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Efficacy and Safety of 0.01% and 0.02% Atropine for the Treatment of Pediatric Myopia Progression Over 3 Years
A Randomized Clinical Trial

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IMPORTANCE The global prevalence of myopia is predicted to approach 50% by 2050, increasing the risk of visual impairment later in life. No pharmacologic therapy is approved for treating childhood myopia progression.

OBJECTIVE To assess the safety and efficacy of NVK002 (Vyluma), a novel, preservative-free, 0.01% and 0.02% low-dose atropine formulation for treating myopia progression.

DESIGN, SETTING, AND PARTICIPANTS This was a double-masked, placebo-controlled, parallel-group, randomized phase 3 clinical trial conducted from November 20, 2017, through August 22, 2022, of placebo vs low-dose atropine, 0.01% and 0.02% (2:2:3 ratio). Participants were recruited from 26 clinical sites in North America and 5 countries in Europe. Enrolled participants were 3 to 16 years of age with −0.50 diopter (D) to −6.00 D spherical equivalent refractive error (SER) and no worse than −1.50 D astigmatism.

INTERVENTIONS Once-daily placebo, low-dose atropine, 0.01%, or low-dose atropine, 0.02%, eye drops for 36 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of participants' eyes responding to therapy (<0.50 D myopia progression at 3 years). Secondary efficacy outcomes included mean change from baseline in SER and axial length at month 36 in a modified intention-to-treat population (mITT; participants 6 to 10 years of age at baseline). Safety measurements for treated participants (3 to 16 years of age) were reported.

RESULTS A total of 576 participants were randomly assigned to treatment groups. Of these, 573 participants (99.5%; mean [SD] age, 8.9 [2.0] years; 315 female [54.7%]) received trial treatment (3 participants who were randomized did not receive trial drug) and were included in the safety set. The 489 participants (84.9%) who were 6 to 10 years of age at randomization composed the mITT set. At month 36, compared with placebo, low-dose atropine, 0.01%, significantly increased the responder proportion (odds ratio [OR], 4.54; 95% CI, 1.15-17.97; P = .03), slowed mean SER progression (least squares mean [LSM] difference, 0.24 D; 95% CI, 0.11 D-0.37 D; P < .001), and slowed axial elongation (LSM difference, −0.13 mm; 95% CI, −0.19 mm to −0.07 mm; P < .001). At month 36, compared with placebo, low-dose atropine, 0.02%, also showed benefit but did not significantly increase the responder proportion (OR, 1.77; 95% CI, 0.50-6.26; P = .37) or slow mean SER progression (LSM difference, 0.10 D; 95% CI, −0.02 D to 0.22 D; P = .10) but did slow mean axial elongation (LSM difference, −0.08 mm; 95% CI, −0.13 mm to −0.02 mm; P = .005). There were no serious ocular adverse events and few serious nonocular events; none were judged as associated with atropine.

CONCLUSIONS AND RELEVANCE Results of this randomized clinical trial suggest efficacy for low-dose atropine, 0.01%, across all 3 main end points compared with placebo. The efficacy and safety observed suggest that low-dose atropine may provide a treatment option for childhood myopia progression.

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Visual Abstract

Supplemental content and Journal Club Slides

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Group Information: The members of the CHAMP Trial Group Investigators appear in Supplement 4.

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T he global prevalence of myopia was estimated at 30% to 34% in 2020 and is predicted to increase to approximately 50% by 2050[1]; 938 million people are projected to develop myopia with refractive error worse than –6 diopters (D) by 2050 with an increased risk of major sequelae.[2] Myopia usually presents at 6 to 12 years of age.[3] Early-onset myopia increases the risk of high myopia[4-6] and complications including glaucoma, cataracts, retinal detachment, and myopic maculopathy.[7,8] Vision correction alone will not alter myopia progression.[9] Multifocal contact lenses and orthokeratology are effective in slowing axial elongation and myopia progression,[10-15] however, no pharmaceutical products are currently approved in the US or Europe to treat myopia progression.

Atropine may block receptors throughout the eye to limit choroidal and scleral thinning and slow eye elongation.[16,17] Low-dose atropine, at concentrations up to 0.05%, has recently emerged as a pharmacologic option to control myopia progression in children.[18-23] The dose-ranging Atropine Treatment of Myopia 2 (ATOM2) trial supported the use of atropine eye drops, including a concentration as low as 0.01% in Asian children.[18] The Low-Concentration Atropine for Myopia Progression (LAMP) study[23] along with other randomized clinical studies of low-dose atropine[19,21,22] demonstrated the efficacy of atropine, 0.01%, in slowing myopia progression with fewer visual adverse effects, compared with higher concentrations of atropine.

