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Two-Year Clinical Trial of the Low-Concentration Atropine for Myopia Progression (LAMP) Study

Phase 2 Report

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Purpose: To evaluate the efficacy and safety of 0.05%, 0.025%, and 0.01% atropine eye drops over 2 years to determine which is the optimal concentration for longer-term myopia control.

Design: Randomized, double-masked trial extended from the Low-Concentration Atropine for Myopia Progression (LAMP) Study.

Participants: Three hundred eighty-three of 438 children (87%) aged 4 to 12 years with myopia of at least −1.0 diopter (D) originally randomized to receive atropine 0.05%, 0.025%, 0.01%, or placebo once daily in both eyes in the LAMP phase 1 study were continued in this extended trial (phase 2).

Methods: Children in the placebo group (phase 1) were switched to receive 0.05% atropine from the beginning of the second-year follow-up, whereas those in the 0.05%, 0.025%, and 0.01% atropine groups continued with the same regimen. Cycloplegic refraction, axial length (AL), accommodation amplitude, photopic and mesopic pupil diameter, and best-corrected visual acuity were measured at 4-month intervals.

Main Outcome Measures: Changes in spherical equivalent (SE) and AL and their differences between groups.

Results: Over the 2-year period, the mean SE progression was 0.55±0.86 D, 0.85±0.73 D, and 1.12±0.85 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively ($P = 0.015$, $P < 0.001$, and $P = 0.02$, respectively, for pairwise comparisons), with mean AL changes over 2 years of 0.39±0.35 mm, 0.50±0.33 mm, and 0.59±0.38 mm ($P = 0.04$, $P < 0.001$, and $P = 0.10$, respectively). Compared with the first year, the second-year efficacy of 0.05% and 0.025% atropine remained similar ($P > 0.1$), but improved mildly in the 0.01% atropine group ($P = 0.04$). For the phase 1 placebo group, the myopia progression was reduced significantly after switching to 0.05% atropine (SE change, 0.18 D in second year vs. 0.82 D in first year [$P < 0.001$]; AL elongated 0.15 mm in second year vs. 0.43 mm in first year [$P < 0.001$]). Accommodation loss and change in pupil size in all concentrations remained similar to the first-year results and were well tolerated. Visual acuity and vision-related quality of life remained unaffected.

Conclusions: Over 2 years, the efficacy of 0.05% atropine observed was double that observed with 0.01% atropine, and it remained the optimal concentration among the studied atropine concentrations in slowing myopia progression. *Ophthalmology 2020;127:910-919 © 2019 by the American Academy of Ophthalmology*

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Myopia is a public health threat worldwide, with increasing prevalence in most regions over the past decades and especially in East Asia.[1–4] Low-concentration atropine eye drops are an emerging therapy for myopia control,[5,6] but their optimal concentration and long-term efficacy remain undefined. In the first-year (phase 1) results of the Low-Concentration Atropine for Myopia Progression (LAMP) study, 0.05% atropine conferred the best treatment-to-side effect ratio among 0.05%, 0.025%, and 0.01% atropine over 1 year.[7] Of note, in the Atropine for the Treatment of Myopia (ATOM) 2 study, 0.01% atropine was more effective in the second year than the first year. The changes in spherical equivalent (SE) and axial length (AL) in the 0.01% atropine group were −0.43 diopter (D) and 0.24 mm, respectively, in the first year, but only −0.06 D and 0.17 mm, respectively in the second year. Interestingly, this effect was not found in higher concentrations of atropine at 0.1% or 0.5%.[8] The authors

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of ATOM 2 therefore concluded that 0.01% atropine has clinically similar efficacy as 0.5% and 0.1% atropine. In contrast, we found 0.05% atropine to be better than 0.025% and 0.01% atropine over 1 year in the LAMP study.[7] We went on to study their longer-term (2-year) efficacies and side effects in phase 2 of this study.

We aimed to answer the following questions in phase 2 of the LAMP study. Which concentration of atropine confers the best efficacy in myopia control over 2 years? Are the efficacies of low-concentration atropine better in the second year than the first year? Are the side effects of low-concentration atropine similar in the first and second year and remain tolerable? What is the efficacy of 0.05% atropine when administered to the placebo self-control group for 1 year? This study reports the phase 2 results of the LAMP study.

Methods

The study design has been described previously for the LAMP study phase 1.[7] In brief, children 4 to 12 years of age with myopic refraction of at least −1.0 D in both eyes, astigmatism of less than 2.5 D, and documented myopic progression of at least 0.5 D in the previous 1 year were enrolled in this double-blinded, single-center clinical trial. After excluding those with ocular diseases, those who underwent previous interventions (such as atropine, pirenzepine, orthokeratology lens, or other optical methods) for myopia control or allergy to atropine, and those with systemic diseases (e.g., cardiac or respiratory illness), the children were randomized to 4 treatment groups—0.05% atropine, 0.025% atropine, 0.01% atropine, and placebo—and then were followed up at 4 months, 8 months, and 12 months.[7] In phase 2 of the study, all children in the placebo group of phase 1 were switched to receive 0.05% atropine at the beginning of the second year until the end of phase 2 (now called the switchover group) owing to ethical considerations because low-concentration atropine was proven effective compared with placebo during the first year. Children in the 0.05%, 0.025%, and 0.01% atropine groups continued to receive the same concentration for the entire 2 years of the study. Participants in the switchover group were informed of the switchover arrangement, but all remained masked to which atropine group they were allocated. Children in the 0.05%, 0.025%, and 0.01% atropine groups remained masked to their treatment groups as in phase 1. Clinical investigators remained masked to all the group allocations as in phase 1. Written informed consent was obtained from parents or guardians, and verbal assent was obtained from the study participants. This study was registered with the Centre for Clinical Research and Biostatistics (CCRB) Clinical Trials Registry, The Chinese University of Hong Kong (identifier, CUHK_CCT00383), and was approved by the ethics committee of The Chinese University of Hong Kong. All procedures were conducted according to the tenets of the Declaration of Helsinki.

