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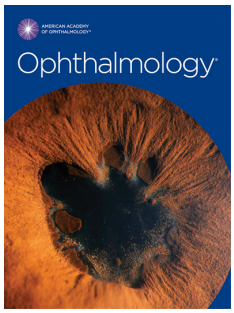

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PII: S0161-6420(19)32356-5

DOI: https://doi.org/10.1016/j.ophtha.2019.12.011

Reference: OPHTHA 11028

To appear in: *Ophthalmology*

Received Date: 19 June 2019

Revised Date: 12 December 2019

Accepted Date: 13 December 2019

Please cite this article as: Yam JC, Li FF, Zhang X, Tang SM, Kei Yip BH, Kam KW, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP, Two-Year Clinical Trial of the Low-concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report, *Ophthalmology* (2020), doi: https://doi.org/10.1016/j.ophtha.2019.12.011.

Two-Year Clinical Trial of the Low-concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report

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Running Head: Low-concentration Atropine for Myopia Progression (LAMP) Study

Financial Disclosure(s): The authors have no proprietary or commercial interest in any materials disclosed in this article.

This study was supported in part by the General Research Fund (GRF), Research Grants Council, Hong Kong (14111515 [JCY]); Health and Medical Research Fund (HMRF), Hong Kong (5160836, [LJC]), and the Direct Grants of the Chinese University of Hong Kong, (4054193 [LJC] and 4054121 & 4054199 [JCY]); the UBS Optimus Foundation Grant 8984 (JCY); the Centaline Myopia Fund [JCY]; and the CUHK Jockey Club Children Eye Care Programme.

HUMAN SUBJECTS: Written informed consents were obtained from parents or guardians, and verbal consent from the study subjects. This study was registered with the Centre for Clinical Research and Biostatistics (CCRB) Clinical Trials Registry, The Chinese University of Hong Kong (registration no: 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.

No animal subjects were used in this study.

Abbreviations and acronyms

BMI = body mass index; IOP = intraocular pressure; VA = visual acuity; logMAR = logarithm of the minimum angle of resolution; D = diopter; VFQ = visual function questionnaires; SE = spherical equivalent; AL= axial length

Abstract

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

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

Participants: Three hundred eighty-three (87%) of the 438 children 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 of the placebo group in phase 1 were switched to receive 0.05% atropine from the beginning of the second year follow up, while 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 measure: 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±0.86D, 0.85±0.73D, and 1.12±0.85D in the 0.05%, 0.025%, 0.01% atropine groups, respectively (P=0.015, P<.001, and P=0.02 for pairwise comparisons); with mean AL changes over two years of 0.39±0.35mm, 0.50±0.33mm, and 0.59±0.38mm (P=0.04, P<0.001, and P=0.10). Compared with the 1st year, the 2nd year efficacy of 0.05% and 0.025% remained similar (p=0.45 and p=0.31), but mildly improved in the 0.01% atropine group (P=0.04). For the phase 1 placebo group, the myopia progression was significantly reduced after switching to 0.05% atropine (SE change 0.18D in second year vs. 0.82D in first year, p<0.001; AL elongated 0.15mm in second year vs 0.43mm 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 two years, the observed efficacy of 0.05% atropine observed was double that observed with 0.01% atropine, and it remained the optimal concentration amongst the studied atropine concentrations in slowing myopia progression.

Background

Myopia is a public health threat worldwide with increasing prevalence in most regions over the past decades especially in East Asia.[1-4] Low-concentration atropine eye drop is an emerging therapy for myopia control,[5 6] but its optimal concentration and long-term efficacy is still not defined. In the first-year (phase 1) results of the Low-concentration Atropine for Myopia Progression (LAMP) study, 0.05% atropine conferred the best treatment-side effect ratio among 0.05%, 0.025%, and 0.01% atropine over one year.[7] Of note, in the ATOM 2 study, 0.01% atropine was more effective in the second year than the first year. The change of SE and AL in the 0.01% atropine group was -0.43 diopter (D) and 0.24mm, respectively, in the first year, but only -0.06D and 0.17mm in the second year. Interestingly, this effect was not found in higher concentration of atropine at 0.1% or 0.5%.[8] The authors of ATOM 2 therefore concluded that there is clinically similar efficacy of 0.01% atropine with 0.5% and 0.1% atropine. In contrast, we found 0.05% atropine better than 0.025% and 0.01% over one year in the LAMP study,[7] we went on to study their longer-term (two years) efficacies and side effects in phase 2 of this study.

