AMERICAN ACADEMY OF OPHTHALMOLOGY®

Efficacy and Safety of Low-Concentration Atropine in Slowing Myopia Progression in Children in Japan: The Randomized, Double-Blind Phase II/III ORANGE Study

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Purpose: To evaluate the efficacy and safety of low-concentration atropine ophthalmic solution for slowing disease progression in children with myopia and assessing rebound phenomenon after treatment cessation.

Design: A randomized, double-masked, placebo-controlled, phase II/III clinical trial in Japan.

Subjects: Children (n = 299) aged 5–15 years with cycloplegic objective spherical equivalent (SE) −1.0 to −6.0 diopters (D) in both eyes.

Methods: Subjects were randomized to atropine 0.01%, 0.025%, or placebo (1 drop once daily before bedtime in both eyes) for 24 months before receiving atropine 0.01%, 0.025%, or placebo for a further 12 months.

Main Outcome Measures: The primary endpoint was mean SE change from baseline at month 24; axial length (AL) change was a secondary endpoint. Safety evaluations included ocular adverse drug reactions (ADRs).

Results: Mean SE change from baseline at month 24 with atropine 0.01%, 0.025%, and placebo was −1.31 (standard deviation [SD]) 0.71), −1.02 (SD 0.86), and −1.65 (SD 0.90) D, respectively; least squares (LS) mean (standard error) differences versus placebo were 0.34 (0.08) D and 0.65 (0.08) D (both $P < 0.0001$). Mean (SD) AL change from baseline at month 24 with atropine 0.01%, 0.025%, and placebo was 0.64 (0.31), 0.51 (0.36), and 0.74 (0.36) mm, respectively; corresponding LS mean (standard error) treatment differences versus placebo were −0.11 (0.03) mm ($P < 0.05$) and −0.23 (0.03) mm ($P < 0.0001$). After a switch to placebo from atropine 0.01%, 0.025%, or placebo, LS mean (standard error) SE change from month 24 to month 36 was −0.61 (0.07), −0.75 (0.07), and −0.40 (0.07) D, respectively, which suggested a small, concentration-dependent myopia progression "rebound" effect, which was not considered to be clinically meaningful. Least squares mean (standard error) AL change from month 24 to month 36 was 0.30 (0.03), 0.32 (0.03), and 0.21 (0.03) mm, respectively. The most common ocular ADR over 24 months was photophobia, mostly mild, occurring in 1.0%–10.9% of children receiving atropine 0.01%, 0.025%, or placebo.

Conclusions: Atropine 0.01% and 0.025% slowed myopia progression in children. There was a small, not clinically meaningful, rebound in myopia progression after the cessation of atropine treatment. Both concentrations were well tolerated.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2026;6:100960*

Supplemental material available at www.ophthalmologyscience.org.

The prevalence of myopia, which is commonly caused by excessive axial length (AL) elongation,[1] has increased markedly in recent years among both adults and children and is expected to affect around 4.8 billion people by 2050.[2]

The global rise in myopia is particularly evident in East and Southeast Asia, where 80%–90% of school leavers (15–16 years of age) are affected. A study of children at 2 schools in Japan found myopia was present in 76.5% of those aged 6–11 years and 94.9% of those aged 12–14 years, suggesting a high prevalence of myopia among Japanese schoolchildren in general.[3] It is speculated that this rise in prevalence may be driven by an increase in near-work activities and a decrease in time spent outdoors.[4,5]

The increasing prevalence of myopia represents not only a growing public health challenge but also an economic problem worldwide, particularly in Southeast Asia, South Asia, and East Asia, where the loss in productivity associated with myopia-related visual impairment is reported to be over twice that in any other region.[6]

Myopia is a progressive condition. High myopia (myopia in which the spherical equivalent [SE] refractive error is less than or equal to −6.00 diopters [D] when ocular accommodation is relaxed[7]) is associated with increased

https://doi.org/10.1016/j.xops.2025.100960
ISSN 2666-9145/25

risk of visual impairment caused by complications such as retinal detachment, myopic maculopathy, and glaucoma.[8]

The development of myopia at an early age (or a longer duration of progression) is a key predictor of high myopia in later childhood and adulthood.[9,10] Slowing the progression of myopia in children is key to preventing the development of high myopia and associated ocular morbidity and typically involves lifestyle changes and optical or pharmacological interventions.[11]

Based on its inhibition of SE growth and axial elongation, the potential use of atropine in slowing myopia progression in children has been widely studied. In early studies assessing atropine 1% in myopia, the frequency and severity of ocular adverse events (AEs) such as mydriasis, photophobia, and the loss of near vision were considered clinically unacceptable[12–15]; rebound after the cessation of treatment with atropine 1% has been previously reported.[16] However, data from subsequent trials in children from Asia have indicated favorable efficacy and safety of atropine eye drops at concentrations <1% for controlling myopia progression.[17–19]

In the Atropine for the Treatment of Myopia 2 study conducted in children in Singapore, significantly larger differences in SE progression and increases in AL were observed with atropine 0.01% compared with 0.1% and 0.5% after 2 years' treatment. However, the absolute differences between groups were clinically small, with an improved safety profile observed with 0.01% compared with the higher concentrations.[17] After treatment cessation at 2 years, atropine 0.01% was associated with the smallest increase in SE progression and AL at 3 years.[20] Although the absence of a control group limits direct efficacy comparison, the observed results with atropine at lower concentrations are promising. The Low-Concentration Atropine for Myopia Progression (LAMP) study of atropine 0.01%, 0.025%, and 0.05% in children showed a concentration-dependent slowing of myopia progression at 2 years.[21] Although all concentrations were well tolerated over 2 years, pupil-size increase was concentration-dependent, and the rate of photophobia was lowest with atropine 0.025%.[21] In an extension of the LAMP study, after treatment cessation at 2 years, SE progression and axial elongation at 3 years were also greater in the higher concentration groups.[22]

Despite these studies, the optimal concentration of atropine that balances efficacy and safety remains unclear, and further research is required to establish this in different patient populations.[23]

Further, in Japan, there are currently no therapies approved to slow the progression of myopia, and physicians are reliant on imported, unapproved preparations or locally prepared, diluted formulations of atropine 1% ophthalmic solution.[24] Reports suggest that locally prepared atropine solutions contain inconsistent formulations with a wide variety of labeling practices for compounding 0.01% atropine.[25] Thus, the development of a novel, aqueous, preservative-free, validated low-concentration atropine ophthalmic solution was initiated for approval by the Pharmaceuticals and Medical Devices Agency in Japan.