Trial medications were administered once every night. They were prepackaged as eye drops in monodose preparations with atropine sulfate concentrations at 0.05%, 0.025%, or 0.01% (0.5-ml unit-concentration, preservative free) by Aseptic Innovative Medicine Co, Ltd, Taipei, Taiwan. Expiry duration for each batch of eye drops was 2 years. Certificates of analysis for 0.05%, 0.025%, and 0.01% atropine were provided by the manufacturer. A drug trial certificate was granted by the Department of Health, Hong Kong Special Administrative Region (SAR). Compliance with trial medication was classified according to the mean number of days a trial medication was used each week as reported by the participants. Compliance rates of more than 75% (i.e., a mean of 5.25 days/week) were considered acceptable. Participants also were offered photochromic glasses (which darken on exposure to sunlight) if they experienced glare or if their parents worried about excessive light exposure, or progressive glasses (reading add) if participants experienced difficulty with near vision. All participants were prescribed with best-corrected spectacles. Validated questionnaires on outdoor time and near work, as well as the Chinese version of the 25-item National Eye Institute Visual Function Questionnaire, were administered to parents at the end of the second year.[9] Examinations in phase 2 were similar to those in phase 1, as described previously.[7] Ophthalmic parameters collected at each visit included distance best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution, near visual acuity under best-corrected distance spectacle correction at 40 cm, and the near point of accommodation with best-corrected distance spectacle correction. Accommodation amplitude was calculated as the inverse of the near point of accommodation. Photopic pupil size and mesopic pupil size were measured by the OPD-Scan III (Nidek, Gamagori, Japan). Cycloplegic autorefraction was performed using an autorefractor (Nidek ARK-510A; Nidek) after the cycloplegic regimen, which consisted of at least 2 cycles of eye drops. In the first cycle, 2 separate eye drops, cyclopentolate 1% (Cyclogyl; Alcon-Convreur, Rijksweg, Belgium) and tropicamide 1% (Santen, Osaka, Japan), were administered to both eyes at 5 minutes apart. A second cycle of the same cycloplegic drops was administered 10 minutes after the first cycle. Maximum cycloplegia to maximally inhibit accommodation is necessary for accurate measurement of refractive errors in children to prevent overestimation of myopia and underestimation of hyperopia.[10] If pupillary light reflex was still present or the pupil size was less than 6.0 mm, a third cycle of the same cycloplegic eye drops would be given 30 minutes after the second cycle. If necessary, further cycles of cycloplegic eye drops might be administered to ensure good dilation of the pupils. Five readings, all of which were less than 0.25 D apart, were obtained and averaged. Spherical equivalent was calculated as spherical power plus half of the cylinder power. Ocular AL was measured on a Zeiss IOL Master (Carl Zeiss Meditec, Inc, Dublin, CA), with an average of 5 readings within a deviation of 0.05 mm or less.

The primary outcome in this study was myopia progression, in terms of SE change, over 2 years (combined phase 1 and phase 2). The secondary outcomes included the change in AL over 2 years; SE change and AL change during the second year; side-effect parameters such as changes in accommodation amplitude, mesopic and photopic pupil sizes, distance BCVA, and near VA; and results of the Chinese version of the 25-item National Eye Institute Visual Function Questionnaire. All parameters, including SE, AL, accommodation amplitude, pupil size, and visual acuity, were monitored from baseline.

During each visit, participants and parents were given an open-ended opportunity to report any side effects, medical illness, or hospitalization since the previous visit. Any adverse events, regardless of whether they appeared relevant to atropine use, were documented, including symptoms related to allergy, glare, blurred near vision, or visual impairment.

Statistical Analysis

All data were analyzed based on the intention-to-treat principle. The mean values of ocular parameters were calculated from both eyes. Changes in parameters were calculated by the difference between the baseline visit and the designated follow-up visit. Our analysis was based on the complete case data without imputation

for those who dropped out of the study before the end of 2 years.[11] The chi-square test and Fisher exact test were used to test for the group difference in categorical data. Generalized estimating equations with robust standard errors for longitudinal data analysis[12,13] were used to adjust the correlation between eyes and to incorporate all valuable data. *P* values were generated by generalized estimating equation models[14] and were adjusted for multiple comparisons with sequential Bonferroni adjustment.[15] To evaluate the potential for confounding, analyses were repeated adjusting for age, gender, and baseline SE (the results were similar to unadjusted; Table S1, available at www.aaojournal.org). The concentration-response effect of atropine on the ophthalmic parameters was confirmed by the coefficient of the treatment groups in the regression model after arranging the treatment groups in the ordinal scale. SPSS statistics software version 24 (IBM Corp, Armonk, NY) was used for data analyses, and *P* values less than 0.05 were considered statistically significant.

Results

In total, 383 of the 438 children (87%) 4 to 12 years of age originally randomized to receive atropine 0.05%, atropine 0.025%, atropine 0.01%, or placebo once daily in both eyes in the LAMP phase 1 study were continued in this extended trial (phase 2), with 102, 91, 97, and 93 participants in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switchover group, respectively (Fig 1). The baseline characteristics of these 383 participants and the 55 participants who dropped out of the study during phase 1 were similar (Table S2, available at www.aaojournal.org). Furthermore, the 350 participants who completed 2 years of follow-up were similar to the 88 participants who did not (Table 1).

