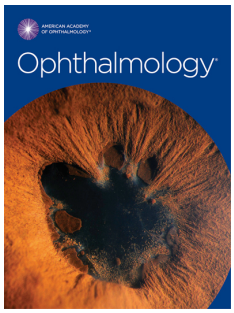
Journal Pre-proof



Effects on Ocular Biometrics by 0.05%, 0.025%, and 0.01% Atropine: Low-concentration Atropine for Myopia Progression (LAMP) Study

Fen-Fen Li, Ka-Wai Kam, Yuzhou Zhang, Shu-Min Tang, Alvin L. Young, Li-Jia Chen, Clement C. Tham, Chi-Pui Pang, Jason C. Yam

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Effects on Ocular Biometrics by 0.05%, 0.025%, and 0.01% Atropine: Low-concentration Atropine for Myopia Progression (LAMP) Study

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Abstract

Background: Anti-myopia effect of 0.01% atropine over placebo affected spherical equivalent (SE) but not axial length (AL) elongation in both ATOM2 study and LAMP study. It is possible that atropine might exert its effect through changes in corneal properties or lens power.

Purpose: To evaluate changes of ocular biometrics in the 0.05%, 0.025%, and 0.01% atropine groups compared to placebo over one year based on the LAMP study.

Design: Double-blinded, randomized, placebo-controlled trial.

Participants: 383 children aged 4 to 12 years, who were randomly assigned to receive 0.05%, 0.025%, 0.01% atropine, or placebo once daily in both eyes and completed the first year of the LAMP study.

Methods: Cycloplegic SE, AL, corneal curvatures, and anterior chamber depth (ACD), were measured by IOL Master. Corneal astigmatism and lens power were calculated. The ocular biometric parameters changes were compared among various groups. Contributions to SE progression from ocular parameters were determined and compared among various groups.

Main outcome measures: Changes in ocular biometrics and their associations with the changes in SE.

Results: Over one year, changes in AL were 0.20±0.25mm, 0.29±0.20mm, 0.36±0.29mm, and 0.41±0.22mm in 0.05%, 0.025%, 0.01% atropine and placebo, respectively ($p<0.001$), with a concentration-dependent response. Corneal power remained stable, and its changes were similar across all atropine concentrations, with -0.02±0.14D, -0.01±0.14D, -0.01±0.12D, and 0.01±0.14D in 0.05%, 0.025%, and 0.01% atropine, and placebo, respectively ($p = 0.10$). Lens power decreased over time in each concentration, but its changes were also similar across all

concentrations, with -0.31±0.43D, -0.38±0.47D, -0.40±0.43D, and -0.41±0.43D in 0.05%, 0.025%, 0.01% atropine and placebo respectively (p=0.24). ACD deepened over time, but its changes remained similar across all concentrations (p=0.41). The contributions to SE progression from the ocular biometric changes including changes of K, AL, and lens power after adjusting for age and gender, in each concentration were similar (p>0.05).

Conclusions: Low-concentrations of atropine 0.05%, 0.025%, and 0.01% have no clinical effect on corneal power and lens power. The anti-myopic effects of low-concentration atropine act mainly on reducing AL elongation, and therefore could reduce risk of subsequent myopia complications.

Keywords: low-concentration atropine; myopia; axial length; corneal curvature; lens power.

Introduction

Myopia is the most common ocular disorder world-wide with especially high prevalence in East Asia.[1-3] The prevalence of myopia and high myopia, defined as refractive errors greater than -6 diopters, is rising and has been predicted to affect approximately 50% and 10% respectively of the world population by the year 2025. [2] Notably, high myopia is associated with excessive axial elongation that can lead to sight-threatening complications, including macular hemorrhage, retinal detachment, cataract, and glaucoma.[4, 5] Given the increasing prevalence of myopia, the visual dysfunction and cost of managing myopia-related complications cast a heavy health burden on affected individuals and society at large. To reduce myopia progression, low-concentration atropine eye drops are an emerging therapy.[6, 7]

In ATOM 2, 0.01% atropine conferred reduction in spherical equivalent (SE) progression by 59% compared to historical control in ATOM1, but had no effect against axial length (AL) elongation.[8] The Low-concentration Atropine for Myopia Progression (LAMP) study demonstrated that 0.05% atropine has the best anti-myopia efficacy among 0.05%, 0.025%, and 0.01% atropine.[9,10] Progression in spherical equivalent in the 0.05%, 0.025%, 0.01% and placebo groups were -0.27±0.61 D, -0.46±0.45 D, -0.59±0.61 D, and-0.81±0.53 D, while reduced AL elongation were 0.20±0.25 mm, 0.29±0.20 mm, 0.36±0.29 mm, and 0.41±0.22 mm, respectively.[9] Of note, the difference in AL elongation between 0.01% atropine and placebo group was not statistically significant.[9] Both ATOM 2 and LAMP studies demonstrated a better anti-myopic effect in terms of SE progression than AL elongation. Gong *et al.* postulated that this distinction between the SE and AL may have been resulted from interactions between atropine effects in the development of the cornea with some changes of corneal power.[11] An animal study of infant marmoset demonstrated that 1% and 0.1% topical atropine could cause lens to move forward and thickened, suggesting its effect on anterior segment.[12]