Currently, compounded low-dose atropine is used off label in the US. These preparations are not of pharmaceutical grade quality and contain preservatives.[24-27] Preservative-free formulations can avoid potential associated toxicities including dry eye and chronic corneal irritation.[28] NVK002 (Vyluma) is a novel, preservative-free, pharmaceutical-grade atropine formulation under development for the treatment of myopia progression.

Here, we report the 3-year results of the Childhood Atropine for Myopia Progression (CHAMP) phase 3 randomized clinical trial that evaluated the efficacy and safety of low-dose atropine at concentrations of 0.01% and 0.02% vs placebo to treat myopia progression in children.

Methods

Trial Design and Oversight

CHAMP was a 3-arm, parallel, randomized, multicenter, double-masked, placebo-controlled, phase 3 trial conducted across 27 clinical sites in North America and 5 countries in Europe. The protocol and the statistical analysis plan (SAP) were developed by the sponsor and are available in Supplement 1 and Supplement 2, respectively. The trial was approved by central and/or local institutional review boards or ethics committees for each clinical site. The trial was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. Before randomization, written informed consent was obtained from parents or legal guardians, and assent was obtained from participants. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Key Points

Question Does low-dose atropine in concentrations of 0.01% and/or 0.02% slow the progression of myopia?

Finding In this randomized clinical trial including 573 participants in the safety set and 489 participants in the modified intention-to-treat set, low-dose atropine treatment demonstrated reduced myopia progression and axial elongation vs placebo over 3 years of therapy.

Meaning Trial results show that the efficacy and safety observed may be supportive of a pharmacological treatment option for myopia progression in children.

The trial included 2 stages (eFigure 1 in Supplement 3). Stage 1 was the 36-month efficacy and safety phase presented herein. Participants were randomly assigned in a 2:2:3 ratio to receive placebo (vehicle), atropine, 0.01%, or atropine, 0.02%, respectively, dosed 1 time per day in each eye at bedtime. The randomization was stratified by age at randomization (<9 years and ≥9 years) and by refractive error (spherical equivalent refractive error [SER] –0.50 to –3.00 D and SER –3.01 to –6.00 D).

The low-dose atropine used in the trial was a preservative-free formulation in the concentrations 0.01% and 0.02% manufactured under Good Manufacturing Practices. It was packaged in sterile, single-use ampules, formulated with standard topical ophthalmic excipients, and was stable at room temperature (eMethods in Supplement 3). Placebo trial medication was of identical formulation but without atropine. Trial sites used Interactive Response Technology (Suvoda), a computer-based randomization and distribution software, to randomly assign participants to treatment groups, and masked trial medication was dispensed accordingly. The randomization list, a permuted block design, was created by Design and Analysis of Trials Associates. The sponsor (Vyluma), site personnel, and trial participants were masked to the identity of treatment throughout the trial.

Trial Participants

Key inclusion criteria included an age of 3 to 17 years or younger (inclusive) at the time of enrollment, myopic SER of –0.50 to –6.00 D in each eye, astigmatism of no more than –1.50 D in each eye, and anisometropic SER of less than 1.50 D. The primary objective was to evaluate myopia progression in participants who were 6 to 10 years of age at randomization. Enrollment of participants from the age range of 11 to 16 years was discontinued after 66 participants. The protocol specified that after enrollment of 50 participants older than 11 years, enrollment could be closed to avoid overenrollment of a subpopulation least likely to benefit. Participants self-identified with the following race and ethnicity categories: American Indian or Alaskan Native, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, White, and other (which included races not shown in the previous list as well as missing race and ethnicity information). Key exclusion criteria included history of any ocular disease or surgery that might confound trial results; this included prior

myopia control treatment including orthokeratology, multifocal contact lenses, or progressive-addition spectacle lenses and chronic use of topical or systemic antimuscarinic/anticholinergic medications. A complete list of inclusion and exclusion criteria is provided in the trial protocol in Supplement 1.

Trial End Points and Assessments

The primary efficacy end point was the proportion of participants' eyes that showed less than 0.50 D myopia progression from baseline (responder analysis) at month 36 for atropine, 0.02%, vs placebo. Secondary end points were defined as the responder analysis for atropine, 0.01%, and change from baseline for SER and axial length for both doses at month 36.

Cycloplegic SER and axial length were measured every 6 months. For each evaluation, 3 to 5 measurements were averaged. The SER for each eye was normalized to a vertex distance of 0 mm (the corneal plane) according to the calculation specified in the SAP. Safety assessments included best-corrected distance visual acuity, photopic pupil size, slitlamp with fundus examination, intraocular pressure every 6 months, and recording of adverse events (AEs) at each visit. AEs were coded using the Medical Dictionary for Regulatory Activities, version 25. In cases of COVID-19–related site closures, virtual visits were conducted by phone, assessing AEs and compliance (Supplement 1).