We aimed to answer the following questions in the phase 2 of the LAMP study: 1) Which concentration of atropine confers the best efficacy in myopia control over two years? 2) Are the efficacies of low-concentration atropine better in the second year than the first year? 3) Are the side effects of low concentration atropine similar in the first and second year, and remained tolerable? 4) What is the efficacy after administration of 0.05% atropine to the placebo self-control group for a 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 aged 4 to 12 years 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 past one year were enrolled in this double-blinded, single centre clinical trial. After excluding those with ocular diseases, previous use of interventions (such as atropine, pirenzepine, orthokeratology lens, or other optical methods) for myopia control, or allergy to atropine, or systemic diseases (e.g., cardiac or respiratory illness), the children were randomized to 4 treatment groups (0.05%, 0.025%, 0.01% atropine, and placebo) and were then 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 till the end of phase 2 (now called the switch-over group) because of ethical considerations since low-concentration atropine were proven effective compared to the placebo group during the first year. Children in the 0.05%, 0.025%, and 0.01% atropine groups remained on the same concentration for the whole 2 years of study. Subjects in the switch-over group were informed of the switch-over arrangement, but all remained masked to which atropine group they have been allocated. Subjects in the 0.05%, 0.025%, and 0.01% atropine group 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 consents were obtained from parents or guardians, and verbal consent from the study subjects. This study was registered with the Centre for Clinical Research and Biostatistics (CCRB) Clinical Trials Registry, The Chinese University of Hong Kong (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 medication was administered once every night. They were pre-packaged as eye drops in mono-dose preparations with atropine sulfate concentrations at 0.05%, 0.025% or

0.01% (0.5ml 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. Drug Trial Certificate was granted by the Department of Health, Hong Kong SAR. Compliance with trial medication was classified according to the mean number of days trial medication was used each week as reported by the subjects. Compliance rates of >75% (i.e., a mean of 5.25 days/week) were considered acceptable. Subjects were also 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 subjects experienced difficulty with near vision. All subjects were prescribed with best-corrected spectacles. Validated questionnaires on outdoor time and near work, as well as CHI-VFQ-25, were administered to parents at the end of the second year. [9] Examinations in phase 2 were similar to 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 (logMAR), near visual acuity under best-corrected distance spectacle correction at 40 cm, the near point of accommodation with best-corrected distance spectacle correction. Accommodation amplitude was calculated as the inverse of near point of accommodation. Photopic pupil size and mesopic pupil size were measured by the OPD-Scan III (Nidek, Japan). Cycloplegic autorefraction was performed using an autorefractor (Nidek ARK-510A, Gamagori, Japan) after the cycloplegic regime, which consisted of at least two cycles of eye drops. In the first cycle, two separate eye drops, cyclopentolate 1% (Cyclogyl, Alcon-Convreur, Rijksweg, Belgium) and tropicamide 1% (Santen, 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. Since maximum cycloplegia to maximally inhibit accommodation is necessary for accurate measurement of refractive errors in children and

thereby 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 less than 0.25 D apart, were obtained and averaged. Spherical equivalent (SE) was calculated as spherical power plus half of the cylinder power. Ocular axial length (AL) was measured on a Zeiss IOL Master (Carl Zeiss Meditec Inc., Dublin, CA), with average of five readings within deviation of 0.05 mm or less.

The primary outcome in this study was myopia progression, in term of SE change, over two years (combined phase 1 and phase 2). The secondary outcomes included the change in AL over two years, SE change and AL change at second year, and side effect parameters, such as changes in accommodation amplitude, mesopic and photopic pupil sizes, distance BCVA, and near VA, and the CHI-VFQ-25. All parameters, including SE, AL, accommodation amplitude, pupil size, and visual acuity, were monitored from baseline.

During each visit, subjects 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. Change of parameters was 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 prior to 2 years. [11] Chi-square test and Fisher's Exact test were used to test for the group

difference in categorical data. Generalized estimating equations (GEEs) 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 Bonferonni adjustment.[15] To evaluate the potential for confounding, analyses were repeated adjusting for age, gender, and baseline SE (the results were similar to unadjusted, Supplemental Table 1). 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 version 24 (IBM Corp., Armonk, NY, USA) was used for data analyses and $P<0.05$ was considered statistically significant.

Results

Totally 383 (87%) of the 438 children aged 4 to 12 years 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), with 102, 91, 97, and 93 subjects in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switch-over group, respectively (Figure 1). The baseline characteristics of these 383 subjects and the 55 subjects who dropped from the study during phase 1 were similar (Supplemental Table 2). Furthermore, the 350 subjects who completed two-years of follow up were similar to the 88 subjects who did not (Table 1).

Changes in SE and AL over 2 years for 0.05%, 0.025%, and 0.01% atropine

At the end of two years, the mean SE change was -0.55±0.86D, -0.85±0.73D, and -1.12±0.85D, in the 0.05%, 0.025% and 0.01% atropine groups, respectively, with significant differences between groups ($P=0.015$, $P<.001$, and $P=0.02$ after Sequential Bonferonni

correction; Table 2 and Figure 2). There was no age-treatment interaction (P=0.52). The respective mean AL changes over two years were 0.39±0.35mm, 0.50±0.33mm, and 0.59±0.38mm (P=0.04, P<.001, and P=0.10 after Sequential Bonferonni correction; Table 2 and Figure 3). The ophthalmic parameters over two years in each visit were summarized in Supplementary Table 3. During the two years, 52.7 %, 32.0%, 22.0% and 27.5% of subjects in the 0.05%, 0.025% and 0.01% atropine and switch-over group, respectively, progressed less than 0.5D; whereas 9.1%, 7.0%, 19.2% and 12.5% progressed by ≥ 2.0D (Figure 4).