The phase II, placebo-controlled, double-masked APPLE study assessed the novel atropine solution, which was developed with the same formulation that was used in the ORANGE study, at concentrations of 0.0025%, 0.005%, and 0.01% in children with mild-to-moderate myopia. The study demonstrated that 12 months of treatment with concentrations of 0.005% and 0.01% were significantly more effective than placebo in inhibiting myopia progression. All 3 concentrations were well tolerated. The study demonstrated that even at very low concentrations, atropine showed dose-related effects, leading to the postulation that children who do not respond to 1 particular dose may respond to a higher dose.[24]

In this randomized, placebo-controlled ORANGE study conducted in Japan, we aimed to determine the optimal clinical concentration for the inhibition of myopia progression in children and evaluate the efficacy and safety of higher concentrations of the novel atropine solution (0.01% and 0.025%). Any potential rebound phenomenon after treatment cessation was also assessed.

Methods

Study Design

The ORANGE study was a phase II/III, randomized, double-masked, parallel-group study conducted at 34 sites in Japan from August 1, 2019, to August 21, 2023. A list of all study investigators is detailed in Supplementary Appendix 1 (available at www.ophthalmologyscience.org). This study was registered at the Japan Registry of Clinical Trials (jRCT2080224816; https://jrct.niph.go.jp/en-latest-detail/jRCT2080224816).

The study protocol was approved by the institutional review board at each study site, and written informed consent for participation in the study was obtained from the participants and their legal guardians. The study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

Subjects

Eligible subjects were children aged 5 to 15 years with a cycloplegic objective SE between −1.0 and −6.0 D in both eyes and with myopia progression of at least −0.5 D SE in both eyes in the year prior to visit 1. Children who had previously used contact lenses and/or drugs to prevent myopia progression, had a history of eye disease (other than myopia) that could affect data interpretation, had a systemic disease that could impact vision or refraction, or had an atropine allergy were excluded from the study.

Interventions

After a 1–14-day observational period, eligible subjects were stratified by age group (5–7, 8–9, 10–11, and 12–15 years) and randomized using a Randomization and Trial Supply Management system facilitated by an investigational drug allocation manager (EPS Corporation) 1:1:1 to atropine 0.01%, atropine 0.025%, or placebo ophthalmic solution for 24 months (treatment period 1; Fig S1, available at www.ophthalmologyscience.org). Neither the study subjects nor the investigators responsible for measuring the study outcomes were aware of the treatments given. The study medication was a sterile, aqueous, preservative-free ophthalmic solution, and each subject received 1 drop once daily in each eye, before bedtime. The study dosage was informed by the efficacy and safety results of the APPLE

study, in which the same atropine formulation but at concentrations of 0.0025%, 0.005%, or 0.01% ophthalmic solution, was administered once daily, at night.[24] The eye drops were administered before bedtime to minimize any photophobia that could be caused by the active ingredient.

After 24 months of treatment (treatment period 1), subjects then received an additional 12 months of treatment (treatment period 2) (Fig S1). Subjects who were initially randomized to atropine 0.01% then received either atropine 0.01% or placebo, whereas those initially randomized to atropine 0.025% then received either atropine 0.025% or placebo. Those who were initially randomized to placebo then received atropine 0.01%, atropine 0.025%, or continued on placebo (Fig S1). Allocation into the initial treatment groups and subsequent switch at month 24 were determined at baseline.

Ophthalmic examinations were conducted at study screening, baseline (randomization), and each visit (4-month intervals) until study end (month 36) or at the time of discontinuation of atropine, whichever was earliest. Study assessments are detailed in Supplementary Appendix 2 (available at www.ophthalmologyscience.org). Adverse events and adverse drug reactions (ADRs; AEs assessed as treatment-related by the study investigator) were monitored throughout the study.

Compliance with the study drug was recorded in a patient diary that was completed by the patient. The patient diary was checked at each hospital visit.

Endpoints

The primary efficacy endpoint was the change from baseline SE at month 24. The secondary efficacy endpoints included changes from baseline SE at months 12 and 36, changes from baseline AL at months 24 and 36, and the proportions of subjects whose SE progressed from baseline by at least −0.5, −0.75, or −1.0 D at month 24. Safety endpoints were the incidence of ADRs based on clinical laboratory data and ophthalmic examinations.

Statistical Analyses

The efficacy analyses were evaluated in the full analysis set, which included subjects who received ≥1 dose of atropine or placebo. A target sample size of 288 subjects (96 subjects in each group) was identified as sufficient to verify the superiority of atropine 0.01% and atropine 0.025% over placebo in SE from 85 subjects per group, on the assumption that 10% of subjects would discontinue the study. Furthermore, this sample size would allow the detection of significant differences between atropine and placebo for the secondary endpoints of change from baseline SE at month 12 and the proportion of subjects with SE progression from baseline of at least −0.5 D at month 24.

The primary endpoint was evaluated by pairwise comparison in a mixed-effects model for repeated measures (MMRM) with baseline SE as the covariate. Change from baseline SE at month 12 and baseline AL at month 24 was also evaluated in an MMRM. An analysis of covariance was used for the statistical analysis of secondary endpoints, including the changes from baseline and month 24 in SE and AL at month 36. The significance level of statistical testing was set at a 2-sided 5%, and the confidence coefficient of the interval estimate was set at a 2-sided 95%. The proportions of subjects whose SE progressed by ≥0.5, 0.75, or 1.0 D from baseline at month 24 were compared by treatment group using Fisher exact method.