Statistical Analysis

Primary and secondary efficacy analyses were performed in the modified intention-to-treat (mITT) data set, which included all participants aged 6 to 10 years at baseline. The mITT set was predefined as the primary analysis population because this age group has been widely studied in the literature. Safety analyses included all participants who were administered at least 1 dose of trial medication. The ITT data set included all participants aged 3 to 16 years of age who were randomly assigned to treatment groups.

At a 2-sided 5% significance level, 136 participants in the atropine, 0.02%, group and 91 participants in the placebo group were estimated to provide 95% power to detect the difference between treatment responder proportions of 0.25 and 0.07. A sample size of 91 in the atropine, 0.01%, group and 91 in the placebo group were estimated to provide 90% power to detect the same treatment difference. To account for dropouts, we planned to randomly assign at least 436 participants into the 6- to 10-year age groups (the primary efficacy population) and at least 483 participants total.

The primary and all secondary end points comprised a fixed sequence set of end points to be tested in order. The responder analysis used a mixed-effects model based on the binomial distribution using a logit function, with progression as the dependent variable, and participant, treatment, visit, eye, baseline age group (<9 or ≥9 years), and SER group (−0.50 to −3.00 D or −3.01 to −6.00 D) as independent variables, including a treatment-by-visit interaction. Random intercept for participants and eye-within participant were included using variance components and compound symmetry covariance structures. The least squares mean (LSM) change from

baseline in SER or axial length was also analyzed using a mixed-effects model (SAP in Supplement 2). All analyses were performed assuming data missing at random, with no imputation for missing data. P values were 2-sided and not adjusted for multiple analyses. A P value < .05 was considered statistically significant. Further details are provided in the SAP in Supplement 2 with analyses using SAS software, version 9.4 (SAS Institute).
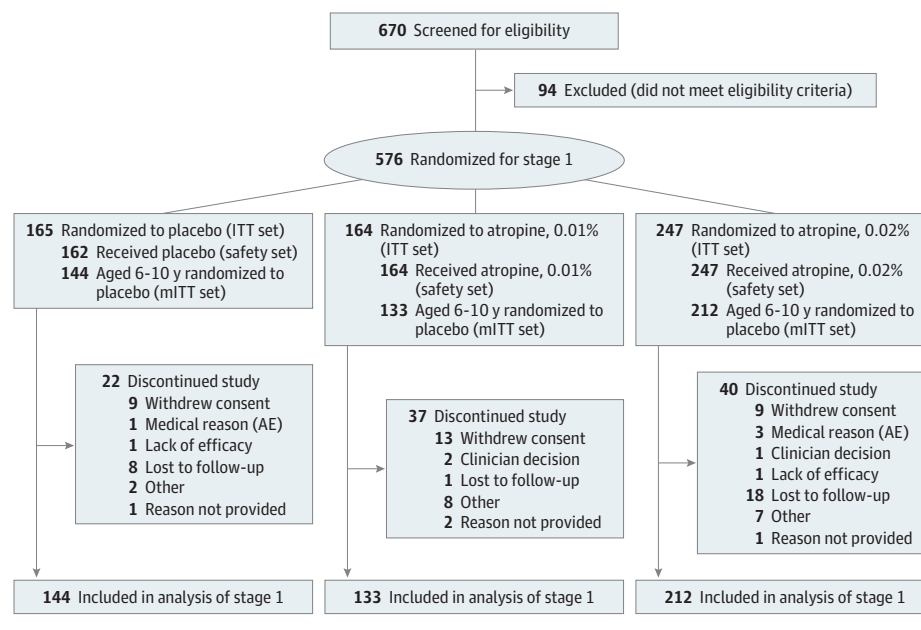
Results

Trial Population

From November 20, 2017, through August 22, 2022, 576 participants were randomly assigned to treatment groups. Of these, 573 participants (99.5%; mean [SD] age, 8.9 [2.0] years; 261 male [45.5%]; 312 female [54.5%]) received trial treatment (3 participants who were randomized did not dose with trial drug) and were included in the safety set. Participants self-identified with the following race and ethnicity groups: 7 American Indian or Alaskan Native (1.2%), 109 Asian (19%), 81 Black or African American (14.1%), 155 Hispanic or Latino (27.1%), 4 Native Hawaiian or Other Pacific Islander (0.7%), 308 White (53.8%), and 64 other (11.2%). The 489 participants (84.9%) who were 6 to 10 years of age at randomization composed the mITT set. Of the 576 randomly assigned participants, 477 (82.8%) completed all 3 years of stage 1, whereas 99 (17.2%) discontinued the trial; this proportion was within the estimated dropout rate of 27%. The main reasons reported for trial discontinuation were loss to follow-up (42 [7.3%]) and withdrawal of consent (31 [5.4%]) (Figure 1). Baseline characteristics were generally balanced among the 3 treatment groups (Table 1; eTable 1 in Supplement 3).