The question remains whether the anti-myopic effect of low concentration atropine is mediated via reduction of axial elongation or other associated biometric changes. Excessive axial elongation causes mechanical stretching and thinning of retina, choroid, and sclera leading to degenerative effects, and subsequent myopic complications such as myopic choroidal neovascularization. Therefore, an effective myopia intervention should prioritize reducing axial elongation. In this report, we evaluated the changes of ocular biometrics and their respective contributions to SE progression in 0.05%, 0.025%, and 0.01% atropine compared to placebo over one year in the LAMP study.

Materials and Methods

Participants

Participants were recruited from the first year of Low-Concentration Atropine for Myopia Progression (LAMP) study,[9] which was a randomized, double-masked, placebo-controlled trial to study the efficacy and safety of topical atropine 0.05%, 0.025%, and 0.01% eye drops in preventing myopia progression in children. Children aged 4 to 12 years with myopic refraction of at least -1.0 D in both eyes and astigmatism of less than 2.5 D were recruited. Excluded were those with systemic diseases or ocular diseases, or previous use of myopia control therapy (such as atropine, pirenzepine, orthokeratology lens, or other optical methods), or history of allergy to atropine (e.g., cardiac or respiratory illness). In Phase 1, the study subjects were randomized to 4 treatment groups (0.05%, 0.025%, 0.01% atropine, and placebo) and followed up at 2 weeks, 4 months, 8 months and 12 months.[9] The trial medications consisted of the appropriate concentration of atropine at 0.05%, 0.025%, or 0.01% (0.50ml unit-concentration, preservative-free), and 0.9% sodium chloride (0.5ml unit-concentration, preservative-free) in placebo group.

All eye drops were prepared in mono-dose preparation by Aseptic Innovative Medicine Co, LTD, Taipei, Taiwan. Each batch of eye drops is valid for 2 years. The Drug Trial Certificate was issued by Department of Health, Hong Kong SAR, China. The LAMP study was registered with the Centre for Clinical Research and Biostatistics (CCRB) Clinical Trials Registry (ChiCTR-TRC-13004032), The Chinese University of Hong Kong (registration no: CUHK_CCT00383). This study conformed to the tenets of the Declaration of Helsinki and was approved by the Ethics committee of the Chinese University of Hong Kong.

Measurements

Examinations in LAMP phase 1 were described previously.[9] All the ocular biometrics in this study were obtained after a complete cycloplegia regime, which consisted of at least two cycles of eye drops. Cycloplegic autorefraction was performed by the autorefractor (Nidek ARK-510A, Gamagori, Japan). Five readings, less than 0.25 D apart, were obtained and averaged. Spherical equivalent refraction (SE) was calculated as spherical power plus half of the cylinder power. Ocular biometric parameters were measured using Zeiss IOL Master (Carl Zeiss Meditec Inc., Dublin, CA), including axial length (AL), anterior chamber depth (ACD), and corneal curvature, including flattest (K1) and steepest corneal curvature (K2). Average corneal curvature (K) was the mean of K1 and K2. Corneal astigmatism (CA) was the absolute difference between the K1 and K2 values. Lens power was calculated using the modified Bennett and Rabbetts formula,[13] by using measured values of SE, K, AL, and ACD. All measurements were performed in both eyes at the initial visit, 2 weeks, and every 4 months for one year.

Statistical analysis

Changes in ocular biometrics parameters were calculated by the difference between the baseline visit and the designated follow up visits. Chi-square test and Fisher exact test were used to test

for the group difference in categorical data, and analysis of variance (ANOVA) for the group difference of continuous data. The means of differences in biometric parameters at every time point from baseline were calculated from both eyes. Missing data values were imputed based on the distribution of other variables in the dataset. P-values were generated by generalized estimating equations (GEEs), in which robust standard errors were used for adjustments of correlation between eyes and multiple comparisons. Both enter procedure and stepwise selection procedure for linear regression were used to detect the relationships between the change in SE (dependent variable) and baseline age, gender, changes in AL, K, lens power. Adjusted R-squared values were used to represent the proportion of the variance in the dependent variable that is predicted from the independent variables in regression models. Seemingly unrelated regressions (SUR) were used to test whether the coefficients in linear regression models on different treatment groups were equal accordingly. Statistical analyses were performed with SPSS statistics version 24 (IBM Corp., Armonk, NY) and Stata software version 14.0 (StataCorp., College Station, TX). In view of a number of statistical comparisons, p values less than 0.01 were considered statistical significant.