Comparison of changes of SE and AL in the second year versus the first year

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

Changes of SE and AL in the switch-over group

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

Changes in accommodation, pupil size, and visual acuity

Changes in accommodation amplitude at the end of two years were 2.05D, 1.66D, 0.63D in the 0.05%, 0.025% and 0.01% atropine groups respectively, which were similar to that of first year, and followed concentration-related response (Table 2, and Supplementary Tables 2-5). Likewise, changes in pupil size at the end of two years were similar to that of first year, and followed concentration-related response (Table 2, and Supplementary Tables 2-5). Distance BCVA and near BCVA in all groups were not affected (Table 2 and Supplementary Tables 2-5).

Adverse events, and vision-related quality of life

Photochromic glasses were needed in about 30% of the subjects, and progressive lens spectacles were not required in general (Table 3). There were more subjects complaining of photophobia at the end of second year if not wearing photochromic glasses (Table 3). Occurrence of allergic conjunctivitis was similar across the groups. (Table 3) Over the two-year period, 17 subjects had 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 subject. In the 0.025% atropine group, 1 subject each had gastroenteritis, pneumonia, appendectomy, or elective circumcision surgery, and 2 subjects had influenza. In the 0.01% atropine group, 1 subject had lip injury requiring surgical repair, 1 subject had influenza, 1 subject had distal radius fracture requiring plaster-casting, and 1 subject each had rash, or pain of leg. In switch-over group, 2 subjects had influenza. Compliance, defined as >75% (average of 5.25 days/week), was 92.6%, 93.0%, 91.3% and 92.5% in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and switch-over group, respectively. There were no differences in the vision-related quality of life among the 0.05%, 0.025%, and 0.01% atropine groups (Supplementary Table 6).

Discussion

This report presents the second-year results (phase 2) of the LAMP study of 4 treatment groups: 0.05%, 0.025% and 0.01% atropine used daily for two years, and switch-over from using placebo after the first year to using 0.05% atropine daily in the second year. The concentration-dependent response remained, and 0.05% atropine continued to be the most effective among 0.05%, 0.025% and 0.01% atropine in myopia control after two years.

Since the ATOM 2 study, use of low concentration atropine including 0.01% has surged in popularity in retarding myopia progression.[11] 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 show that 0.05% atropine is the optimal concentration over a two-year period. Due to the switch-over design in the placebo group, there is no data on the natural myopia progression over two years. Nevertheless, based on the predictive model by Donovan et al.,[13] Progression (Asians) = -0.014*Age^2+0.39*Age-3.16, the predicted natural progression of our original placebo group should be -0.73D in the second year, giving a total progression of -1.55D in two years. Using this for comparison, 0.05%, 0.025%, and 0.01% atropine could achieve respectively 64.5%, 45.2%, and 27.7% reduction of SE progression over two years.

Comparisons between our study and ATOM 2 study was summarized in table 4. It appeared that 0.5% and 0.1% atropine in ATOM 2 [10] achieved better effect than 0.05% atropine in our present study, consistent with the concentration-dependent response. Notably, 0.01% in the ATOM 2 study had similar anti-myopia effect to 0.05% atropine in our study, but stronger than our 0.01% atropine (Table 4). In a retrospective case-control study of 57 children aged 6-12 years, 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 non-treatment controls.[16] In another retrospective study with mean follow up of 4.5 years, the

0.05% to 0.1% atropine treatment group had a mean myopia progression rate at -0.23D/year, compared to -0.86D/year in non-treatment controls.[17] The finding was consistent with our results, although these studies were retrospective in design, and provided no axial length data. A low progression rate of -0.1D/year was also reported in a case-control retrospective study of 60 Caucasian children receiving 0.01% atropine based on non-cycloplegic refraction with no axial length measurement.[17] Of note, direct comparisons of our data with other studies should be interpreted with cautions, 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 2D in two 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 up atropine concentration or combined therapy with other interventions for poor responders should be considered in future clinical trials.[18]

In ATOM 2, 0.01% atropine was similar to 0.1%, and 0.5% in efficacy over two years, with mean SE progression at -0.49 D, -0.38 D and -0.30 D, respectively (Table 4).[10, 13] Efficacy in the second year was significantly better when compared with the first year in the 0.01% group, but not the 0.1% and 0.5% groups (Table 4).[13] Similarly in our study, the efficacy of 0.01% in the second year was mildly better than the first year (Table 2) with an improvement of 0.12 D, in line with 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 at the second year was due to cumulative effect over time. Atropine at 0.01%, atropine may not have reached its concentration threshold, and therefore, the treatment effect takes time to reach their maximal effect. This can be more prominent at the initial period of treatment, but with accumulation of atropine over time, it is possible the efficacy would reach a plateau. On the other hand, for the higher concentrations

of 0.025% and 0.05%, they likely have reached their maximal effect at the initial period, and therefore, no further better efficacy over time was noted. Furthermore, the role of natural slowing down in the progression with age would be more prominent in the 0.01% atropine group compared with 0.025% and 0.05% because of the weaker efficacy of the treatment effect of 0.01% atropine.