Efficacy

The proportion of responder eyes was 17.5% (44 of 252) in the placebo group, 28.5% (57 of 200) in the atropine, 0.01%, group, and 22.1% (81 of 366) in the atropine, 0.02%, group (Table 2). The primary outcome of the difference vs placebo was significant for atropine, 0.01% (odds ratio [OR], 4.54; 95% CI, 1.15-17.97; P = .03) but was not significant for atropine, 0.02% (OR, 1.77; 95% CI, 0.50-6.26; P = .37) at 3 years. Atropine, 0.01%, was associated with significantly higher responder rates than placebo at all time points, whereas atropine, 0.02%, was significant vs placebo only at month 12 (OR, 4.78; 95% CI, 1.75-13.04; P = .002) (Figure 2A; eTable 2 in Supplement 3). Post hoc analysis comparing atropine, 0.01% and 0.02%, showed comparable efficacy (eTable 3 in Supplement 3). Post hoc evaluation of confounding therapies indicated that exclusion of data associated with confounding therapies led to an increased treatment effect size (eTable 4 in Supplement 3) noted subsequently in the Discussion.

The change in SER from baseline (LSM) at month 36 was −1.28 D (95% CI, −1.37 to −1.19 D) in the placebo group, −1.04 D (95% CI, −1.14 to −0.94 D) in the atropine, 0.01%, group, and −1.18 D (95% CI, −1.26 to −1.10 D) in the atropine, 0.02%, group (Table 2). The LSM difference for atropine, 0.01% vs placebo was 0.24 D (95% CI, 0.11-0.37 D; P < .001). There was a smaller

Figure 1. Participant Disposition

670 Screened for eligibility

94 Excluded (did not meet eligibility criteria)

576 Randomized for stage 1

165 Randomized to placebo (ITT set)
162 Received placebo (safety set)
144 Aged 6-10 y randomized to placebo (mITT set)

164 Randomized to atropine, 0.01% (ITT set)
164 Received atropine, 0.01% (safety set)
133 Aged 6-10 y randomized to placebo (mITT set)

247 Randomized to atropine, 0.02% (ITT set)
247 Received atropine, 0.02% (safety set)
212 Aged 6-10 y randomized to placebo (mITT set)

22 Discontinued study
 9 Withdrew consent
 1 Medical reason (AE)
 1 Lack of efficacy
 8 Lost to follow-up
 2 Other
 1 Reason not provided

37 Discontinued study
13 Withdrew consent
 2 Clinician decision
 1 Lost to follow-up
 8 Other
 2 Reason not provided

40 Discontinued study
 9 Withdrew consent
 3 Medical reason (AE)
 1 Clinician decision
 1 Lack of efficacy
18 Lost to follow-up
 7 Other
 1 Reason not provided

144 Included in analysis of stage 1

133 Included in analysis of stage 1

212 Included in analysis of stage 1

AE indicates adverse event; ITT, intention to treat; mITT, modified intention to treat.

Table 1. Baseline Demographic and Clinical Characteristics (Intention-to-Treat Set)

Characteristic	Placebo (n = 165)	Atropine, 0.01% (n = 164)	Atropine, 0.02% (n = 247)
Age, mean (SD), y	8.8 (1.8)	9.0 (2.1)	9.0 (2.1)
< 9 y, No. (%)	63 (38.2)	64 (39.0)	94 (38.1)
≥ 9 y, No. (%)	102 (61.8)	100 (61.0)	153 (61.9)
Sex, No. (%)			
Female	94 (57.0)	85 (51.8)	136 (55.1)
Male	71 (43.0)	79 (48.2)	111 (44.9)
Ethnicity, No. (%)			
Hispanic or Latino	47 (28.5)	44 (26.8)	64 (25.9)
Not Hispanic	112 (67.9)	114 (69.5)	171 (69.2)
Race, No. (%)			
American Indian or Alaskan Native	1 (0.6)	3 (1.8)	3 (1.2)
Asian	26 (15.8)	29 (17.7)	54 (21.9)
Black or African American	27 (16.4)	23 (14.0)	31 (12.6)
Native Hawaiian or Other Pacific Islander	3 (1.8)	1 (0.6)	0
White	93 (56.4)	84 (51.2)	132 (53.4)
Other (including missing)[a]	15 (9.1)	24 (14.6)	27 (10.9)
Refractive error range, No. (%)			
Less myopic (SER: −0.50 to −3.00 D)	111 (67.3)	110 (67.1)	164 (66.4)
More myopic (SER: −3.01 to −6.00 D)	54 (32.7)	54 (32.9)	83 (33.6)

Abbreviations: D, diopter; SER, spherical equivalent refractive error.