Results

Baseline parameters among all groups

Among the 438 children recruited for the LAMP study, 383 (87%) completed the first-year follow up and were included in this report: 102 children in the 0.05% atropine group, 91 in 0.025% atropine, 97 in 0.01% atropine, and 93 in the placebo group. The baseline ocular biometrics, average corneal curvature (K), flattest K (K1), steepest K (K2), corneal astigmatism (CA), anterior chamber depth (ACD), and calculated lens power, were similar among all groups

(Table 1). These parameters were also similar in those 55 children who had not completed the first year follow up (Table 1).

Ocular biometrics change over one year

The one-year changes in ocular biometric parameters, including AL, K, ACD, and lens power, in the 0.05%, 0.025%, 0.01% atropine and placebo group were summarized in Table 2, Table 3 and Figure 1. Over one year, changes in AL were 0.20±0.25mm, 0.29±0.20mm, 0.36±0.29mm, and 0.41±0.22mm in 0.05%, 0.025%, and 0.01% atropine, and placebo, respectively ($p<0.001$), with a concentration-dependent response. Average K remained stable in each group (Table 3), with -0.02±0.14D, -0.01±0.14D, -0.01±0.12D, and 0.01±0.14D in 0.05%, 0.025%, and 0.01% atropine and placebo respectively (Table 2, overall p-value = 0.10). Corneal astigmatism (CA) increased over time in each concentration (Table 3), but its changes remained similar across all concentrations (Table 2, overall p value=0.74). Lens power decreased over time in each group (Table 3), but its changes were also similar across all concentrations, with -0.31±0.43 D, -0.38±0.47 D, -0.40±0.43 D, and -0.41±0.43 D in 0.05%, 0.025%, 0.01%, and placebo respectively (p-value=0.24; Table 2). ACD deepened over time (Table 3), but its changes remained similar across all concentrations (p-value = 0.41; Table 2).

Ocular biometrics change accompanied with myopia progression

The contributions to SE progression from the ocular biometric changes including changes of K, AL, and lens power after adjusting for age and gender, in each concentration were summarized in Table 4. In all atropine concentrations, the myopia progression was mainly accounted by AL elongation, which contributed more than 70% of the myopia progression, followed by lens power and corneal power (Table 4). Considering change in AL, K, and lens power, the multiple regression model explained 97.0%, 93.0%, 95.6%, and 96.1% for SE change in 0.05%, 0.025%,

0.01% atropine and the placebo respectively (Table 4, Model 3). In the placebo group, linear regression showed that the coefficient of AL was -2.73, which meant 1mm AL change accounted for -2.73D SE change. As for other components, 1D lens power change for -0.65D SE change, and 1D K change accounted for -1.05D SE change (Table 4, Model 4). The coefficient of change in AL, K, and lens power were all similar among all atropine concentrations by using seemingly unrelated regressions (Table 4, Model 4).

Discussion

Although other ocular biometrics were thought to contribute to the anti-myopia effects of low concentration atropine,[11,14] this study demonstrates that the reduction in AL elongation accounted for most of the effect. The largest reduction in AL elongation was observed in 0.05% atropine followed by 0.025%, and 0.01% atropine compared with placebo in a concentration-dependent response. There were no differences in change of corneal curvatures and lens power caused by any atropine concentrations compared to placebo over one year. Notably, contributions to SE progression from axial length, corneal and lens power in each atropine concentration and placebo were similar. AL elongation contributed the majority of SE progression. Thus, the anti-myopic effect of low-concentration atropine was mainly achieved by retardation of axial elongation.

There are potential explanations for the different effects on SE progression and AL elongation by low-concentration atropine. First, our study demonstrated that AL alone contributed to the SE variance ranging from 72% to 81%. (Table 4) Since the changes in corneal power and lens power were similar in atropine at low concentrations and placebo, while the AL changes follow a concentration-dependent effect across the concentrations, therefore, change in SE and AL during myopia progression would not be completely parallel, and their ratio is around

193 0.7 to 0.8. This could explain the observation from LAMP study that compared with placebo, a
194 27% in SE reduction and 12% axial elongation were achieved in 0.01% atropine, 43% in SE
195 reduction and 29% in AL elongation in 0.025% atropine, and 67% in SE reduction and 51% in
196 AL elongation in 0.05% atropine. [9] The remaining SE variance in all concentrations were
197 accounted by lens and corneal factors. Notably, our study showed no significant effect on corneal
198 curvature and lens power of low concentration atropine compared with placebo; and showed
199 similar contributions to SE progression from axial length, corneal curvatures and lens power
200 between all atropine concentrations and placebo. This further ascertained that the anti-myopia
201 effect of atropine was mediated via retarding of axial elongation. Second, children's AL
202 elongation includes both normal age-related growth, albeit small, and additional myopia
203 associated growth. Therefore, SE change correlates only part of the AL elongation. That can
204 partly explain why atropine's effect on total AL elongation would be less than that of SE
205 progression.

