efficacy and safety

Data category	Region	Study CTD	Phase	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Study 012703LT 5.3.3.2-2	I	Patients with low to moderate myopia aged 5 to 15 years	10	0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily for 7 days (Study Instillation Period I) and for approximately 12 months (Study Instillation Period II)	Pharmacokinetics Safety
	Japan	Study 012702LT 5.3.5.1-1	II/III	Patients with low to moderate myopia aged 5 to 15 years	299	Placebo, 0.01% atropine ophthalmic solution, or 0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily at bedtime for 24 months (Treatment Period I) and 12 months (Treatment Period II)	Efficacy Safety
Reference	Foreign	Study 012701LT 5.3.5.1-2	II	Patients with low to moderate myopia aged 6 to 11 years	100	Placebo, 0.0025% atropine ophthalmic solution, 0.005% atropine ophthalmic solution, or 0.01% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily at bedtime for 12 months	Efficacy Safety

7.1 Evaluation data

7.1.1 Japanese phase I study (CTD 5.3.3.2-2, Study 012703LT, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, uncontrolled study was conducted in Japanese patients with low to moderate myopia aged 5 to 15 years[6)] (target sample size, 10 patients [≥3 patients weighing <30 kg, ≥3 patients weighing ≥30 kg and <40 kg, ≥3 patients weighing ≥40 kg]) in Japan to evaluate the pharmacokinetics and safety of the 0.025% atropine ophthalmic solution [for the pharmacokinetic study data, see Section 6.2.1].

This study consisted of the observation period (1-14 days), Study Instillation Period I (7 days), and Study Instillation Period II (approximately 12 months).

After the observation period, the 0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose in the evening (19:00) once daily for 7 days during Study Instillation Period I and then applied in both eyes at 1 drop per dose once daily at bedtime for 12 months during Study Instillation Period II.

6) Patients meeting the following main inclusion criteria were included. Patients who had used contact lens or drugs for the purpose of slowing the progression of myopia were excluded.
(a) The objective spherical equivalent under cycloplegia is −1.0 D to −6.0 D in both eyes.
(b) The refraction examination within 1 year before screening indicated progression of myopia in both eyes (as a guide, the spherical equivalent is worsened by ≥0.5 D).

A total of 10 patients who received the study drug were included in the safety analysis population. During Study Instillation Period I, none discontinued the study, and during Study Instillation Period II, 1 patient discontinued the study because of use of prohibited concomitant drugs.

During Study Instillation Periods I and II, adverse events occurred in 60% (6 of 10) of patients. No serious adverse events including deaths occurred.

Adverse events considered causally related to the study drug occurred in 40% (4 of 10) of patients (glare in 3 patients and visual impairment in 1 patient).

7.1.2 Japanese phase II/III study (CTD 5.3.5.1-1, Study 012702LT, [redacted] 20[redacted] to [redacted] 20[redacted])

A double-masked, placebo-controlled, randomized, parallel-group study was conducted in Japanese patients with low to moderate myopia aged 5 to 15 years[6] (target sample size, 288 patients,[7] 96 per group) in Japan to evaluate the efficacy and safety of the atropine ophthalmic solution.

This study consisted of the observation period (1-14 days), Treatment Period I (24 months), and Treatment Period II (12 months). After the observation period, subjects were randomized into the placebo group, 0.01% atropine group, and 0.025% atropine group in a ratio of 1:1:1 for Treatment Period I. For Treatment Period II, subjects in the 0.01% atropine group during Treatment Period I were randomized into the placebo group (0.01%/P group) and 0.01% atropine group (0.01%/0.01% group) in a ratio of 1:1; those in the 0.025% atropine group during Treatment Period I were randomized into the placebo group (0.025%/P group) and 0.025% atropine group (0.025%/0.025% group) in a ratio of 1:1; those in the placebo group during Treatment Period I were randomized into the placebo group (P/P group), 0.01% atropine group (P/0.01% group), and 0.025% atropine group (P/0.025% group) in a ratio of 2:1:1.[8]

During Treatment Period I, placebo, 0.01% atropine ophthalmic solution, or 0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily at bedtime for 24 months in a double-masked manner. During Treatment Period II, placebo, 0.01% atropine ophthalmic solution, or 0.025% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily at bedtime for 12 months in a double-masked manner[9] (Figure 1).

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7) On the assumption that a difference in change in objective spherical equivalent under cycloplegia from baseline to Month 24 between the 0.01% atropine group and placebo group was 0.57 D with the SD of 0.8 D, the number of subjects required to detect the difference with a power of 90% at a two-sided significance level of 5% in t-test was determined to be 43 per group. Then, in view of the following points, the target sample size of 288 subjects (96 per group) was specified: For the 0.025% atropine group, the same number of subjects as that for the 0.01% atropine group was considered to provide an adequate power based on the expected dose-response relationship; the test was needed to secure the power to detect a difference in change in objective spherical equivalent under cycloplegia from baseline to Month 12, the secondary endpoint, between the groups; and 10% of the subjects were assumed to discontinue the study.

8) Randomization was performed using age category (4 categories of 5-7, 8-9, 10-11, and 12-15 years) as an allocation factor.

9) After the data lock at Month 24, code break was implemented, but even during Treatment Period II and thereafter, the investigators, sub-investigators, subjects, and study staff at the study sites remained masked.

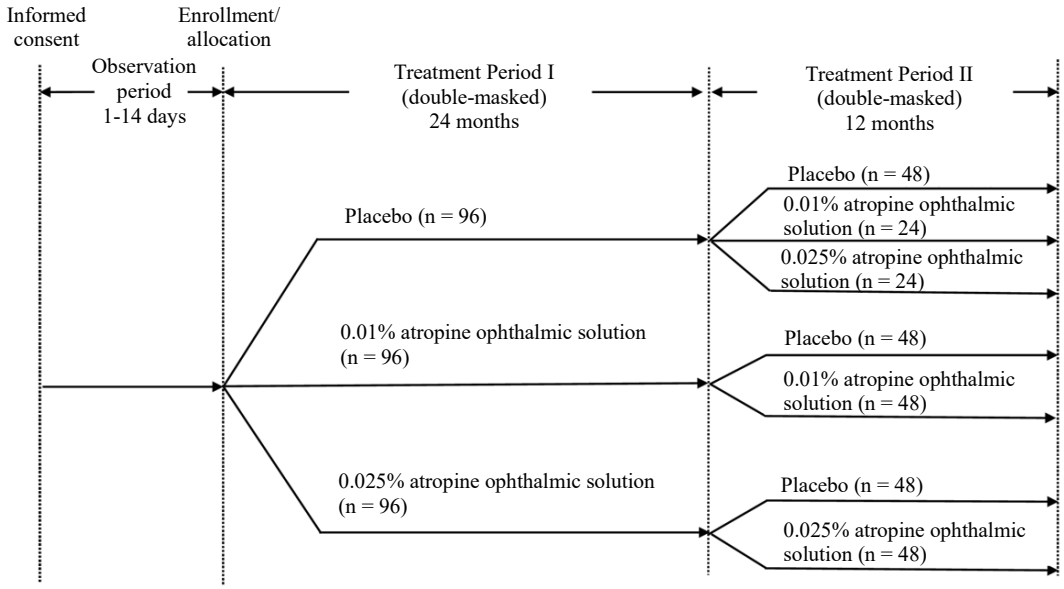

Figure 1. Study design (Study 012702LT)

A total of 299 subjects who were randomized and received the study drug (99 in the placebo group, 99 in the 0.01% atropine group, 101 in the 0.025% atropine group) were included in the safety analysis population and full-analysis set (FAS). The FAS was used as the primary efficacy analysis population.

During Treatment Period I, 39 subjects (9 in the placebo group, 15 in the 0.01% atropine group, 15 in the 0.025% atropine group) discontinued the study, and 4 subjects (2 in the placebo group, 1 in the 0.01% atropine group, 1 in the 0.025% atropine group) discontinued the study treatment, mainly because of consent withdrawal in 37 subjects (9 in the placebo group, 14 in the 0.01% atropine group, 14 in the 0.025% atropine group), adverse events in 1 subject (1 in the 0.025% atropine group), and the other reasons in 1 subject (1 in the 0.01% atropine group). A total of 256 subjects (43 in the P/P group, 24 in the P/0.01% group, 21 in the P/0.025% group, 43 in the 0.01%/P group, 40 in the 0.01%/0.01% group, 41 in the 0.025%/P group, 44 in the 0.025%/0.025% group) entered Treatment Period II. During this period, 16 subjects (2 in the P/P group, 3 in the P/0.01% group, 2 in the P/0.025% group, 2 in the 0.01%/P group, 6 in the 0.01%/0.01% group, 0 in the 0.025%/P group, 1 in the 0.025%/0.025% group) discontinued the study mainly because of consent withdrawal in 15 subjects (2 in the P/P group, 3 in the P/0.01% group, 2 in the P/0.025% group, 1 in the 0.01%/P group, 6 in the 0.01%/0.01% group, 0 in the 0.025%/P group, 1 in the 0.025%/0.025% group).

For efficacy,[10)] Table 7 shows results on a change in objective spherical equivalent[11)] under cycloplegia[12)] from baseline to Month 24, the primary endpoint, demonstrating superiority of 0.01% and 0.025% atropine over placebo. Figure 2 shows changes from baseline in objective spherical equivalent under cycloplegia over time up to Month 36.