[a] Other includes races other than those listed in the table and missing race and ethnicity.

treatment effect for atropine, 0.02% vs placebo (LSM difference, 0.10 D; 95% CI, −0.02 to 0.22 D; P = .10). Although the primary end point was defined at 36 months, compared with placebo, atropine, 0.01%, also reduced mean SER progression at month 24 (LSM change, 0.22 D; 95% CI, 0.08-0.35 D; P = .002), and atropine, 0.02%, reduced mean SER progression at month 12 (LSM change, 0.12 D; 95% CI, 0-0.24 D; P = .05) (Figure 2B; eTable 2 in Supplement 3).

Regarding axial length, the LSM change from baseline at month 36 was 0.81 mm (95% CI, 0.76-0.85 mm) in the

placebo group, 0.68 mm (95% CI, 0.63-0.72 mm) in the atropine, 0.01%, group, and 0.73 mm (95% CI, 0.69-0.76 mm) in the atropine, 0.02%, group (Table 2). The LSM difference for atropine, 0.01%, vs placebo was −0.13 mm (95% CI, −0.19 to −0.07 mm; P < .001) and for atropine, 0.02%, vs placebo was −0.08 mm (−0.13 to −0.02 mm; P = .005). Both doses also reduced axial length elongation compared with placebo at month 12 (atropine, 0.01%, LSM difference, −0.07 mm; 95% CI, −0.13 to −0.01 mm; P = .03; atropine, 0.02%, LSM difference, −0.06 mm; 95% CI, −0.12 to −0.01 mm; P = .02) and

Table 2. Efficacy Measures (Modified Intention-to-Treat Set)

End point	Placebo (n = 144)	Atropine, 0.01% (n = 133)	Atropine, 0.02% (n = 212)
Responder analysis: <0.50 D myopia progression at month 36			
No. of eyes	252	200	366
No. (%) of responder eyes	44 (17.5)	57 (28.5)	81 (22.1)
Odds ratio for low-dose atropine/placebo (95% CI)	NA	4.54 (1.15 to 17.96)	1.77 (0.50 to 6.26)
P value	NA	.03	.37
Cycloplegic refraction: mean change from baseline in SER			
Baseline			
No. of eyes	282	266	424
Mean SER (SD), D	−2.45 (1.13)	−2.41 (1.17)	−2.42 (1.17)
Median (IQR)	−2.38 (1.66)	−2.20 (1.53)	−2.26 (1.57)
Month 36			
No. of eyes	252	200	366
Mean SER (SD), D	−3.72 (1.42)	−3.41 (1.49)	−3.61 (1.53)
Median (IQR)	−3.73 (2.05)	−3.28 (2.02)	−3.51 (2.10)
Least squares mean change (95% CI) from baseline at month 36, D	−1.28 (−1.37 to −1.19)	−1.04 (−1.14 to −0.94)	−1.18 (−1.26 to −1.10)
Least squares mean difference (95% CI) between low-dose atropine and placebo, D	NA	0.24 (0.11 to 0.37)	0.10 (−0.02 to 0.22)
P value	NA	<.001	.10
Biometric measure: mean change from baseline in axial length			
Baseline			
No. of eyes	281	266	419
Mean axial length (SD), mm	24.33 (0.84)	24.37 (0.81)	24.30 (0.87)
Median (IQR)	24.40 (1.20)	24.39 (1.09)	24.29 (1.14)
Month 36			
No. of eyes	252	200	366
Mean axial length (SD), mm	25.09 (0.88)	25.12 (0.87)	25.01 (0.98)
Median (IQR)	25.13 (1.29)	25.09 (1.27)	25.01 (1.26)
Least squares mean change (95% CI) from baseline at month 36, mm	0.81 (0.76 to 0.85)	0.68 (0.63 to 0.72)	0.73 (0.69 to 0.76)
Least squares mean difference (95% CI) between low-dose atropine and placebo, mm	NA	−0.13 (−0.19 to −0.07)	−0.08 (−0.13 to −0.02)
P value	NA	<.001	.005

Abbreviations: D, diopter; NA, not applicable; SER, spherical equivalent refractive error.

month 24 (atropine, 0.01%, LSM difference, −0.12 mm; 95% CI, −0.18 to −0.06 mm; P < .001; atropine, 0.02%, LSM difference, −0.07 mm; 95% CI, −0.12 to −0.02 mm; P = .01) (Figure 2C; eTable 2 in Supplement 3). The SER change from baseline and axial length change from baseline were correlated (placebo, Pearson r = −0.79; 95% CI, −0.83 to −0.74; P < .001; atropine, 0.01%, Pearson r = −0.74; 95% CI, −0.80 to −0.68; P < .001; atropine, 0.02%, Pearson r = −0.85; 95% CI, −0.88 to −0.82; P < .001) (eFigure 2 in Supplement 3).