206 In LAMP study, only effect on SE progression, but not AL elongation, in 0.01% atropine
207 group reached statistical significance. While sample size in LAMP study is adequate, it is
208 powered primarily based on SE change. A larger sample size is needed to detect the difference of
209 AL elongation between 0.01% and placebo groups. On the other hand, comparisons of 0.01%
210 atropine in ATOM2 with historical placebo in ATOM1 (effect, -8%)[8] might have been largely
211 influenced by the different modalities in biometric measurements, IOL Master (non-contact
212 partial coherence interferometry) was used in ATOM2 and A-scan ultrasonography in
213 ATOM1.[15, 16] Direct comparisons between ATOM2 study and LAMP study should be cautious
214 because of differences in subject cohorts and preparations of the eye drops. Of note, 0.01%
215 atropine showed the effect on pupils and accommodation in ATOM2, but not in LAMP, although

same measurements method were employed in both studies. This may suggest a potential biological difference of the drops between both studies, and therefore different efficacies.

The strength of this study lies in its double-blinded, placebo-controlled randomization design of a relatively large sample of study subjects followed up in a year. In performing repeated biometry measures, the possible bias would be minimized by using GEEs including data from both eyes to assess changes over time. Measurements were done with IOL Master after complete cycloplegia, which avoided the effect of accommodation. Our study allowed direct comparisons between different atropine concentrations with placebo to ascertain the atropine effects on ocular biometric parameters. There are some limitations in this study. First, this current study only reported the first-year period of atropine treatment compared to placebo. Longer term ocular biometric changes, including after cessation of treatment, will have to be further evaluated in subsequent phases of the LAMP study. Second, lens power was not measured directly but calculated based on Bennett and Rabbetts formula. Nevertheless, this calculation is considered as an acceptable estimate of in vivo lens power from infancy to adulthood. [17, 18]

Conclusions

In summary, low concentration atropine eye drops have no significant effects on corneal curvature and lens power. Its anti-myopia effects are mediated via reducing axial elongation, but not other ocular biometric parameters, and therefore could reduce the risk of subsequent myopia complications.

Abbreviation and acronyms:

LAMP study=low-concentration atropine for myopia progression study; D=diopters; SE= spherical equivalent refraction; AL=axial length; ACD=anterior chamber depth; K1=flattest corneal curvature; K2=steepest corneal curvature; CA=corneal astigmatism.

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 (ChiCTR-TRC-13004032), 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.

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Figure Legends

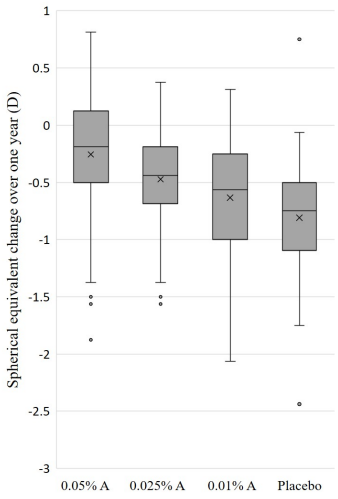
Figure 1. Box plots of changes in refractive error and ocular biometrics in treatment groups over one year. A. Change in refractive error in treatment groups over one year. B. Change in axial length in treatment groups over one year. C. Change in corneal power in treatment groups over one year. D. Change in lens power in treatment groups over one year. E. Change in anterior chamber depth in treatment groups over one year.

D= diopters.

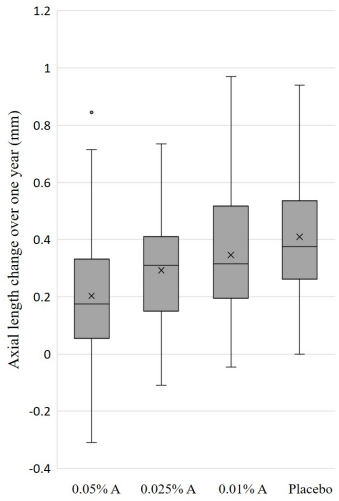
Precis:

Low-concentration of atropine 0.05%, 0.025%, and 0.01% have no clinical effect on corneal power and lens power. The anti-myopic effects of 0.05% and 0.025% atropine act mainly on reducing axial length elongation, and therefore could reduce risk of subsequent myopia complications.