10) The efficacy evaluation was performed on the eye with more progressed myopia at baseline based on the objective spherical equivalent (efficacy evaluation eye) for each subject. For subjects with both eyes of the same objective spherical equivalent, the right eye was deemed as the efficacy evaluation eye.

11) Using an auto ref-keratometer, spherical power and cylinder power were measured 5 times for each eye, and from results on spherical power and cylinder power in each measurement, the objective spherical equivalent was calculated according to the following formula. Using calculated values in 5 measurements, the mean objective spherical equivalent was determined for each eye. The concerned mean was used in the analysis.
"Objective spherical equivalent = spherical power + cylinder power × 1/2"

12) Two doses of 1% cyclopentolate hydrochloride ophthalmic solution were instilled as a cycloplegic at an interval of 5 minutes, and at 45 minutes after the last dose, the cycloplegia condition was checked. When the (sub)investigator considered the condition inadequate, another dose was instilled.

Table 7. Change in objective spherical equivalent under cycloplegia from baseline to Month 24 (Study 012702LT, FAS)

	Objective spherical equivalent		Change in objective spherical equivalent[a),b)]	Difference between groups [95% CI][b)]	*P* value[b),c)]
	Baseline	Month 24			
Placebo	-3.14 ± 1.13 (99)	-4.78 ± 1.40 (93)	-1.64 ± 0.06		
0.01% atropine	-3.01 ± 1.12 (99)	-4.31 ± 1.27 (86)	-1.30 ± 0.06	0.34 [0.17, 0.51]	< 0.0001
0.025% atropine	-3.08 ± 1.05 (101)	-4.12 ± 1.37 (87)	-1.01 ± 0.06	0.64 [0.47, 0.81]	< 0.0001

Mean ± SD (number of subjects evaluated)

a) Least squares mean ± standard error (SE)

b) Analysis based on mixed effects model for repeated measures (MMRM) using the objective spherical equivalent at baseline as a covariate, treatment group, timepoint, interaction between treatment group and timepoint, and interaction between objective spherical equivalent at baseline and timepoint as fixed effects, and subjects as a random effect. The degree of freedom was adjusted according to the Kenward-Roger method, and the variance component structure was assumed as a covariance structure.

c) Two-sided significance level of 5%. Multiplicity of the test was controlled using a closed testing procedure as follows: Firstly, a comparison between placebo and 0.025% atropine was performed; and then only when a statistically significant difference was observed, a comparison between placebo and 0.01% atropine was performed.

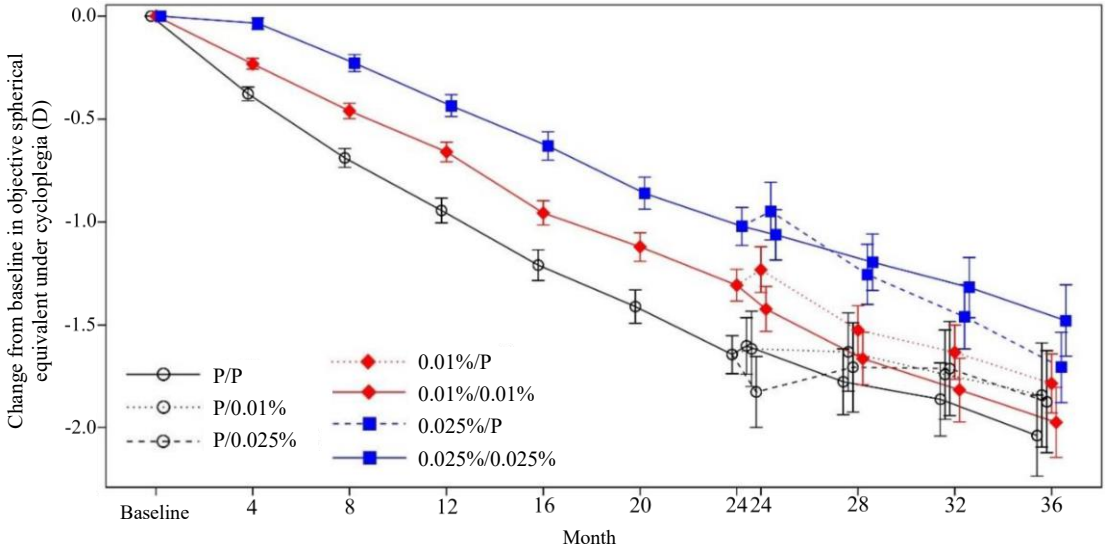

Figure 2. Change from baseline in objective spherical equivalent under cycloplegia over time (Study 012702LT, mean ± SE, observed case [OC], FAS)

During Treatment Period I, adverse events occurred in 73.7% (73 of 99) of subjects in the placebo group, 81.8% (81 of 99) of subjects in the 0.01% atropine group, and 83.2% (84 of 101) of subjects in the 0.025% atropine group. No deaths occurred. Serious adverse events occurred in 3.0% (3 of 99) of subjects in the placebo group (viral pharyngitis, COVID-19, and Campylobacter gastroenteritis in 1 subject each), 1.0% (1 of 99) of subjects in the 0.01% atropine group (inguinal hernia), and 3.0% (3 of 101) of subjects in the 0.025% atropine group (COVID-19 in 2 subjects and humerus fracture in 1 subject). All events were assessed as causally unrelated to the study drug. Adverse events considered as causally related to the study drug occurred in 1.0% (1 of 99) of subjects in the placebo group, 5.1% (5 of 99) of subjects in the 0.01% atropine group, and 16.8% (17 of 101) of subjects in the 0.025% atropine group. The events reported by ≥2 subjects in any group were photophobia (1 subject in the placebo group, 4 subjects in the 0.01% atropine group, 11 subjects in the 0.025% atropine group), visual impairment (0 subjects, 0 subjects, subjects), vision blurred (0 subjects, 0 subjects, 2 subjects), and headache (0 subjects, 1 subject, 2 subjects).

During Treatment Period II, adverse events occurred in 53.5% (23 of 43) of subjects in the P/P group, 58.3% (14 of 24) of subjects in the P/0.01% group, 52.4% (11 of 21) of subjects in the P/0.025% group, 69.8% (30 of 43) of subjects in the 0.01%/P group, 55.0% (22 of 40) of subjects in the 0.01%/0.01% group, 51.2% (21 of 41) of subjects in the 0.025%/P group, and 56.8% (25 of 44) of subjects in the 0.025%/0.025% group. No deaths occurred. A serious adverse event occurred in 2.3% (1 of 43) of subjects in the P/P group (upper limb fracture), but the event was assessed as causally unrelated to the study drug. Adverse events considered causally related to the study drug occurred in 9.5% (2 of 21) of subjects in the P/0.025% group (visual impairment and pupillary disorder in 1 subject each) and 2.5% (1 of 40) of subjects in the 0.01%/0.01% group (photophobia).

7.2 Reference data

7.2.1 Foreign phase II study (Reference CTD 5.3.5.1-2, Study 012701LT, November 2017 to April 2020)

A double-masked, placebo-controlled, randomized, parallel-group study was conducted in non-Japanese patients with low to moderate myopia aged 6 to 11 years[13] (target sample size; 100 patients,[14] 25 per group) in Singapore to evaluate the efficacy and safety of the atropine ophthalmic solution.

This study consisted of the treatment period (12 months) and follow-up period (6 months).

Subjects were randomized into the placebo group, 0.0025% atropine group, 0.005% atropine group, and 0.01% atropine group in a ratio of 1:1:1:1.[15] During the treatment period, placebo, 0.0025% atropine ophthalmic solution, 0.005% atropine ophthalmic solution, or 0.01% atropine ophthalmic solution was applied in both eyes at 1 drop per dose once daily at bedtime for 12 months in a double-masked manner. During the follow-up period, the progression of myopia from Month 12 was evaluated without the study treatment.

Of 100 subjects who were randomized and received the study drug (26 in the placebo group, 24 in the 0.0025% atropine group, 24 in the 0.005% atropine group, 26 in the 0.01% atropine group), 99 subjects (26, 24, 24, 25) were included in the safety analysis population and FAS, and the remaining 1 subject[16] (the 0.01% atropine group) was excluded. The FAS was used as the primary efficacy analysis population. Of the safety analysis population, 2 subjects (the 0.0025% atropine group) discontinued the study during the treatment period because of the adverse events and consent withdrawal in 1 subject each. During the follow-up period, 3 subjects (the 0.01% atropine group) discontinued the study because of other reasons (impact of COVID-19 spread).

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13) Patients meeting the following main inclusion criteria were included. Patients who had used contact lens or drugs for the purpose of slowing the progression of myopia were excluded.
   (a) The objective spherical equivalent under cycloplegia is −1.0 D to −6.0 D in both eyes (−1.0 D not inclusive, −6.0 D inclusive).
   (b) For both eyes, myopia is or is predicted to be progressed with the spherical equivalent worsened by ≥−0.5 D within 12 months based on the change in refraction examination or lens power.

14) On the assumption that the mean change in objective spherical equivalent under cycloplegia from baseline to Month 12 of treatment, the primary endpoint, was −0.43 D in the atropine group and −0.76 D in the placebo group with the common SD of 0.5 D, the number of subjects required to detect a statistical significant difference between the atropine group and placebo group with a power of 62.8% (at a two-sided significance level of 5% in t-test) and 74.4% (at a two-sided significance level of 10% in t-test) was determined to be 25 per group.