Changes in Spherical Equivalent and Axial Length over 2 Years for the 0.05%, 0.025%, and 0.01% Atropine Groups

At the end of 2 years, the mean SE change was −0.55±0.86 D, −0.85±0.73 D, and −1.12±0.85 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively, with significant differences between groups ($P = 0.015$, $P < 0.001$, and $P = 0.02$ after sequential Bonferroni correction; Table 2; Fig 2). No age−treatment interaction was observed ($P = 0.52$). The respective mean AL changes over 2 years were 0.39±0.35 mm, 0.50±0.33 mm, and 0.59±0.38 mm ($P = 0.04$, $P < 0.001$, and $P = 0.10$ after sequential Bonferroni correction; Table 2; Fig 3). The ophthalmic parameters over 2 years in each visit were summarized in Table S3 (available at www.aaojournal.org). During the 2 years, 52.7 %, 32.0%, 22.0%, and 27.5% of participants in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switchover groups, respectively, progressed less than 0.5 D, whereas 9.1%, 7.0%, 19.2%, and 12.5% of participants in the respective groups progressed by 2.0 D or more (Fig 4).

Comparison of Changes in Spherical Equivalent and Axial Length in the Second Year versus the First Year

During the second year, the mean SE progression was −0.30±0.44 D, −0.39±0.48 D, and −0.48±0.44 D in the 0.05%, 0.025%, and 0.01% atropine groups, with respective AL elongation of 0.18±0.16 mm, 0.22±0.18 mm, and 0.25±0.18 mm (Table 2). The SE progression in the 0.05% and 0.025% atropine groups was similar in the second and first years, but better in the second year in the 0.01% atropine group (Table 2). Axial length elongation in the second year was similar to that in the first year in the 0.05% atropine group but was less in the 0.025% and 0.01% atropine groups (Table 2).

Changes in Spherical Equivalent and Axial Length in the Switchover Group

For the switchover group, mean SE progression and AL elongation were −0.18±0.49 D and 0.15±0.18 mm, respectively, during the second year. From the baseline at the beginning of this study, SE progression and AL elongation has been −1.00±0.77 D and 0.58±0.33 mm over 2 years (Table 2).

Changes in Accommodation, Pupil Size, and Visual Acuity

Changes in accommodation amplitude at the end of 2 years were 2.05 D, 1.66 D, and 0.63 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively, which were similar to that of the first year and followed a concentration-related response (Table 2; Tables S2−S5, available at www.aaojournal.org). Likewise, changes in pupil size at the end of 2 years were similar to those at the end of the first year and followed a concentration-related response (Table 2; Tables S2−S5, available at www.aaojournal.org). Distance BCVA and near BCVA in all groups were not affected (Table 2; Tables S2−S5, available at www.aaojournal.org).

Adverse Events and Vision-Related Quality of Life

Photochromic glasses were needed in approximately 30% of participants, and progressive lens spectacles were not required in general (Table 3). More participants reported photophobia at the end of the second year if not wearing photochromic glasses (Table 3). Occurrence of allergic conjunctivitis was similar across the groups (Table 3). Over the 2-year period, 17 participants showed severe adverse events requiring hospitalization, but none was related to the topical atropine therapy. In the 0.05% atropine group, gastroenteritis, influenza, asthmatic attack, and body injury each occurred in 1 participant. In the 0.025% atropine group, 1 participant each experienced gastroenteritis, pneumonia, appendectomy, or elective circumcision surgery, and 2 participants experienced influenza. In the 0.01% atropine group, 1 participant sustained a lip injury requiring surgical repair, 1 participant experienced influenza, 1 participant sustained a distal radius fracture requiring plaster casting, and 1 participant each experienced rash or leg pain. In the switchover group, 2 participants experienced influenza. Compliance was 92.6%, 93.0%, 91.3%, and 92.5% in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switchover groups, respectively. No differences were observed in vision-related quality of life among the 0.05%, 0.025%, and 0.01% atropine groups (Table S6, available at www.aaojournal.org).

Discussion

This report presents the second-year results (phase 2) of the LAMP study of 4 treatment groups: 0.05% atropine, 0.025% atropine, and 0.01% atropine used daily for 2 years and switching over from using a placebo during the first year to using 0.05% atropine daily during the second year. The concentration-dependent response remained, and 0.05%