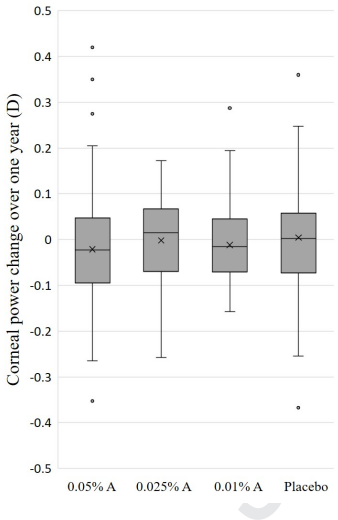
A.


Spherical equivalent change over one year (D)
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
0.05% A
0.025% A
0.01% A
Placebo

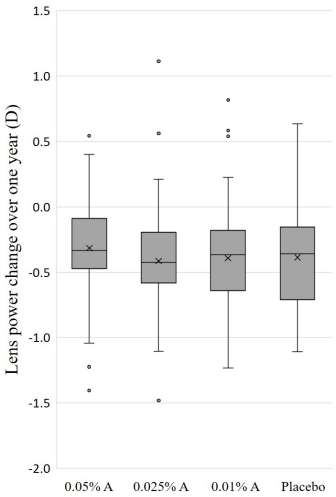
B.


Axial length change over one year (mm)
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0.05% A
0.025% A
0.01% A
Placebo

C.


Corneal power change over one year (D)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
0.05% A
0.025% A
0.01% A
Placebo

D.


Lens power change over one year (D)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0.05% A
0.025% A
0.01% A
Placebo

E.

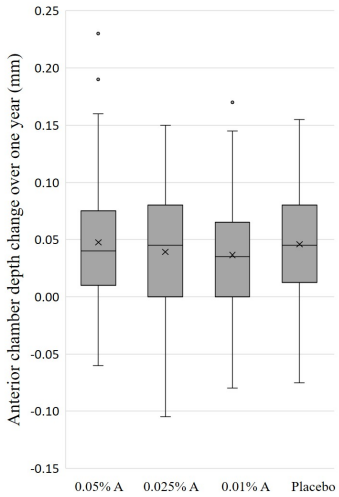

Anterior chamber depth change over one year (mm)
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
0.05% A
0.025% A
0.01% A
Placebo

Table 1. Baseline demographics and ocular parameters of study subjects

	Completed one year (N=383)				Loss to follow-up (N=55)			
	0.05% Atropine (n=102)	0.025% Atropine (n=91)	0.01% Atropine (n=97)	Placebo (n=93)	0.05% Atropine (n=7)	0.025% Atropine (n=17)	0.01% Atropine (n=13)	Placebo (n=18)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, years	8.5 (1.69)	8.5 (1.67)	8.4 (1.76)	8.5 (1.8)	9.0 (2.31)	8.7 (2.03)	7.4 (1.95)	8.1 (1.78)
Gender, Male, %	53 (52.0%)	60 (65.9%)	53 (54.6%)	58 (62.4%)	2 (28.6%)	5 (35.3%)	6 (46.2%)	8 (44.4%)
Spherical equivalent, D	-3.95 (1.64)	-3.83 (1.81)	-3.95 (1.9)	-4.1 (1.91)	-3.84 (1.06)	-3.59 (2.16)	-3.67 (2.62)	-3.71 (3.07)
Axial length, mm	24.86 (0.9)	24.92 (0.89)	24.79 (1.02)	24.9 (0.99)	24.83 (0.53)	24.67 (1.16)	24.36 (0.53)	24.72 (1.33)
Average K, D	43.77 (1.45)	43.71 (1.28)	43.91 (1.32)	43.75 (1.27)	43.55 (1.14)	43.80 (1.42)	43.80 (1.29)	43.52 (0.89)
Flattest K, D	43.01 (1.38)	43 (1.18)	43.18 (1.3)	43.05 (1.21)	42.97 (1.04)	42.78 (1.40)	43.13 (1.10)	42.88 (0.87)
Steepest K, D	44.52 (1.61)	44.41 (1.44)	44.44 (1.39)	44.44 (1.39)	44.13 (1.31)	44.09 (1.50)	44.47 (1.56)	44.15 (0.95)
ACD, mm	3.74 (0.18)	3.76 (0.25)	3.72 (0.22)	3.72 (0.22)	3.78 (0.21)	3.66 (0.27)	3.58 (0.24)	3.69 (0.25)
CCT, µm	551.1 (29.53)	549.0 (30.41)	545.3 (31.73)	545.3 (31.73)	541.3 (29.85)	555.1 (30.08)	549.8 (21.22)	541.3 (22.72)
IOP, mmHg	15.8 (2.39)	15.8 (2.13)	15.5 (2.26)	15.5 (2.53)	17.3 (2,87)	16.2 (1.29)	15.9 (2.17)	16.2 (2.99)
Corneal astigmatism, D	1.51 (0.82)	1.41 (0.62)	1.47 (0.76)	1.39 (0.63)	1.15 (0.58)	1.32 (0.61)	1.34 (0.79)	1.27 (0.38)
Lens power, D	22.7 (1.36)	22.5 (1.20)	22.8 (1.45)	22.7 (1.3)	23.0 (1.77)	23.4 (1.86)	23.8 (1.84)	23.2 (1.59)