15) Randomization was performed using age category (3 categories of 6-7, 8-9, and 10-11 years) as an allocation factor.

16) After the first dose of the study drug, the informed consent of this subject was found to have a defect. The subject then discontinued the study and was excluded from all analysis populations.

For the efficacy,[10] Table 8 shows results on a change in objective spherical equivalent[12] under cycloplegia[17] from baseline to Month 12, the primary endpoint. Atropine at 0.005% and 0.01% tended to suppress worsening of the objective spherical equivalent compared to placebo. Figure 3 shows changes from baseline in objective spherical equivalent under cycloplegia over time up to Month 18.

Table 8. Change in objective spherical equivalent under cycloplegia from baseline to Month 12 (Study 012701LT, FAS)

	Objective spherical equivalent		Change in objective spherical equivalent[a),b)]	Difference between groups [95%CI][b)]
	Baseline	Month 12		
Placebo	-3.93 ± 1.13 (26)	-4.48 ± 1.13 (26)	-0.60 ± 0.06	
0.0025% atropine	-3.00 ± 1.11 (24)	-3.61 ± 1.18 (22)	-0.49 ± 0.07	0.11 [-0.08, 0.29]
0.005% atropine	-3.80 ± 1.35 (24)	-4.13 ± 1.23 (24)	-0.37 ± 0.07	0.23 [0.06, 0.41]
0.01% atropine	-3.25 ± 1.11 (25)	-3.64 ± 0.95 (25)	-0.35 ± 0.06	0.25 [0.07. 0.43]

Mean ± SD (number of subjects evaluated)
a) Least squares mean ± SE
b) Analysis based on MMRM using the objective spherical equivalent at baseline as a covariate.

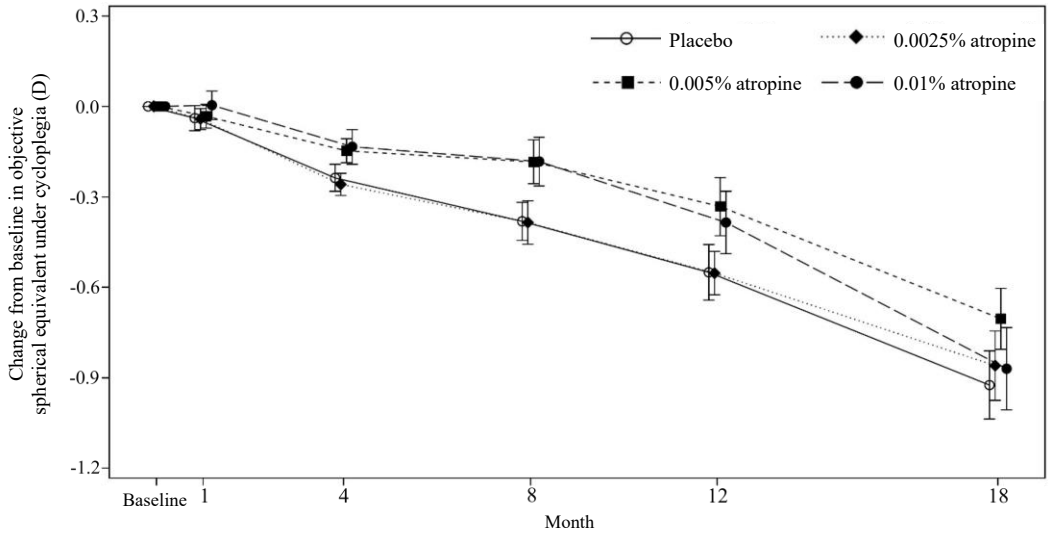

Figure 3. Change from baseline in objective spherical equivalent under cycloplegia over time (Study 012701LT, mean ± SE, OC, FAS)

Adverse events occurred in 7.7% (2 of 26) of subjects in the placebo group, 37.5% (9 of 24) of subjects in the 0.0025% atropine group, 58.3% (14 of 24) of subjects in the 0.005% atropine group, and 44.0% (11 of 25) of subjects in the 0.01% atropine group. No serious adverse events including deaths occurred.

Adverse events considered causally related to the study drug occurred in 8.3% (2 of 24) of subjects in the 0.0025% atropine group (eye pain and eye pain/glare/vision blurred in 1 subject each) and 8.0% (2 of 25) of subjects in the 0.01% atropine group (glare).

[17] One drop of 0.5% proparacaine ophthalmic solution was instilled as a cycloplegic, and then 3 doses of 1% cyclopentolate ophthalmic solution were instilled at an interval of 5 minutes.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the rationale for designing the plan of the Japanese phase II/III study (Study 012702LT):

Because there were no drugs or medical devices approved for the indication of slowing the progression of myopia in Japan, Study 012702LT was designed to examine the superiority of the atropine ophthalmic solution over placebo.

The study population was specified as patients with myopia aged ≥5 and ≤15 years in view of onset age of myopia, which typically develops at the age of approximately 6 to 8 years and progresses through the age of 15 to 16 years (*Cochrane Database of Systematic Reviews.* 2011;7:CD004916), age at which examination and observation are feasible, and the length of the follow-up period. In addition, because the intended indication of the atropine ophthalmic solution is to slow the progression of myopia, patients with low to moderate progressive myopia in both eyes on which the refraction examination within 1 year before screening indicated worsening of the spherical equivalent by ≥0.5 D.

In view of the following points, the primary endpoint in Study 012702LT was specified as a change in objective spherical equivalent under cycloplegia from baseline to Month 24:

- A report of the World Health Organization (WHO) (WHO. The impact of myopia and high myopia) describes that a response of myopia to treatment with the atropine ophthalmic solution should be assessed based on a change in objective spherical equivalent after 2 years of treatment, and then continuation or discontinuation of the treatment should be chosen.
- The objective spherical equivalent is an index allowing objective assessment and measured as an index of progression of myopia in clinical settings.

To evaluate the worsening of myopia after the completion of treatment with atropine ophthalmic solution and the efficacy and safety of atropine ophthalmic solution applied for >2 years, a 12-month Treatment Period II followed Treatment Period I. In Treatment Period II, patients received placebo or continued the atropine ophthalmic solution from Treatment Period I at the same concentration (Figure 1).

The applicant's explanation about the efficacy of atropine in slowing the progression of myopia based on results in Study 012702LT:

The results on a change in objective spherical equivalent under cycloplegia from baseline to Month 24, the primary endpoint, demonstrated superiority of 0.01% and 0.025% atropine over placebo (Table 7).

Many subjects discontinued the study during Treatment Period I [see Section 7.1.2] and discontinuation of 1% atropine ophthalmic solution led to rapid progression of myopia (*Ophthalmology.* 2006;113:2285-91, *Ophthalmology.* 2009;116:572-9). The applicant considered that the possibility of such a rebound could not be ruled out even for the 0.01% and 0.025% atropine ophthalmic solutions. For the change in objective spherical equivalent under cycloplegia from baseline to Month 24, the primary endpoint, the main analysis was performed assuming that missing values were attributable to random missing measurements (Missing at random). However, to investigate an

effect of the study discontinuation on the efficacy evaluation, a sensitivity analysis with missing values imputed by a different method (Tipping point analysis assuming "Missing not at random") was performed. For this investigation, changes in objective spherical equivalent under cycloplegia from baseline to Month 24 in the 0.01% atropine group and 0.025% atropine group were calculated assuming "Missing at random" for missing data. When −0.75 D and −2.69 D were added to the calculated changes, the *P* value exceeded 0.05. These values were deemed as Tipping points. When the obtained Tipping points (−0.75 D and −2.69 D) were added to the estimated changes (−1.30 D and −1.01 D, respectively [see Table 7]) in objective spherical equivalent in the 0.01% atropine group and 0.025% atropine group in the main analysis, the results (−2.05 D and −3.70 D, respectively) were both below the estimated change in objective spherical equivalent from baseline to Month 24 in the placebo group (−1.64 D [see Table 7]). Based on the changes in objective spherical equivalent under cycloplegia over Treatment Period II (Figure 2) and other findings, the change in objective spherical equivalent after discontinuation of atropine is unlikely to become below that in the placebo group. These Tipping Points are considered clinically irrelevant. The results from the main analysis were thus determined to be robust.

Table 9 shows results on the secondary endpoints.

Table 9. Results on secondary endpoints (Study 012702LT, FAS)

Endpoint	Placebo	0.01% atropine	0.025% atropine
Change in objective spherical equivalent under cycloplegia from baseline to Month 12[a)]	-0.95 ± 0.06	-0.66 ± 0.06	-0.44 ± 0.06
Change in axial length from baseline to Month 24[a)]	0.74 ± 0.02	0.63 ± 0.02	0.51 ± 0.02
Proportion of subjects with the objective spherical equivalent under cycloplegia worsened by ≥1.0 D from baseline to Month 24[b)]	79.6 (74/93)	64.0 (55/86)	46.0 (40/87)

a) Least squares mean ± SE. Calculated according to MMRM using the baseline value as a covariate, treatment group, timepoint, interaction between treatment group and timepoint, and interaction between baseline value and timepoint as fixed effects, and subjects as a random effect.
b) % (number of applicable subjects/number of subjects evaluated).

Table 10 shows results of a sub-group analysis on the primary endpoint by patient characteristic in Study 012702LT. In any sub-group, the results on efficacy were more favorable in the 0.01% atropine group and 0.025% atropine group than in the placebo group.