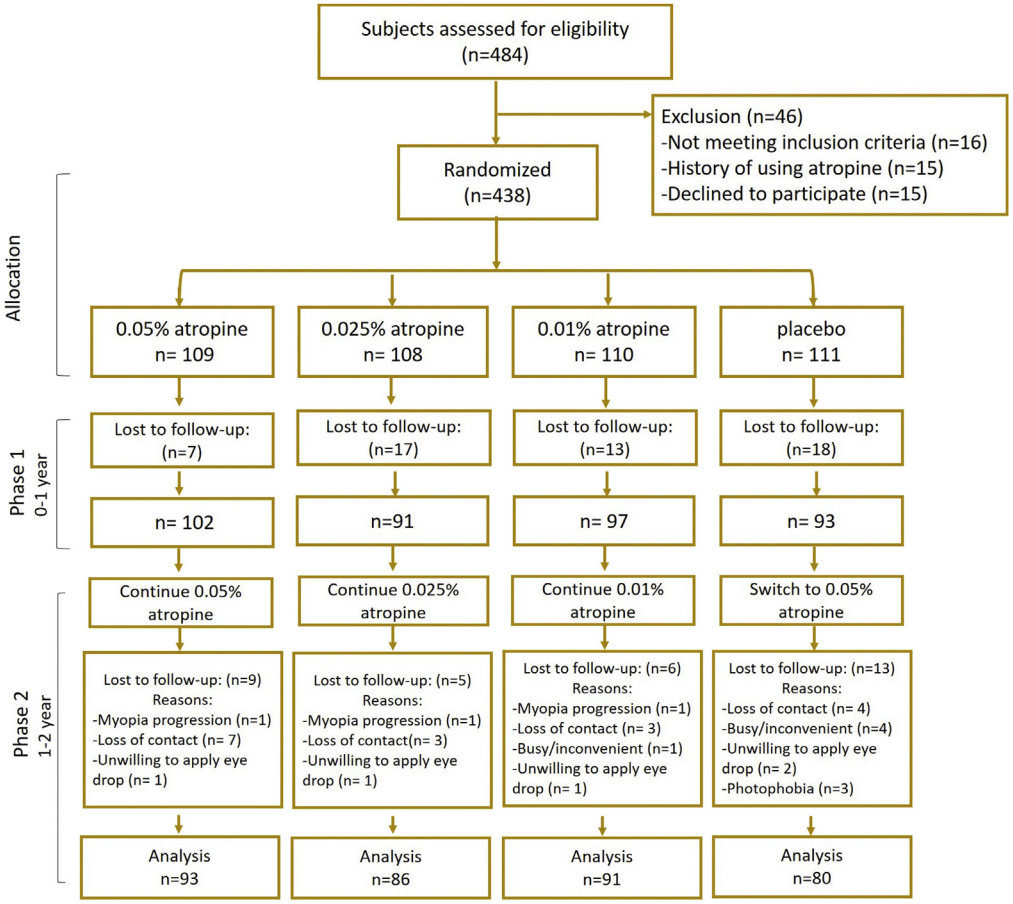

Figure 1. Participant flowchart in the Low-Concentration Atropine for Myopia Progression Study.

atropine continued to be the most effective among 0.05%, 0.025%, and 0.01% atropine groups for myopia control after 2 years.

Since the ATOM 2 study, use of low-concentration atropine, including 0.01%, has surged in popularity in retarding myopia progression.[6] In the LAMP study, atropine 0.05% was demonstrated to be better than 0.01% and 0.025% atropine in myopia control over 1 year.[7] Results of the present LAMP study phase 2 also showed that 0.05% atropine is the optimal concentration over a 2-year period. Because of the switchover design in the placebo group, no data are available on natural myopia progression over 2 years. Nevertheless, based on the predictive model by Donovan et al,[16] progression (Asians) $= -0.014 \times \text{age}^2 + 0.39 \times \text{age} - 3.16$, the predicted natural progression of our original placebo group should have been −0.73 D in the second year, giving a total progression of −1.55 D over 2 years. Using this for comparison, 0.05%, 0.025%, and 0.01% atropine could achieve 64.5%, 45.2%, and 27.7% reduction of SE progression, respectively, over 2 years.

Comparisons between our study and the ATOM 2 study are summarized in Table 4. It seems that 0.5% and 0.1% atropine in ATOM 2[8] achieved a better effect than 0.05% atropine in the present study, consistent with the concentration-dependent response. Notably, 0.01% atropine in the ATOM 2 study showed a similar antimyopia effect as 0.05% atropine in our study, but a stronger effect than 0.01% atropine in our study (Table 4). In a retrospective case-control study of 57 children 6 to 12 years of age, 0.05% atropine achieved a myopia progression rate of −0.28±0.26 D/year over 19.95±9.04 months versus −0.75±0.35 D/year over 21.47±10.02 months in the nontreatment controls.[17] In another retrospective study with mean follow-up of 4.5 years, the 0.05% to 0.1% atropine treatment group showed a mean myopia progression rate of −0.23 D/year compared with −0.86 D/year in nontreatment controls.[18] The finding was consistent with our results, although these studies were retrospective in design and provided no AL data. A low progression rate of −0.1 D/year also was reported in a case-control retrospective study of 60 white children receiving 0.01% atropine based on noncycloplegic refraction with no AL measurement.[18] Of note, direct comparisons of our data with data from other studies should be interpreted with caution because of differences in study designs, cohorts, age groups, and manufacturers of eye drops.

Of note, 9.1% children in the 0.05% atropine group progressed more than 2 D in 2 years. In addition, the standard deviations in SE progression and AL elongation in all treatment groups were not small, indicating large variations in myopia control among individuals. Therefore, stepping

Table 1. Baseline Demographic Characteristics in the 0.05% Atropine, 0.025% Atropine, 0.01% Atropine, and Placebo-to-0.05% Atropine Groups for Those Who Completed 2 Years of Treatment versus Those Who Did Not Complete 2 Years of Treatment