Statistical testing of the primary and secondary endpoints was conducted using a fixed sequence method to adjust for the multiplicity between the 0.01% and 0.025% concentrations and between multiple secondary endpoints to control the overall type 1 error rate. For the primary endpoint, the first comparison was made between atropine 0.025% and placebo, and then, if statistical significance was observed, between atropine 0.01% and placebo. The secondary endpoints were only tested if the primary endpoint showed a statistically significant difference for both concentrations (0.01% and 0.025%) versus placebo. This fixed sequence method was applied to the following endpoints: progression of patients showing SE progression of ≥0.5 D at month 24 and change from baseline in SE at month 12. If a statistically significant difference of the primary endpoint was detected for only 1 concentration, then the fixed sequence testing of the secondary endpoints was only conducted for that concentration. The safety analysis set comprised subjects who received ≥1 dose of atropine or placebo and who had any safety data recorded. The numbers of subjects with AEs and ADRs during the treatment periods were tabulated to demonstrate the occurrence and incidence of each event by treatment group.

Results

Subject Disposition, Baseline Characteristics, and Treatment

A total of 347 subjects were enrolled in the ORANGE study. Of these, 299 met the study eligibility criteria and were randomized to treatment with atropine 0.01% (n = 99), atropine 0.025% (n = 101), or placebo (n = 99) (Fig 1). Subject characteristics were similar across treatment groups (Table 1). Overall, mean age was 9.4 (standard deviation [SD] 1.88) years, and 59.5% of subjects were female. All subjects were Asian and had a mean cycloplegic SE of −3.08 (SD 1.10) D and AL of 24.6 (SD 0.80) mm.

A total of 244 subjects (81.6%) completed 24 months of treatment (treatment period 1) and 240 subjects (80.3%) completed an additional 12 months of treatment (treatment period 2). Treatment compliance during the first 24 months of the study (treatment period 1) was 96.1% (atropine 0.01%), 95.1% (atropine 0.025%), and 96.5% (placebo). Between months 24 and 36, compliance was 95.1% (continued on atropine 0.01%), 97.3% (continued on atropine 0.025%), and 97.1% (continued on placebo). For subjects switched from atropine 0.01% or 0.025% to placebo, compliance was 97.1% and 95.7%, respectively. For those who switched from placebo to atropine 0.01% or 0.025%, compliance was 94.2% and 97.6%, respectively.

Efficacy

Changes in SE at Months 24 and 12. Mean (SD) change from baseline SE at month 24 in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively, was −1.31 (0.71), −1.02 (0.86), and −1.65 (0.90) D (Fig 2). The least squares (LS) mean (± standard error) treatment differences in MMRM analysis of the change from baseline SE at month 24 for atropine 0.01% and 0.025% versus placebo were 0.34 (±0.09) and 0.64 (±0.09) D (both $P < 0.0001$), respectively.

Mean change from baseline SE at month 12 in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively, was −0.66 (SD 0.47), −0.44 (SD 0.53), and