Pupil mydriasis leading to photophobia and blurred near vision due to loss of accommodation remained important side effects of atropine eye drops. In this two-year study, we noted all concentrations were well-tolerated over the two years. Pupil size increase was concentration-dependent, with an increase in photopic pupil sizes of 1.25mm, 0.67mm, and 0.60mm in 0.05%, 0.025%, and 0.01% atropine group, respectively. The change in pupil size did not increase with time. An increase of ≥3mm in photopic pupil size could be a threshold of significant discomfort.[19, 20] Therefore, concentrations below 0.05% atropine should be tolerable. Also, photophobia rate at two years was 8.6%, 4.7%, and 5.5% for the 0.05%, 0.025% and 0.01% atropine groups, respectively. Accommodation amplitude loss, respectively at -2.05D, -1.66D, and -0.63D, remained similar to the first-year results for 0.05%, 0.025%, and 0.01% atropine. Of note, there was increased proportion of subjects needing photochromic glasses in the switch-over group, up to 55%. In our study design, parents could choose photochromic glasses either because of children's complain of photophobia or parental concerns on side effects of pupil dilatation. In the switch-over group, parents were informed switching over to treatment group, (while the exact treatment concentration was not revealed), it was possible that parents tended to choose photochromic lens for protection of side effect. Distance and near vision were similar in all groups. Vision-related quality of life was similar across all groups at the end of two years. Altogether, we suggested that the side effects of low concentration atropine remained stable over time, and were well tolerated.

One main limitation of the study is the switch-over of the placebo group to 0.05% atropine during the second year. The switch-over was based on ethical consideration once we have proven myopia slowing effect of low-concentration atropine as compared with the placebo group at the end of the first year. Therefore, our study did not have the placebo-compared efficacy of 0.05%, 0.025%, and 0.01% over two years. Nevertheless, our results include an arm-to-arm comparison among 0.05%, 0.025%, and 0.01% over two-year period, on a randomized control design to determine the optimal concentrations. Additionally, our results based on the complete case without imputation, therefore, 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 two years with 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 ATOM 1 and ATOM 2 studies. There were previous postulations in that atropine continuously administered for two years may lead to stabilization effect, and therefore could be stopped afterwards. However, the subsequent rebound phenomenon observed affects the treatment regimen and wean off strategy. Therefore, we plan for our phase 3 (third year) study randomization of each of the three groups 0.05%, 0.025%, and 0.01% into wash out group and treatment-continued group, in order to evaluate 1) efficacy of 0.05%, 0.025%, and 0.01% atropine group over three years; 2) whether treatment should be stopped after two 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 in children whose myopia refraction and axial length

progressed during the washout period, to determine the long-term efficacy of low concentration atropine at a five-year period.

In summary, results of LAMP phase 2 study as reported here show that 0.05% atropine is the best concentration amongst the concentrations studied for myopia control over a two-year period, although 0.01% atropine was mildly more effective in the second year than the first year, but not in 0.05% and 0.025% atropine. 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 two years.

Acknowledgments

We thank all the study subjects and their parents for participating in this clinical trial. We thank Mr. Yuzhou Zhang from the Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong for his support on statistical analysis. We are very grateful to Ms Mandy P.H. Ng from the Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong for her overall coordination and logistic arrangements on the trial.

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Figure Legends

Figure 1. Subject flowchart of Low-concentration Atropine for Myopia Progression (LAMP) study.

Figure 2. Change in spherical equivalent in treatment groups over 2 years.

D= diopters; Switch-over group: placebo group during first year and was then switched over to 0.05% atropine group at the beginning of the second year.

Error bars represent one standard error.

Figure 3. Change in and axial length in treatment groups over 2 years.

Switch-over group: placebo group during first year and was then switched over to 0.05% atropine group at the beginning of the second year.

Error bars represent one standard error.

Figure 4. Distribution of the various rates of progression of myopia at LAMP phase 1 (12 months) and phase 2 (24 months).

Progression of myopia according to severity with atropine 0.05%, 0.025%, 0.01%, and placebo switch over to 0.05% atropine group.

Table 1. Demographics at the baseline characteristics in Atropine 0.05%, 0.025%, 0.01% and placebo-switched-to-0.05% atropine groups who completed 2 years versus those who have not completed 2 years.