SE= spherical equivalent, AL= axial length, K= corneal curvature, CCT=central corneal thickness; IOP= intraocular pressure; ACD= anterior chamber depth.
SE and AL data were based on previous LAMP phase 1.
*Significant level set at p <0.01.

Table 2. Changes in refractive error and ocular biometrics in 0.05%, 0.025%, 0.01% atropine and placebo groups in each visit.

Change between	3) 0.05% atropine (n=102) Mean	SD	2) 0.025% atropine (n=91) Mean	SD	1) 0.01% atropine (n=97) Mean	SD	0) Placebo (n=93) Mean	SD	Overall p value	P-value in pair comparisons (1 vs 0, 2 vs 0, 3 vs 0, 1 vs 2, 1 vs 3, 2 vs 3)
Baseline and 4 months										
Δ Spherical equivalent (D)	-0.02	0.39	-0.19	0.31	-0.27	0.31	-0.34	0.32	<.001*	(0.43, 0.002*, <.001*, 0.34, <.001*, 0.001*)
Δ Axial length (mm)	0.07	0.14	0.12	0.11	0.14	0.12	0.17	0.10	<.001*	(0.31, 0.008*, <.001*, 0.99, 0.006*, 0.006*)
Δ average K (D)	-0.02	0.15	0.00	0.14	0.00	0.15	0.02	0.14	0.15	(0.99, 0.99, 0.13, 0.99, 0.99, 0.99)
Δ Lens Power (D)	-0.19	0.46	-0.19	0.37	-0.19	0.36	-0.21	0.35	0.94	(0.99, 0.99, 0.99, 0.99, 0.99, 0.99)
Δ ACD (mm)	0.01	0.06	0.01	0.09	0.003	0.06	0.01	0.07	0.82	(0.99, 0.99, 0.99, 0.99, 0.99, 0.99)
Δ Flattest K (D)	-0.07	0.16	-0.04	0.15	-0.03	0.16	-0.03	0.15	0.11	(0.99, 0.99, 0.15, 0.99, 0.22, 0.70)
Δ Steepest K (D)	0.03	0.26	0.05	0.22	0.04	0.25	0.07	0.22	0.81	(0.99, 0.99, 0.84, 0.99, 0.99, 0.99)
Δ Corneal astigmatism (D)	0.10	0.30	0.09	0.26	0.07	0.30	0.10	0.25	0.78	(0.99, 0.99, 0.99, 0.99, 0.99, 0.99)
Baseline and 8 months										
Δ Spherical equivalent (D)	-0.12	0.48	-0.36	0.37	-0.47	0.44	-0.60	0.45	<.001*	(0.24, <.001*, <.001*, 0.22, <.001*, <.001*)
Δ Axial length (mm)	0.13	0.18	0.21	0.16	0.25	0.17	0.31	0.16	<.001*	(0.16, <.001*, <.001*, 0.30, <.001*, 0.004*)
Δ average K (D)	-0.02	0.17	-0.01	0.15	-0.01	0.14	0.02	0.16	0.29	(0.99, 0.99, 0.33, 0.99, 0.99, 0.99)
Δ Lens Power (D)	-0.26	0.43	-0.27	0.42	-0.30	0.38	-0.34	0.36	0.23	(0.99, 0.58, 0.39, 0.99, 0.99, 0.99)
Δ ACD (mm)	0.03	0.06	0.02	0.08	0.02	0.07	0.03	0.05	0.36	(0.99, 0.99, 0.99, 0.99, 0.99, 0.65)
Δ Flattest K (D)	-0.10	0.19	-0.08	0.16	-0.06	0.16	-0.05	0.16	0.02	(0.99, 0.58, 0.01*, 0.99, 0.13, 0.89)
Δ Steepest K (D)	0.06	0.27	0.06	0.23	0.05	0.25	0.08	0.27	0.74	(0.99, 0.99, 0.99, 0.99, 0.99, 0.99)
Δ Corneal astigmatism (D)	0.17	0.32	0.13	0.28	0.11	0.31	0.13	0.31	0.32	(0.99, 0.99, 0.99, 0.99, 0.39, 0.99)
Baseline and 12 months										
Δ Spherical equivalent (D)	-0.27	0.61	-0.46	0.45	-0.59	0.61	-0.81	0.53	<.001*	(0.006*, <.001*,<.001*, 0.05, <.001*, 0.01*)
Δ Axial length (mm)	0.20	0.25	0.29	0.20	0.36	0.29	0.41	0.22	<.001*	(0.18, <.001*, <.001*, 0.02, <.001*, 0.006*)
Δ average K (D)	-0.02	0.14	-0.01	0.14	-0.01	0.12	0.01	0.14	0.08	(0.53, 0.47, 0.06, 0.99, 0.99, 0.99)
Δ Lens Power (D)	-0.31	0.43	-0.38	0.47	-0.40	0.43	-0.41	0.43	0.24	(0.99, 0.99, 0.34, 0.99, 0.76, 0.99)
Δ ACD (mm)	0.05	0.06	0.04	0.08	0.04	0.06	0.05	0.07	0.41	(0.76, 0.99, 0.99, 0.99, 0.99, 0.99)
Δ Flattest K (D)	-0.11	0.17	-0.09	0.17	-0.08	0.17	-0.07	0.13	0.11	(0.99, 0.99, 0.11, 0.99, 0.54, 0.99)
Δ Steepest K (D)	0.06	0.26	0.06	0.22	0.06	0.22	0.09	0.25	0.46	(0.81, 0.99, 0.99, 0.99, 0.99, 0.99)
Δ Corneal astigmatism (D)	0.16	0.33	0.15	0.29	0.13	0.30	0.17	0.30	0.74	(0.99, 0.99, 0.99, 0.99, 0.99, 0.99)

