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ORIGINAL RESEARCH

STudy of Atropine to Reduce (STAR) Myopia Progression in Children: 24-Month Results of a Randomized, Double-Masked, Vehicle-Controlled Trial of Atropine Sulfate 0.01% and 0.03%

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ABSTRACT

***Introduction*:** Pediatric myopia is rising globally, with high myopia associated with sight-threatening complications later in life. Low-dose atropine has been shown to slow myopia progression, with most studies conducted in Asian populations using compounded formulations. We evaluated the efficacy and safety of atropine sulfate ophthalmic solution at two concentrations for slowing myopia progression in a predominantly white population.

***Methods*:** STAR was a randomized, double-masked, vehicle-controlled, phase 3 clinical study conducted in Europe and the USA. Children ($N=847$) aged 3–14 years with myopia between −0.50 and −6.00 diopters (D) were dosed after 1:1:1 randomization to vehicle, atropine sulfate 0.01% or 0.03% once daily before bedtime for 48 months. The primary endpoint was mean annual progression rate (APR) of myopia, measured by cycloplegic autorefraction, through month 24.

***Results*:** Mean APR at 24 months was −0.44 D/year (vehicle), −0.31 D/year (atropine sulfate 0.01%), and −0.32 D/year (atropine sulfate 0.03%), with differences versus vehicle of 0.13 D (95% CI 0.06–0.20; $p=0.0003$) and 0.12 D (95% CI 0.05–0.19; $p=0.0009$), respectively. In Fast Progressor Subgroup 1 (progression −0.50 D/year or worse at baseline), differences versus vehicle were 0.21 D ($p<0.0001$) for atropine sulfate 0.01% and 0.15 D ($p=0.0023$) for atropine sulfate 0.03%. In Fast Progressor Subgroup 2 (progression −0.75 D/year or worse at baseline), differences versus vehicle were 0.19 D ($p=0.0008$) for atropine sulfate 0.01% and 0.11 D ($p=0.0397$) for atropine sulfate 0.03%. TEAEs were similar across groups. Photophobia was the most common ocular event (16.7% vehicle, 24.1% atropine sulfate 0.01%, 30.4% atropine sulfate 0.03%). Treatment discontinuation was similar across groups (18.7% vehicle, 19.7%

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atropine sulfate 0.01%, 18.6% atropine sulfate 0.03%).
Conclusion: Atropine sulfate 0.01% and 0.03% effectively slowed myopia progression in children, with greatest efficacy in Fast Progressors Subgroup 1. Both concentrations were well tolerated with manageable side effects, supporting atropine sulfate as a treatment option for pediatric myopia.
Clinical Trial Registration: ClinicalTrials.gov identifier NCT03918915.

PLAIN LANGUAGE SUMMARY

Myopia (near-sightedness) is becoming increasingly common worldwide, especially in children. When left untreated, it can worsen over time and lead to serious eye complications later in life. This study tested whether low-dose atropine sulfate eye drops could safely slow myopia worsening (progression) in children aged 3–14 years. The STudy of Atropine to Reduce (STAR) myopia progression was a randomized study of atropine sulfate 0.01% and 0.03%. A total of 847 participants received either atropine sulfate eye drops (at concentrations of 0.01% or 0.03%) or a vehicle (eye drops without active medication) once daily before bedtime for 48 months. Results showed that both atropine concentrations significantly slowed myopia progression compared with vehicle. Children receiving atropine 0.01% had 0.13 diopters less myopia worsening at 2 years than those receiving vehicle, while those using atropine 0.03% had 0.12 diopters less worsening. The treatment worked particularly well for children who had a history of faster myopia progression (−0.50 and −0.75 diopters per year or worse). Both atropine concentrations were well tolerated, with few children stopping treatment due to side effects. The most common side effect across all groups was increased sensitivity to light, which was generally mild. On the basis of these results, atropine 0.01% received marketing authorization by the European Medicines Agency on June 2, 2025, for slowing myopia progression in children. This study provides important evidence that atropine eye drops can be an effective option for managing childhood myopia, potentially reducing the risk of serious eye complications later in life.

Keywords: Annual progression rate; APR; Atropine sulfate 0.01%; Atropine sulfate 0.03%; Children; Low-dose atropine; Pediatric myopia; Slowing of myopic progression; Spherical equivalent refraction; STAR

Key Summary Points

Why carry out this study?

Pediatric myopia prevalence is increasing globally, with estimates suggesting up to 50% of the world's population may be affected by 2050; high myopia (spherical equivalent refraction −6.00 diopters [D] or worse) significantly increases the risk of vision-threatening complications.