	Completed 2 years (N=350)				Not completed 2 years (N=88)			
	0.05% Atropine (n=93)	0.025% Atropine (n=86)	0.01% Atropine (n=91)	Switch-over group # (n=80)	0.05% Atropine (n=16)	0.025% Atropine (n=22)	0.01% Atropine (n=19)	Switch-over group # (n=31)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	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)
Gender (Male, %)	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/m2)	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 (um)	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 (hours per day)[a]	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)
Nearwork (dioptic hours per day)[b]	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)

#Switch-over group: subjects receiving placebo during the first year, and were then switch over to 0.05% atropine group at the beginning of the second year.
VA = visual acuity; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; D = diopter
a, outdoor activity = outdoor exercise + outdoor leisure activity;
b, nearwork = 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	3) 0.05% Atropine (N=93) Mean	SD	2) 0.025% Atropine (N=86) Mean	SD	1) 0.01% Atropine (N=91) Mean	SD	0) Switch-over group (N=80) Mean	SD	Pairwise comparisons p values (3 vs 2, 3 vs 1, 2 vs 1)
Spherical equivalent (SE), D									
Baseline to 24 months	-0.55	0.86	-0.85	0.73	-1.12	0.85	-1.00	0.77	(0.015*, <.001*, 0.02*)
A. Baseline to 12 months	-0.25	0.61	-0.46	0.45	-0.64	0.56	-0.82	0.49	(0.004*, <.001*, 0.01*)
B. 12 months to 24 months	-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*		<.001*		
Axial length, mm									
Baseline to 24 months	0.39	0.35	0.50	0.33	0.59	0.38	0.58	0.33	(0.04*, <.001*, 0.10)
A. Baseline to 12 months	0.20	0.24	0.29	0.20	0.35	0.24	0.43	0.21	(0.012*, <.001*, 0.049*)
B. 12 months to 24 months	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*		<.001*		
Photopic pupil size, mm									
Baseline to 24 months	1.25	1.13	0.67	0.87	0.60	0.84	1.18	1.30	(<.001*, <.001*, 0.99)
A. Baseline to 12 months	1.02	1.02	0.81	0.89	0.55	0.77	0.10	1.10	(0.22, <.001*, 0.02*)
B. 12 months to 24 months	0.21	1.00	-0.12	0.93	0.05	0.95	1.08	1.24	(0.04*, 0.22, 0.21)
# p value	<.001*		<.001*		<.001*		<.001*		
Mesopic pupil size, mm									
Baseline to 24 months	0.69	0.64	0.34	0.62	0.26	0.58	0.62	0.75	(<.001*, <.001*,0.99)
A. Baseline to 12 months	0.56	0.62	0.41	0.61	0.27	0.44	0.01	0.55	(0.14, <.001*, 0.03*)
B. 12 months to 24 months	0.13	0.51	-0.05	0.57	-0.02	0.45	0.61	0.65	(0.02*, 0.01*, 0.59)
# p value	<.001*		<.001*		<.001*		<.001*		
Accommodation amplitude, D									
Baseline to 24 months	-2.05	3.19	-1.66	2.79	-0.63	3.06	-1.79	2.86	(0.99, <.001*, 0.02*)
A. Baseline to 12 months	-1.96	2.89	-1.70	2.50	-0.21	2.84	-0.22	2.75	(0.99, <.001*, <.001*)
B. 12 months to 24 months	-0.10	2.48	-0.01	2.37	-0.41	2.52	-1.58	2.26	(0.99, 0.38, 0.26)
# p value	<.001*		<.001*		0.61		0.001*		
Distance VA, logMAR									
Baseline to 24 months	-0.03	0.06	-0.03	0.06	-0.04	0.06	-0.03	0.06	(0.68, 0.44, 0.34)
A. Baseline to 12 months	-0.02	0.06	-0.02	0.06	-0.03	0.07	-0.02	0.05	(0.99, 0.32, 0.16)
B. 12 months to 24 months	-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 months	-0.01	0.09	-0.01	0.08	-0.02	0.09	0.02	0.10	(0.99, 0.62, 0.86)
A. Baseline to 12 months	-0.003	0.10	-0.003	0.08	-0.03	0.11	-0.02	0.10	(0.99, 0.13, 0.1)
B. 12 months to 24 months	-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		

Switch-over group: placebo first year then switch over to 0.05% atropine group at the beginning of the second year; D = diopter; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; VA = visual acuity.

Mean was calculated with both eye data. p value was generated by the generalized estimating equation model, which incorporated all the valuable data. Sequential Bonferonni correction was applied for the pairwise comparisons.

p value was the comparison between A and B.

*Significant was set at 0.05.

Table 3. Side effects and adverse events over two years.