Prespecified subgroup analyses for baseline characteristics, analyzed for both responder rate and SER change from baseline, were consistent with overall outcomes, generally showing a positive treatment effect vs placebo across all subgroups. No treatment-by-subgroup interaction was identified (eFigure 3 in Supplement 3).

Prespecified analyses of the efficacy of atropine, 0.01% and 0.02% vs placebo across all 3 end points in the ITT population (eTable 5 in Supplement 3) showed similar results as in the mITT population (Table 2; eTable 2 in Supplement 3).

Compliance with dosing (as measured by the return of used and unused ampules) in the ITT set was high (eTable 6 in Supplement 3).

Safety

Both low-dose atropine concentrations were safe and well tolerated. In the safety analysis, there was no increase in treatment-emergent AEs (TEAEs) associated with nonocular antimuscarinic function with low-dose atropine treatments (0% in atropine, 0.01%; 0.8% in atropine, 0.02%) vs placebo (2.5%), and there were no serious ocular TEAEs. TEAEs were defined as any new or worsening of an existing AE that occurred or worsened between the first dose date and the last dose date of stage 1. Serious nonocular TEAEs were reported in 13 participants (2.3%), including 4 in the placebo group (2.5%), 1 in the atropine, 0.01%, group (0.6%), and 8 in the atropine, 0.02%, group (3.2%). One serious TEAE, a seizure, occurred in a participant taking placebo with prior history of seizures (Table 3; eTable 7 in Supplement 3).

Figure 2. Change in Ophthalmic Parameters Over Time

A Proportion of mITT set with <0.50-diopter myopia progression (responder)
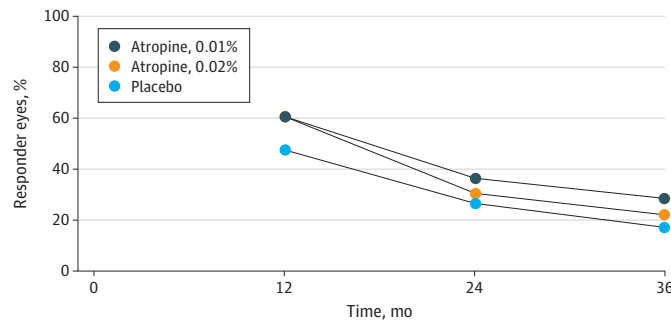
Atropine, 0.01%, No. of eyes		216	194	200
OR (95% CI) low-dose atropine/placebo		3.90 (1.35 to 11.26)	3.39 (1.00 to 11.44)	4.54 (1.15 to 17.97)
P value		.01	.05	.03
Atropine, 0.02%, No. of eyes		360	346	366
OR (95% CI) for low-dose atropine/placebo		4.78 (1.75 to 13.04)	1.52 (0.49 to 4.70)	1.77 (0.50 to 6.26)
P value		.002	.46	.37
Placebo, No. of eyes		244	238	252

B Least squares mean change from baseline in SER (mITT set)
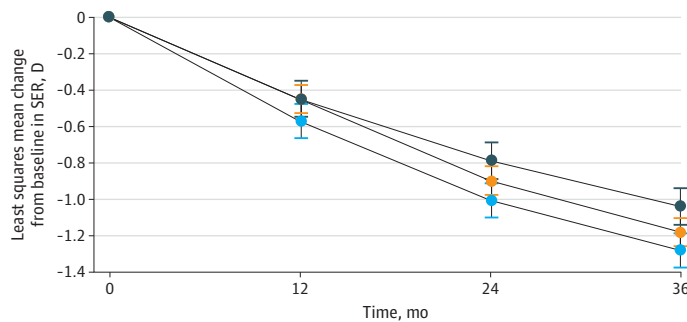
Atropine, 0.01%, No. of eyes	266	216	194	200
Least squares mean difference (95% CI) for low-dose atropine–placebo, D		0.12 (−0.01 to 0.25)	0.22 (0.08 to 0.35)	0.24 (0.11 to 0.37)
P value		.08	.002	<.001
Atropine, 0.02%, No. of eyes	424	360	346	366
Least squares mean difference (95% CI) for low-dose atropine–placebo, D		0.12 (0.00 to 0.24)	0.11 (−0.01 to 0.23)	0.10 (−0.02 to 0.22)
P value		.05	.08	.10
Placebo, No. of eyes	282	244	236	252