Despite emerging evidence supporting low-dose atropine for slowing pediatric myopia progression, approved pharmaceutical options have been limited or non-existent in many regions, with the majority of previous studies conducted in Asian populations using compounded formulations.

The 48-month STudy of Atropine to Reduce (STAR) myopia progression is currently the longest and largest randomized controlled study of atropine for myopia control in a predominantly white population from the USA and Europe, testing a formulation (atropine sulfate) with deuterium oxide, which stabilizes low-dose atropine at near physiological pH levels.

What was learned from the study?
Atropine sulfate 0.01% and 0.03% significantly reduced the mean annual progression rate of myopia compared with vehicle at 24 months, with effects observed as early as 6 months and sustained throughout the 24 months; in patients with myopia progression of −0.50 D per year or worse, atropine sulfate significantly reduced annual progression rate.
The 24-month safety data demonstrated a well-tolerated profile with low discontinuation rates, minimal impact on corneal health, and manageable side effects.

INTRODUCTION

Myopia is defined as a spherical equivalent refraction (SER) of −0.50 diopters (D) or worse [1] and presents a significant global health concern, with estimates predicting that it may impact up to 50% of the world's population and up to 40% of children and adolescents by 2050 [2, 3]. Its prevalence varies by region and age group. In 2000, the highest prevalence rate estimates of myopia were in the 20–24-year and 25–29-year age groups [2]. In the 2020s, the prevalence rate estimate for the total global population was 33.9%. Among specific regions, East Asia presented the highest prevalence rate estimate at 51.6%, followed by Southeast Asia at 46.1% and Western Europe at 36.7% [2].

A key anatomical feature of myopia is excessive axial elongation of the eye, leading to negative refractive error [4]. The development and progression of myopia are influenced by multiple factors [5]. Genetic factors play a notable role, with children who have one or both parents with myopia experiencing a substantially increased risk of developing myopia themselves [6]. Ethnicity also contributes to myopia risk; in a study of 2353 12-year-old Australians, children of East Asian descent had substantially greater odds of having myopia compared with European white children (odds ratio 11.0; 95% confidence interval [CI] 7.0, 17.4) [7]. In the same study, the role of environmental factors on myopia development was evidenced; for example, continuous reading (>30 min) and near-work activities, such as close (<30 cm) reading distance, were shown to increase the probability of developing myopia [7].

Of particular concern is high myopia, defined as an SER of −6.00 D or worse, which substantially increases the risk of vision-threatening complications [8]. It has been demonstrated that each additional diopter of myopia is associated with a 58% increased risk of myopic maculopathy, 30% increased risk of retinal detachment, 21% increased risk of posterior subcapsular cataract, and 20% increased risk of open-angle glaucoma [9]. Childhood-onset myopia is of particular concern, as early-onset disease (< 12 years old) is predictive of faster progression and longer progression duration compared with onset after age 12 years, which consequently increases the risk of vision-threatening complications, such as retinal detachment, myopic macular degeneration, open-angle glaucoma, and posterior subcapsular cataracts [9, 10].

Current management of myopia primarily involves optical correction through spectacles or contact lenses, which addresses refractive error but does not affect the underlying disease progression [11]. However, emerging evidence supports management approaches that may delay myopia progression, including optical interventions such as specialized spectacles [12, 13], orthokeratology [14, 15], and multifocal contact lenses [16, 17]. Behavioral modifications, particularly increased outdoor time [18, 19] and control of near-work activities [20], have also been demonstrated to play a significant role in myopia management.

Pharmacological approaches, including antimuscarinic agents, have also shown promise and are extensively studied [21]. Within this class, several options have been investigated: (1) atropine at higher concentrations (0.5–1.0%) demonstrated significant efficacy in the ATOM1 trial, but has been associated with substantial adverse effects, such as photophobia [22]; (2) low-dose atropine (LDA; 0.01–0.05%) has shown a varying balance of efficacy and tolerability across multiple clinical studies [23–25]; (3) other muscarinic agents, such

as pirenzepine, have shown limited efficacy in early trials, but development was discontinued as a result of pirenzepine's comparatively lower efficacy than alternative treatments, such as LDA [26–28]. LDA has emerged as the most promising pharmacological approach, demonstrating efficacy in several landmark clinical trials [22, 24, 25]. In these trials, LDA consistently slowed myopia progression and resulted in minimal side effects compared with higher concentrations.

Despite substantial evidence supporting various interventions, approved treatment options for delaying myopia progression have been largely unavailable in many regions [11], leaving clinicians without standardized, regulatory-approved solutions. Currently available compounded atropine formulations (pharmacy-prepared low-concentration formulations) face several challenges, including variable concentration and stability that may affect clinical outcomes, variable pH (which can affect the bioavailability of the drug to the target receptors), limited shelf life requiring frequent replacement, inconsistent quality between preparations, and absence of formal efficacy and safety studies required for regulatory approval [29, 30]. These limitations highlight the need for a stable, standardized atropine formulation with robust clinical data and regulatory approval, to address the growing public health concern that pediatric myopia presents.