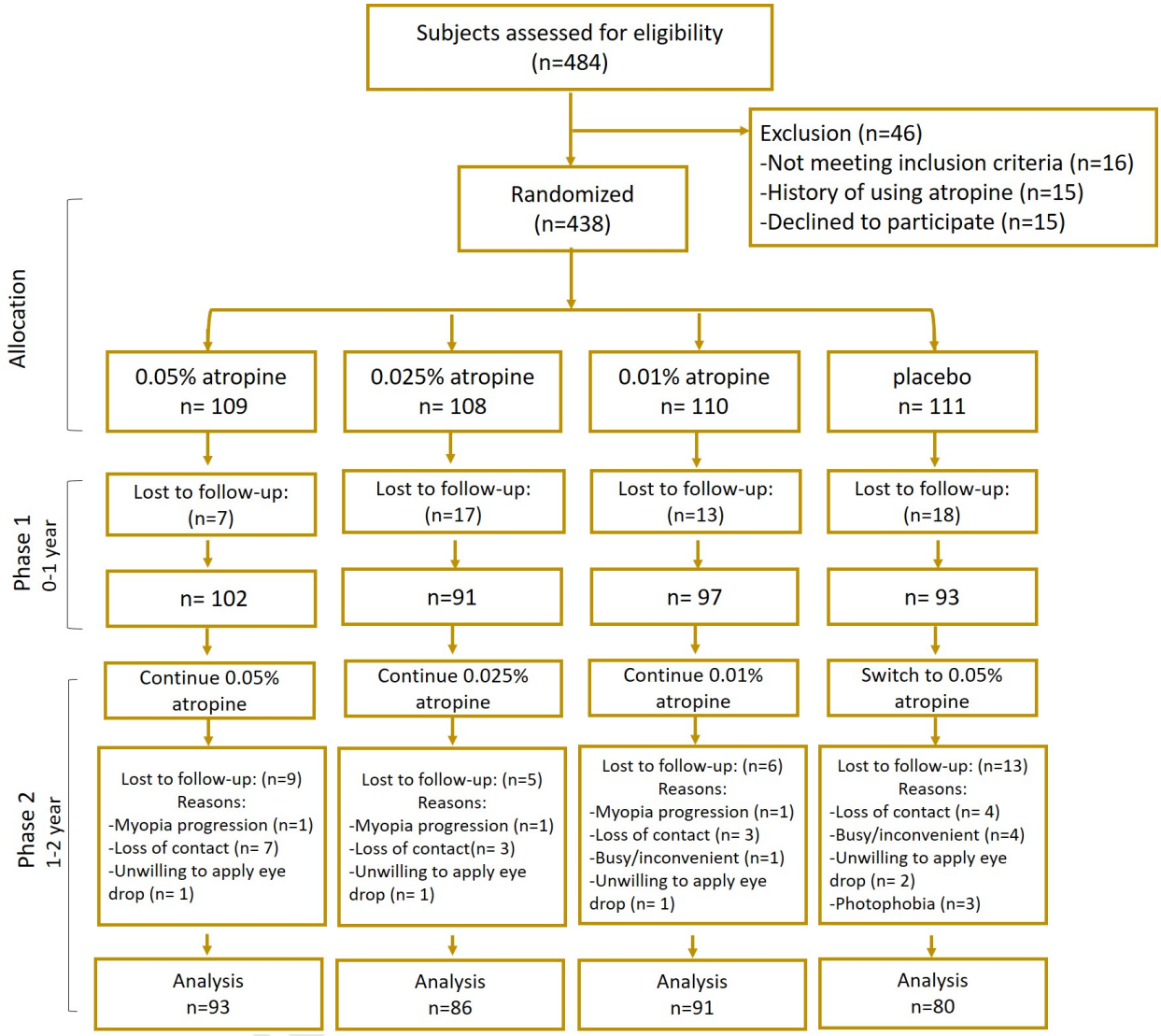
	0.05% Atropine (n=93)		0.025% Atropine (n=86)		0.01% Atropine (n=91)		Switch-over group (n=80)	
	over 1 year	over 2 years	over 1 year	over 2 years	over 1 year	over 2 years	over 1 year	over 2 years
Photochromic glasses needed	29 (31.2%)	31 (33.3%)	35 (40.7%)	38 (44.2%)	30 (33.0%)	31 (34.1%)	40 (50.0%)	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%)