C Least squares mean change from baseline in axial length (mITT set)
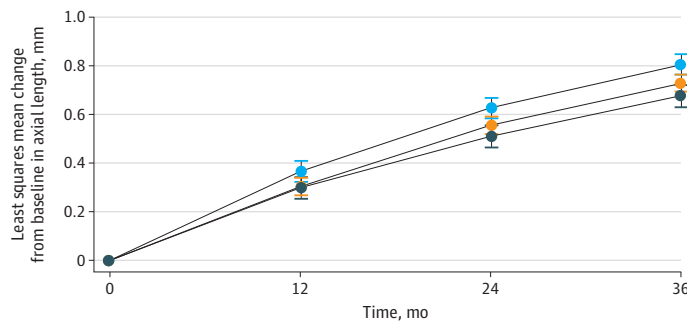
Atropine, 0.01%, No. of eyes	266	213	196	200
Least squares mean difference (95% CI) for low-dose atropine–placebo, mm		−0.07 (−0.13 to −0.01)	−0.12 (−0.12 to −0.06)	−0.13 (−0.19 to −0.07)
P value		.03	<.001	<.001
Atropine, 0.02%, No. of eyes	419	355	341	361
Least squares mean difference (95% CI) for low-dose atropine–placebo, mm		−0.06 (−0.12 to −0.01)	−0.07 (−0.12 to −0.02)	−0.08 (−0.13 to −0.02)
P value		.02	.01	.005
Placebo, No. of eyes	281	241	240	252

A, Proportion with less than 0.50-diopter (D) myopia progression (responder) (modified intention-to-treat [mITT] set). P value for odds ratio (OR) (low-dose atropine/placebo). B, Least squares mean change from baseline in spherical equivalent refractive error (SER; mITT set). P value for least squares mean difference (low-dose atropine – placebo). C, Least squares mean change from baseline in axial length (mITT set). P value for least squares mean difference (low-dose atropine – placebo).

Table 3. Treatment-Emergent Adverse Events (Safety Set)

Characteristic	No. (%)			
	Placebo (n = 162)	Atropine, 0.01% (n = 164)	Atropine, 0.02% (n = 247)	Total (n = 573)
Any treatment-emergent adverse event, No. (%)	116 (71.6)	98 (59.8)	163 (66.0)	377 (65.8)
Serious ocular treatment-emergent adverse event, No. (%)	0	0	0	0
Serious nonocular treatment-emergent adverse event, No. (%)	4 (2.5)	1 (0.6)	8 (3.2)	13 (2.3)
Any treatment-emergent adverse event leading to permanent discontinuation of trial drug, No. (%)	10 (6.2)	0	5 (2.0)	15 (2.5)
Treatment-emergent adverse events (partial list), No. (%)[a]				
Photophobia	5 (3.1)	4 (2.4)	11 (4.5)	20 (3.5)
Allergic conjunctivitis	5 (3.1)	3 (1.8)	11 (4.5)	19 (3.3)
Eye irritation	6 (3.7)	1 (0.6)	2 (0.8)	9 (1.6)
Mydriasis (enlarged pupil)	0	2 (1.2)	4 (1.6)	6 (1.0)
Blurred vision	0	2 (1.2)	4 (1.6)	6 (1.0)
Eyelid swelling	0	3 (1.8)	1 (0.4)	4 (0.7)
Eyelid irritation	1 (0.6)	0	2 (0.8)	3 (0.5)
Elevated heart rate	1 (0.6)	0	2 (0.8)	3 (0.5)
Seizure	1 (0.6)	0	0	1 (0.2)

[a] eTable 1 in Supplement 3 contains a complete list.

The incidence of any TEAE was similar between placebo (116 of 162 participants [71.6%]), atropine, 0.01% (98 of 164 participants [59.8%]), and atropine, 0.02% (163 of 247 participants [66.0%]). The most common ocular TEAEs were photophobia, allergic conjunctivitis, eye irritation, mydriasis, and blurred vision (Table 3; eTable 7 in Supplement 3).

Discussion

The CHAMP trial demonstrated that atropine, 0.01%, produced a treatment effect that slowed myopia progression compared with placebo for all efficacy measures (eg, increasing the number of responders, slowing SER progression, and reducing axial length elongation) in participants aged 6 to 10 years.

The treatment effect observed with atropine, 0.01%, is clinically meaningful as reflected in the increased number of responders to therapy compared with placebo (28.5% vs 17.5%; a difference of 11%; 95% CI, 3%-18.5%). Although no reference exists to show that this difference is clinically meaningful, the predefined threshold for a responder eye was myopia progression of less than 0.50-D SER from baseline at 3 years. This is a stringent criterion for defining myopia control[29] and indicative of clinically negligible progression or stable myopia.[30] Compared with placebo, atropine, 0.01%, resulted in a greater proportion of responders at months 12, 24, and 36 and reduced mean SER progression at months 24 and 36 compared with placebo.