The STudy of Atropine to Reduce (STAR) myopia progression evaluated the efficacy and safety of two low-dose atropine sulfate ophthalmic solutions (0.01% and 0.03%) versus vehicle in slowing myopia progression in children aged 3–14 years. The active ingredient in the atropine sulfate formulation is atropine, an anticholinergic drug that competitively blocks muscarinic receptors from stimulation by acetylcholine [31].

Here, we present the 24-month analysis of STAR, a 48-month study designed to evaluate product safety and efficacy over 36 months, followed by a 4th-year randomized withdrawal phase. This interim time point is relevant, as the 24-month duration is the most frequently reported time point in published myopia control studies, allowing for meaningful comparisons with the existing literature, and was the time point required for approval by the European Medicines Agency (EMA).

METHODS

Study Design

The study was a multicenter, randomized, double-masked, parallel-group, vehicle-controlled phase 3 study (STAR study, NCT03918915) conducted over 48 months at 47 clinical sites across the USA (41) and Europe (6). The study comprised two sequential parts: Part 1, primary 36-month treatment period with 1:1:1 randomization at baseline, and Part 2, 12-month randomized withdrawal period starting at month 36.

In line with EMA guidance, the primary objective of the STAR study at the 24-month interim time point was to evaluate the mean annual progression rate (APR) of myopia through month 24. Secondary objectives of the study included (1) assessing the effects of atropine sulfate on axial length (AL); (2) evaluating the long-term safety profile in the pediatric population; and (3) assessing treatment effects in specific subgroups, including fast progressors and different age cohorts.

Ethical Approval

The protocol and informed consents/assents were approved by the required institutional review boards or ethics committees, and the study was conducted in accordance with Good Clinical Practice guidelines and tenets of the Declaration of Helsinki. Before any protocol-required procedure, written informed consent was obtained from parents or legal guardians; participants aged 6 years and above provided self-assent. Prior to randomization, the participant or parent/guardian administered one drop of an artificial tear to each eye to demonstrate cooperation and compliance with eyedrop instillation. This study followed the Consolidated Standards of Reporting Trial (CONSORT) reporting guidelines.

Study Population

Eligible participants were children aged 3–14 years at screening with myopia between

– 0.50 D and – 6.00 D in both eyes, as determined by cycloplegic autorefraction. Additional inclusion criteria were astigmatism 1.50 D or better in both eyes, anisometropia 1.00 D or better in both eyes, best-corrected visual acuity (BCVA) of 75 letters (Snellen equivalent 20/32) or better, and a normal posterior segment based on dilated fundus examination. For participants with baseline myopia less than – 0.75 D, a documented history of myopia progression of – 0.50 D in the previous 6–12 months was required. Participants with myopia progression of – 0.75 D or worse were required to use refractive correction while awake (single-vision eyeglasses or soft, daily-wear, single-vision contact lenses) that met study investigators' criteria.

Key exclusion criteria included medical conditions predisposing the participant to degenerative myopia, such as Marfan syndrome or Stickler syndrome, or conditions that may affect visual function or development, such as diabetes mellitus or chromosome anomaly; current use of a monoamine oxidase inhibitor; ocular inflammation or infection in either eye, including blepharitis, conjunctivitis, keratitis, and scleritis; past, present, or future plans to use orthokeratology, rigid gas-permeable, bifocal, progressive-addition, multifocal, or other lenses to reduce myopia progression; previous use of atropine, pirenzepine, or other antimuscarinic agent for myopia; and history of or planned future ocular surgery.

Randomization and Masking

Participants were randomized 1:1:1 to receive vehicle, atropine sulfate 0.01%, or atropine sulfate 0.03% using a computer-generated randomization schedule via an interactive web response system. Randomization was stratified by age groups (3 to < 6 years [3.1%], 6 to < 9 years [21.8%], 9 to < 12 years [39.1%], and 12 to 14 years [36.0%]) and baseline SER (– 0.50 D to – 3.0 D [61.7%], > – 3.0 D to – 6.0 D [38.1%]) (Fig. 1).

To maintain masking, all study medications were packaged in identical bottles and provided by Sydnexis, Inc. Investigators, participants, caregivers, and study staff remained masked to treatment assignment throughout the study.