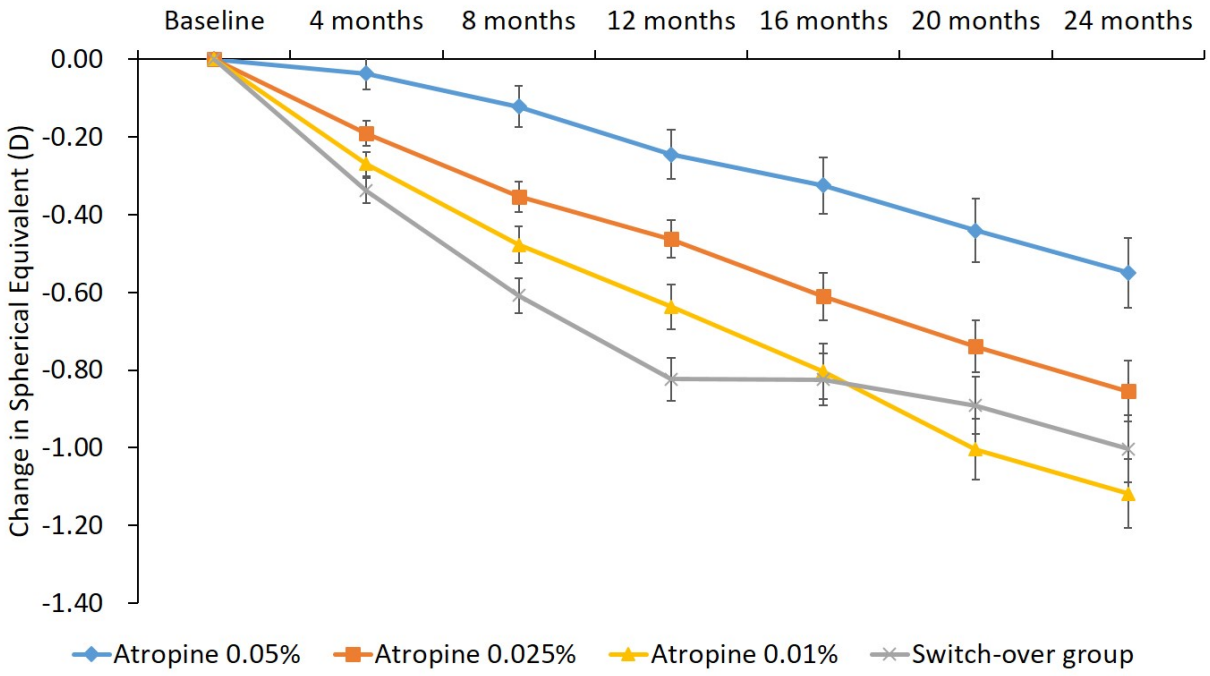
Only subjects at 2-year follow-up were included.

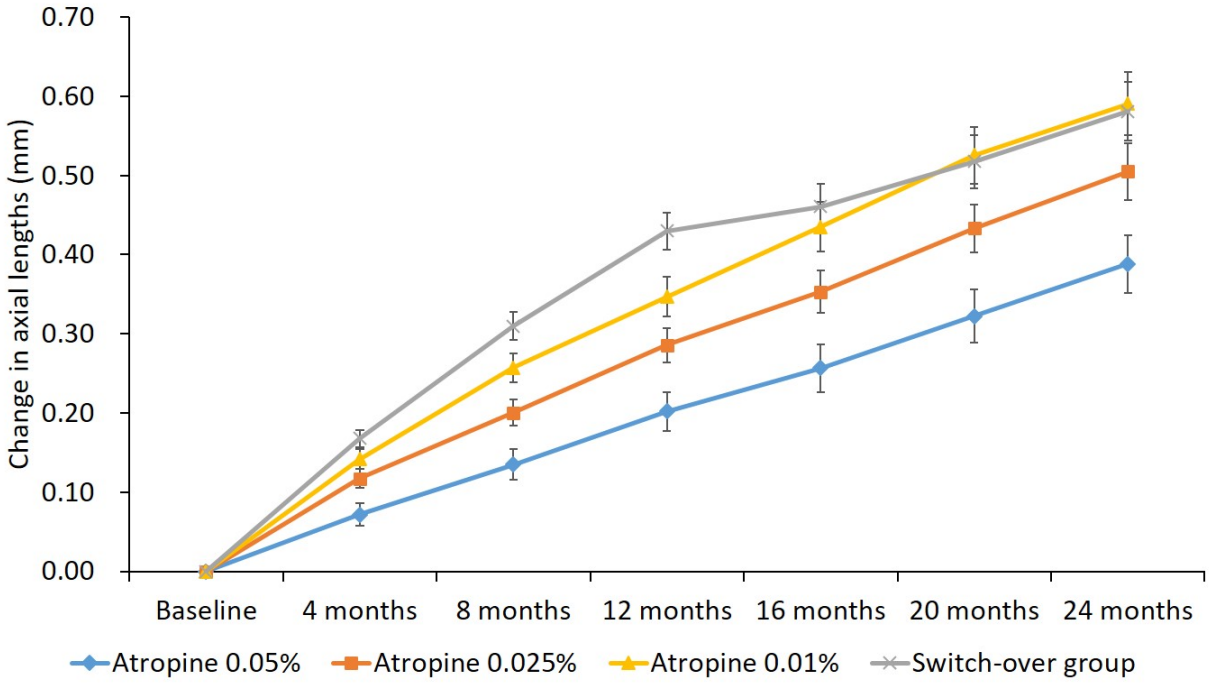
Table 4. Comparison between LAMP study and ATOM2 study over two years.