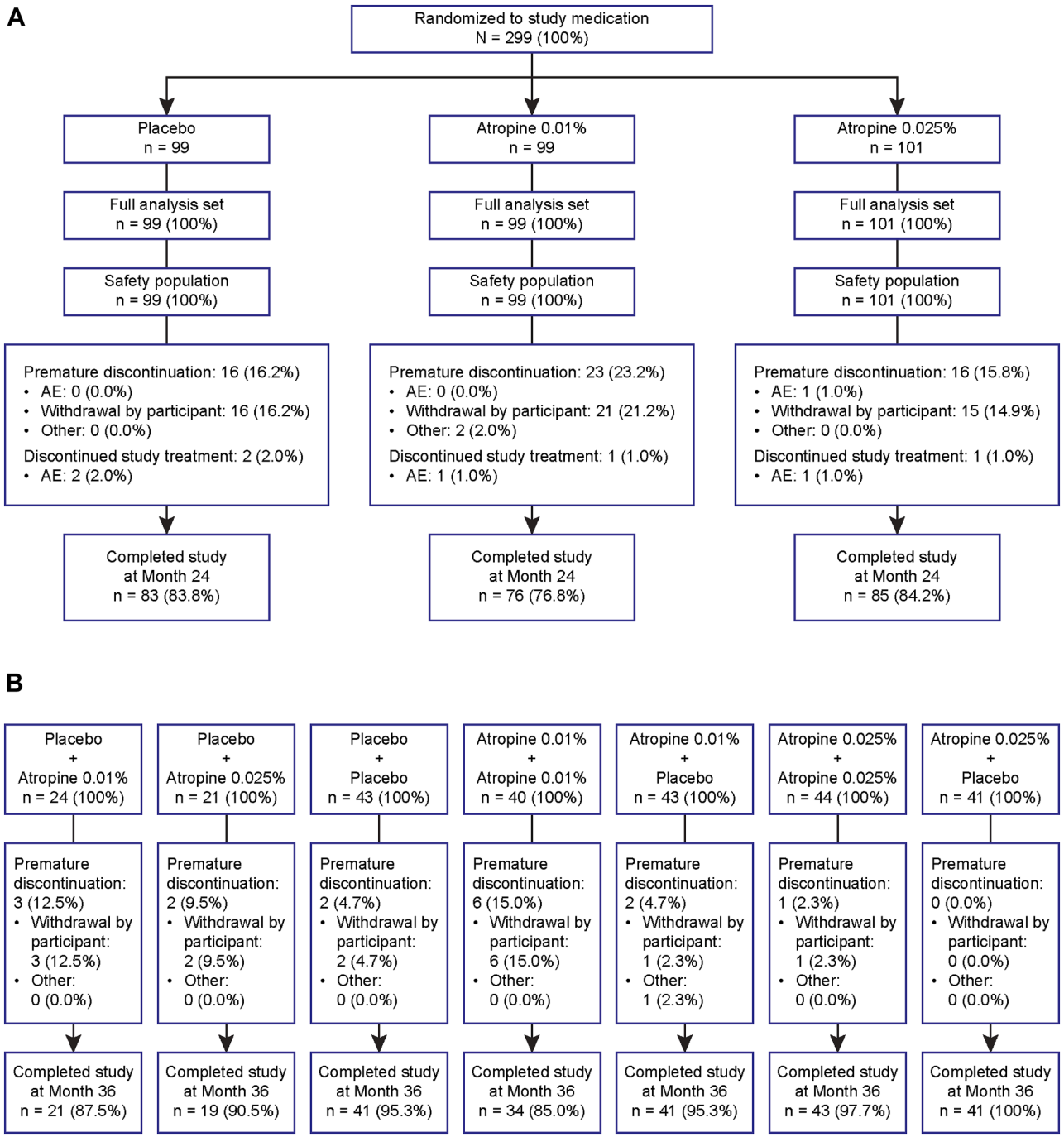

Figure 1. Subject disposition in (**A**) treatment period 1 and (**B**) treatment period 2. Flowchart of subjects enrolled in treatment period 1 and treatment period 2. AE = adverse event.

−0.95 (SD 0.59) D (Fig 2). Based on the MMRM analysis, the LS mean (± standard error) treatment differences in the change in SE at month 12 for atropine 0.01% and 0.025% versus placebo were 0.29 (±0.08) D ($P = 0.0006$) and 0.52 (±0.08) D ($P < 0.0001$), respectively.

Changes in AL at Month 24. Mean change from baseline AL at month 24 in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively, was 0.64 (SD 0.31), 0.51 (SD 0.36), and 0.74 (SD 0.36) mm (Fig 3). Based on the MMRM analysis, the LS mean (± standard error) treatment differences in the change in AL at month 24 for atropine 0.01% and 0.025% versus placebo were −0.11 (±0.03) mm ($P < 0.05$) and −0.23 (±0.03) mm ($P < 0.0001$), respectively.

SE Progression at Month 24. Spherical equivalent worsened from baseline at month 24 in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively, by ≥0.5 D in 82.6%, 70.1%, and 91.4% of subjects (difference [95%

Table 1. Baseline Characteristics

Characteristic	Placebo (n = 99)	Atropine 0.01% (n = 99)	Atropine 0.025% (n = 101)	Overall (N = 299)
Age, yrs	9.5 (1.9)	9.4 (1.9)	9.4 (1.9)	9.4 (1.9)
Female, n (%)	61 (61.6)	54 (54.5)	63 (62.4)	178 (59.5)
Race, n (%)				
Asian	99 (100)	99 (100)	101 (100)	299 (100)
Cycloplegic objective spherical equivalent, D	−3.14 (1.13) n = 99	−3.01 (1.12) n = 98	−3.08 (1.05) n = 101	−3.08 (1.10) N = 298
Axial length, mm	24.58 (0.83)	24.61 (0.77)	24.60 (0.83)	24.60 (0.80)
Noncycloplegic best-corrected distance logMAR VA	−0.007 (0.084)	0.001 (0.088)	−0.004 (0.093)	−0.003 (0.088)
Noncycloplegic best-corrected near logMAR VA	0.068 (0.122)	0.054 (0.115)	0.050 (0.111)	0.057 (0.116)
Photopic pupil size, mm	4.84 (1.11)	4.99 (1.06)	4.83 (0.98)	4.89 (1.05)

D = diopters; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.
Data are mean (standard deviation) unless stated otherwise.

confidence interval] vs. placebo: 8.8% [−19.4, 1.2]; $P = 0.1163$ and 21.3% [−32.9, −8.4]; $P = 0.0003$, respectively), and by ≥0.75 D in 79.1%, 56.3%, and 84.9% of subjects (difference [95% confidence interval] vs. placebo: 5.8% [−17.6, 5.6]; $P = 0.3340$ [nominal] and 28.6% [−41.3, −14.6]; $P < 0.0001$ [nominal], respectively). Treatment differences versus placebo for the proportions of subjects with ≥1.0 D SE worsening from baseline at month 24 were statistically significant for both atropine 0.01% and 0.025% ($P = 0.0297$ [nominal] and $P < 0.0001$ [nominal], respectively; Table 2).

Change in SE and AL at Month 36 from Baseline and from Month 24. Least squares mean (± standard error) change from baseline SE at month 36 was −1.77 (0.17), −1.71 (0.17), and −2.05 (0.17) D in the atropine 0.01% + placebo, atropine 0.025% + placebo, and placebo + placebo groups, respectively (Table 3). After cessation of treatment after 2 years, the LS mean change (± standard error) in SE from month 24 to month 36 was −0.61 (±0.07), −0.75 (±0.07), and −0.40 (±0.07) D in the atropine 0.01% + placebo, atropine 0.025% + placebo, and placebo + placebo groups, respectively (Table 3). This suggested a small, concentration-dependent "rebound" in SE progression; however, this was not considered clinically meaningful.

Similar results were observed with changes in AL after treatment cessation at month 24. The LS mean (± standard error) change from baseline AL at month 36 was 0.89 (0.07), 0.82 (0.07), and 0.97 (0.07) mm in the atropine 0.01% + placebo, atropine 0.025% + placebo, and placebo + placebo groups, respectively. After a switch at month 24 from either atropine 0.01% or 0.025% to placebo, LS mean change (± standard error) in AL from month 24 to month 36 was 0.30 (±0.03), 0.32 (±0.03), and 0.21 (±0.03) in the atropine 0.01% + placebo, atropine 0.025% + placebo, and placebo + placebo groups, respectively. Changes in SE and AL from baseline to month 36 in subjects who continued atropine 0.01% and atropine 0.025% or who were switched from the placebo at month 24 to either atropine concentration are available in Supplementary Appendix 3 (available at www.ophthalmologyscience.org).

Safety

Treatment Period 1. Adverse drug reactions were reported in 5 (5.1%), 17 (16.8%), and 1 (1.0%) subjects in treatment period 1 in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively. One ADR event (moderate visual impairment) led to the study discontinuation of 1 subject in the atropine 0.025% group (Table 4). This visual impairment was classified as near vision disturbance (accommodation dysfunction) and resolved after treatment cessation. Ocular ADRs occurred in 5, 16, and 1 subjects for each event in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively (Table 4).