Intervention

Participants received one drop of assigned study medication (vehicle, atropine sulfate 0.01%, or atropine sulfate 0.03%) in each eye every night for 36 months. Previous myopia control treatments were prohibited; single-vision corrective lenses were required to be worn full time and contact lenses were to be removed at night. The atropine sulfate solution in the study medication was formulated with benzalkonium chloride (BAK, 0.01%) as a preservative. The study medication formulation also contained deuterium oxide (D_2O), which stabilizes low-dose atropine at near physiological pH levels [30, 32]. Parents/caregivers were instructed to administer the study medication at bedtime, apply gentle pressure to the inner canthus for 1–2 min after administration, and wait at least 15 min between administering eyedrops and any other ophthalmic medications. Treatment compliance was monitored via a phone questionnaire or web-based application, first weekly for the first 6 months, then monthly.

Assessment Schedule and Procedures

Participants attended scheduled visits at screening, baseline, and months 3, 6, then every 6 months thereafter until month 48 or early termination, with telephone visits at week 2 and between clinic visits from months 9 to 39 and additional visits at months 42 and 48 for the randomized withdrawal period.

At each visit, cycloplegic autorefraction was performed using a standardized protocol: one drop of 1% cyclopentolate was applied two times to each eye, with 5 min between drops. The autorefraction occurred at least 40 min (but no more than 60 min) after the second drop of 1% cyclopentolate had been instilled. The mean for each eye was then averaged to obtain the SER for both eyes.

AL was measured at sites equipped with the necessary technology (covering at least 50% of study participants) using optical biometry

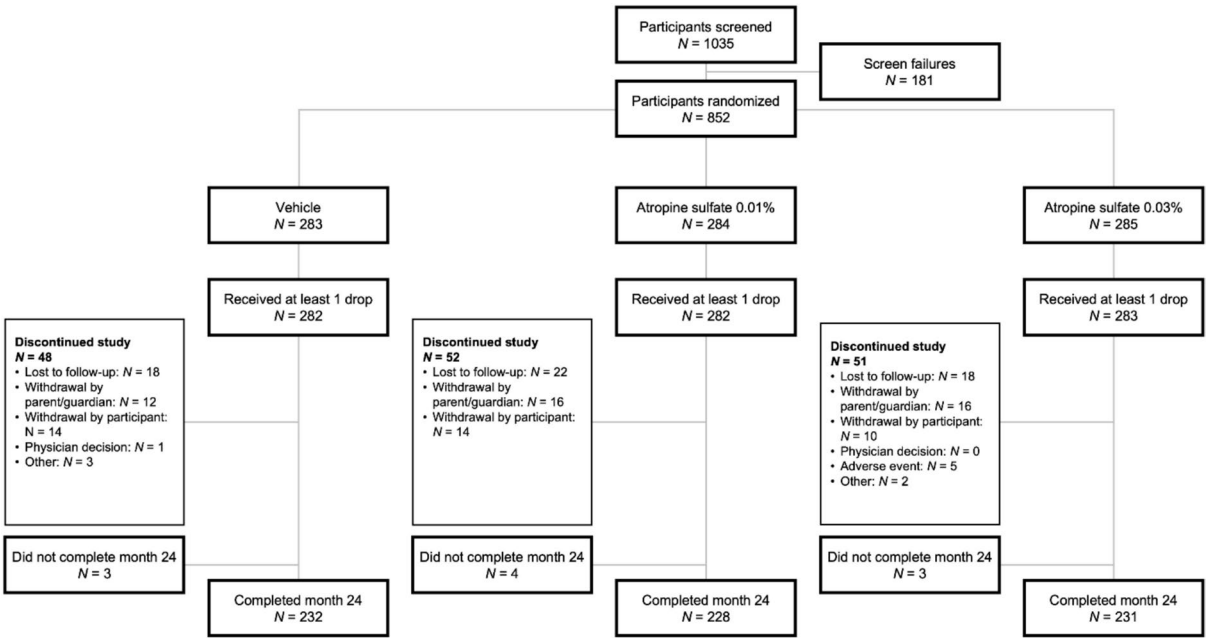

Fig. 1 Participant flow. CONSORT flow chart showing screening, randomization, follow-up, and analysis population. Includes numbers of participants at each stage and reasons for discontinuation

devices including IOLMaster® (Carl Zeiss Meditec AG, Jena, Germany), Lenstar® 900 (Haag-Streit AG, Köniz, Switzerland), or Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar, Germany). Three consecutive measurements were averaged at each time point. Many recruitment sites lacked the necessary facilities to perform AL measurements, and the COVID-19 pandemic further impacted the ability to collect these measurements during in-person follow-up visits.

Visual function assessments included BCVA using Early Treatment Diabetic Retinopathy Study charts at 4 m, near BCVA using the ATS4 Near Acuity Test at 40 cm, binocular accommodative amplitude prior to cycloplegia using the push-up method, and pupil diameter was measured prior to cycloplegia using a hand-held pupil card (graded in 0.5 mm increments) provided to the sites.

