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(54) **Title:** COMPOSITION AND/OR METHOD FOR REDUCING AND/OR PREVENTING MYOPIA PROGRESSION COMPRISING ATROPINE

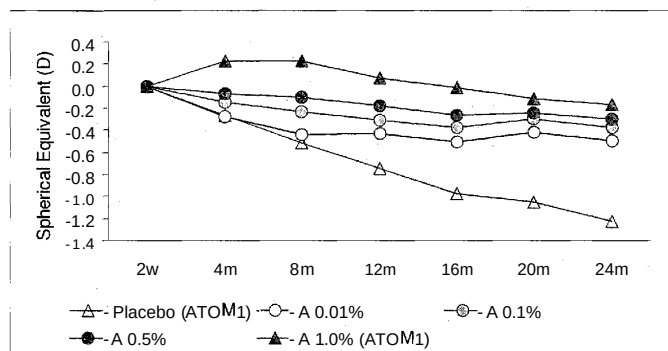


Figure 5

(57) **Abstract:** The invention relates to a composition and/or method for reducing and/or preventing myopia progression. The composition comprises an ultra-low atropine concentration. The composition comprises less than 0.025% atropine. For example, the composition comprises about 0.01% atropine. The ultra-low atropine composition reduces and/or prevents myopia progression with negligible side effects, such as loss of accommodation, mydriasis, near-vision blur, allergic conjunctivitis and dermatitis.

**COMPOSITION AND/OR METHOD FOR REDUCING AND/OR
PREVENTING MYOPIA PROGRESSION COMPRISING ATROPINE**

Field of the invention

The present invention relates to a composition and/or method for reducing and/or preventing myopia progression. In particular, the invention relates to an ultra-low concentration atropine solution for reducing and/or preventing myopia progression.

Background of the invention

Myopia (nearsightedness or short sightedness) is a type of refractive error of the eye, in which the visual image is focused in front of the retina, typically resulting in blurred vision of distant objects. Myopia is especially prevalent among Asians and has been reported to be as high as 70-90% in Asian countries. Myopia may be corrected by prescription lenses (for example, spectacles or contact lenses) or refractive surgery (for example, LASIK or phakic intraocular lens implantation).

After onset of myopia, which typically occurs during early childhood, its progression is often difficult to control. Atropine is a non-specific muscarinic antagonist. Atropine at 1.0% and 0.5% has been demonstrated through randomised trials to be effective in slowing myopia progression (Shih *et al.*, 1999). The safety profile, and associated side-local and systemic effects of atropine (i.e. its effect on pupil size and accommodation), however, has often been a source of concern, and has greatly deterred the use of this medication for myopia control. Every unit increase in pupil size results in an exponential increase in the amount of light entering the eye, and this may cause glare and photophobia. The long term effect of excessive amounts of ultraviolet light entering an eye which has been chronically dilated with atropine may potentially increase the risk of cataract or macular degeneration. Atropine also decreases accommodation amplitude (ability to focus on near objects), thus reducing near vision so that children may require bifocal or progressive glasses to read or see close objects.

In atropine in the treatment of myopia study 1 (ATOM1), 1 % atropine was reported to be effective in slowing the progression of myopia (Chua *et al.*, 2006). Side effects were recognised with 1 % atropine treated eyes, including blurring of near vision in the

atropine-treated eye (likely due to cycloplegia) and anisocoria or uneven pupil size, (likely due to mydriasis).

5 In a retrospective non-randomized study, Lee *et al.*, (2006) found that myopia in 21 children aged 6-12 years on 0.05% atropine progressed at a rate of 0.28 ± 0.26 D per year, compared to 0.75 ± 0.35 D per year in 36 consecutive untreated clinic patients. Negative side effects including photophobia and hampered near vision were reported in the subjects.

10 In another retrospective review of 50 pre-myopic children, 24 of whom were started on 0.025% atropine, Fang *et al.*, (2010) noted that subsequent myopia shift was less (-0.14 ± 0.24 D) in the 0.025% atropine group, compared to controls (-0.58 ± 0.34 D). Both the control group and the 0.025% atropine group exhibited photophobia although the difference was not significant. None of the subjects complained of near-vision blur.

It is desirable to provide an atropine composition for reducing and/or preventing myopia progression with negligible or minimal side effects.

15 Summary of the invention

The present composition provides an ultra-low concentration atropine composition for reducing and/or preventing myopia progression.

According to a first aspect, the present invention provides a composition for reducing and/or preventing myopia progression comprising less than 0.025% atropine.

20 According to another aspect, the invention relates to the use of atropine in the preparation of a composition for reducing and/or preventing myopia progression, wherein the composition comprises less than 0.025% atropine.

The invention also provides a method for reducing and/or preventing myopia progression comprising administering to a subject a composition comprising less than
25 0.025% atropine.

Brief description of the figures

Figure 1 is a flow chart illustrating the study design of ATOM1.

Figure 2 is a graph showing mean spherical equivalent change from baseline from ATOM1.

5 Figure 3 is a graph showing mean axial length change from baseline from ATOM1.

Figure 4 is a flow chart illustrating the study design of ATOM2.

Figure 5 is a graph showing the mean change in spherical equivalent for groups from baseline 2 to 24 months with 0.01%, 0.1% and 0.5% atropine from ATOM2 and 1% atropine and placebo from ATOM1.

10 Figure 6 is a graph illustrating progression of myopia according to severity (pooled eyes) with 0.01%, 0.1% and 0.5% atropine from ATOM2 and 1% atropine and placebo from ATOM1. Myopia progression from baseline 2 is classified as severe (if > 1 D), moderate (0.5-0.99 D) and mild (if <0.5 D).

15 Figure 7 is a graph illustrating the main change in axial lengths from baseline 2 to 24 months from ATOM2.

Figure 8 is a graph illustrating the changes in spherical equivalent in groups from ATOM2 after stopping atropine for 1 year.

Figure 9 is a graph illustrating the changes in axial length in groups from ATOM2 after stopping atropine for 1 year.

20 Definitions

The term "about" when used in conjunction with a value, for example about 0.01%, means a value reasonably close to the value. For example, for 0.01%, 0.006%, 0.007%, 0.008%, 0.009%, 0.0095%, 0.0099%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014% would be included. In particular, it would include the value itself.

25

"Accommodation" refers to the process by which the eye adjusts to a near focus, to maintain a clear image (focus) on an object as its distance changes.

"Amblyopia" (also known as "lazy eye") refers to a decrease of vision, either unilaterally or bilaterally, with no apparent structural abnormality in the eye. In amblyopia, visual stimulation either fails to transmit or is poorly transmitted through the optic nerve to the brain.

"Anisocoria" refers to a condition where the pupils of the eyes are uneven in size.

"Cycloplegia" refers to paralysis of the ciliary muscle of the eye, resulting in a loss of accommodation.

10 "Mydriasis" refers to a condition where the pupil of the eye is dilated due to disease, trauma or the use of drugs. Mydriasis may be associated with glare intolerance and photophobia.

"Photophobia" refers to a condition of sensitivity to light. In ordinary medical terms, photophobia is not a morbid fear or phobia, but an experience of discomfort or pain to the eyes due to light exposure.

"Strabismus" (also known as "crossed eyes") refers to a condition in which the two eyes do not line up in the same direction, and therefore do not look at the same object at the same time.

Detailed description of the invention

20 The composition of the present invention comprises an ultra-low concentration of atropine, i.e. less than 0.025% atropine. The concentration of atropine in the composition may be any value less than 0.025%, for example, the composition may comprise 0.001 to 0.0249% atropine; 0.005% to 0.0249% atropine, 0.01 to 0.0249% atropine, 0.005 to 0.02% atropine, 0.05 to 0.015% atropine or 0.008 to 0.012% atropine.