A previous review has shown that the anatomical end point of change in axial length correlates with refractive changes,[29] which was also shown in our analysis (eFigure 2 in Supplement 3). Because of its objective nature, axial length elongation is emerging as an important end point for monitoring myopic progression.[29] Biometric measurements demonstrated that both atropine, 0.01% and 0.02%, slowed axial elongation, compared with placebo at all time points measured over 3 years. The clear efficacy of atropine, 0.01%, in slowing myopia progression and axial elongation may lead to less frequent or delayed changes in glasses, progression to less severe correction, and potential reduction of long-term sequelae, which could lead to vision loss later in life such as myopic maculopathy.[31]

CHAMP was a 3-year, placebo-controlled, phase 3 clinical trial of atropine, 0.01% and 0.02%, conducted in children with myopia. Previous studies showing the benefit of low-dose atropine[19,21-23,32] were conducted at a single site or multiple sites in Asia. The ATOM2 study[32] provided evidence of dose-dependent effects in the range of 0.01% to 0.5% but did not include a placebo group. The other 4 studies[19,21-23] were placebo-controlled for 1 or 2 years, with treatment effects generally consistent with atropine, 0.01%, over the same period. The Western Australia-ATOM trial used a single site and showed a statistically significant benefit for atropine, 0.01%, after 1 year but not at the 2-year time point. The authors ascribe this result to a loss of fast myopia progressors in the placebo group during the second year of the trial.[20]

The CHAMP trial results support the possibility that atropine, 0.01%, eye drops as applied in this trial may be a safe and effective pharmacologic option for individuals similar to those enrolled in this trial. AEs potentially associated with topical atropine included photophobia or blurred vision, although the incidence of these AEs were low compared with placebo in this trial (Table 3; eTable 7 in Supplement 3).

Although atropine, 0.02%, slowed axial elongation compared with placebo, the responder analysis and SER progression were associated with $P > .05$; however, in a post hoc analysis comparing the 2 active doses, we observed comparable results between atropine, 0.01% and 0.02% (eTable 3 in

Supplement 3). Other studies of atropine, 0.01% and 0.02% (or 0.025%), showed small, nonsignificant differences between the lower and higher concentrations in SER change from baseline.[23,33]

To further understand the results of atropine, 0.02%, another post hoc analysis was conducted, which excluded the data after treatment cessation for participants who discontinued trial medication but stayed in the trial through month 36, while switching to other myopia therapies (ie, orthokeratology, multifocal contact lenses, or compounded atropine) (eTable 4 in Supplement 3). This analysis showed an increased difference between atropine, 0.02%, and placebo in the proportion of responders (OR increased from 1.8; $P = .37$ in the mITT set to an OR of 2.5; $P = .16$ in this post hoc analysis) and in the mean difference of SER change from baseline (LSM difference increased from 0.10 D; $P = .10$ to 0.15 D; $P = .01$). There was a clear confounding effect due to the inclusion of the data from these participants in mITT after they stopped trial medication and went on to other treatments, which likely contributed to the atropine, 0.02%, results as reported.

In evaluating our results, a higher-than-expected placebo responder rate was observed (17% vs the assumed 7% in the protocol). However, on review of more recently available data, the observed placebo myopia progression rate in CHAMP appears within the range of the progression rate observed in control arms of other myopia therapy studies (eTable 8 in Supplement 3).[11,20,34,35]

The CHAMP trial demonstrated that both atropine concentrations, 0.01% and 0.02%, exhibited a safety profile notable for minimal ocular AEs and no increase in nonocular antimuscarinic AEs compared with placebo. Other potential therapies for the treatment of myopia progression include defocus-incorporated multiple-segment lenses, multifocal contact lenses, and orthokeratology. Atropine is generally considered suitable in younger children, when compared with CLs or other devices.[36-38] The future myopia treatment paradigm may involve initiation of therapy earlier in the disease progression and may include a combination of low-dose atropine and device-based therapies.[39-43]

Strengths and Limitations

A strength of this trial was the placebo-controlled design over 3 years of treatment in a US and European population. Trial limitations include potential bias introduced by those participants who discontinued trial medication and switched to confounding treatments and the relatively lower representation of participants in the range of 3 to 5 years and 11 to 17 years of age.

Conclusions

Results from this multicenter, randomized clinical trial demonstrated that a preservative-free formulation of atropine, 0.01%, slows myopia progression among participants 6 to 10 years of age. Atropine, 0.01%, significantly increased the proportion of eyes with less than 0.5-D myopia progression after 3 years of treatment. This dose also reduced both SER progression and axial elongation vs placebo over the same period. A smaller treatment effect was observed for atropine, 0.02%.

From a risk/benefit perspective, the efficacy and safety observed suggests that low-dose atropine may provide a treatment option for children aged 3 to 17 years with myopia progression, which may lead to less frequent or delayed change in glasses, progression to less severe correction, and potentially reduce long-term sequelae, which could lead to vision loss later in life, such as myopic maculopathy.[31] In the population studied, low-dose atropine could provide an important early treatment option for young children.

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