Table 10. Change in objective spherical equivalent under cycloplegia from baseline to Month 24 by patient characteristic (Study 012702LT)

Patient characteristic		Placebo		0.01% atropine		0.025% atropine		Difference between atropine and placebo [95% CI]	
		Baseline	Change	Baseline	Change	Baseline	Change	0.01% atropine	0.025% atropine
Overall population		-3.14 ± 1.13 (99)	-1.65 ± 0.90 (93)	-3.01 ± 1.12 (99)	-1.31 ± 0.71 (86)	-3.08 ± 1.05 (101)	-1.02 ± 0.86 (87)	0.34 [0.10, 0.58]	0.62 [0.36, 0.88]
Age	5-9 years	-3.04 ± 1.03 (55)	-1.88 ± 0.86 (52)	-2.79 ± 1.00 (55)	-1.60 ± 0.63 (52)	-3.05 ± 0.97 (56)	-1.36 ± 0.87 (52)	0.28 [-0.01, 0.57]	0.53 [0.19, 0.86]
	10-15 years	-3.28 ± 1.24 (44)	-1.35 ± 0.86 (41)	-3.30 ± 1.20 (44)	-0.86 ± 0.59 (34)	-3.12 ± 1.15 (45)	-0.53 ± 0.58 (35)	0.48 [0.14, 0.83]	0.82 [0.48, 1.16]
Sex	Male	-3.41 ± 1.25 (38)	-1.57 ± 1.00 (37)	-2.95 ± 1.19 (45)	-1.26 ± 0.73 (41)	-3.20 ± 1.10 (38)	-1.00 ± 0.73 (35)	0.32 [-0.07, 0.71]	0.58 [0.16, 0.99]
	Female	-3.00 ± 1.02 (61)	-1.69 ± 0.83 (56)	-3.07 ± 1.06 (54)	-1.36 ± 0.69 (45)	-3.01 ± 1.04 (63)	-1.04 ± 0.95 (52)	0.33 [0.03, 0.64]	0.65 [0.31, 0.99]
Objective spherical equivalent	<−3.0 D	-4.10 ± 0.82 (47)	-1.59 ± 0.98 (43)	-4.17 ± 0.84 (39)	-1.14 ± 0.72 (33)	-4.00 ± 0.72 (48)	-1.05 ± 0.82 (41)	0.45 [0.05, 0.86]	0.54 [0.15, 0.94]
	≥−3.0 D	-2.28 ± 0.48 (52)	-1.69 ± 0.82 (50)	-2.26 ± 0.40 (60)	-1.41 ± 0.69 (53)	-2.25 ± 0.40 (53)	-1.00 ± 0.91 (46)	0.28 [-0.02, 0.57]	0.69 [0.34, 1.04]
Axial length	<24.5 mm	-2.71 ± 0.85 (52)	-1.78 ± 0.93 (48)	-2.61 ± 0.86 (48)	-1.63 ± 0.56 (44)	-2.59 ± 0.82 (47)	-1.13 ± 1.02 (41)	0.16 [-0.17, 0.48]	0.65 [0.24, 1.06]
	≥24.5 mm	-3.62 ± 1.21 (47)	-1.50 ± 0.85 (45)	-3.37 ± 1.20 (50)	-1.00 ± 0.71 (41)	-3.50 ± 1.05 (54)	-0.92 ± 0.70 (46)	0.51 [0.17, 0.84]	0.58 [0.26, 0.90]

Mean ± SD (number of subjects evaluated)

Table 11 shows results on each endpoint at Month 36 in Study 012702LT. For the change in objective spherical equivalent under cycloplegia from baseline to Month 36, a difference [95% confidence interval (CI)] between the 0.01%/0.01% or 0.025%/0.025% group and P/P group was 0.06 [−0.47, 0.60] and 0.56 [0.04, 1.09], respectively, indicating that the results tended to be more favorable in the 0.025%/0.025% group than in the P/P group. The proportion of subjects with the objective spherical equivalent under cycloplegia worsened by ≥1.0 D from baseline to Month 36 did not clearly differ between the 0.01%/0.01% group and P/P group but was smaller in the 0.025%/0.025% group than in the P/P group.

Table 11. Results on each endpoint at Month 36 (Study 012702LT)

Endpoint	P/P	P/0.01%	P/0.025%	0.01%/P	0.01%/0.01%	0.025%/P	0.025%/0.025%
Change from baseline in objective spherical equivalent under cycloplegia[a)]	-2.04 ± 1.27	-1.84 ± 1.16	-1.87 ± 1.05	-1.79 ± 0.91	-1.97 ± 0.99	-1.71 ± 1.10	-1.48 ± 1.12
Change from baseline in axial length[a)]	0.96 ± 0.52	0.90 ± 0.50	0.84 ± 0.44	0.89 ± 0.41	0.93 ± 0.45	0.83 ± 0.49	0.72 ± 0.46
Proportion of subjects with the objective spherical equivalent under cycloplegia worsened by ≥1.0 D from baseline[b)]	80.5 (33/41)	71.4 (15/21)	83.3 (15/18)	80.5 (33/41)	82.4 (28/34)	68.3 (28/41)	59.5 (25/42)

a) Mean ± SD
b) % (number of applicable subjects/number of subjects evaluated)

The above results on the primary and secondary endpoints in Study 012702LT are considered to have demonstrated that atropine has the efficacy in slowing the progression of myopia.

PMDA's view:
The study design of Study 012702LT (control, study population, primary endpoint, and treatment period) was found to have no major problems.

In view of the results in Study 012702LT presented below, atropine is shown to have the efficacy in slowing the progression of myopia.

- The results on a change in objective spherical equivalent under cycloplegia from baseline to Month 24, the primary endpoint, demonstrated superiority of 0.01% and 0.025% atropine over placebo.
- The progression of myopia is deemed to be greatly affected by elongation of axial length (*Diagnosis and treatment of pediatric myopia* [in Japanese]. Miwa-Shoten Ltd. 2023;p39-70). The changes in axial length from baseline to Month 24 tended to be smaller in both 0.01% and 0.025% atropine groups than in the placebo group. The results on the other secondary endpoints supported those on the primary endpoint.
- The change in objective spherical equivalent under cycloplegia from baseline to Month 36 tended to be more favorable in the 0.025%/0.025% group than in the P/P group. The proportion of subjects with the objective spherical equivalent under cycloplegia worsened by ≥1.0 D from baseline tended to be smaller in the 0.025%/0.025% group than in the P/P group.

7.R.2 Safety

Based on the clinical study data submitted for the present application and the reviews in Sections 7.R.2.1 and 7.R.2.2 below, use of atropine requires attention particularly to the events associated with its mydriatic effect such as photophobia. PMDA, however, has concluded that atropine has acceptable safety where appropriate caution is advised on such events beforehand.

7.R.2.1 Safety profile of atropine

The applicant's explanation about safety profile of atropine:

In the Japanese phase I study (Study 012703LT), adverse events occurred in 60% (6 of 10) of subjects, and adverse events reported by ≥2 subjects were glare, visual impairment (4 subjects each), and pyrexia (2 subjects). Adverse events considered causally related to the study drug were glare in 30.0% (3 of 10) of subjects and visual impairment in 10.0% (1 of 10) of subjects, and all of them were mild in severity and resolved without treatment.

Table 12 shows an overview of adverse events in Treatment Period I and Treatment Period II of the Japanese phase II/III study (Study 012702LT). In Treatment Period I of Study 012702LT, incidences of serious adverse events and adverse events leading to treatment discontinuation were low in all groups. Any of the serious adverse events (COVID-19 in 2 subjects, inguinal hernia and humerus fracture in 1 subject each) in the 0.01% and 0.025% atropine groups were assessed as causally unrelated to the study drug. Of the adverse events leading to treatment discontinuation in Treatment Period I, photophobia in 1 subject in the 0.01% atropine group and glare, visual impairment, and photophobia in 1 subject each in the 0.025% atropine group were assessed as causally related to the study drug. Neither serious adverse events nor adverse events leading to treatment discontinuation occurred in Treatment Period II, except in the P/P group. In addition, the adverse events considered causally related to the study drug (photophobia in 1 subject in the 0.01%/0.01% group, visual impairment and pupillary disorder in 1 subject each in the P/0.025% group) were all mild or moderate in severity and resolved.