25 Accordingly, the composition may comprise 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine. In particular, the composition comprises about 0.01%

atropine. More in particular, the composition comprises 0.01%. The composition may further comprise at least one pharmaceutically acceptable excipient.

The composition according to any aspect of the invention may be for use in reducing and/or preventing myopia progression and/or treating myopia. Accordingly, the invention includes a method of reducing and/or preventing myopia progression comprising administering to a subject a composition according to any aspect of the invention. The composition is for administration to the eye. In particular, the composition is for topical administration to the eye. More in particular, the composition is an eye-drop composition

10 After onset, myopia typically progresses during childhood and may only stabilise in adulthood. Accordingly, the composition is suitable for reducing and/or preventing myopia progression in subjects where myopia is still progressing and/or has not stabilised, even in late adulthood. For example, the composition is suitable for reducing and/or preventing myopia progression in subjects from 3 to 30 years old, where myopia
15 is still progressing and/or has not stabilised. In particular, the composition is suitable for reducing and/or preventing myopia in children from 6 to 12 years old.

Accordingly, the invention also provides a method for reducing and/or preventing myopia progression comprising administering to a subject a composition according to any aspect of the invention.

20 In a study (Example 2), 400 children were administered either 0.01%, 0.05% or 0.1% atropine nightly to both eyes and myopia progression was monitored over a period of 2 years. The results of this study showed that 0.01% atropine was found to induce negligible side-effects (for example: loss of accommodation, mydriasis, allergic conjunctivitis, dermatitis) compared to atropine at 0.1% and 0.05% and retains
25 comparable efficacy in controlling myopia progression.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention.

EXAMPLES

Example 1 First atropine in the treatment of myopia study (ATOM1)

5 In ATOM1, 400 children aged 6-12 years with spherical equivalents of -1.00 D and -6.00 D were randomly assigned to having 1% atropine or placebo medication in one eye (Chua *et al.*, 2006). The design of the study is illustrated in Figure 1 and summarised below. The results from ATOM1 are compared and also used in Example 2.

Summary of ATOM 1

10 **Purpose:** To evaluate the efficacy and safety of topical atropine, a nonselective muscarinic antagonist, in slowing the progression of myopia and ocular axial elongation in Asian children.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Subjects: 400 children aged 6 to 12 years with refractive error of spherical equivalent -1.00 to -6.00 D and astigmatism of -1.50 D or less.

15 **Intervention:** Subjects (the children) were assigned with equal probability to receive either 1 % atropine or vehicle eye-drops once nightly for 2 years. Only 1 eye of each subject was chosen through randomization for treatment.

20 **Main Outcome Measures:** The main efficacy outcome measures were change in spherical equivalent refraction as measured by cycloplegic autorefraction and change in ocular axial length as measured by ultrasonography. The primary safety outcome measure was the occurrence of adverse events.

25 **Results:** 346 (86.5%) subjects completed the 2-year study. After 2 years, the mean progression of myopia and of axial elongation in the placebo-treated control eyes was -1.20 ± 0.69 D (Figure 2) and 0.38 ± 0.38 mm (Figure 3), respectively. In the atropine-treated eyes, myopia progression was -0.28 ± 0.92 D (Figure 2), whereas the axial length remained essentially unchanged compared with baseline (-0.02 ± 0.35 mm, Figure 3). The changes in refractive error and axial length in the non-treated eyes of

subjects in both the atropine group and placebo-control group paralleled that of the placebo-treated eyes (Figures 2 and 3). The differences in myopia progression and axial elongation between the 2 groups were -0.92 D (95% confidence interval, -1.10 to -0.77 D; $P < 0.001$) and 0.40 mm (95% confidence interval, 0.35-0.45 mm; $P < 0.001$), respectively. No serious adverse events related to atropine were reported. In this study, glare and photophobia were minimized with the use of photochromatic lenses. 54 subjects withdrew from the study. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%), and others (0.5%).

- 10 **Conclusions:** Topical 1% atropine was effective in slowing the progression of low and moderate myopia and ocular axial elongation in Asian children.

Example 2: Second atropine in the treatment of myopia study (ATOM2)

In ATOM2, the effect of lower doses of atropine in preventing myopia progression and the visual side effects (pupil dilation, loss of accommodation and near-vision blur) were assessed.

(i) Summary of ATOM 2

Purpose: To compare efficacy and visual side-effects of 3 lower doses of atropine: 0.5%, 0.1% and 0.01%.

20 **Design:** Single-center, double-masked, randomized study. The design of ATOM2 is illustrated in Figure 4.

Subjects: 400 children aged 6-12 years with myopia of at least -2.0 D and astigmatism of -1.50 D or less.

25 **intervention:** Subjects (the children) were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1% and 0.01% atropine, to be administered once nightly to both eyes for 2 years. Cycloplegic refraction, axial length, accommodation amplitude, pupil diameter and visual acuity were noted at baseline, 2 weeks and then every 4 months for 2 years.

Main outcome measure: Myopia progression at 2 years. Changes were noted and differences between groups were compared using the Huber-White robust standard error to allow for data clustering of two eyes per subject.

Results: The mean myopia progression at 2 years was -0.30 ± 0.60 D, -0.38 ± 0.60 D and -0.49 ± 0.63 D in the 0.5%, 0.1% and 0.01% atropine groups respectively ($p=0.02$ between 0.01 and 0.5% groups; other $p>0.05$). In comparison, myopia progression in ATOM1 was -1.20 ± 0.69 D in the placebo group and -0.28 ± 0.92 in the 1% atropine group. The mean increase in axial length was 0.27 ± 0.25 mm, 0.28 ± 0.28 mm and 0.41 ± 0.32 mm in the 0.5%, 0.1% and 0.01% groups ($p<0.01$ between the 0.01% and 0.1% groups and between the 0.01% and 0.5% groups). Differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups, however, were small and may be considered clinically insignificant. 0.01% atropine had negligible effect on accommodation and pupil size and no effect on near visual acuity. Allergic conjunctivitis and dermatitis were the most common adverse effect noted; with 16 cases in 0.1% and 0.5% atropine groups, none in the 0.01% group.

Conclusion: 0.01% atropine has negligible side-effects compared to atropine at 0.1% and 0.5% and retains comparable efficacy in controlling myopia progression.

(ii) ATOM2 in detail

Methods

Children aged between 6-12 years with myopic refraction of at least 2.0 D in both eyes, astigmatism of less than 1.5 D and a documented myopic progression of at least 0.5 D in the past year were enrolled in a double-masked single-centre clinical trial. Excluded were those with ocular pathology (eg. amblyopia, strabismus), previous use of atropine or pirenzepine, an allergy to atropine, or systemic ill health (eg. cardiac or respiratory illness). Written informed consent was obtained from parents or guardians and verbal assent was obtained from children. The study was conducted according to the tenets of the Declaration of Helsinki, with ethics approval from the Singapore Eye Research Institute Review Board.

Subjects (the children) were randomized to receive 0.5%, 0.1% or 0.01% atropine once nightly in both eyes at an allocation ratio of 2:2:1 in six strata defined by gender and age-groups of 6-7, 8-10 and 11-12 years to ensure gender and age balance across the three treatment arms. Trial medications were pre-packaged so that bottles were pre-labelled with subject number and of similar appearance. Trial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzaikonium chloride as preservative (Ashwood Laboratories Ltd, Macau).