Photophobia was the most common ADR and was reported in 4 subjects in the atropine 0.01% group, 11 subjects in the atropine 0.025% group, and 1 subject in the placebo group (Table S1, available at www.ophthalmologyscience.org). Photophobia was assessed as moderate in 1 subject in each of the atropine 0.025% and placebo groups; all other cases were mild. Other ocular ADRs included visual impairment (2 mild; 1 moderate) in 3 subjects and glare (moderate) in 1 subject (Table S1).

Treatment Period 2. Adverse drug reactions were reported in 2 (9.5%) subjects in the placebo + atropine 0.025% group and 1 (2.5%) subject in the atropine 0.01% + atropine 0.01% group in treatment period 2 (Table S2, available at www.ophthalmologyscience.org). No ADRs led to study discontinuation in treatment period 2. Adverse drug reactions reported were photophobia (mild) in the atropine 0.01% + atropine 0.01% group (1 subject), visual impairment (moderate) in the placebo + atropine 0.025% group (1 subject), which was classified as near vision disturbance and resolved without requiring treatment discontinuation, and pupillary disorder (mild) in the placebo + atropine 0.025% group (1 subject).

Pupil size increased from baseline to month 24 in the atropine 0.01% and 0.025% groups by a respective mean of 0.49 (SD 0.95) and 0.74 (SD 0.90) mm, and from baseline to month 36 in the atropine 0.01% + atropine 0.01% (by 0.41 [SD 0.85] mm), atropine 0.025% + atropine 0.025% (by 0.61 [SD 0.76] mm), placebo + atropine 0.01% (by

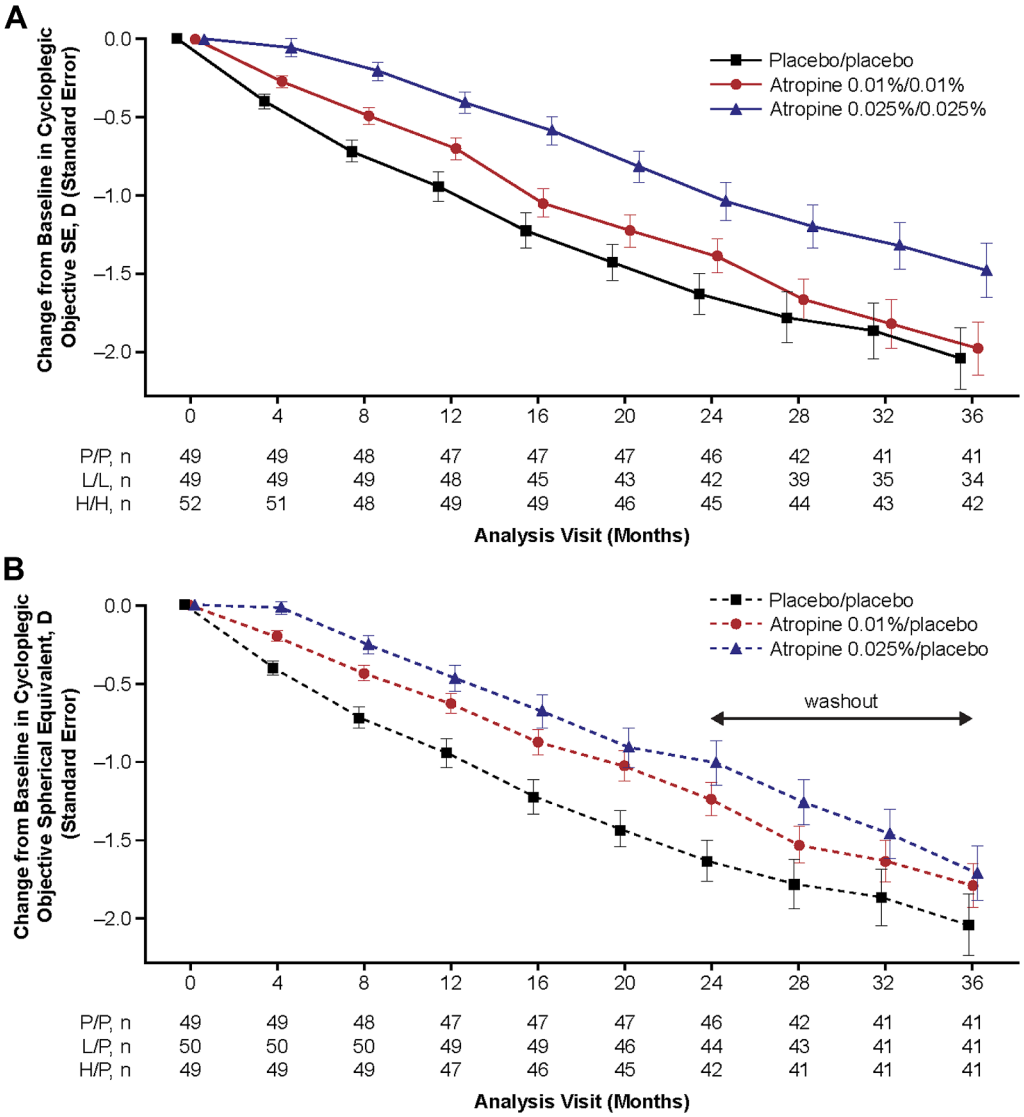

Figure 2. Change from baseline in cycloplegic objective SE to month 36 in the (**A**) nonswitch and (**B**) switch groups. Mean (± standard error) change in SE from baseline over 36 months. Data are presented separately for the treatment groups receiving atropine 0.01%, atropine 0.025%, and the placebo group. The bottom panel shows subjects that were subsequently switched from atropine 0.01% or 0.025% to placebo compared with the placebo group. In subjects who were switched from the study drug to placebo, the washout period began at month 24 after cessation of treatment with the study drug. Negative values indicate progression. D = diopters; H/H = atropine 0.025% + atropine 0.025%; H/P = atropine 0.025% + placebo; L/L = atropine 0.01% + atropine 0.01%; L/P = atropine 0.01% + placebo; P/P = placebo + placebo; SE = spherical equivalent.