Table 12. Incidences of adverse events (Study 012702LT, safety analysis population)

	Treatment Period I			Treatment Period II						
	Placebo	Atropine 0.01%	Atropine 0.025%	P/P	P/0.01%	P/0.025%	0.01% /P	0.01% /0.01%	0.025%/ P	0.025%/ 0.025%
Number of subjects evaluated	99	99	101	43	24	21	43	40	41	44
All adverse events	73 (73.7)	81 (81.8)	84 (83.2)	23 (53.5)	14 (58.3)	11 (52.4)	30 (69.8)	22 (55.0)	21 (51.2)	25 (56.8)
Serious adverse events	3 (3.0)	1 (1.0)	3 (3.0)	1 (2.3)	0	0	0	0	0	0
Adverse events leading to treatment discontinuation	2 (2.0)	1 (1.0)	2 (2.0)	0	0	0	0	0	0	0
Adverse events considered causally related to the study drug	1 (1.0)	5 (5.1)	17 (16.8)	0	0	2 (9.5)	0	1 (2.5)	0	0
Major adverse events[a)]										
Conjunctivitis allergic	11 (11.1)	14 (14.1)	15 (14.9)	4 (9.3)	1 (4.2)	2 (9.5)	2 (4.7)	3 (7.5)	2 (4.9)	1 (2.3)
Hordeolum	8 (8.1)	10 (10.1)	7 (6.9)	1 (2.3)	0	1 (4.8)	0	1 (2.5)	0	3 (6.8)
Photophobia	2 (2.0)	4 (4.0)	11 (10.9)	0	0	0	0	1 (2.5)	0	0
Chalazion	3 (3.0)	4 (4.0)	2 (2.0)	3 (7.0)	0	0	3 (7.0)	0	0	1 (2.3)
Conjunctivitis	0	4 (4.0)	2 (2.0)	0	0	0	0	0	0	0
Dry eye	1 (1.0)	3 (3.0)	1 (1.0)	0	1 (4.2)	0	0	1 (2.5)	2 (4.9)	0
Ocular hyperaemia	0	3 (3.0)	0	0	0	0	0	0	0	0
Visual impairment	0	0	3 (3.0)	0	0	1 (4.8)	0	0	0	0
Nasopharyngitis	25 (25.3)	35 (35.4)	34 (33.7)	4 (9.3)	2 (8.3)	3 (14.3)	13 (30.2)	5 (12.5)	1 (2.4)	7 (15.9)
Eczema	5 (5.1)	10 (10.1)	4 (4.0)	1 (2.3)	1 (4.2)	0	0	1 (2.5)	0	3 (6.8)
COVID-19	7 (7.1)	8 (8.1)	5 (5.0)	9 (20.9)	3 (12.5)	2 (9.5)	5 (11.6)	6 (15.0)	10 (24.4)	10 (22.7)
Pyrexia	11 (11.1)	4 (4.0)	6 (5.9)	4 (9.3)	0	0	3 (7.0)	1 (2.5)	2 (4.9)	1 (2.3)
Seasonal allergy	8 (8.1)	8 (8.1)	7 (6.9)	0	1 (4.2)	3 (14.3)	3 (7.0)	2 (5.0)	2 (4.9)	1 (2.3)
Influenza	4 (4.0)	7 (7.1)	8 (7.9)	1 (2.3)	0	0	1 (2.3)	0	0	0
Ligament sprain	1 (1.0)	7 (7.1)	4 (4.0)	0	0	0	1 (2.3)	1 (2.5)	2 (4.9)	0
Acne	5 (5.1)	6 (6.1)	8 (7.9)	2 (4.7)	2 (8.3)	2 (9.5)	1 (2.3)	2 (5.0)	1 (2.4)	0
Headache	3 (3.0)	5 (5.1)	5 (5.0)	2 (4.7)	0	1 (4.8)	0	0	0	0
Rhinitis allergic	7 (7.1)	4 (4.0)	6 (5.9)	1 (2.3)	1 (4.2)	2 (9.5)	1 (2.3)	2 (5.0)	2 (4.9)	1 (2.3)
Sinusitis	1 (1.0)	4 (4.0)	2 (2.0)	1 (2.3)	0	0	0	0	0	0
Gastroenteritis	5 (5.1)	3 (3.0)	2 (2.0)	0	0	1 (4.8)	2 (4.7)	1 (2.5)	0	0
Skin papilloma	2 (2.0)	3 (3.0)	5 (5.0)	0	0	0	0	0	0	0
Stomatitis	1 (1.0)	3 (3.0)	5 (5.0)	1 (2.3)	0	0	1 (2.3)	0	0	0
Rhinitis	1 (1.0)	3 (3.0)	3 (3.0)	2 (4.7)	0	0	0	0	1 (2.4)	1 (2.3)
Streptococcal infection	4 (4.0)	3 (3.0)	1 (1.0)	0	0	0	0	0	0	0
Arthralgia	3 (3.0)	3 (3.0)	0	0	0	0	0	0	0	0
Varicella	1 (1.0)	3 (3.0)	0	0	0	0	0	0	0	0
Dry skin	2 (2.0)	3 (3.0)	3 (3.0)	1 (2.3)	0	1 (4.8)	1 (2.3)	0	0	0
Hand dermatitis	1 (1.0)	3 (3.0)	2 (2.0)	0	0	0	0	0	2 (4.9)	1 (2.3)
Arthropod sting	1 (1.0)	3 (3.0)	0	0	1 (4.2)	0	1 (2.3)	0	0	0
Otitis externa	0	2 (2.0)	3 (3.0)	1 (2.3)	0	0	1 (2.3)	0	0	2 (4.5)
Urticaria	2 (2.0)	2 (2.0)	4 (4.0)	1 (2.3)	1 (4.2)	0	0	0	1 (2.4)	0
Dental caries	3 (3.0)	1 (1.0)	1 (1.0)	1 (2.3)	0	0	0	1 (2.5)	0	0
Contusion	1 (1.0)	1 (1.0)	5 (5.0)	2 (4.7)	0	0	1 (2.3)	0	0	1 (2.3)
Pharyngitis	1 (1.0)	0	4 (4.0)	2 (4.7)	0	0	0	1 (2.5)	0	0

Number of subjects with event (incidence %)

a) Adverse events reported by ≥3 subjects in any group are individually listed.

Based on results in Studies 012703LT and 012702LT, the safety of atropine in patients with myopia is considered to have no major problem.

PMDA's view:

In view of the submitted clinical study data and applicant's explanation, the safety profile of atropine in patients with myopia has raised no serious concerns. Atropine has acceptable safety on the premise that appropriate cautions are provided for the events reviewed in the section below. In the section below, the events that more commonly occurred during use of the atropine ophthalmic solution than during the use of placebo and events concerned based on the pharmacological action of atropine are continuously discussed in terms of the incidence and need for precautions.

7.R.2.2 Photophobia and glare

The applicant's explanation about the risk of photophobia and glare during use of atropine:
Photophobia and glare during use of atropine are considered attributable to increased light rays entering the eye in association with mydriasis induced by atropine.

Photophobia during use of the atropine ophthalmic solution occurred in 15 subjects (4 in the 0.01% atropine group and 11 in the 0.025% atropine group) in Treatment Period I of Study 012702LT and 1 subject (the 0.01%/0.01% group) in Treatment Period II. In Study 012702LT, photophobia was mild in 15 subjects and moderate in 1 subject in severity and all resolved or were resolving without discontinuation of atropine, except for events in 3 subjects (mild in 2 subjects and moderate in 1 subject).

Glare during use of the atropine ophthalmic solution occurred in 4 subjects in Study 012703LT and 1 subject (0.025% atropine group) in Treatment Period I of study 012702LT. The events were mild in 4 subjects (Study 012703LT) and moderate in 1 subject (Treatment Period I of Study 012702LT) in severity. Although the moderate event in 1 subject led to discontinuation of the study, the other events were resolving or resolved without discontinuation of atropine.

As shown above, photophobia and glare are unlikely to hamper continued use of atropine. The risk of these events is considered manageable with cautionary advice given in the package insert, i.e., the patient developing photophobia or any other event associated with mydriatic effect after using atropine should not use play equipment with a risk of fall or engage in machine operation until the symptom resolves; patients should wear sunglasses where necessary and avoid looking directly at the sun or intense light source. To promote proper use of atropine, reference materials for healthcare professionals and patient leaflets will be prepared, in which information including the occurrence of relevant events and measures to be taken against these events will be offered.

PMDA's view:
In view of its pharmacological action, the use of atropine may cause an event associated with its mydriatic effect such as photophobia and glare. However, based on their occurrence in the clinical studies, photophobia or glare triggered by atropine is unlikely to pose a clinically serious problem. Thus, the risk of these events is considered manageable by means of, via the package insert, informing the occurrence of events and advising patients who have developed any of these events after using atropine not to engage in machine operation until the symptom resolves. Thus, the applicant's explanation has been accepted.

7.R.3 Clinical positioning and indication

The applicant's explanation about clinical positioning and indication of atropine:
Myopia is defined as a condition with objective spherical equivalent ≥−0.5 D. High myopia is considered as a risk factor of severe complications with visual impairment such as retinal detachment, myopic maculopathy, and glaucoma (*Lancet.* 2012;379:1739-48). Slowing the progression of myopia is expected to prevent a decrease in QOL and severe ocular complications with visual impairment, and

in Japan, atropine ophthalmic solutions, orthokeratology, and multifocal soft contact lens have been actually used for the purpose of slowing the progression of myopia, but none of them are approved for the indication of slowing the progression of myopia.

The foreign clinical study data and results from the meta-analysis showed that the 0.01% atropine ophthalmic solution was effective in slowing the progression of myopia and had more favorable ocular safety than 0.1% to 1% atropine ophthalmic solutions (*Ophthalmology.* 2012;119:347-54, *Am J Ophthalmol.* 2014;157:451-7, etc.). Preferred use of ophthalmic solutions containing atropine at lower concentrations than those for the other treatments is suggested (*Eye [Lond].* 2019;33:3-13).

Study 012702LT of atropine in patients with low to moderate myopia aged 5 to 15 years showed that the 0.01% and 0.025% atropine ophthalmic solutions have not only the efficacy in slowing the progression of myopia [see Section 7.R.1] but also acceptable safety without any major problems [see Section 7.R.2].

Based on the above, atropine can be a new therapeutic option for slowing the progression of myopia.