After assessment at the time of enrolment (baseline), the subjects were re-assessed 2 weeks after starting atropine (baseline 2), and then at 4, 8, 12, 16, 20 and 24 months. At each visit, best-corrected distance logMar visual acuity (BCVA) was assessed by an optometrist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity was assessed using best-corrected distance spectacle correction with a reduced LogMar reading chart placed at 40cm under well-lit conditions. The near point of accommodation (NPA) was measured using a RAF rule using best-corrected distance spectacle correction. Subjects were instructed to move the target inwards till the N5 print became slightly blurred, and then outwards till it just became clear. Accommodation amplitude was calculated as the inverse of NPA. Mesopic pupil size was measured with the Procyon 3000 pupillometer (Lion House, Red Lion Street, London, UK), using the Meso-Hi (4 lux) setting. Photopic pupil size was measured using the Neuroptics pupillometer (Neuroptics Inc, Irvine, CA, USA) while the subjects were viewing a target placed at 3m, after at least 10 seconds of exposure to lamps providing 300 lux of luminance. In both cases, at least 5 pupil size readings (with range <0.5 mm) were recorded and averaged.

Cycloplegic autorefraction was determined 30 minutes after 3 drops of cyclopentolate 1% (Cyclogyl, Alcon-Convreur) were administered at 5 minutes apart using a Canon RK-F1 autorefractor (Canon Inc. Ltd, Tochigiken, Japan). Five readings, all of which had to be less than 0.25 D apart, were obtained and averaged. Spherical equivalent was calculated as sphere plus half cylinder power. The Zeiss IOL Master (Carl Zeiss Meditec Inc, CA, USA), a non-contact partial coherence interferometry, was used to measure the ocular axial length. Five readings, with a maximum-minimum deviation of 0.05 mm or less, were taken and averaged.

Parents or guardians, subjects (the children) and study investigators were kept masked to the assigned dosage of trial medications. Each subject (child) kept a diary of usage of the trial medication. Compliance level of each subject was classified according to mean number of frequency of using atropine per week as reported by subjects over the
5 first 24 months. Subjects with 75% compliance rate (≥ 5.25 days/week) were considered compliant.

The primary end-point was myopia progression over 2 years. Since a hyperopic shift may occur after commencing atropine, myopic progression was calculated from the second baseline, when the subjects had been on trial medication for 2 weeks. Level of
10 myopia progression in each eye was further categorized as being mild (<0.5 D), moderate (0.5 to 0.99 D) or severe (>1.0 D).

Secondary end-points included myopia progression at one year, change in axial length at one and two years, and side-effect parameters such as changes in accommodation amplitude, mesopic and photopic pupil size and best-corrected distance and near
15 visual acuity. Myopia and axial changes were noted from second baseline, while accommodation, pupil size and visual acuity were monitored from first baseline. Any adverse events, regardless of whether they appeared relevant to atropine use, were documented.

Statistical analysis

20 All analyses were based on intention to treat principle and performed in statistical software Stata (version 10.1, Stata Corp., College Station, TX). For demographic and other person-level data such as compliance and ever experiencing adverse events, Fisher's exact test was used to test for difference in proportion of subjects between treatment groups and ANOVA for difference in means between treatment groups.
25 Endpoints from both eyes were pooled in a combined analysis using the Huber-White robust standard errors to allow for the correlation between eyes within person 25. Results on left and right eyes were very similar. For example, mean difference (95% CI) in 2-year myopia progression between left and right eyes were -0.01 (-0.06, 0.03). For brevity and better precision, this report shows analyses pooling both eyes with
30 robust standard errors for clustered data. The global null hypothesis of no difference

between 3 treatment groups was tested first, followed by pair-wise comparisons. Nominal level of statistical significance (p-value) was reported, i.e. no adjustment for multiple comparison. Interpretation will begin with considering the global null hypothesis between 3 groups in order to prevent inflated type I error rate. Placebo and
5 atropine treated eyes in ATOM1 were used for reference in secondary analyses.

Results

A total of 400 children were recruited into the study, with 161 , 155 and 84 children in the 0.5%, 0.1% and 0.01% atropine treatment arms respectively (Figure 4). There were almost equal numbers of males and females and 91% of children were of ethnic
10 Chinese origin (Table 1). No differences were noted in demographics, baseline refractive error, accommodation, pupil diameter or best corrected visual acuity between groups (Table 1). Correlation between change in spherical equivalent and axial length over 2 years was high (correlation coefficients. 82, $p<0.001$), and suggests good measurement validity.

Table 1: Characteristics at baseline and second baseline (ie. 2 weeks after starting trial medication)

Variables	Atropine(A) dose			p-value ^a
	A 0.01% (n 84)	A 0.1% (n 155)	A 0.5% (n 161)	
Age (yr), mean (sd)	9.5 (1.5)	9.7 (1.6)	9.7 (1.5)	0.95
Female, %	48.8	46.5	47.2	0.95
Chinese %	90.5	92.3	90.0	0.99
Spherical equivalent (D)				
- baseline	-4.5 (1.5)	-4.8 (1.5)	-4.7 (1.8)	0.40
- second baseline	-4.5 (1.5)	-4.5 (1.4)	-4.3 (1.8)	0.67
Axial length (mm)				
- baseline	25.1 (1.0)	25.2 (0.8)	25.2 (0.9)	0.94
- second baseline	25.2 (1.0)	25.1 (0.8)	25.1 (0.9)	0.93
Accommodation (D)				
- baseline	16.2 (3.4)	16.7 (3.0)	15.8 (3.4)	0.01
- second baseline	11.3 (4.3)	3.8 (2.5)	2.2 (1.2)	<0.001
Mesopic pupil diameter (mm)				
- baseline	3.9 (0.6)	3.9 (0.6)	4.0 (0.7)	0.21
- second baseline	5.2 (0.8)	7.2 (0.7)	7.8 (0.5)	<0.001
Photopic pupil diameter (mm)				
- baseline	4.7 (0.7)	4.6 (0.7)	4.6 (0.7)	0.63
- second baseline	5.8 (0.8)	7.4 (0.7)	7.9 (0.6)	<0.001
BCVA distant (logMar)				
- baseline	0.01 (0.05)	0.01 (0.06)	0.02 (0.06)	0.56
- second baseline	0.01 (0.05)	0.01 (0.05)	0.01 (0.06)	0.86
Near vision (logMar)				
- baseline	0.04 (0.09)	0.04 (0.08)	0.04 (0.07)	0.38
- second baseline	0.06 (0.08)	0.29 (0.18)	0.48 (0.16)	<0.001

a. Fisher's exact test for binary demographic variables; ANOVA for age; Huber-White robust standard error for clustered data (both eyes pooled) on ocular parameters

- 5 Two-year primary endpoint data were available for 355 of 400 (88.8%) subjects. 44 subjects withdrew participation on their own accord; 9 (10.7%), 14 (9.0%) and 21 (13.0%) from the 0.01%, 0.1% and 0.5% treatment group respectively (p=0.43); 1 subject did not turn up for the second year assessment. Compliance, defined as >75% expected usage was 98.7%, 96.8% and 98.8% in the 0.5%, 0.1% and 0.01% arms
- 10 (p=0.53) in the 2 year period.