0.51 [SD 0.86] mm), placebo + atropine 0.025% (by 0.42 [SD 0.83] mm), and placebo + placebo (by 0.16 [SD 0.74] mm) groups. The increased pupil sizes observed at month 24 with atropine 0.01% and 0.025% had resolved by month 28 in the atropine 0.01% + placebo and atropine 0.025% + placebo groups (change from baseline pupil size, −0.00 [SD 0.72] and 0.02 [SD 0.087] mm, respectively). Intraocular pressure changes from baseline at month 24 were small across treatment groups, with mean values of 0.27 (SD 2.27), −0.08 (SD 2.34), and 0.35 (SD 2.11) mmHg in the atropine 0.01%, atropine 0.025%, and placebo groups, respectively. There were no serious ADRs and no deaths in the study.

Discussion

In this randomized, placebo-controlled study, treatment with the novel atropine sulfate ophthalmic solution at concentrations of 0.01% or 0.025% slowed disease progression in a concentration-dependent manner for up to 2 years in Japanese children with myopia. After cessation of treatment after 2 years, a small, concentration-dependent "rebound" in SE progression was observed over 12 months that was not considered to be clinically meaningful, suggesting that efficacy may be maintained for up to 36 months in children.

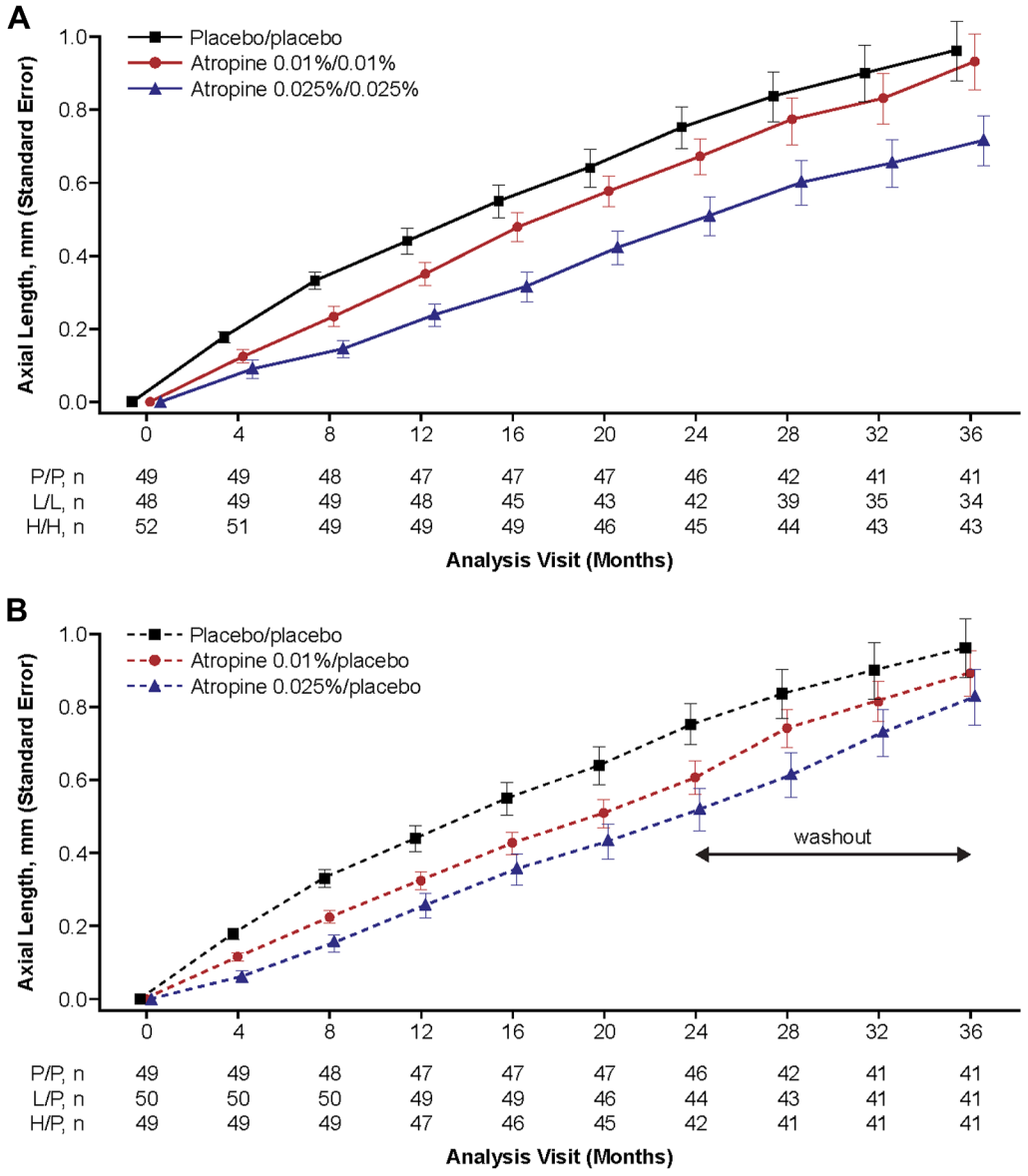

Figure 3. Change from baseline in AL to month 36 in the (**A**) nonswitch and (**B**) switch groups. Mean (± standard error) change in AL from baseline over 36 months. Data are presented separately for the treatment groups receiving atropine 0.01%, atropine 0.025%, and the placebo group. The bottom panel shows subjects who were subsequently switched from atropine 0.01% or 0.025% to placebo compared with the placebo group. In subjects who were switched from the study drug to placebo, the washout period began at month 24, after cessation of treatment with the study drug. Increases in AL are associated with progression. AL = axial length; H/H = atropine 0.025% + atropine 0.025%; H/P = atropine 0.025% + placebo; L/L = atropine 0.01% + atropine 0.01%; L/P = atropine 0.01% + placebo; P/P = placebo + placebo.