Because Study 012702LT included patients with progressive myopia aged 5 to 15 years, in whom the objective spherical equivalent under cycloplegia was −1.0 D to −6.0 D in both eyes, PMDA asked the applicant to explain whether use of atropine can be recommended for the other patient population than that in the concerned study and whether the intended indication of atropine and precautions in the package insert are appropriate.

The applicant's explanation:
In view of the following points, besides patients aged 5 to 15 years corresponding to the study population in Study 012702LT, there are other patients who need atropine, and the efficacy can be expected in these patients as well. The applicant therefore considers it almost unnecessary to limit patients eligible for atropine by age.

- Myopia is known to develop mostly at the age of approximately 6 to 8 years but actually develops at the age of 16 years or later in a certain number of individuals, and elongation of axial length is found in some patients with adolescent- or adult-onset myopia as well (*JAMA Ophthalmol.* 2022;140:162-9, *Clin Exp Optom.* 2023;106:422-6).
- Age when the progression of myopia reaches the stable state is known to be generally around mid-teens but greatly varies from individual to individual. The progression is ongoing in a certain proportion of adults (*Invest Ophthalmol Vis Sci.* 2019;60:184-203).
- In Study 012702LT, the effectiveness of atropine in preteens (aged 10-15 years) did not tend to be lower than that in early-school children (aged 5-9 years) [see Section 7.R.1].
- In Study 012702LT, patients aged <5 years were not enrolled. In a foreign clinical study of 0.01% to 0.05% atropine ophthalmic solutions, patients with myopia aged 4 years received 0.05% or 0.025% atropine ophthalmic solution, but no safety concerns were reported (*Ophthalmology.* 2024;131:1011-20).

In Japan, myopia is defined as a condition with objective spherical equivalent ≥−0.5 D (https://www.myopiasociety.jp/ member/guideline/ [last accessed on September 12, 2024]), and for myopia with objective spherical equivalent ≥−0.5 D, therapeutic interventions should be considered because myopia is a risk factor of severe complications with visual impairment such as retinal detachment, myopic maculopathy, and glaucoma (*Invest Ophthalmol Vis Sci.* 2021;62:1-5). Also, in Study 012702LT, the efficacy did not clearly differ between subgroups based on the objective spherical equivalent under cycloplegia [see Section 7.R.1]. Based on the above, the applicant considers that atropine can be recommended for patients in whom myopia has been diagnosed.

For the progression rate of myopia, Study 012702LT included patients with progressive myopia in whom the refraction examination within 1 year before screening indicated worsening of the spherical equivalent by ≥0.5 D. But the past extent of the progression of myopia would not serve as a definitive indicator of future extent of the progression; and therapeutic interventions are recommended to slow the progression of myopia that is progressing irrespective of its extent (*Eye.* 2024;38:450-4). Therefore, atropine can be recommended irrespective of the rate.

However, children are known to be at potential risk of pseudomyopia owing to ciliary muscle tonus, etc., and it is important that myopia is clearly distinguished from other eye diseases such as pseudomyopia and amblyopia. Prior to atropine treatment, the eligibility of the patient must be confirmed based on accurate diagnosis of myopia.

Based on the above, the applicant considers that the indication of atropine should be “Slowing the progression of myopia,” and the package insert should include the following precautions:

- In view of possible pseudomyopia owing to tonic accommodation, myopia must be diagnosed under appropriate cycloplegia prior to atropine treatment.
- Patients should be confirmed to have no other concomitant eye diseases such as amblyopia which need to be prioritized in treatment.

In addition, the applicant plans to implement measures for promoting proper use of atropine such as preparation of materials for healthcare professionals in cooperation with related academic societies to ensure that eligible patients are appropriately selected.

PMDA’s view:
The Japanese phase II/III study in patients with myopia (Study 012702LT) showed that the atropine ophthalmic solution has the efficacy in slowing the progression of myopia [see Section 7.R.1], and acceptable safety will be assured with appropriate precautions taken [see Section 7.R.2]. Atropine can be positioned as a therapeutic option for slowing the progression of myopia.

In light of the applicant’s explanation, the indication “slowing the progression of myopia” is of no particular problem. However, the characteristics of patients participated in Study 012702LT (age, extent of myopia, etc.) should be mentioned in the “Clinical Studies” section of the package insert, with advice that patient selection be based on the age and state of myopia of the study participants. To assure patient eligibility for atropine, the “Precautions Concerning Indication” section should provide

specific advice on diagnosis for patient selection and require further confirmation that patients have no other concomitant eye diseases such as amblyopia which need to be prioritized in treatment. Furthermore, it is important to take measures to promote proper use of atropine, including prompt preparation of guidance materials in cooperation with related academic societies for this purpose.

7.R.4 Dosage and administration

7.R.4.1 Dosage and administration of atropine

PMDA asked the applicant to explain the rationale for the dosage regimen of the atropine ophthalmic solution in the Japanese phase II/III study (Study 012702LT) and justification of the proposed dosage and administration.

The applicant's explanation:

The dosage regimen in Study 012702LT was specified as once-daily application at 1 drop per dose based on results from foreign clinical studies of atropine ophthalmic solutions at low concentrations (*Ophthalmology.* 2012;119:347-54, *Am J Ophthalmol.* 2014;157:451-7), and to reduce the effect attributable to the pharmacological action of atropine such as photophobia, application at bedtime was specified. Doses in Study 012702LT were specified as atropine concentrations of 0.01% and 0.025% in view of the following points:

- Foreign clinical studies conducted in patients with myopia to evaluate the efficacy and safety of 0.01% to 1% atropine ophthalmic solutions (*Ophthalmology.* 2006;113:2285-91, *Ophthalmology.* 2009;116:572-9, etc.) showed that atropine at the lowest concentration of 0.01% slowed the progression of myopia.
- A foreign clinical study conducted in patients with myopia to evaluate the efficacy and safety of 0.01% to 0.05% atropine ophthalmic solutions confirmed the safety of the atropine ophthalmic solutions at up to 0.05% but showed increases in incidence of photophobia and pupil size at 2 weeks of application in a concentration-dependent manner, suggesting that safety concerns would be lower at 0.025% than at 0.05% (*Ophthalmology.* 2019;126:113-24).
- In the Japanese phase I study (Study 012703LT), once-daily application of the 0.025% atropine ophthalmic solution for 12 months raised no safety problems.

Based on the following results in Study 012702LT in addition to the above, the atropine concentration for the proposed product was specified as 0.025%, and the proposed dosage and administration was specified as once-daily application at 1 drop per dose at bedtime.

- Results on a change in objective spherical equivalent under cycloplegia from baseline to Month 24, the primary endpoint, demonstrated superiority of 0.01% and 0.025% atropine over placebo, and the efficacy tended to be higher in the 0.025% atropine group than in the 0.01% atropine group [see Section 7.1.2]. Results on a change in axial length from baseline to Month 24, the secondary endpoint, showed that the elongation tended to be suppressed in an atropine-concentration dependent manner [see Section 7.R.1].
- For the change in objective spherical equivalent under cycloplegia from baseline to Month 36, a difference [95% CI] between the 0.025%/0.025% group and P/P group was 0.56 [0.04, 1.08], indicating that the results tended to be more favorable in the 0.025%/0.025% group than in the P/P

group, whereas no clear difference was observed between the 0.01%/0.01% group and P/P group [see Section 7.R.1].

- In Treatment Period I, the incidence of adverse events considered causally related to atropine was higher in the 0.025% atropine group than in the 0.01% atropine group, but all of them were mild or moderate and non-serious. Most of the subjects with adverse events considered causally related to atropine were recovering or recovered from the events after continued use of atropine. Atropine was considered to raise no major safety concerns at either concentration [see Section 7.R.2.1].
- Concerning rapid progression of myopia after cessation of atropine, a change in objective spherical equivalent under cycloplegia after switchover to placebo in Treatment Period II tended to be greater in the 0.025% atropine group than in the 0.01% atropine group, but no clinically-relevant rapid worsening of myopia was observed [see Section 7.R.4.3].

PMDA's view:
The applicant's explanation is understandable. PMDA considers it not problematic to specify the atropine concentration as 0.025% for the proposed product and the dosage and administration as "Once-daily application at 1 drop per dose at bedtime."

7.R.4.2 Duration of treatment with atropine

The applicant's explanation about duration of treatment with atropine and judgment for the necessity of continued treatment:
Published literature on atropine ophthalmic solutions at low concentrations suggest that these solutions did not slow the progression of myopia in some patients (*Ophthalmology*. 2012;119:347-54). As with the above literature, in the Japanese phase II/III study (Study 012702LT), 16.7% and 13.8% of the subjects in the 0.025% atropine group had the objective spherical equivalent under cycloplegia that was worsened from baseline to Month 12 by ≥−1.0 D and from baseline to Month 24 by ≥−2.0 D, respectively; some patient did not respond to atropine. Therefore, the following will be advised: After starting treatment with atropine, periodic examination should be performed to monitor the progression of myopia; and the treatment should not be aimlessly prolonged for patients not responding to atropine.