Change in myopic progression and axial length

A clinically small, dose related response on myopic progression was noted between the 3 treatment arms (Figure 5). An initial hyperopia shift of 0.3 to 0.4 D was noted in the 0.1% and 0.5% groups but not in the 0.01% group (Table 1). At the end of 1 year, there

was a significant difference in myopia progression between the 0.5% atropine group and the 0.01% ($p < 0.001$) and 0.1% ($p = 0.01$) groups, but no statistical significant difference between 0.01% and 0.1% groups. The final myopia progression over 2 years was -0.49 ± 0.60 D, -0.38 ± 0.60 D and -0.30 ± 0.63 D in the atropine 0.01%, 0.1% and 5 0.5% groups respectively ($p = 0.07$), with significant difference only between the 0.01% and 0.5% groups (Table 2). There was no significant difference in spherical equivalent levels between groups ($p = 0.20$). Fifty percent of the 0.01% group had progressed by less than 0.5 D, compared to 58% and 63% in the 0.1 and 0.5% group respectively, with approximately 18% progressing by > 1.0 D in all 3 groups (Figure 6).

Table 2: Ophthalmology parameters at 2nd annual visit

	Atropine (A) dose (mean (SD))			p-value
	A 0.01%	A 0.1%	A 0.5%	
Spherical equivalent (D)				
- at 1 year	-4.9 (1.5)	-4.8 (1.4)	-4.6 (1.9)	0.26
- at 2 years	-5.1 (1.5)	-4.9 (1.3)	-4.7 (1.7)	0.20
- mean change over 1 year	-0.43 (0.52)	-0.31 (0.50)	-0.17 (0.47)	<0.001 ^{A,C}
- mean change over 2 years	-0.49 (0.63)	-0.38 (0.60)	-0.30 (0.60)	0.07 ^A
Axial length (mm)				
- at 1 year	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
- at 2 years	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08 ^B
- mean change over 1 year	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001 ^{A,B}
- mean change over 2 years	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002 ^{A,B}
Accommodation (D)				
- at 1 year	11.7 (4.3)	6.0 (3.4)	3.6 (3.2)	<0.001 ^{A,B,C}
- at 2 years	11.8 (3.2)	6.8 (3.4)	4.0 (2.6)	<0.001 ^{A,B,C}
- mean change over 1 year	-4.4 (4.9)	-10.9 (4.0)	-12.4 (3.3)	<0.001 ^{A,B,C}
- mean change over 2 years	-4.6 (4.2)	-10.1 (4.3)	-11.8 (4.4)	<0.001 ^{A,B,C}
Mesopic pupil size (mm)				
- at 1 year	5.1 (0.9)	6.7 (1.0)	7.5 (1.1)	<0.001 ^{A,B,C}
- at 2 years	5.1 (0.9)	6.7 (1.1)	7.5 (1.2)	<0.001 ^{A,B,C}
- mean change over 1 year	1.15 (0.78)	2.77 (1.03)	3.50 (1.05)	<0.001 ^{A,B,C}
- mean change over 2 years	1.15 (0.71)	2.71 (1.12)	3.56 (1.14)	<0.001 ^{A,B,C}
Photopic pupil size (mm)				
- at 1 year	5.6 (0.8)	7.0 (1.0)	7.7 (1.0)	<0.001 ^{A,B,C}
- at 2 years	5.5 (0.8)	6.9 (1.0)	7.8 (1.1)	<0.001 ^{A,B,C}
- mean change over 1 year	0.91 (0.78)	2.42 (0.91)	3.11 (1.08)	<0.001 ^{A,B,C}
- mean change over 2 years	0.74 (0.75)	2.25 (1.01)	3.11 (1.10)	<0.001 ^{A,B,C}
BCVA distant (logMar)				
- at 1 year	-0.005 (0.042)	-0.003 (0.054)	-0.003 (0.054)	0.99
- at 2 years	-0.001 (0.057)	0.005 (0.054)	0.011 (0.057)	0.25
- mean change over 1 year	-0.02 (0.05)	-0.02 (0.06)	-0.03 (0.05)	0.21
- mean change over 2 years	-0.02 (0.06)	0.01 (0.06)	-0.01 (0.06)	0.44
Near vision (logMar)				
- at 1 year	0.03 (-0.06)	0.15 (0.15)	0.35 (0.18)	<0.001 ^{A,B,C}
- at 2 years	0.01 (0.07)	0.10 (0.13)	0.29 (0.18)	<0.001 ^{A,B,C}
- mean change over 1 year	-0.01 (0.10)	0.10 (0.16)	0.32 (0.19)	<0.001 ^{A,B,C}
- mean change over 2 years	-0.02 (0.08)	0.06 (0.13)	0.25 (0.19)	<0.001 ^{A,B,C}

BCVA: best-corrected visual acuity

Myopia progression and axial length: change from second baseline; other parameters: change from initial baseline

- 5 P-values for test of global null hypotheses of all groups being the same are shown. Pairwise comparison P-values are represented by A: significant (P<0.05) difference between 0.01% and 0.5% atropine, B: significant difference between 0.01% and 0.1% atropine, and C: significant difference between 0.1% and 0.5% atropine.

With respect to axial length, change at 1 year was larger in the 0.01% group (0.24 ± 0.19 mm) than in the 0.1% (0.13 ± 0.18 mm) and 0.5% (0.11 ± 0.17 mm) groups (p<0.001) (Figure-7). Pair-wise comparison showed statistically-significant difference

between 0.01% and the other two groups ($p < 0.001$). This difference persisted till the end of the 24 month period (Table 2).

Changes in accommodation, pupil diameter and visual acuity

There was no difference in accommodation, mesopic and photopic pupil diameter between groups at baseline (Table 1). However, significant dose-related differences quickly became evident by second baseline visit (Table 1). Changes within the 0.01% group were significantly less than in the 2 other groups. Accommodation amplitude in the 0.01% group was only reduced to 11.3 D compared to 3.8 D and 2.2 D in the 0.1% and 0.5% groups (Table 1). In functional terms, this meant that near visual acuity was not significantly impaired in the 0.01% group, while deficiencies were noted in the 2 other groups. Mean best-corrected distant visual acuity was not affected by atropine use (Table 2), although 10% of subjects did encounter mild distance blur (Table 3).

Table 3. Adverse event and serious adverse events

	Atropine (A) dose			Exact test p-value ^a
	A 0.01% (n=84)	A 0.1% (n=155)	A 0.5% (n=161)	
	Number of episode /number of children (% children)			
Adverse Events				
Allergic conjunctivitis	0/0 (0)	7/6 (4)	7/7 (4)	0.16
Dermatitis involving eyelids	0/0 (0)	2/1 (1)	4/3 (2)	0.54
Stye/chalazion	2/2 (2)	16/12 (8)	16/12 (7)	0.22
Loss of distant BCVA > 1 line	11/11 (13)	20/20 (13)	13/13 (8)	0.38
Others, eye-related	2/1 (1)	2/2 (2)	3/3 (2)	1.00
Others, non eye-related	306/69 (82)	470/122 (78)	477/132 (82)	0.73
Severe Adverse Events				
Events requiring hospitalisation	1/1 (1)	3/3 (2)	3/3 (2)	1.00

a. Fisher's exact test for proportion of children with adverse events

Pupil size, under both photopic and mesopic conditions, in the 0.01% group increased by only 1 mm, while pupils in the 0.1% and 0.5% groups were about 3 mm larger (Table 2). While the atropine effect on pupil diameter remained unchanged over time,

the accommodation appeared to improve in the 0.1% and 0.5% groups over time (Table 2). The mean accommodation amplitude in the 0.5% group, for example, fell from 15.8 D at baseline to 2.2 D at the second baseline visit but rose to 3.6 D and 4.1 D by the end of the first and second years. Changes in 0.01% group were less, varying
5 from 16.2 D to 11.3 D, 11.7 D and 11.8 D over the same time-period.