After 12 months, atropine 0.01% and 0.025% had reduced SE progression by 0.29 and 0.52 D, and after 24 months, by 0.34 and 0.65 D, respectively. In addition, after 24 months, atropine 0.01% and 0.025% had reduced AL elongation by 0.11 and 0.23 mm, respectively. Although direct comparisons cannot be made because of the differences in study designs and atropine formulations, these results are broadly similar to the data reported from other placebo-controlled studies, including Japan Atropine for the Treatment of Myopia, LAMP, and Childhood Atropine for Myopia Progression.[18,26,27] In the Japan Atropine for the Treatment of Myopia study, atropine 0.01% reduced SE progression by a respective 0.08 D and 0.22 D at 12 months and 24 months, and AL elongation by 0.14 mm at 24 months in Japanese children.[26] Similarly, in the LAMP study in China, atropine 0.01% and 0.025% reduced SE progression by 0.38 and 0.35 D, respectively, after 36 months in children.[22] The Childhood Atropine for Myopia Progression study, conducted at sites in Europe and North America, also reported comparable outcomes, with atropine 0.01% reducing SE progression by 0.24 D and AL by 0.13 mm after 36 months in children.[27] However, in the European Myopia Outcome Study of Atropine in Children study,[28] SE progression did not differ between

Table 2. Progression of ≥0.5, 0.75, or 1.0 D from Baseline in Objective Spherical Equivalent at Month 24

Parameter	Statistics	Placebo (n = 99)	Atropine 0.01% (n = 99)	Atropine 0.025% (n = 101)
0.5-D worsening	n/N (%)	85/93 (91.4)	71/86 (82.6)	61/87 (70.1)
	95% confidence of difference*	NA	−19.4 to 1.2	−32.9 to −8.4
	P value†	NA	0.1163	0.0003
0.75-D worsening	n/N (%)	79/93 (84.9)	68/86 (79.1)	49/87 (56.3)
	95% confidence of difference*	NA	−17.6 to 5.6	−41.3 to −14.6
	P value†	NA	0.3340‡	<0.0001‡
1.0-D worsening	n/N (%)	74/93 (79.6)	55/86 (64.0)	40/87 (46.0)
	95% confidence of difference*	NA	−28.9 to −2.1	−46.6 to −19.1
	P value†	NA	0.0297‡	<0.0001‡

D = diopters; NA = not available.
*Atropine minus placebo.
†Fisher exact test versus placebo.
‡Nominal *P* value.

the atropine 0.01% and placebo groups (0.10 D; $P = 0.07$) at 24 months, although AL growth was lower in the treatment group.

As described above, this study appears to demonstrate greater numerical efficacy in the change in AL and SE from baseline when compared with other myopia control studies with atropine. The varying efficacy between this and other concentrations of atropines may be attributed to the alternative formulation of the study drug, which allows for better penetration into the intraocular tissue, notably the posterior sclera, the assumed site of action.[14] Ultimately, mechanistic studies are warranted to fully elucidate the differences in efficacy between formulations of atropine, along with further head-to-head efficacy studies.

After cessation of atropine treatment at month 24, the change in SE progression from month 24 to 36, generally known as "rebound," was −0.61, −0.75, and −0.40 D in the atropine 0.01% to placebo, atropine 0.025% to placebo, and placebo groups, respectively, showing a small, concentration-dependent progression in SE after treatment cessation. The change for atropine 0.01% in the current study was consistent with the −0.65 D change in SE progression reported in Japan Atropine for the Treatment of Myopia at month 36 after cessation of atropine 0.01% eye drops at month 24.[29] A recent meta-analysis of rebound after cessation of a range of myopia control interventions reported annualized SE progression for atropine at low concentrations (0.01%−0.05%), ranging from −0.41 D to −0.78 D, and AL increases from 0.20 to 0.48 mm. Findings from this analysis highlight the varying magnitude of rebound across studies. Although some reported rapid myopia progression after discontinuing low-dose atropine, others did not observe a significant rebound effect.[30] The rebound reported in the ORANGE study was not considered clinically meaningful or to affect the beneficial effect of the initial atropine treatment.

Although the efficacy of atropine increases in a concentration-dependent manner, a corresponding increase in AEs has been reported previously.[21,31] In addition, the relationship between mydriatic effects and atropine concentration in the iris has also been reported. Therefore, the study drug was formulated with the aim of appropriately reaching the posterior ocular area—the site of action—while minimizing the occurrence of AEs, such as mydriatic effects, caused by the penetration of atropine to the anterior segment of the eye.[14,32] Furthermore, the preservative-free composition of the study drug may provide advantageous tolerability for patients in this treatment group, as preservatives that are often found in topical ocular medications can lead to the increased severity of ocular surface disease symptoms.[33]

Table 3. Change from Baseline and Month 24 in Cycloplegic Objective Spherical Equivalent at Month 36 (Treatment Period 2)

Treatment Group	Least Squares Mean	Standard Error	95% CI	Nominal *P* Value
		Change from baseline to month 36		
Placebo + placebo	−2.045	0.1725	NA	NA
Atropine 0.01% + placebo	−1.772	0.1729	−0.211 to 0.758	0.2666
Atropine 0.025% + placebo	−1.714	0.1725	−0.151 to 0.814	0.1762
		Change from month 24 to month 36		
Placebo + placebo	−0.396	0.0701	NA	NA
Atropine 0.01% + placebo	−0.612	0.0691	−0.413 to −0.020	0.0313
Atropine 0.025% + placebo	−0.750	0.0700	−0.552 to −0.156	0.0006

NA = not available; CI = confidence interval.
Full analysis set. The analysis of covariance model includes treatment as fixed effects and baseline as the covariate.