Concerning continued treatment for slowing the progression of myopia, an increase of 1.0 D in myopia leads to an exponential increase of a risk of ocular complications, and thus to reduce the risk of future ocular complications, the treatment for slowing the progression of myopia should be continued until the progression stabilizes (*Journal of the Eye.* 2023;40:141-9). Atropine is expected to slow the progression of myopia and thus cannot be expected to be effective in patients with stabilized myopia. In this view, whether the progression of myopia has been stabilized is considered as one of the criteria for necessity of continued treatment with atropine. However, while the progression of myopia has been reported to stabilize generally in mid-teens, it greatly varies individually and in some cases, myopia progressed even in patients in their 20s (*Invest Ophthalmol Vis Sci.* 2019;60:M184-203). The applicant thus considers it difficult to specify time of cessation of atropine by age or duration of treatment. After starting the treatment with atropine, myopia progression should be evaluated periodically, and whether to continue the treatment should be individually judged. For this purpose, guidance materials for healthcare professionals will be prepared in cooperation with related academic

societies to provide reference information, so that physicians can make appropriate decisions about when to terminate atropine.

PMDA's view:
The applicant's explanation is understandable. The following should be advised: after the start of atropine, myopia progression should be evaluated periodically; for those who are not responding to atropine, the treatment should not be prolonged aimlessly.

In terms of the provision of reference information that helps physicians make a right decision on when to terminate atropine, it is important to prepare guidance materials promptly in cooperation with related academic societies and provide in an appropriate manner.

7.R.4.3 Progression of myopia in response to cessation of atropine

Cessation of treatment with an atropine ophthalmic solution led to rapid progression of myopia that was faster than the natural course (without treatment) or progression observed during the treatment (*Ophthalmology.* 2006;113:2285-91, *Ophthalmology.* 2009;116:572-9). In the Japanese phase II/III study (Study 012702LT), slopes of changes from baseline in objective spherical equivalent under cycloplegia at and after Month 24 indicated a particularly worsening trend in the 0.025%/P group compared with the other groups (Figure 2). PMDA asked the applicant to explain the possibility of rapid progression of myopia after cessation of atropine and the possibility of the concerned phenomenon becoming a clinically relevant problem.

The applicant's explanation:
The possibility of rapid progression of myopia after cessation of the treatment for myopia should be observed for at least 12 months after cessation of the treatment (*Invest Ophthalmol Vis Sci.* 2019;60:M132-60) and such possibility was investigated based on changes in objective spherical equivalent and axial length at Month 36, 12 months after cessation of atropine in Study 012702LT.

Table 13 shows changes in objective spherical equivalent under cycloplegia and axial length from Month 24 to Month 36 in Study 012702LT. The changes tended to be greater in the groups with cessation of the atropine ophthalmic solution at Month 24 (0.01%/P group and 0.025%/P group) than in the P/P group. Proportions of subjects with the objective spherical equivalent under cycloplegia worsened by ≥1.0 D from Month 24 to Month 36 were 14.6% (6 of 41 subjects) in the P/P group, 14.6% (6 of 41 subjects) in the 0.01%/P group, and 25.0% (10 of 40 subjects) in the 0.025%/P group; the proportion in the 0.025%/P group tended to be greater than those in the other groups.

Table 13. Changes in objective spherical equivalent under cycloplegia and axial length from Month 24 to Month 36
(Study 012702LT, Treatment Period II, FAS)

Treatment group	No. of subjects evaluated	Change from Month 24 to Month 36	
		Objective spherical equivalent under cycloplegia (D)[a)]	Axial length (mm)[a)]
P/P	41	-0.42 ± 0.48	0.22 ± 0.16
0.01%/P	41	-0.60 ± 0.42	0.30 ± 0.16
0.025%/P	40	-0.74 ± 0.44	0.32 ± 0.26

a) Mean ± SD

The progression of myopia immediately after switchover from atropine to placebo tended to be faster in patients with higher spherical equivalent at baseline when atropine was used for slowing the progression of myopia (*Front Pharmacol.* 2024;15:1343698), and potential effects of the spherical equivalent and axial length just after cessation of atropine (just before switchover to placebo) on the progression rate of myopia after cessation of atropine cannot be ruled out. To compare changes in objective spherical equivalent or axial length in the 0.01%/P group and 0.025%/P group with that in the P/P group with such effects eliminated, the following procedure was applied: Firstly, the timepoint when the change from baseline in the P/P group approximated that from baseline to Month 24 in the 0.01%/P group or 0.025%/P group was identified as the base point; and then the change from Month 24 to Month 36 in the 0.01%/P group or 0.025%/P group was compared with that from the base point to 12 months later in the P/P group. The time points (base points) when the change in objective spherical equivalent from baseline in the P/P group approximated those from baseline to Month 24 in the 0.01%/P group and 0.025%/P group were identified as Months 16 and 12, respectively. The time points (base points) when the change in axial length from baseline in the P/P group approximated those from baseline to Month 24 in the 0.01%/P group and 0.025%/P group were identified as Months 20 and 16, respectively. The changes from these base points to 12 months later are shown in Table 14. The changes from the base point to 12 months later in the 0.01%/P group and 0.025%/P group were not greatly different from those in the P/P group, and no rapid worsening trend was observed.

Table 14. Changes in objective spherical equivalent and axial length from the base point to 12 months later
(Study 012702LT)

Treatment group	Objective spherical equivalent under cycloplegia			Axial length		
	Time of evaluation (Month)		Change in objective spherical equivalent under cycloplegia (D)[b)]	Time of evaluation (Month)		Change in axial length (mm)[b)]
	Base point[a)]	12 months after base point		Base point[a)]	12 months after base point	
0.01%/P	24	36	-0.60 ± 0.42	24	36	0.30 ± 0.16
P/P	16	28	-0.55 ± 0.42	20	32	0.26 ± 0.20
0.025%/P	24	36	-0.74 ± 0.44	24	36	0.32 ± 0.26
P/P	12	24	-0.68 ± 0.40	16	28	0.28 ± 0.17

a) Month 24 for the 0.01%/P group and 0.025%/P group. For the P/P group, timepoint when the change in objective spherical equivalent from baseline approximated that from baseline to Month 24 in the 0.01% atropine/P group or 0.025% atropine/P group.
b) Mean ± SD

The change in objective spherical equivalent from baseline to Month 36 (mean ± SD) was −2.04 ± 1.27 D in the P/P group, −1.79 ± 0.91 D in the 0.01%/P group, and −1.71 ± 1.10 D in the 0.025%/P group, and the change in axial length from baseline to Month 36 (mean ± SD) was 0.96 ± 0.52 mm in the P/P group, 0.89 ± 0.41 mm in the 0.01%/P group, and 0.83 ± 0.49 mm in the 0.025%/P group. The changes in the groups with cessation of atropine at Month 24 (0.01%/P group and 0.025%/P group)

were smaller than that in the placebo only group (P/P group), showing no worsening trend of myopia in comparison with the placebo only group.

As presented above, changes in objective spherical equivalent under cycloplegia and axial length from Month 24 to Month 36 in Study 012702LT showed that an extent of the progression of myopia in the groups with cessation of atropine at Month 24 (0.01%/P group and 0.025%/P group) tended to be greater than that in the P/P group, but at least no such rapid worsening of myopia that exceeded the progression rate in treatment-naive patients (P/P group) was observed at 12 months after cessation of atropine. The progression of myopia after cessation of atropine is considered unlikely to become a clinically relevant problem.

PMDA's view:
In Study 012702LT, the changes in objective spherical equivalent under cycloplegia and axial length from Month 24 to Month 36 tended to be greater in the groups with cessation of the atropine ophthalmic solution at Month 24 than in the placebo only group in a concentration-dependent manner. In view of this finding, the possibility of rapid progression of myopia after cessation of atropine cannot be ruled out. The applicant compared the changes in objective spherical equivalent under cycloplegia and axial length from the base point to 12 months later in the 0.01%/P group and 0.025%/P group with those in the P/P group (Table 14). However, the progression of myopia is reported to be faster in younger age (*Invest Ophthalmol Vis Sci.* 2023;64:7), and in view of the base point in the P/P group which came earlier than that in the atropine group, such comparison is not considered appropriate for evaluation of an extent of the progression of myopia after cessation of the atropine ophthalmic solution. On the other hand, the changes in objective spherical equivalent from baseline to Month 36 (12 months after cessation) in the groups with cessation of the atropine ophthalmic solution at Month 24 does not tend to be greater than those in the placebo only group (P/P group), and thus a risk of the progression of myopia faster than the natural course is not suggested at least within 12 months after cessation of the atropine ophthalmic solution. The progression of myopia after cessation of atropine is considered unlikely to become a clinically relevant problem.

In conclusion, healthcare professionals should be informed of possible rapid progression of myopia after cessation of atropine via guidance materials.

7.R.5 Post-marketing investigations

The safety profile of atropine in Japanese patients has been proven in extensive clinical experience with approved ophthalmic ointments and ophthalmic solutions containing a higher concentration of atropine than the drug product. The results from the Japanese phase I and Japanese phase II/III studies raised no concerns to be addressed in the clinical setting. For these reasons, the applicant currently intends to conduct early post-marketing phase vigilance and routine pharmacovigilance activities on Ryjusea Mini, but no post-marketing surveillance.

PMDA's view:
Based on review results in Sections 7.R.1, 7.R.2, and the applicant's explanation, there are no concerns to be addressed for the post-marketing use of Ryjusea Mini in patients with myopia, and

post-marketing surveillance myopia have to be conducted in this population immediately after approval where early post-marketing phase vigilance and routine pharmacovigilance activities will be underway, and information provision to healthcare professionals about adverse events of special interest in use of the drug product, collection of safety information of the drug product, and practice of proper safety measures based on current and future information are ensured by these activities. However, if any new issue to be addressed arises in the post-marketing use of the drug product, the applicant should promptly discuss the implementation of post-marketing surveillance as additional pharmacovigilance activities.