Δ =change, K= corneal curvature, ACD= anterior chamber depth, D=diopter.

Generalized estimating equations (GEEs) were performed for change in ophthalmic parameters with treatment group and time and interaction of time and group included, followed by testing the treatment effects at each time point in both eyes. Pair-comparisons were performed after the overall treatment group effect.
*Significant level set at p < 0.01.

Table 3. Corneal parameters and lens power at each time point.

	3) 0.05% atropine (n=102)		2) 0.025% atropine (n=91)		1) 0.01% atropine (n=97)		0) Placebo (n=93)		*Group overall p-value*	*Time*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*		
Average K (D)										*0.26*
2 weeks	*43.78*	*1.41*	*43.64*	*1.30*	*43.93*	*1.30*	*43.78*	*1.24*	*0.16*	
4 months	*43.78*	*1.43*	*43.71*	*1.27*	*43.93*	*1.30*	*43.80*	*1.23*	*0.72*	
8 months	*43.78*	*1.45*	*43.69*	*1.24*	*43.91*	*1.29*	*43.79*	*1.25*	*0.74*	
12 months	*43.77*	*1.44*	*43.69*	*1.27*	*43.91*	*1.31*	*43.78*	*1.23*	*0.24*	
Flattest K (D)										*<.001**
2 weeks	*43.01*	*1.35*	*42.96*	*1.21*	*43.17*	*1.27*	*43.06*	*1.16*	*0.18*	
4 months	*42.97*	*1.39*	*42.97*	*1.17*	*43.17*	*1.26*	*43.06*	*1.17*	*0.72*	
8 months	*42.94*	*1.41*	*42.92*	*1.14*	*43.13*	*1.27*	*43.03*	*1.19*	*0.72*	
12 months	*42.93*	*1.39*	*42.91*	*1.16*	*43.11*	*1.26*	*43.00*	*1.18*	*0.73*	
Steepest K (D)										*<.001**
2 weeks	*44.53*	*1.59*	*44.34*	*1.45*	*44.59*	*1.45*	*44.44*	*1.35*	*0.34*	
4 months	*44.58*	*1.56*	*44.45*	*1.43*	*44.69*	*1.43*	*44.53*	*1.36*	*0.73*	
8 months	*44.62*	*1.60*	*44.45*	*1.42*	*44.70*	*1.41*	*44.55*	*1.39*	*0.74*	
12 months	*44.61*	*1.59*	*44.47*	*1.45*	*44.71*	*1.45*	*44.57*	*1.36*	*0.74*	
Corneal astigmatism (D)										*<.001**
2 weeks	*1.51*	*0.78*	*1.39*	*0.64*	*1.45*	*0.75*	*1.39*	*0.61*	*0.23*	
4 months	*1.62*	*0.78*	*1.48*	*0.62*	*1.52*	*0.75*	*1.47*	*0.62*	*0.74*	
8 months	*1.68*	*0.82*	*1.54*	*0.65*	*1.57*	*0.74*	*1.52*	*0.68*	*0.54*	
12 months	*1.68*	*0.81*	*1.56*	*0.65*	*1.60*	*0.73*	*1.57*	*0.67*	*0.69*	
Anterior Chamber Depth, ACD (mm)										*<.001**
2 weeks	*3.73*	*0.20*	*3.75*	*0.24*	*3.70*	*0.27*	*3.71*	*0.22*	*0.20*	
4 months	*3.75*	*0.19*	*3.77*	*0.24*	*3.72*	*0.24*	*3.72*	*0.22*	*0.29*	
8 months	*3.77*	*0.19*	*3.78*	*0.23*	*3.74*	*0.24*	*3.75*	*0.22*	*0.22*	
12 months	*3.78*	*0.20*	*3.81*	*0.24*	*3.76*	*0.24*	*3.77*	*0.22*	*0.31*	
Bennett-Rabbetts Lens Power (D)										*<.001**
2 weeks	*22.7*	*1.39*	*22.5*	*1.34*	*22.8*	*1.43*	*22.7*	*1.34*	*0.18*	
4 months	*22.6*	*1.38*	*22.4*	*1.24*	*22.7*	*1.40*	*22.6*	*1.30*	*0.39*	
8 months	*22.5*	*1.34*	*22.2*	*1.19*	*22.6*	*1.37*	*22.4*	*1.30*	*0.14*	
12 months	*22.5*	*1.35*	*22.1*	*1.22*	*22.5*	*1.34*	*22.3*	*1.26*	*0.12*	