Safety assessments comprised comprehensive ophthalmic examinations, including slit-lamp biomicroscopy, corneal staining assessment using fluorescein with standardized grading (none, trace, mild, moderate, severe), intraocular pressure measurement, ophthalmoscopy, vital signs, and adverse event (AE) monitoring with special attention to known atropine effects.

Statistical Analysis

For the EMA-mandated primary endpoint, group sample sizes of 280 per treatment arm achieved greater than 90% power to detect a reduction of 0.18 D or more in the APR between atropine sulfate and vehicle, assuming a common standard deviation (SD) of 0.60 D. Power calculations were based on a two-sample *t* test evaluated at a one-sided 0.025 significance level. The study was powered to compare each atropine concentration versus vehicle with control of multiplicity; however, it was not powered for comparisons between the 0.01% and 0.03% concentrations.

Group sample sizes of 280 in each treatment arm were assigned to achieve at least 90% power to detect a difference in the percentage of participants with myopic progression (−0.75 D or worse) of 15% or greater between the atropine sulfate arms and vehicle (US Food and Drug Administration-related primary endpoint).

Power calculations were based on the chi-squared test with a significance level of 0.025.

Analysis populations included the full analysis set (FAS, $n=847$): all randomized participants who received ≥ 1 dose of study drug; safety analysis set ($n=847$): all participants who received any study drug; and per-protocol analysis set (PPS, $n=773$): FAS participants without significant protocol deviations and with at least one post-baseline spherical equivalent (SE) measurement. Fast Progressor Subgroups 1 ($n=291$) and 2 ($n=225$) included FAS participants with progression −0.50 D/year or worse and −0.75 D/year or worse, respectively, based on historical refraction, where available.

Primary efficacy analysis employed a mixed model for repeated measures (MMRM), with fixed effects for treatment, baseline age category, visit, visit-by-treatment interaction, with baseline SE as a covariate, and compound symmetry covariance. Least squares mean differences between treatment groups were calculated with 95% CIs. Intercurrent events were taken into account in the efficacy analyses, as missing data related to discontinuations for AE and a reason other than AE were multiply imputed assuming missing not at random and missing at random, respectively. A hierarchical gate-keeping procedure controlled type I error for both the 0.01% and 0.03% concentrations via a truncated Hochberg test, with truncation parameter $\gamma=0.8$, starting with the primary endpoint (APR) followed by secondary endpoints, including APR for Fast Progressor Subgroups 1 and 2. Secondary endpoints were analyzed using MMRM for continuous variables, a Cochran–Mantel–Haenszel test for binary outcomes, and Kaplan–Meier analysis for time-to-event data. Multiple sensitivity analyses, including PPS analysis, multiple imputation assuming different strategies for intercurrent events, and tipping point analysis, assessed robustness.

According to the hierarchical testing and associated analysis methods, if all previous endpoints in the testing hierarchy reached statistical significance, both atropine sulfate groups were to be combined and compared as pooled versus vehicle for the analysis of efficacy in Fast Progressor Subgroups 1 and 2. Both individual and pooled comparisons were included in the outputs.

RESULTS

Baseline Characteristics

The STAR study enrolled 852 children randomized in a 1:1:1 ratio to receive atropine sulfate 0.01%, atropine sulfate 0.03%, or a vehicle. Of these, 847 participants (282 in the vehicle group, 282 in the atropine sulfate 0.01% group, and 283 in the atropine sulfate 0.03% group) received at least one dose of the study medication, comprising the FAS. Demographic and baseline characteristics were well matched across groups (Table 1).

Completion rates at 24 months were consistent between groups: 82.0% (vehicle), 80.3% (atropine sulfate 0.01%), and 81.1% (atropine sulfate 0.03%). Compliance rates remained high at greater than 97% across all groups up to 24 months, without significant differences.

Primary Efficacy Endpoint

Both concentrations of atropine sulfate significantly reduced the mean APR compared with vehicle at 24 months (Fig. 2). The mean APR from baseline to month 24 in the FAS was −0.44 D (95% CI −0.50, −0.38) for vehicle, −0.31 D (95% CI −0.37, −0.25) for atropine sulfate 0.01%, and −0.32 D (95% CI −0.38, −0.26) for atropine sulfate 0.03%. Treatment effects at month 24 were 0.13 for atropine sulfate 0.01% versus vehicle (95% CI 0.06, 0.20; $p=0.0003$), and 0.12 for atropine sulfate 0.03% versus vehicle (95% CI 0.05, 0.19; $p=0.0009$). Treatment effects were observed as early as month 6 and were sustained through 24 months (Table 2).