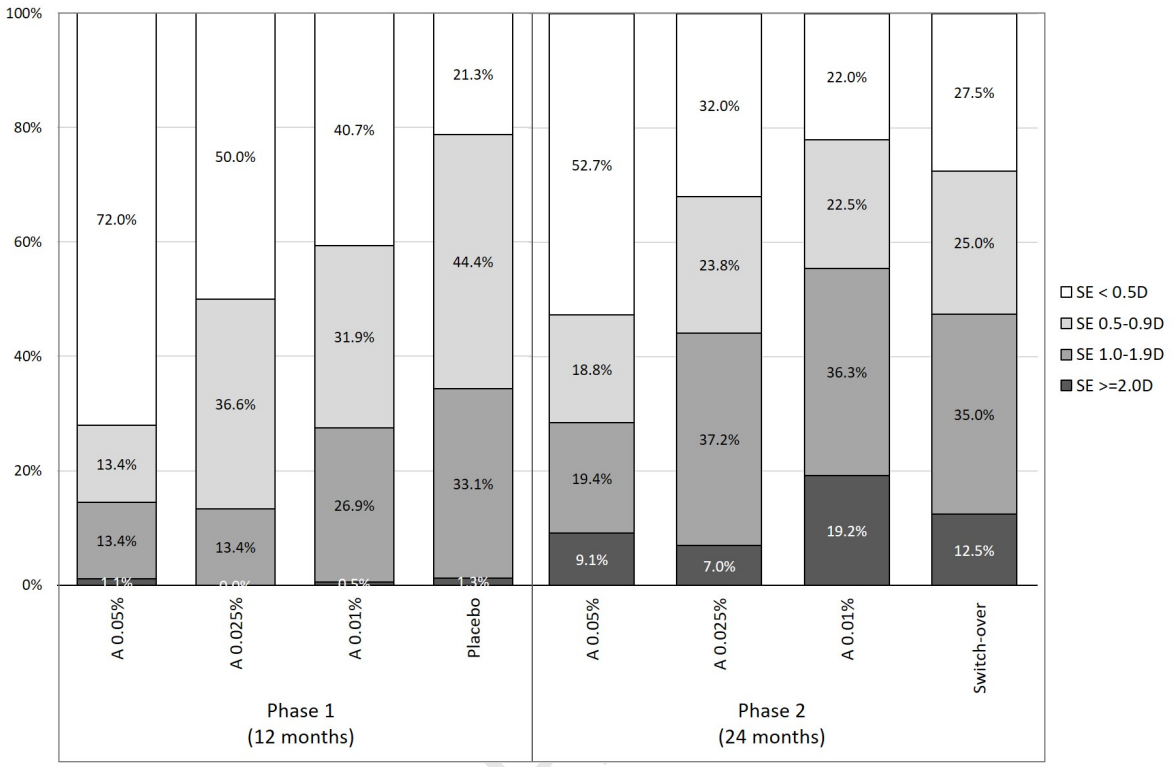
	ATOM2 study			LAMP study			
	0.5% atropine	0.1% atropine	0.01% atropine	0.05% atropine	0.025% atropine	0.01% atropine	Placebo
Change of SE, D							
First year	-0.17	-0.31	-0.43	-0.25	-0.46	-0.64	-0.82
Second year	-0.13	-0.07	-0.06	-0.30	-0.39	-0.48	
Total 2 years	-0.3	-0.38	-0.49	-0.55	-0.85	-1.12	
Change of 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 years	0.27	0.28	0.41	0.39	0.50	0.59	

ATOM2 data from Chia, A., et al. Ophthalmology 2012; 119(2): 347-354.


Subjects assessed for eligibility (n=484)
Exclusion (n=46)
-Not meeting inclusion criteria (n=16)
-History of using atropine (n=15)
-Declined to participate (n=15)
Randomized (n=438)
Allocation
0.05% atropine n= 109
0.025% atropine n= 108
0.01% atropine n= 110
placebo n= 111
Phase 1 0-1 year
Lost to follow-up: (n=7)
Lost to follow-up: (n=17)
Lost to follow-up: (n=13)
Lost to follow-up: (n=18)
n= 102
n=91
n= 97
n= 93
Phase 2 1-2 year
Continue 0.05% atropine
Continue 0.025% atropine
Continue 0.01% atropine
Switch to 0.05% atropine
Lost to follow-up: (n=9) Reasons: -Myopia progression (n=1) -Loss of contact (n= 7) -Unwilling to apply eye drop (n= 1)
Lost to follow-up: (n=5) Reasons: -Myopia progression (n=1) -Loss of contact(n= 3) -Unwilling to apply eye drop (n= 1)
Lost to follow-up: (n=6) Reasons: -Myopia progression (n=1) -Loss of contact (n= 3) -Busy/inconvenient (n=1) -Unwilling to apply eye drop (n= 1)
Lost to follow-up: (n=13) Reasons: -Loss of contact (n= 4) -Busy/inconvenient (n=4) -Unwilling to apply eye drop (n= 2) -Photophobia (n=3)
Analysis n=93
Analysis n=86
Analysis n=91
Analysis n=80


Baseline
4 months
8 months
12 months
16 months
20 months
24 months
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
-1.40
Change in Spherical Equivalent (D)
Atropine 0.05%
Atropine 0.025%
Atropine 0.01%
Switch-over group


0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Change in axial lengths (mm)
Baseline
4 months
8 months
12 months
16 months
20 months
24 months
Atropine 0.05%
Atropine 0.025%
Atropine 0.01%
Switch-over group



Precis

Low-concentration atropine 0.05% doubled the efficacy of 0.01% in reducing myopia progression over two years, and remained well tolerated and safe, without affecting the vision-related quality of life.