	Completed 2 Years (n = 350)				Did Not Complete 2 Years (n = 88)			
	0.05% Atropine (n = 93)	*0.025% Atropine (n = 86)*	*0.01% Atropine (n = 91)*	*Switchover Group* (n = 80)*	*0.05% Atropine (n = 16)*	*0.025% Atropine (n = 22)*	*0.01% Atropine (n = 19)*	*Switchover Group* (n = 31)*
Age (yrs)	8.32 (1.71)	8.48 (1.69)	8.35 (1.8)	8.41 (1.87)	9.3 (1.59)	8.45 (1.87)	7.79 (1.9)	8.39 (1.63)
Male gender, no. (%)	50 (53.8%)	56 (65.1%)	48 (52.7%)	49 (62.3%)	5 (31.3%)	10 (45.5%)	10 (52.6%)	16 (51.6%)
BMI (kg/m^2)	16.65 (3.63)	16.52 (2.34)	16.56 (2.97)	16.16 (3.13)	17.57 (3.12)	15.79 (2.38)	17.11 (3.08)	16.11 (4.05)
Spherical equivalent (D)	−3.93 (1.63)	−3.88 (1.83)	−3.99 (1.94)	−4.31 (1.96)	−3.98 (1.53)	−3.41 (1.96)	−3.59 (2.25)	−3.33 (2.42)
Axial length (mm)	24.88 (0.91)	24.94 (0.9)	24.78 (1.02)	24.96 (1.02)	24.77 (0.74)	24.64 (1.05)	24.53 (0.77)	24.64 (1.11)
Central corneal thickness (μm)	551.35 (29.28)	548.88 (29.84)	546.25 (26.75)	546.05 (31.37)	550.13 (29.01)	555.52 (32.39)	544.53 (28.59)	538.37 (28.67)
IOP (mmHg)	15.72 (2.04)	15.85 (1.94)	15.52 (2.1)	15.54 (2.28)	16.27 (1.52)	15.97 (1.54)	15.65 (1.62)	15.31 (2.22)
Photopic pupil size (mm)	3.82 (0.68)	3.74 (0.63)	3.61 (0.59)	3.82 (0.8)	3.73 (0.88)	3.75 (0.86)	3.51 (0.49)	3.62 (0.63)
Mesopic pupil size (mm)	6.76 (0.74)	6.78 (0.64)	6.62 (0.67)	6.66 (0.55)	6.58 (0.89)	6.68 (0.92)	6.49 (0.86)	6.74 (0.82)
Accommodation amplitude (D)	12.65 (2.84)	12.49 (2.31)	11.82 (2.95)	11.93 (2.38)	13 (2.19)	11.75 (1.79)	12.77 (1.6)	12.99 (2.49)
Distance VA (logMAR)	0.01 (0.06)	0.01 (0.07)	0.01 (0.06)	0.02 (0.06)	0.00 (0.08)	0.02 (0.08)	0.03 (0.08)	0.00 (0.06)
Near VA (logMAR)	0.02 (0.08)	0.01 (0.07)	0.03 (0.09)	0.02 (0.08)	0.02 (0.09)	0 (0.08)	−0.01 (0.08)	0.01 (0.08)
Outdoor activity (hrs/day)†	2.29 (0.97)	2.04 (1.00)	2.20 (0.95)	2.29 (0.88)	2.22 (0.98)	2.04 (0.99)	1.97 (0.92)	2.08 (0.99)
Near work (dioptic hrs/day)‡	15.82 (4.25)	15.89 (4.77)	16.05 (4.45)	15.24 (5.37)	14.66 (6.37)	12.6 (5.89)	16.51 (4.31)	14.24 (6.61)

BMI = body mass index; D = diopter; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.
Data are mean (standard deviation) unless otherwise indicated.
*Participants receiving placebo during the first year who were switched over to 0.05% atropine at the beginning of the second year.
†Outdoor exercise plus outdoor leisure activity.
‡Near work = 3 × (homework + reading + playing cell phone) + 2 × (using computer + playing video game) + 1 × (watching TV).

Table 2. Comparisons between the First Year and the Second Year in Ophthalmic Parameters

Change	0.05% Atropine (n = 93)		0.025% Atropine (n = 86)		0.01% Atropine (n = 91)		Switchover Group* (n = 80)		P Values, Pairwise Comparisons (0.05% vs. 0.025%, 0.05% vs. 0.01%, 0.025% vs. 0.01% Groups)
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Spherical equivalent (D)									
Baseline to 24 mos	−0.55	0.86	−0.85	0.73	−1.12	0.85	−1.00	0.77	0.015†, < 0.001†, 0.02†
Baseline to 12 mos	−0.25	0.61	−0.46	0.45	−0.64	0.56	−0.82	0.49	0.004†, < 0.001†, 0.01†
12 mos to 24 mos	−0.30	0.44	−0.39	0.48	−0.48	0.44	−0.18	0.49	0.32, 0.002†, 0.14
P value‡	0.45		0.31		0.04†		< 0.001†		
Axial length (mm)									
Baseline to 24 mos	0.39	0.35	0.50	0.33	0.59	0.38	0.58	0.33	0.04†, < 0.001†, 0.10
Baseline to 12 mos	0.20	0.24	0.29	0.20	0.35	0.24	0.43	0.21	0.012†, < 0.001†, 0.049†
12 mos to 24 mos	0.18	0.16	0.22	0.18	0.25	0.18	0.15	0.18	0.32, 0.009†, 0.25
P value‡	0.57		0.02†		0.001†		< 0.001†		
Photopic pupil size (mm)									
Baseline to 24 mos	1.25	1.13	0.67	0.87	0.60	0.84	1.18	1.30	< 0.001†, < 0.001†, 0.99
Baseline to 12 mos	1.02	1.02	0.81	0.89	0.55	0.77	0.10	1.10	0.22, < 0.001†, 0.02†
12 mos to 24 mos	0.21	1.00	−0.12	0.93	0.05	0.95	1.08	1.24	0.04†, 0.22, 0.21)
P value‡	< 0.001†		< 0.001†		< 0.001†		< 0.001†		
Mesopic pupil size (mm)									
Baseline to 24 mos	0.69	0.64	0.34	0.62	0.26	0.58	0.62	0.75	< 0.001†, < 0.001†, 0.99
Baseline to 12 mos	0.56	0.62	0.41	0.61	0.27	0.44	0.01	0.55	0.14, < 0.001†, 0.03†
12 mos to 24 mos	0.13	0.51	−0.05	0.57	−0.02	0.45	0.61	0.65	0.02†, 0.01†, 0.59
P value‡	< 0.001†		< 0.001†		< 0.001†		< 0.001†		
Accommodation amplitude (D)									
Baseline to 24 mos	−2.05	3.19	−1.66	2.79	−0.63	3.06	−1.79	2.86	0.99, < 0.001†, 0.02†
Baseline to 12 mos	−1.96	2.89	−1.70	2.50	−0.21	2.84	−0.22	2.75	0.99, < 0.001†, < 0.001†
12 mos to 24 mos	−0.10	2.48	−0.01	2.37	−0.41	2.52	−1.58	2.26	0.99, 0.38, 0.26
P value‡	< 0.001†		< 0.001†		0.61		0.001†		
Distance VA (logMAR)									
Baseline to 24 mos	−0.03	0.06	−0.03	0.06	−0.04	0.06	−0.03	0.06	0.68, 0.44, 0.34
Baseline to 12 mos	−0.02	0.06	−0.02	0.06	−0.03	0.07	−0.02	0.05	0.99, 0.32, 0.16
12 mos to 24 mos	−0.01	0.05	−0.01	0.05	−0.01	0.06	−0.01	0.05	0.99, 0.96, 0.93
P value‡	0.42		0.62		0.11		0.24		
Near VA (logMAR)									
Baseline to 24 mos	−0.01	0.09	−0.01	0.08	−0.02	0.09	0.02	0.10	0.99, 0.62, 0.86
Baseline to 12 mos	−0.003	0.10	−0.003	0.08	−0.03	0.11	−0.02	0.10	0.99, 0.13, 0.1
12 mos to 24 mos	−0.004	0.08	−0.006	0.08	0.01	0.11	0.01	0.08	0.99, 0.38, 0.30
P value‡	0.87		0.75		0.06		0.051		