Secondary Efficacy Endpoints

Fewer participants experienced myopia progression worse than −0.75 D at 12 months and 24 months in the atropine groups compared

Table 1 Baseline demographic and clinical characteristics: full analysis set

Characteristic	Vehicle (*n* = 282)	Atropine sulfate 0.01% (*n* = 282)	Atropine sulfate 0.03% (*n* = 283)	Total (*N* = 847)
Age (years), mean ± SD	10.4 ± 2.42	10.4 ± 2.44	10.2 ± 2.46	10.3 ± 2.44
Age group, *n* (%)				
3 to < 6 years	9 (3.2)	8 (2.8)	9 (3.2)	26 (3.1)
6 to < 9 years	61 (21.6)	62 (22.0)	62 (21.9)	185 (21.8)
9 to < 12 years	110 (39.0)	110 (39.0)	111 (39.2)	331 (39.1)
12–14 years	102 (36.2)	102 (36.2)	101 (35.7)	305 (36.0)
Sex, *n* (%)				
Male	133 (47.2)	115 (40.8)	127 (44.9)	375 (44.3)
Female	149 (52.8)	167 (59.2)	156 (55.1)	472 (55.7)
Race, *n* (%)				
White	198 (70.2)	190 (67.4)	192 (67.8)	580 (68.5)
Black/African American	21 (7.4)	35 (12.4)	22 (7.8)	78 (9.2)
Asian	47 (16.7)	46 (16.3)	55 (19.4)	148 (17.5)
Other	11 (3.9)	7 (2.5)	5 (1.8)	23 (2.8)
Ethnicity, *n* (%)				
Hispanic or Latino	81 (28.7)	74 (26.2)	71 (25.1)	226 (26.7)
Non-Hispanic or Latino	201 (71.3)	208 (73.8)	212 (74.9)	621 (73.3)
Baseline SER (D), mean ± SD	− 2.70 ± 1.27	− 2.73 ± 1.37	− 2.65 ± 1.29	− 2.69 ± 1.31
SER category, *n* (%)				
− 0.5 D to − 3.0 D	170 (60.3)	176 (62.4)	177 (62.5)	523 (61.7)
> − 3.0 D to − 6.0 D	111 (39.4)	106 (37.6)	106 (37.5)	323 (38.1)
> − 6.0 D or ≤ − 0.5 D	1 (0.4)	0	0	1 (0.1)
APR prior to baseline, mean ± SD	− 0.62 ± 1.28	− 0.58 ± 1.18	− 0.58 ± 1.74	− 0.59 ± 1.43
Axial length (mm), mean ± SD	24.49 ± 0.89	24.51 ± 0.95	24.33 ± 0.93	24.44 ± 0.92

APR annual progression rate, *D* diopters, *SD* standard deviation, *SER* spherical equivalent refraction

with vehicle: 17.2% and 35.7%, respectively, for vehicle, 8.6% and 25.6% for atropine sulfate 0.01%, and 7.8% and 22.4% for atropine sulfate 0.03% (Supplementary material, Fig. S1). At month 24, treatment differences for myopia progression were 10.0% lower in atropine sulfate 0.01% than vehicle (95% CI 2.5, 17.5; $p = 0.0091$), and 13.3% lower in atropine sulfate 0.03% than vehicle (95% CI 5.9, 20.7; $p = 0.0005$). At month 24 in Fast Progressor Subgroup 1, the atropine sulfate 0.01% group experienced a mean change from baseline in