Generalized estimating equations were performed for ophthalmic parameters with treatment group, followed by testing the treatment effects at each time point in both eyes.

**Significant level set at $p < 0.01$.*

Table 4. Linear regression for change in spherical equivalent and ocular biometrics.

Variables	0.05% atropine			0.025% atropine			0.01% atropine			Placebo		
	β	SE	p-value	β	SE	p-value	β	SE	p-valu	β	SE	p-valu
Model 1[£]												
Δ Axial length (mm)	-2.21	0.11	<.001*	-1.77	0.11	<.001*	-2.07	0.10	<.001*	-2.11	0.13	<.001*
Adjusted R-squared		80.4%			72.6%			81.2%			75.3%	
Model 2[£]												
Δ Axial length (mm)	-2.67	0.09	<.001*	-2.28	0.09	<.001*	-2.64	0.07	<.001*	-2.74	0.10	<.001*
Δ Lens power (D)	-0.54	0.06	<.001*	-0.47	0.04	<.001*	-0.57	0.04	<.001*	-0.61	0.05	<.001*
Adjusted R-squared		89.3%			87.9%			93.7%			90.2%	
Model 3[£]												
Δ Axial length (mm)	-2.77	0.05	<.001*	-2.46	0.07	<.001*	-2.73	0.06	<.001*	-2.77	0.06	<.001*
Δ Lens power (D)	-0.71	0.03	<.001*	-0.56	0.04	<.001*	-0.65	0.04	<.001*	-0.64	0.03	<.001*
Δ Corneal power (D)	-1.21	0.08	<.001*	-1.04	0.13	<.001*	-0.85	0.14	<.001*	-1.03	0.09	<.001*
Adjusted R-squared		97.0%			93.0%			95.6%			96.1%	
Model 4[¶]												
Δ Axial length (mm)	-2.79	0.05	<.001*	-2.43	0.08	<.001*	-2.74	0.07	<.001*	-2.73	0.07	<.001*
Δ Lens power (D)	-0.71	0.03	<.001*	-0.58	0.04	<.001*	-0.66	0.04	<.001*	-0.65	0.03	<.001*
Δ Corneal power (D)	-1.21	0.08	<.001*	-1.07	0.13	<.001*	-0.90	0.14	<.001*	-1.05	0.09	<.001*
Gender (M1,F2)	-0.01	0.02	0.50	-0.04	0.02	0.07	-0.05	0.02	0.02	-0.07	0.02	0.003*
Age	-0.01	0.01	0.23	0.01	0.01	0.14	0.002	0.01	0.86	0.011	0.01	0.14
Adjusted R-squared		97.0%			93.2%			95.7%			96.4%	

Δ =change over one year; D=diopter; β=coefficient; SE= standard error.
£Model 1, 2, 3 are the equations using 'stepwise' selection procedure in linear regression models
¶Model 4 is the equation using 'enter' procedure in linear regression model.
*Significant level set at $p < 0.01$.