D = diopter; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.
Mean was calculated with data from both eyes. *P* value was generated by the generalized estimating equation model, which incorporated all the valuable data. Sequential Bonferroni correction was applied for the pairwise comparisons.
*Placebo first year then switched over to 0.05% atropine at the beginning of the second year.
†Significant was set at 0.05.
‡Comparison between baseline to 12 mos and 12 to 24 mos.

up atropine concentration or combined therapy with other interventions for poor responders should be considered in future clinical trials.[19]

In the ATOM 2, 0.01% atropine was similar to 0.1% atropine and 0.5% atropine in efficacy over 2 years, with a mean SE progression of −0.49 D, −0.38 D, and −0.30 D, respectively (Table 4).[8] Efficacy in the second year was significantly better when compared with the first year in the 0.01% atropine group, but not when compared with the 0.1% and 0.5% atropine groups (Table 4).[8] Similarly in our study, the efficacy of 0.01% in the second year was mildly better than that in the first year (Table 2), with an improvement of 0.12 D, in line with the results of ATOM 2, but at a smaller magnitude. This phenomenon was not observed in the higher concentrations of 0.05% and 0.025% (Table 4). We postulate the better efficacy in 0.01% atropine during the second year was the result of a cumulative effect over time. At 0.01%, atropine may not have reached its concentration threshold, and therefore, the treatment effect took time to reach its maximum. This can

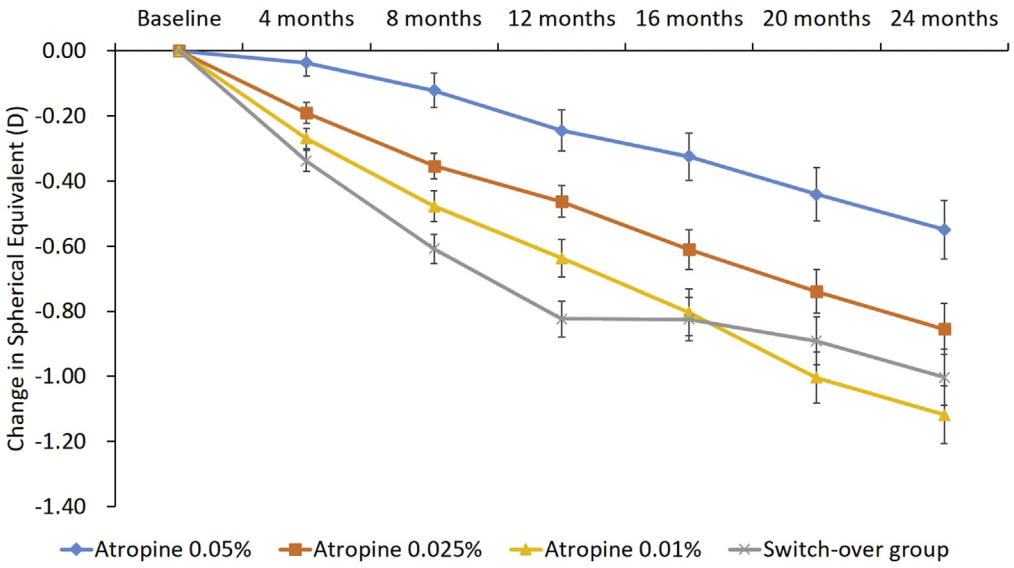

Figure 2. Graph showing change in spherical equivalent in treatment groups over 2 years. The switchover group received placebo during first year and was then switched over to 0.05% atropine at the beginning of the second year. D = diopter. Error bars represent 1 standard error.

be more prominent during the initial period of treatment, but with accumulation of atropine over time, it is possible that the efficacy reaches a plateau. However, for the higher concentrations of 0.025% and 0.05%, treatment likely has reached its maximal effect during the initial period, and therefore, no further better efficacy over time was noted. Furthermore, the role of natural slowing down in progression with age would be more prominent in the 0.01% atropine group compared with the 0.025% and 0.05% atropine groups because of the weaker efficacy of the treatment effect of 0.01% atropine.

Pupil mydriasis leading to photophobia and blurred near vision resulting from loss of accommodation remained important side effects of atropine eye drops. In this 2-year study, we noted all concentrations were well tolerated over the 2 years. Pupil size increase was concentration dependent, with an increase in photopic pupil sizes of 1.25 mm, 0.67 mm, and 0.60 mm in 0.05%, 0.025%, and 0.01% atropine groups, respectively. The change in pupil size did not increase with time. An increase of 3 mm or more in photopic pupil size could be a threshold of significant discomfort.[20,21] Therefore, concentrations of less than 0.05% atropine should be tolerable. Also, the photophobia rate at 2 years was 8.6%, 4.7%, and 5.5% for the 0.05%, 0.025%, and 0.01% atropine groups, respectively. Accommodation amplitude loss at −2.05 D, −1.66 D, and −0.63 D remained similar to the first-year results for the 0.05%, 0.025%, and 0.01% atropine groups, respectively. Of note,