Changes in spherical equivalent (myopia) and axial length after stopping atropine for 1 year (between 24 and 36 months)

356 children (89%) entered into the wash-out phase of the ATOM2 study. On cessation of atropine, there was a rebound increase in myopia was noted in all 3 groups which
10 was greater in 0.5% atropine eyes ($-0.87 \pm 0.52D$) than in 0.1% atropine ($-0.68 \pm 0.45D$) and 0.01% atropine ($-0.28 \pm 0.33D$) eyes ($p < 0.001$). This resulted in overall progression over the 36 month period being significantly less in the 0.01% atropine eyes ($-0.72 \pm 0.72D$) than in the 0.1% atropine ($-1.04 \pm 0.83D$) and 0.5% atropine eyes ($-1.15 \pm 0.81 D$) (Figure 8).

15 During the same period, there was a significantly greater increase in axial length in the 0.1% atropine and 0.5% atropine eyes compared to the 0.01% atropine eyes (Figure 9). Overall change in axial length, however, was not significantly different between groups.

Adverse events

20 Majority of the adverse events were deemed to be unrelated to study treatment (eg. flu-like illness) (Table 3). Adverse reactions directly attributable to atropine included allergic conjunctivitis, which occurred in 13 subjects (4.1%) in 0.1% atropine and 0.5% atropine groups. in 3 (1.2%) subjects, symptoms were severe enough to warrant ceasing trial medication. Four subjects in the 0.1% and 0.5% groups (1.3%) had allergy
25 related dermatitis of the eyelids. Six subjects had other eye symptoms, 5 of which could be attributed to atropine including 1 case of irritation and another of blur in the 0.01% atropine group, and 2 cases of ocular irritation and 1 with intolerable glare in the 0.5% atropine group.

Seven subjects had a severe adverse event requiring hospitalization. In the 0.01% group, one subject had acute gastric pain. In the 0.1% atropine group, there was 1 case each of appendicitis, respiratory infection and Ewing's sarcoma. In the 0.5% atropine group, there was 1 case each of tachycardia, dengue fever and gastroenteritis.

- 5 None of these events are thought to be associated with atropine.

Discussion

- At the end of 2 years, the mean myopia and axial length progression in the ATOM1 study was -0.28 ± 0.92 D and -0.02 ± 0.35 mm in the 1% atropine eyes compared to -1.20 ± 0.69 D and 0.38 ± 0.38 mm in the placebo eyes. The progression of myopia in the ATOM2 subjects lie in a dose-related manner between these two extremes (Figure 5).

In ATOM2, the progression of myopia in subjects on 0.5% atropine was -0.17 ± 0.47 D over 1 year, and -0.30 ± 0.60 D over 2 years. This was similar to the progression noted in subjects on 1% atropine in the ATOM1 study (Figure 5).

- 15 Changes in myopia and axial lengths outcome in the 0.1% atropine group were very similar to the 0.5% atropine group. The myopia progression was initially larger in the 0.1% atropine at 1 year (-0.31 D vs -0.17 D, $p=0.01$) but this gap had closed by the second year (-0.38 D vs -0.30 D, $p=0.25$). In terms of effect on other ocular parameters, accommodation (-10.9 D vs -12.4 D), mesopic pupil diameter (2.7mm vs 20 3.5mm) and photopic pupil diameter (2.2 D vs 3.1 D) were also less in the 0.1% atropine compared to the 0.5% atropine group, making the overall efficacy-side-effect profile of 0.1 % atropine better than 0.5% atropine.

- The changes in spherical equivalent and axial lengths upon stopping atropine is interesting. There was a rebound increase in myopia and axial length which was 25 greater in higher dose atropine. The change in the 0.01% group, however, was more gradual with overall change in spherical equivalent being less in the 0.01% group compared to all other groups.

The subjects from ATOM1 were slightly younger (mean age: 9.2 versus 9.6 years), had lower spherical equivalents (mean spherical equivalent -3.4 versus -4.7 D) and smaller

axial lengths (mean axial length 24.8 versus 25.2 mm) than those in the ATOM2 group. Nevertheless, the reduction in myopia progression with atropine eyedrops observed in both studies with otherwise similar study profiles and methodologies was consistent and should be regarded as definitive outcomes in these studies. Axial lengths were
5 measured differently between the two studies with A-scan ultrasonography used in ATOM1 (Chua *et al.*, 2006) and IOLmaster in ATOM2. Thus, the axial lengths of ATOM1 and ATOM2 have not been compared in Figure 7.

In designing ATOM2, 0.01% atropine was initially assumed to have minimal effect, and thus act as a potential control; hence the lower allocation of subjects to this group.
10 However, contrary to expectations, 0.01% atropine also had significant clinical efficacy on reducing myopia progression not dissimilar to the higher concentrations, but unlike the other concentrations, had negligible effect on accommodation and pupil size. The myopia progression rate in this group ($-0.49 \text{ D} \pm 0.63 \text{ D}$ at 2 years) was much less than the $-1.20 \pm 0.69 \text{ D}$ at 2 years in the ATOM1 placebo groups. Compared with the 2
15 higher doses, the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared to the 0.5% group and similarly, the difference in axial length increase was statistically larger than both the 0.1% and 0.5% group. However, absolute differences between groups were clinically small with differences in myopic progression and axial length increase of only 0.19 D and 0.13 mm over 2 years (Table
20 2, Figures 5 and 7). Most importantly, the ocular side-effect profile was significantly better with accommodation remaining at 11.8 D, mean pupil size of 5 mm and a mean near logMar vision of 0.01. In other words, 0.01% atropine was still clinically effective in reducing myopia progression, but did not cause side-effects normally associated with higher concentrations of atropine.

25 Overall, atropine-related adverse effects were uncommon at the 0.01% dose. Allergic reactions were most frequent; with 3.2% experiencing allergic conjunctivitis and 0.8% experiencing an allergy-associated dermatitis, all of which were in the 0.1% or 0.5% groups. It should be noted that the benzalkonium preservative in the 0.01% atropine eyedrop formulation may be at least partly responsible for these allergies. A number of
30 subjects (1.1%) also noted at least 1 line loss in distance best-corrected vision (Table 3). These effects are reversible on stopping medication (Tong *et al.*, 2009). There are no long-term studies on the effect of atropine on the eye and continued vigilance is

necessary, but so far there are no known long-term adverse effects associated with its use (North and Kelly, 1987).

The strength of ATOM2 was its randomised double-blind design and low drop out rate. Instead of a placebo group, the comparison was based on external (historical and
5 population) controls. The non-inclusion of a placebo group was a decision based on findings from the ATOM1 study, which clearly showed the efficacy of atropine treatment compared to placebo, rendering a placebo arm unethical. The more important aspect of this trial remained the comparison of low dose versus high dose not only in terms of efficacy, but also in terms of the visual side effects of atropine. ATOM2 was otherwise
10 designed to have largely similar study parameters so that direct comparison with ATOM1 was deemed appropriate.

In conclusion, the results of ATOM2 suggest that 0.5%, 0.1% and 0.01% atropine remain effective in reducing myopia progression, as compared to placebo treatment, and that the clinical differences in myopia progression between these 3 groups are
15 small. In terms of side-effects, 0.5% and 0.1% atropine formulations were still noted to cause visual side-effects of accommodation loss and pupil dilation, but the 0.01% atropine formulation had no or negligible effect on accommodation or pupil dilation. The lowest concentration of 0.01% atropine appears to retain efficacy and is thus a viable concentration for reducing myopia progression in children, whilst attaining a
20 clinically significant improved safety profile in terms of accommodation, pupil size and near visual acuity, and subsequently much reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer adverse events, and exhibited much less myopic rebound after it was stopped. These findings collectively suggest that 0.01% atropine nightly appears to be a safe and effective regime for slowing myopia
25 progression in children, with minimal impact on visual function in children.