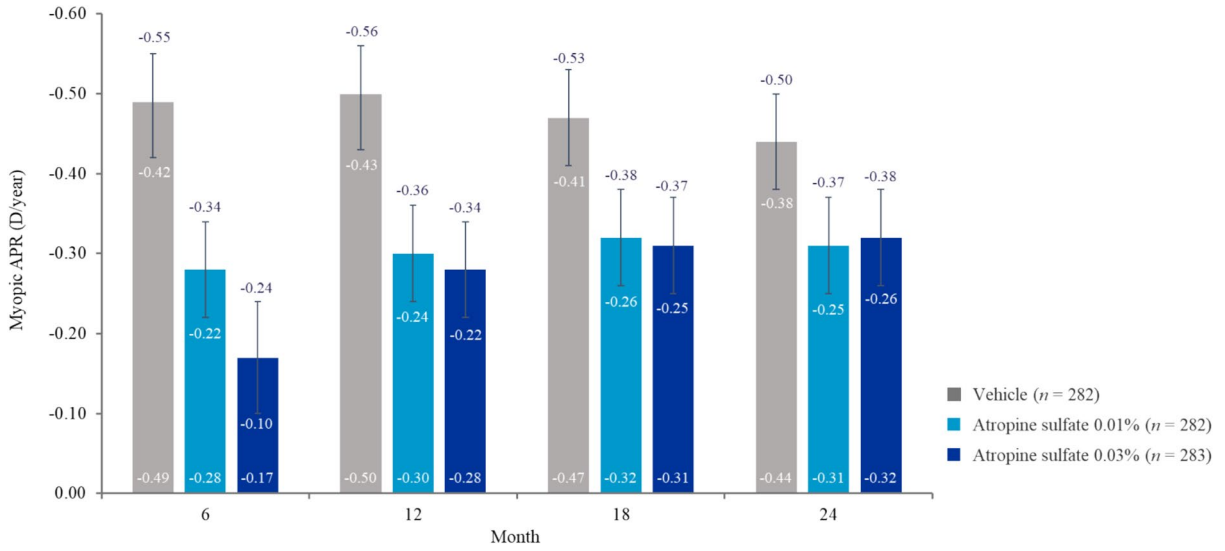

Fig. 2 Primary efficacy outcome. Annual progression rate of myopia at month 24 by treatment and month: full analysis set. *APR* annual progression rate, *D* diopters

the SE that was 0.39 D less (95% CI 0.19, 0.59; $p=0.0001$) than the vehicle group (Supplementary material, Fig. S2).

AL changes at 24 months were analyzed in a subset of participants ($n=413$) with available measurements. The mean changes were 0.40 mm (95% CI 0.34, 0.47) for vehicle, 0.35 mm (95% CI 0.29, 0.41) for atropine sulfate 0.01%, and 0.36 mm (95% CI 0.30, 0.42) for atropine sulfate 0.03%. Differences were −0.05 mm ($p=0.1526$) and −0.04 mm ($p=0.2510$) for atropine sulfate 0.01% and 0.03%, respectively, versus vehicle. Differences at 12 months were −0.05 mm ($p=0.1360$) and −0.06 mm ($p=0.0702$).

Subgroup Analyses

In Fast Progressor Subgroup 1 (progression −0.50 D/year or worse prior to baseline, $n=291$), the mean (least squares means) APR from baseline to month 24 was −0.55 D (95% CI −0.64, −0.46) in the vehicle group and −0.37 D (95% CI −0.44, −0.29) in the combined atropine sulfate group. For the pooled atropine sulfate group, a statistically significant difference of 0.18 D (95% CI 0.10, 0.26) in mean APR was shown compared with vehicle ($p<0.0001$). Of note, each comparison of atropine sulfate 0.01% versus vehicle and atropine sulfate 0.03% versus vehicle was nominally significant ($p<0.0001$ and $p=0.0023$, respectively) (Fig. 3).s

In Fast Progressor Subgroup 2 (progression −0.75 D/year or worse at baseline, $n=225$), the mean (least squares means) APR from baseline to month 24 was −0.53 D (95% CI −0.63, −0.43) in the vehicle group and −0.38 D (95% CI −0.47, −0.30) in the combined atropine sulfate group. For the pooled atropine sulfate group, a statistically significant difference of 0.15 D (95% CI 0.06, 0.25) in mean APR was shown compared with vehicle ($p=0.0018$). Of note, atropine sulfate 0.01% versus vehicle and atropine sulfate 0.03% versus vehicle were nominally significant ($p=0.0008$ and $p=0.0397$, respectively) (Fig. 4).

In the FAS, age-stratified analyses showed consistent efficacy across age groups at month 24. In the 3 to <12 years subgroup ($n=181/180/182$ for vehicle/atropine sulfate 0.01%/0.03%), differences in APR versus vehicle were 0.19 D (95% CI 0.10, 0.29; $p=0.0001$) for atropine sulfate 0.01% and 0.16 D (95% CI 0.06, 0.25; $p=0.0016$) for atropine sulfate 0.03%. In the 6–14 years subgroup ($n=273/273/274$), differences were 0.18 D (95% CI 0.05, 0.19; $p=0.0014$) for atropine sulfate 0.01% and 0.11 D (95% CI 0.04, 0.18; $p=0.0019$) for atropine sulfate 0.03%.