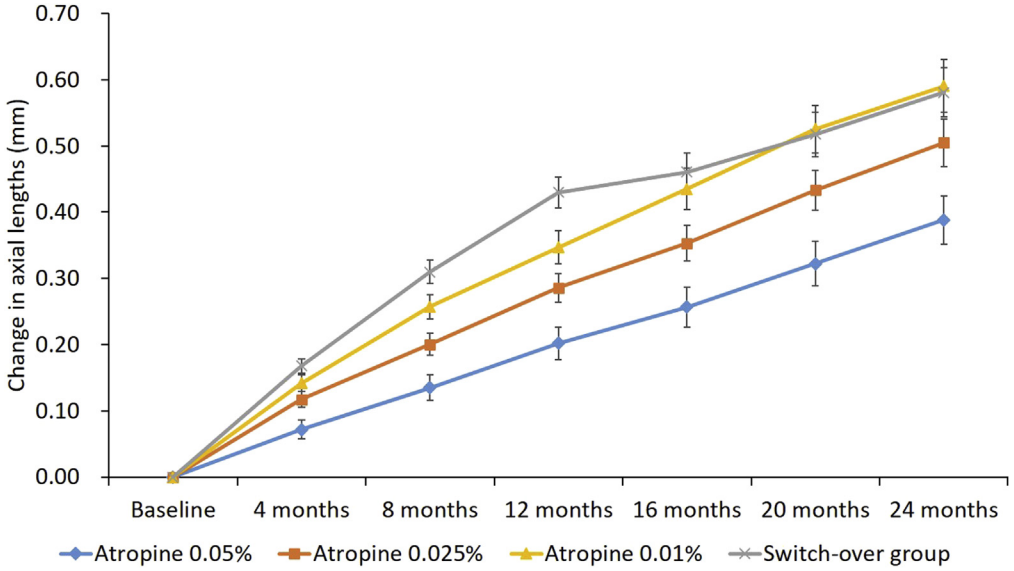

Figure 3. Graph showing change in and axial length in treatment groups over 2 years. The switchover group received placebo during first year and was then switched over to 0.05% atropine at the beginning of the second year. Error bars represent 1 standard error.

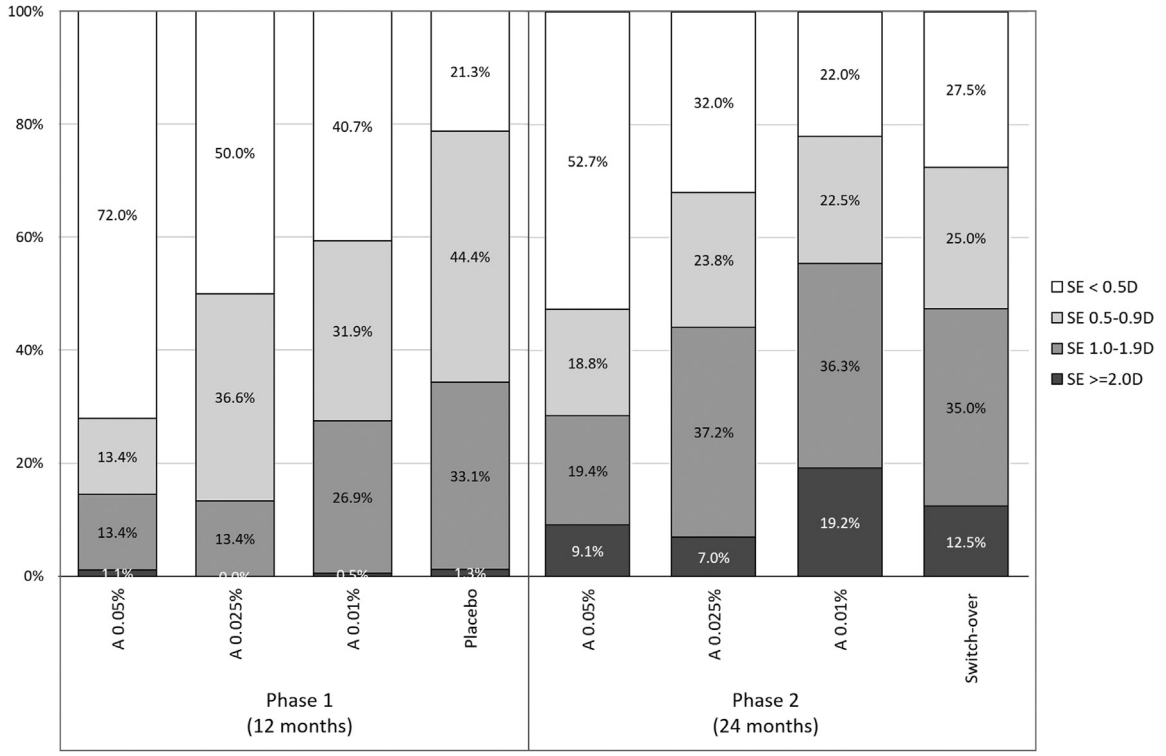

Figure 4. Bar graph showing the distribution of the various rates of progression of myopia during the Low-Concentration Atropine for Myopia Progression Study phase 1 (12 months) and phase 2 (24 months). Progression of myopia according to severity with 0.05% atropine, 0.025% atropine, 0.01% atropine, and placebo switchover to 0.05% atropine group. A = atropine; D = diopter; SE = spherical equivalent.

an increased proportion of participants required photochromic glasses in the switchover group, up to 55%. In our study design, parents could choose photochromic glasses either because of children reporting photophobia or parental concerns regarding the side effects of pupil dilatation. In the switchover group, parents were informed of switching over to a treatment group (while the exact treatment concentration was not revealed); it was possible that parents tended to choose photochromic lenses for protection against side effects. Distance and near vision were similar in all groups. Vision-related quality of life was similar across all groups at the end of 2 years. Altogether, we observed that the side effects of low concentration atropine remained stable over time and were well tolerated.