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Claims

1. A composition for reducing and/or preventing myopia progression comprising less than 0.025% atropine.
2. The composition according to claim 1; comprising 0.001% to 0.0249% atropine.
- 5 3. The composition according to any one of the preceding claims; comprising 0.005% to 0.02% atropine.
4. The composition according to any one of the preceding claims, comprising 0.005% to 0.015 % atropine.
- 10 5. The composition according to claim 1, wherein the composition comprises 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine.
- 15 6. The composition according to any one of the preceding claims, wherein the composition comprises about 0.01 % atropine.
7. The composition according to any one of the preceding claims, wherein the composition comprises 0.01% atropine.
8. The composition according to any one of the preceding claims, further comprising at least one pharmaceutically acceptable excipient.
- 20 9. The composition according to any one of the preceding claims, wherein the composition is for administration to the eye.
10. The composition according to any one of the preceding claims, wherein the composition is an eye-drop composition.
- 25 11. The composition according to any one of claims 1 to 10, for use in reducing and/or preventing myopia progression and/or treating myopia.

12. A method for reducing and/or preventing myopia progression comprising administering to a subject a composition according to any one of claims 1 to 10.
13. Use of atropine in the preparation of a composition for reducing and/or preventing myopia progression, wherein the composition comprises less than
5 0.5% atropine.
14. Use according to claim 13, wherein the composition comprises 0.001% to 0.0249% atropine.
15. Use according to claim 13 or 14, wherein the composition comprises 0.005 to 0.02% atropine.
- 10 16. Use according to any one of claims 13 to 15, wherein the composition comprises 0.005 to 0.015% atropine.
17. Use according to any one of claims 13 to 16, wherein the composition comprises 0.008 to 0.012% atropine.
18. Use according to claim 13, wherein the composition comprises 0.001%,
15 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.011%, 0.012%, 0.013%, 0.014%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.021%, 0.022%, 0.023%, 0.024%, 0.0245% or 0.0249% atropine.
19. Use according to any one of claims 13 to 18, wherein the composition comprises about 0.01% atropine.
- 20 20. Use according to any one of claims 13 to 19, wherein the composition comprises 0.01% atropine.
21. Use according to any one of claims 10 to 15, wherein the composition further comprises at least one pharmaceutically acceptable excipient.
22. Use according to any one of claims 10 to 16, wherein the composition is for
25 administration to the eye.