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 5.3.5.1-1) 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 atropine has efficacy in slowing the progression of myopia, and that atropine has acceptable safety in view of its benefits. Atropine offers a new therapeutic option for slowing the progression of myopia and thus is clinically meaningful. PMDA considers that the indication, dosage and administration, and post-marketing investigations should be further discussed at the Expert Discussion.

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

Review Report (2)

November 8, 2024

Product Submitted for Approval

Brand Name	Ryjusea Mini Ophthalmic Solution 0.025%
Non-proprietary Name	Atropine Sulfate Hydrate
Applicant	Santen Pharmaceutical Co., Ltd.
Date of Application	February 28, 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 review in Section "7.R.1 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of atropine in slowing the progression of myopia was demonstrated.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

In view of the review in Section "7.R.2 Safety" of the Review Report (1), use of atropine requires attention particularly to the events associated with its mydriatic effect such as photophobia. PMDA, however, has concluded that atropine has acceptable safety where appropriate caution is advised on such events beforehand.

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA and made the following comments:

- It is desirable that healthcare professionals be provided with specific measures against photophobia or other events associated with the mydriatic effect of atropine occurred.

In this view, PMDA instructed the applicant to appropriately provide the measures against photophobia and other potential events associated with the mydriatic effect of atropine, in not only the

package insert but also reference materials for healthcare professionals and patient leaflets. The applicant appropriately responded.

1.3 Clinical positioning and indication

PMDA's conclusions:

In view of the review in Section "7.R.3 Clinical positioning and indication" of the Review Report (1), atropine can be positioned as a therapeutic option for slowing the progression of myopia.

While the indication of atropine, "slowing the progression of myopia," is of no particular problem, the characteristics of patients participated in Study 012702LT (age, extent of myopia, etc.) should be mentioned in the "Clinical Studies" section of the package insert, with advice in the "Precautions Concerning Indication" section that patient selection be based on the age and state of myopia of the study participants. To assure patient eligibility, physicians should be provided with proper advice on diagnosis for patient selection and reminded that selected patients must not have other concomitant eye diseases such as amblyopia which need to be prioritized in treatment. It is important, as proposed by the applicant, to take measures to promote proper use of atropine in cooperation with related academic societies so as to assure appropriate selection of patients eligible for atropine.

The expert advisors supported the above conclusion of PMDA at the Expert Discussion, and made the following comments:

- To appropriately select patients in need of atropine treatment, it is important that the measures to promote proper use be presented in the clinical practice guidelines, etc. in cooperation with related academic societies.
- From the viewpoints of appropriate myopia management and proper use of atropine, healthcare professionals need to understand clearly that atropine is intended to slow the progression of myopia but not to improve myopia, and that treated patients will remain dependent on glasses or other visual correction in daily living.

In these views, PMDA instructed the applicant to offer the following advice in the "Precautions Concerning Indication" section. The applicant responded appropriately.

Precautions Concerning Indication

- Atropine should be administered to patients with myopia confirmed under appropriate cycloplegia (pseudomyopia may occur owing to tonic accommodation). It must be ensured that the patient does not have amblyopia or other concomitant eye diseases which need to be prioritized in treatment.
- Eligible patients must be selected by physicians with a full understanding of the knowledge presented in the "Clinical Studies" section and the characteristics of the patients enrolled in the clinical study (age, state of myopia, etc.).

1.4 Dosage and administration

1.4.1 Dosage and administration of atropine

In view of the review in Section "7.R.4.1 Dosage and administration of atropine" of the Review Report (1), PMDA has concluded that there is no problem in specifying the atropine concentration as 0.025%, and the dosage regimen as "once-daily application at 1 drop per dose at bedtime."

The expert advisors supported PMDA's conclusion above at the Expert Discussion.

1.4.2 Duration of treatment with atropine

PMDA's conclusions:

As discussed in Section "7.R.4.2 Duration of treatment with atropine" of the Review Report (1), healthcare professionals should be advised to perform periodic examination to monitor the progression of myopia; and the treatment should not be prolonged aimlessly for patients not responding to atropine. The reference information that helps physicians make a right decision on when to terminate atropine, which were proposed by the applicant, should be offered in a proper manner in cooperation with related academic societies.

The expert advisors supported above conclusions of PMDA at the Expert Discussion. PMDA instructed the applicant to offer the following advice in the "Precautions Concerning Dosage and Administration" section. The applicant responded appropriately.

Precautions Concerning Dosage and Administration

Myopia progression should be evaluated periodically. The treatment should not be prolonged aimlessly for those not responding to atropine.

1.4.3 Progression of myopia in response to cessation of atropine

PMDA's conclusion:

Based on the discussion in Section "7.R.4.3 Progression of myopia in response to cessation of atropine" of the Review Report (1), myopia progression after cessation of atropine is unlikely to become a major clinical concern. Possible rapid progression of myopia after cessation of atropine should be cautioned in the guidance materials.

The expert advisors supported above conclusion of PMDA at the Expert Discussion, and made the following comments:

- Possible rapid progression of myopia after cessation of atropine should be informed through the guidance materials. Healthcare professionals should be advised to continue periodic refraction test or axial length measurement even after the completion of atropine treatment.

Accordingly, PMDA instructed the applicant to caution via the guidance materials that atropine may cause rapid progression of myopia, and that periodic refraction test or axial length measurement be continued even after the completion of atropine treatment. The applicant responded appropriately.

1.5 Risk management plan (draft)

PMDA's conclusion:

Based on the review in Section "7.R.5 Post-marketing investigations" of the Review Report (1), post-marketing surveillance in patients with myopia will not have to be conducted immediately after approval where early post-marketing phase vigilance and routine pharmacovigilance activities will be underway, which will ensure the provision of information about atropine-associated adverse events of special interest, collection of safety information of the drug product, and practice of proper safety measures based on current and future information. However, if any new issue to be addressed arises in the post-marketing use of atropine, the applicant should promptly discuss the implementation of post-marketing surveillance as additional pharmacovigilance activity.

The expert advisors supported the above conclusion of PMDA at the Expert Discussion. PMDA has concluded that the risk management plan (draft) for atropine should include additional pharmacovigilance activities and risk minimization activities presented in Table 15, and that the applicant should conduct these activities.

Table 15. Summary of additional pharmacovigilance activities and additional risk minimization activities

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Dissemination of information through early post-marketing phase vigilance

2. Overall Evaluation

PMDA's conclusion:

As a result of the above review, the product may be approved for the indication and the dosage and administration below, with the following condition. The present application is for the new indication and the new dosage form, and the re-examination period for the indication of the present application is 4 years. The drug product is not classified as a biological product or a specified biological product, and is classified as a powerful drug.

Indication

Slowing the progression of myopia

Dosage and Administration

The usual dosage is 1 drop of the ophthalmic solution applied once daily at bedtime.

Approval Conditions

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

Appendix

List of Abbreviations

0.01%/0.01% group	Group of patients who were treated with 0.01% atropine ophthalmic solution in Treatment Period I, followed by 0.01% atropine ophthalmic solution in Treatment Period II of Study 012702LT
0.01%/P group	Group of patients who were treated with 0.01% atropine ophthalmic solution in Treatment Period I, followed by placebo ophthalmic solution in Treatment Period II of Study 012702LT
0.025%/0.025% group	Group of patients who were treated with 0.025% atropine ophthalmic solution in Treatment Period I, followed by 0.025% atropine ophthalmic solution in Treatment Period II of Study 012702LT
0.025%/P group	Group of patients who were treated with 0.025% atropine ophthalmic solution in Treatment Period I, followed by placebo ophthalmic solution in Treatment Period II of Study 012702LT
Atropine	Atropine Sulfate Hydrate
$AUC_{0\text{-}60min}$	Area under the plasma concentration-time curve zero to 60 minutes
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve zero to 24 hours
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve zero to infinity
CI	Confidence interval
C_{max}	Maximum concentration
CTD	Common technical document
CQA	Critical quality attribute
FAS	Full analysis set
HEK293 cells	Human embryonic kidney cells 293
HPLC	High performance liquid chromatography
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3B guideline	"Revision of Guideline on Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001 dated June 24, 2003)
IC_{50}	50% inhibitory concentration
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLC-PK1 cells	Lewis lung cancer porcine kidney 1 epithelial cells
LOCF	Last observation carried forward
MATE	Multidrug and toxin extrusion protein
MF	Master file
MMRM	Mixed effects model for repeated measures
OC	Observed case
OCT	Organic cation transporter
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
P/P group	Group of patients who were treated with placebo ophthalmic solution in Treatment Period I, followed by placebo ophthalmic solution in Treatment Period II of Study 012702LT
P/0.01% group	Group of patients who were treated with placebo ophthalmic solution in Treatment Period I, followed by 0.01% atropine ophthalmic solution in Treatment Period II of Study 012702LT
P/0.025% group	Group of patients who were treated with placebo ophthalmic solution in Treatment Period I, followed by 0.025% atropine ophthalmic solution in Treatment Period II of Study 012702LT
(Q)SAR	(Quantitative) structure-activity relationship
QOL	Quality of life
t_{max}	Time to reach maximum concentration
$t_{1/2}$	Elimination half-life
Ryjusea Mini	Ryjusea Mini ophthalmic solution 0.025%