One main limitation of the study is the switchover of the placebo group to 0.05% atropine during the second year. The switchover was based on ethical consideration after we proved the myopia-slowing effect of low-concentration atropine as compared with placebo at the end of the first year. Therefore, our study did not show placebo-compared efficacy for the 0.05% atropine, 0.025% atropine, and 0.01% atropine groups over 2 years. Nevertheless, our

Table 3. Side Effects and Adverse Events over 2 Years

	0.05% Atropine (n = 93)		0.025% Atropine (n = 86)		0.01% Atropine (n = 91)		Switchover Group (n = 80)	
	Over 1 Year	*Over 2 Years*	*Over 1 Year*	*Over 2 Years*	*Over 1 Year*	*Over 2 Years*	*Over 1 Year*	*Over 2 Years*
Photochromic glasses needed	29 (31.2)	31 (33.3)	35 (40.7)	38 (44.2)	30 (33.0)	31 (34.1)	40 (50.0)	44 (55.0)
Progressive glasses needed	0	1 (1.1)	0	1 (1.2)	1 (1.0)	2 (2.2)	1 (1.3)	1 (1.3)
Photophobia with photochromic glasses	2 (2.2)	4 (4.3)	3 (3.5)	1 (1.2)	1 (1.0)	1 (1.0)	1 (1.3)	3 (3.8)
Photophobia without photochromic glasses	0	4 (4.3)	3 (3.5)	3 (3.5)	1 (1.0)	5 (5.5)	0	4 (5.0)
Allergic conjunctivitis	2 (2.2)	9 (9.7)	5 (5.8)	10 (11.6)	7 (7.7)	11 (12.1)	7 (8.8)	7 (8.8)
Hospitalization	3 (3.2)	4 (4.3)	5 (5.8)	6 (7.0)	3 (3.3)	5 (5.5)	2 (2.5)	2 (2.5)

Data are no. (%). Only participants who completed the 2-year follow-up were included.

Table 4. Comparison between the Low-Concentration Atropine for Myopia Progression (LAMP) Study and the Atropine for the Treatment of Myopia 2 (ATOM2) Study over 2 Years

	Atropine for the Treatment of Myopia 2 Study*			Low-Concentration Atropine for Myopia Progression Study			
	0.5% Atropine	*0.1% Atropine*	*0.01% Atropine*	*0.05% Atropine*	*0.025% Atropine*	*0.01% Atropine*	*Placebo*
Change in SE (D)							
First year	−0.17	−0.31	−0.43	−0.25	−0.46	−0.64	−0.82
Second year	−0.13	−0.07	−0.06	−0.30	−0.39	−0.48	
Total over 2 yrs	−0.3	−0.38	−0.49	−0.55	−0.85	−1.12	
Change in AL (mm)							
First year	0.11	0.13	0.24	0.20	0.29	0.35	0.43
Second year	0.16	0.15	0.17	0.18	0.22	0.25	
Total 2 over yrs	0.27	0.28	0.41	0.39	0.50	0.59	

AL = axial length; D = diopter; SE = spherical equivalent.
*Atropine for the Treatment of Myopia 2 data from ref. 8.

results include an arm-to-arm comparison among 0.05% atropine, 0.025% atropine, and 0.01% atropine over a 2-year period in a randomized control design to determine optimal concentrations. Additionally, our results are based on the complete case without imputation; therefore, an unmeasured confounder may exist and could bias the estimated treatment effect. Furthermore, our study was not powered to evaluate the differences in adverse events among all groups.

The phase 1 results of the LAMP study confirmed the efficacy of low-concentration atropine compared with placebo, along with a concentration-dependent response. In the first year, 0.05% atropine was the best concentration. Herein, the phase 2 results confirmed 0.05% atropine remained the best concentration after 2 years with a concentration-dependent response. One remaining question is the rebound phenomenon after cessation of atropine 1%, 0.5%, 0.1%, and 0.01%, as observed in the ATOM 1 and ATOM 2 studies. Previous postulations suggested that atropine continuously administered for 2 years may lead to a stabilization effect, and therefore could be stopped afterward. However, the subsequent rebound phenomenon observed affected the treatment regimen and weaning-off strategy. Therefore, we are planning for a phase 3 (third-year) study randomization of each of the 3 groups—0.05% atropine, 0.025% atropine, and 0.01% atropine—into a washout group and treatment-continued group to evaluate (1) efficacy of 0.05% atropine, 0.025% atropine, and 0.01% atropine over 3 years; (2) whether treatment should be stopped after 2 years of atropine; and (3) the rebound phenomenon of 0.05%, 0.025%, and 0.01% atropine after cessation of treatment. Finally, we plan to conduct phase 4 of the study to resume atropine treatment in children whose myopia refraction and AL progressed during the washout period to determine the long-term efficacy of low-concentration atropine over a 5-year period.

In summary, the results of the LAMP phase 2 study as reported herein show that 0.05% atropine is the best concentration among the concentrations studied for myopia control over a 2-year period, although 0.01% atropine was mildly more effective in the second year than the first year, but 0.05% and 0.025% atropine were not more effective in the second year than the first year. All concentrations of atropine were well tolerated without apparent adverse effects on the quality of life. The efficacy of 0.05% atropine observed was double that observed with 0.01% atropine in SE progression over 2 years.

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Footnotes and Financial Disclosures

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No animal subjects were included in this study.

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Data collection: Yam, Li, Tang

Obtained funding: Yam, Chen

Overall responsibility: Yam, Li, Zhang, Tang, Yip, Kam, Ko, Young, Tham, Chen, Pang

Abbreviations and Acronyms:
AL = axial length; **ATOM** = Atropine for the Treatment of Myopia; **BCVA** = best-corrected visual acuity; **BMI** = body mass index; **D** = diopter; **IOP** = intraocular pressure; **LAMP** = Low-Concentration Atropine for Myopia Progression; **SE** = spherical equivalent; **VA** = visual acuity; **VFQ** = visual function questionnaire.

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