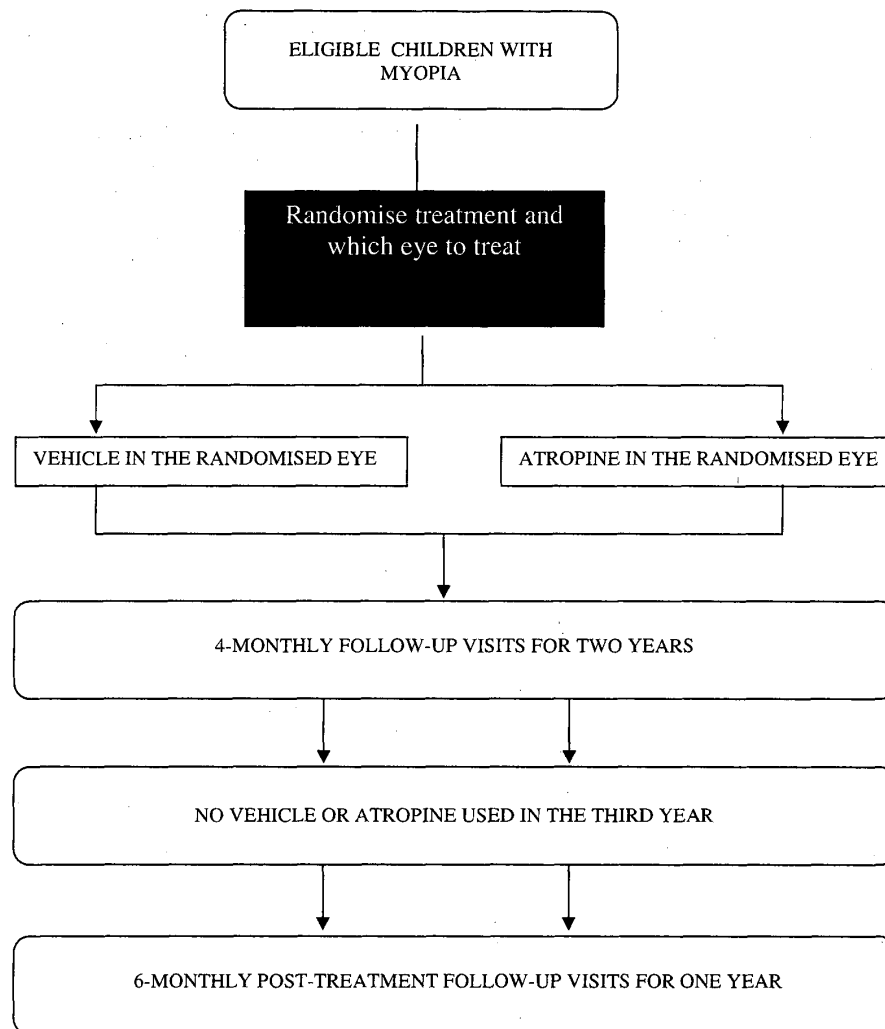


Figure 1

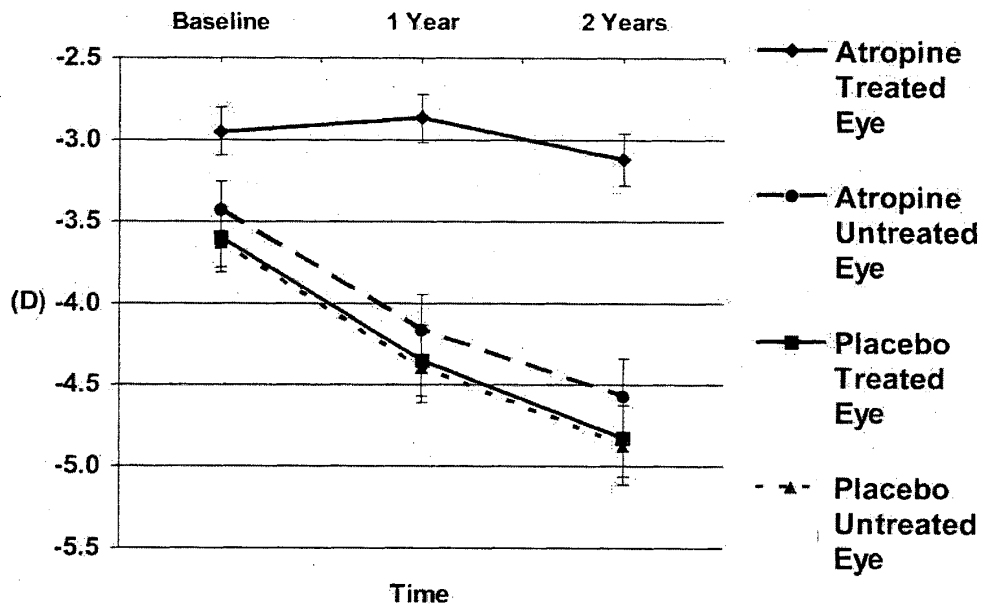


Figure 2

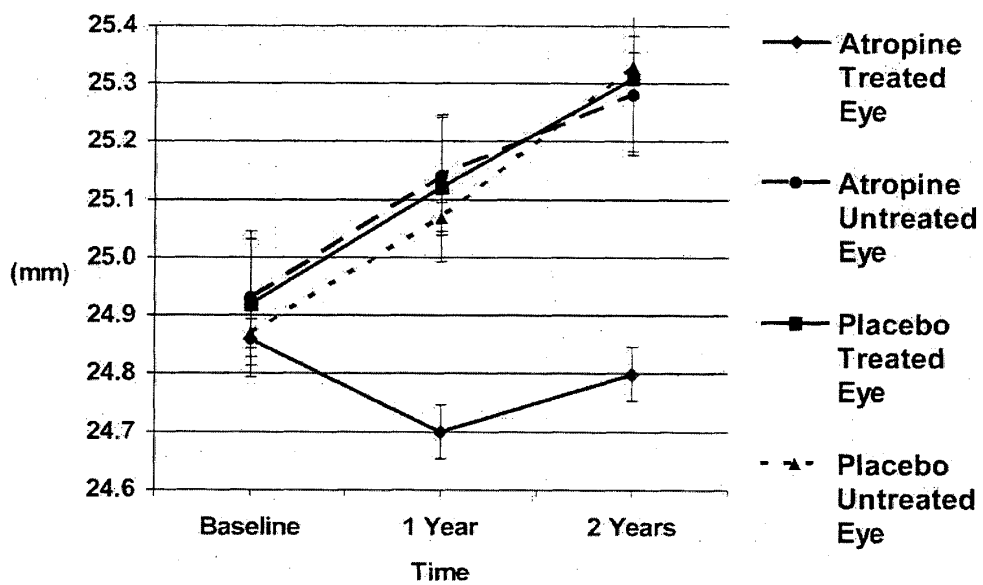


Figure 3

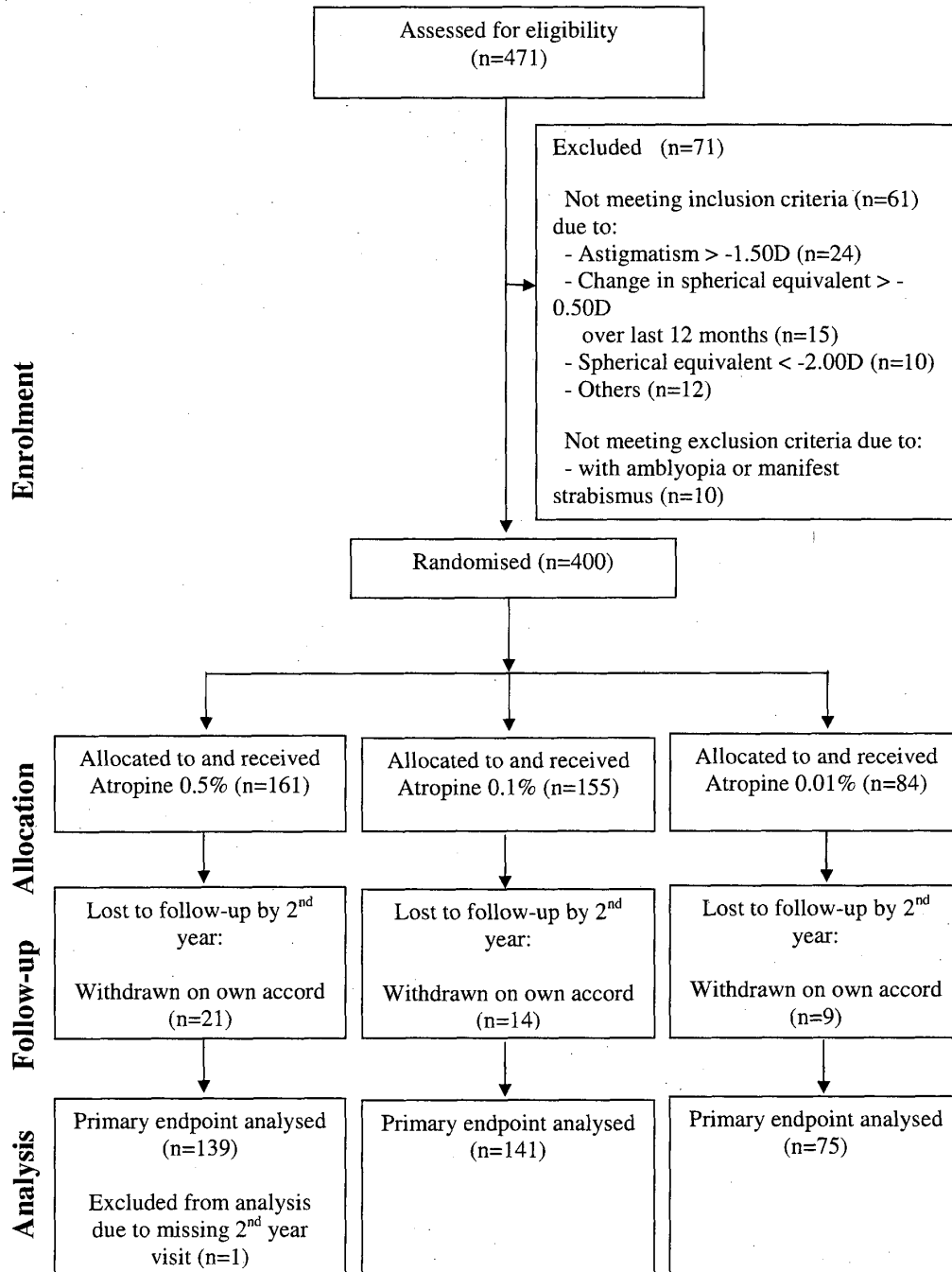


Figure 4

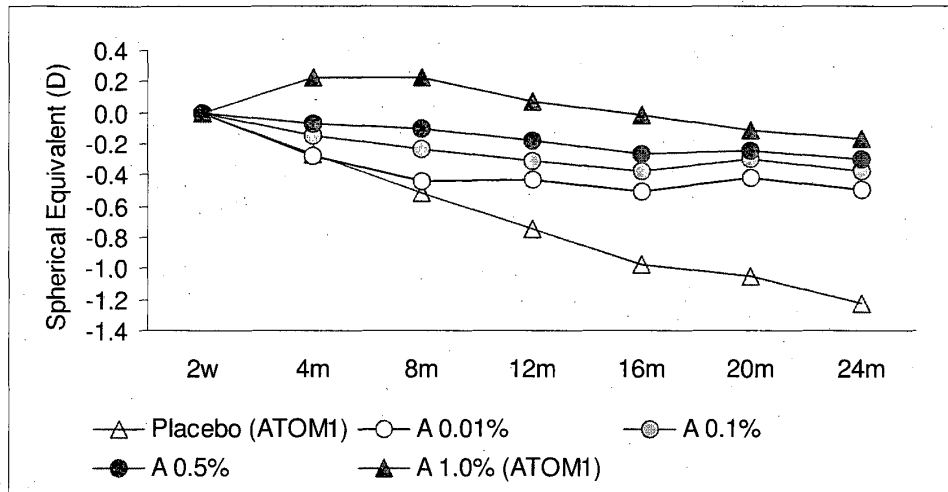


Figure 5

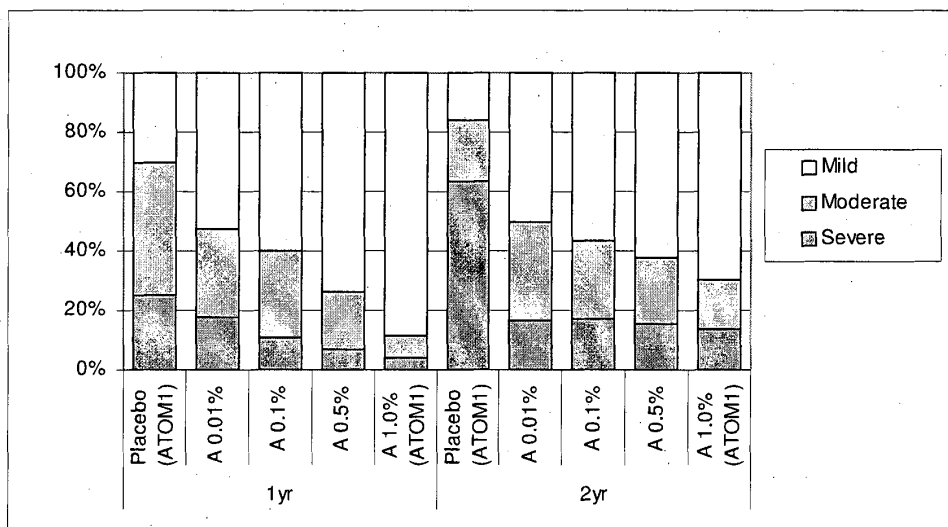


Figure 6

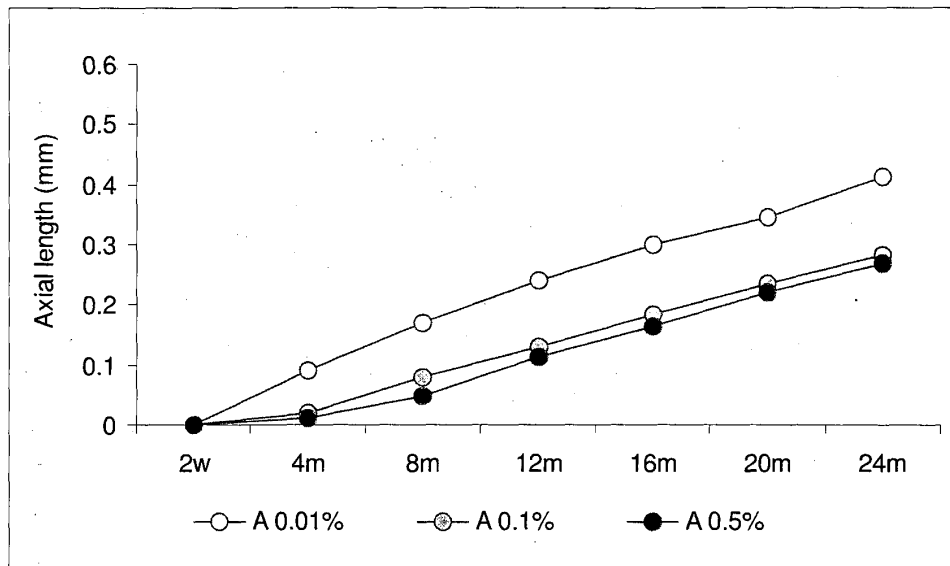


Figure 7

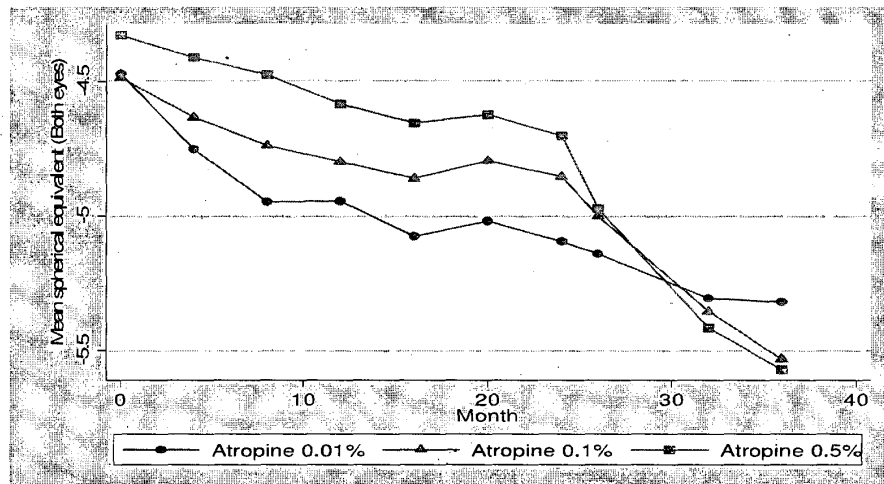


Figure 8

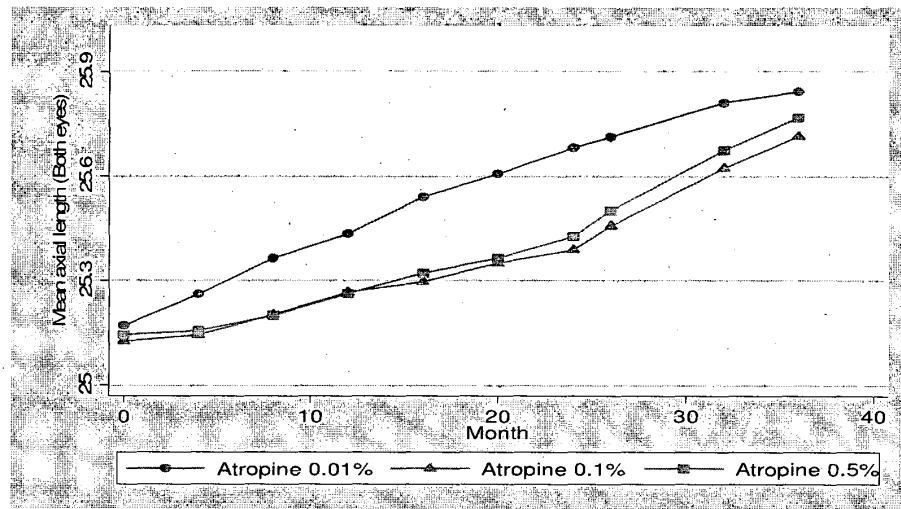


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2012/000174

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/46 (OCT 2005) A61P 27/10 (OCT 2005)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, WPI, EPODOC: atropine, atropen, hyoscyamine, cytopaz, anaspaz, myopia, short sightedness, near sightedness; Clinical trials.gov website: myopia, atropine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 July 2012

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT7SG2012/000174
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	'Safety and Efficacy Study of 0.5%, 0.1% & 0.01% Atropine Treatment to Both Eyes in Treatment of Myopia in Children.' [retrieved 28 June 2012] Retrieved from the internet, URL: http://clinicaltrials.gov/ct2/show/NCT00371124?term=ATROPINE&rank=18 published 30 August 2010. whole document	1-22
X	US 2007/0254914 A1 (WU, P-C. et al.) 01 November 2007 paragraphs 0015, 0017	1-22
X	SHIH, Y-F. et al. 'Effects of Different Concentrations of Atropine on Controlling Myopia in Myopic Children.' Journal of Ocular Pharmacology and Therapeutics. 1999. 15(1):85-90 page 86, 2nd paragraph	13, 21-22
X	FANG, P-C. et al. 'Prevention of Myopia Onset with 0.025% Atropine in Premyopic Children'. 'Journal of Ocular Pharmacology and Therapeutics. 2010 Aug; 26(4):341-5. page 342	13, 21-22
P,X	CHIA, A. et al. 'Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2).' Ophthalmology. Feb 2012. 119(2):347-54. whole document	1-22

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INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/SG2012/000174	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2007/0254914 A1	01 Nov 2007	US 2007254914 A1	01 Nov 2007
End of Annex			
<u>Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.</u> Form PCT/ISA/210 (Family Annex)(July 2009)			