Table 4. Safety Events in Treatment Period 1

Subjects with Any Safety Event, n (%)	Placebo (n = 99)	Atropine 0.01% (n = 99)	Atropine 0.025% (n = 101)
ADRs	1 (1.0)	5 (5.1)	17 (16.8)
Serious ADRs	0 (0.0)	0 (0.0)	0 (0.0)
ADRs leading to study discontinuation	0 (0)	0 (0)	1 (1.0)
Death	0 (0)	0 (0)	0 (0)
Subjects with any ocular ADRs	1 (1.0)	5 (5.1)	16 (15.8)
Serious ocular ADRs	0 (0.0)	0 (0.0)	0 (0.0)
Ocular ADRs leading to study discontinuation	0 (0)	0 (0)	1 (1.0)
Subjects with any nonocular ADRs	0 (0.0)	2 (2.0)	2 (2.0)
Serious nonocular ADRs	0 (0.0)	0 (0.0)	0 (0.0)
Nonocular ADRs leading to study discontinuation	0 (0)	0 (0)	0 (0)

ADR = adverse drug reaction.
Safety analysis set. Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term.

The incidence of ADRs at 24 months was higher with atropine 0.025% than with 0.01% in this study, with a greater likelihood of AEs with a higher atropine concentration, consistent with previous reports.[31] Photophobia was the most common ADR and was reported in 4.0% and 10.9% of subjects treated with atropine 0.01% and 0.025%, respectively. This is consistent with photophobia or glare, blurred vision, and hypersensitivity reactions that were identified in a recent review as the 3 most common AEs with atropine.[31] Photophobia was mostly mild, indicating that atropine at both concentrations was well tolerated.

Consistent with the LAMP study,[21] a concentration-dependent increase in pupil size was reported in the ORANGE study. After 24 months, the mean change from baseline in pupil diameter with atropine 0.025% was 0.74 mm in the ORANGE study and 0.67 mm in the LAMP study. For atropine 0.01%, the mean change was 0.49 mm (ORANGE) and 0.60 mm (LAMP), respectively. Significant increases in pupil diameter with atropine 0.01% and 0.02% eye drops, reported previously in children with myopia, were not found to be associated with photophobia.[34] The overall incidence and severity of ADRs and results for other safety parameters in this study suggest a favorable safety and tolerability profile for atropine ophthalmic solution at both 0.01% and 0.025% concentrations (1 drop, once daily in both eyes). Given that the efficacy of atropine was concentration-dependent, the optimal concentration in these Japanese patients was considered to be 0.025%.

The strengths of the ORANGE study included the randomized, double-masked, placebo-controlled study design, the inclusion of AL measurement in addition to the standard measurement of cycloplegic SE for myopia assessment, and the assessment of changes in SE after treatment cessation. However, there were certain study limitations. The efficacy and safety of atropine 0.01% and 0.025% were not assessed in children <5 years of age and those with high (severe) myopia; therefore, the results of the ORANGE study may not be generalizable to these groups of children. Although atropine 0.01% and 0.025% were found to be effective after 36 months of use, additional benefits may be apparent with a longer-term study duration. Further analyses are required to identify the efficacy of atropine 0.01% and 0.025% in subjects with high (severe) myopia.

In conclusion, the results of the ORANGE study reported here show that both atropine 0.01% and 0.025% were well tolerated and effective in slowing the progression of myopia in terms of changes from baseline SE and AL, with no sudden deterioration in SE upon treatment cessation. Atropine 0.025% was considered to be the optimal concentration to reduce the progression of myopia in Japanese children who were part of the ORANGE study population.

Acknowledgments

The authors would like to thank the participants, their families, and all investigators involved in this study. The authors also thank Yoshiaki Yamada, Hiromi Akai, and Toru Nishio of Japan Medical Affairs at Santen Pharmaceutical Co., Ltd., for reviewing the discussion for medical accuracy. Medical writing support, including assisting the authors with development of the outline and initial draft and incorporation of comments, was provided by Linda Brown, BSc (Hons), and Abbie Rodger, BSc (Hons), and editorial support, including fact checking, referencing, figure preparation, formatting, proofreading, and submission, was provided by Isobel Markham, MSc, and Jess Fawcett, BSc, all of Core (a division of Prime, London, UK), supported by Santen according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460). The sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Footnotes and Disclosures

Originally received: June 3, 2025.
Final revision: September 26, 2025.
Accepted: September 26, 2025.
Available online: October 9, 2025. Manuscript no. XOPS-D-25-00397.

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Data Availability: Data underlying the findings described in this manuscript may be requested in accordance with Santen's data sharing policy.

Data presented in this manuscript were presented at the American Academy of Ophthalmology (AAO) annual meeting (October 18−21, 2024, Chicago, IL, USA) and at the Japanese Society for Myopia Research General Meeting (May 18−19, 2024, Tokyo, Japan).

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

K.O.-M.: Research Grant − Tomey Corporation; Consultant − Santen Pharmaceutical Co., Ltd., CooperVision outside the submitted work.

Y.M. and Y.Y.: Employee − Santen Pharmaceutical Co., Ltd.

This study was supported by Santen Pharmaceutical Co., Ltd. The sponsor or funding organization participated in the design of the study, conducting the study, data collection, data management, and data analysis of the manuscript.

Kyoko Ohno-Matsui, MD, PhD, an editorial board member of this journal, was recused from the peer-review process of this article and had no access to information regarding its peer review.

Support for Open Access publication was provided by Santen Pharmaceutical Co, Ltd.

HUMAN SUBJECTS: Human subjects were included in this study. The study protocol was approved by the institutional review board at each study site, and written informed consent for participation in the study was obtained from the subjects and their legal guardians. The study was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

No animal subjects were used in this study.

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Obtained funding: N/A

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Abbreviations and Acronyms:
ADR = adverse drug reaction; **AE** = adverse event; **AL** = axial length; **D** = diopters; **LAMP** = Low-Concentration Atropine for Myopia Progression; **LS** = least squares; **MMRM** = mixed-effects model for repeated measures; **SD** = standard deviation; **SE** = spherical equivalent.

Keywords:
Atropine, Axial length, Children, Myopia, Spherical equivalent.

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