Table 2 Summary of efficacy outcomes at month 24: full analysis set

Outcome	Vehicle ($n = 282$)	Atropine sulfate 0.01% ($n = 282$)	Atropine sulfate 0.03% ($n = 283$)
Primary endpoint			
Mean APR (D/year), LS mean (95% CI)	− 0.44 (− 0.50, − 0.38)	− 0.31 (− 0.37, − 0.25)	− 0.32 (− 0.38, − 0.26)
Difference vs. vehicle (95% CI)		0.13 (0.06, 0.20)	0.12 (0.05, 0.19)
p value		0.0003	0.0009
Secondary endpoints			
Proportion with progression worse than − 0.75 D, *n* (%)	100.70 (35.72)	72.00 (25.55)	63.40 (22.40)
Difference vs. vehicle (95% CI)		− 10.00 (− 17.49, − 2.46)	− 13.30 (− 20.68, − 5.94)
p value		0.0091	0.0005
Mean change in axial length (mm)	($n = 139$)	($n = 139$)	($n = 135$)
LS mean (95% CI)[a]	0.40 (0.34, 0.47)	0.35 (0.29, 0.41)	0.36 (0.30, 0.42)
Difference vs. vehicle (95% CI)		− 0.05 (− 0.13, 0.02)	− 0.04 (− 0.12, 0.03)
p value		0.1526	0.2510

APR annual progression rate, *CI* confidence interval, *D* diopters, *LS* least squares

[a]Axial length measurements were available in a subset of participants

No significant sex- or ethnicity-based differences were noted.

Safety Outcomes Through Month 24

Both atropine sulfate concentrations exhibited favorable safety profiles. At month 24, no participants in the atropine sulfate 0.01% group had to be uptitrated to atropine sulfate 0.03% for escape medication. Treatment-emergent AEs (TEAEs), defined as events of any causality, were reported by 64.9% (vehicle), 61.3% (atropine sulfate 0.01%), and 70.0% (atropine sulfate 0.03%) of participants (Table 3). TEAEs leading to study drug discontinuation were reported in 0.7% (vehicle), 0.7% (atropine sulfate 0.01%), and 2.5% (atropine sulfate 0.03%) of participants.

Non-ocular TEAEs occurred in 47.5% (vehicle), 39.4% (atropine sulfate 0.01%), and 44.9% (atropine sulfate 0.03%) of participants. The most frequent non-ocular TEAE was headache (14.9% vehicle, 10.6% atropine sulfate 0.01%, 14.5% atropine sulfate 0.03%). No serious systemic AEs were considered treatment related.

Ocular TEAEs were reported by 40.1% (vehicle), 42.9% (atropine sulfate 0.01%), and 55.5% (atropine sulfate 0.03%) of participants (Table 4). Common ocular TEAEs included photophobia (16.7% vehicle, 24.1% atropine sulfate 0.01%, 30.4% atropine sulfate 0.03%) and blurred

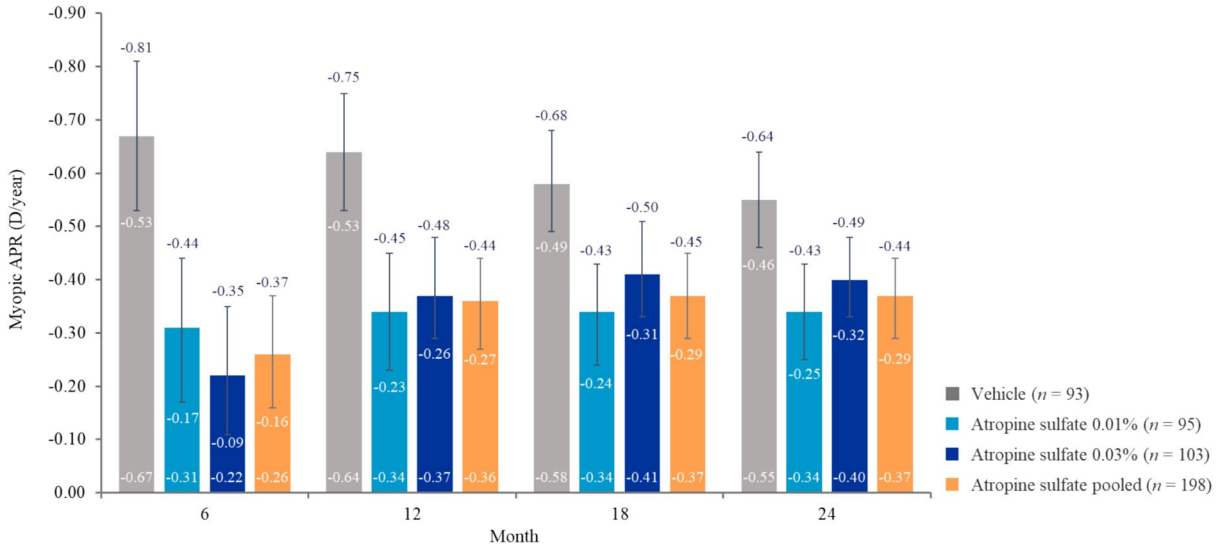

Fig. 3 Annual progression rate of myopia at month 24 in Fast Progressor Subgroup 1 (progression − 0.50 D/year or worse at baseline). *APR* annual progression rate, *D* diopters

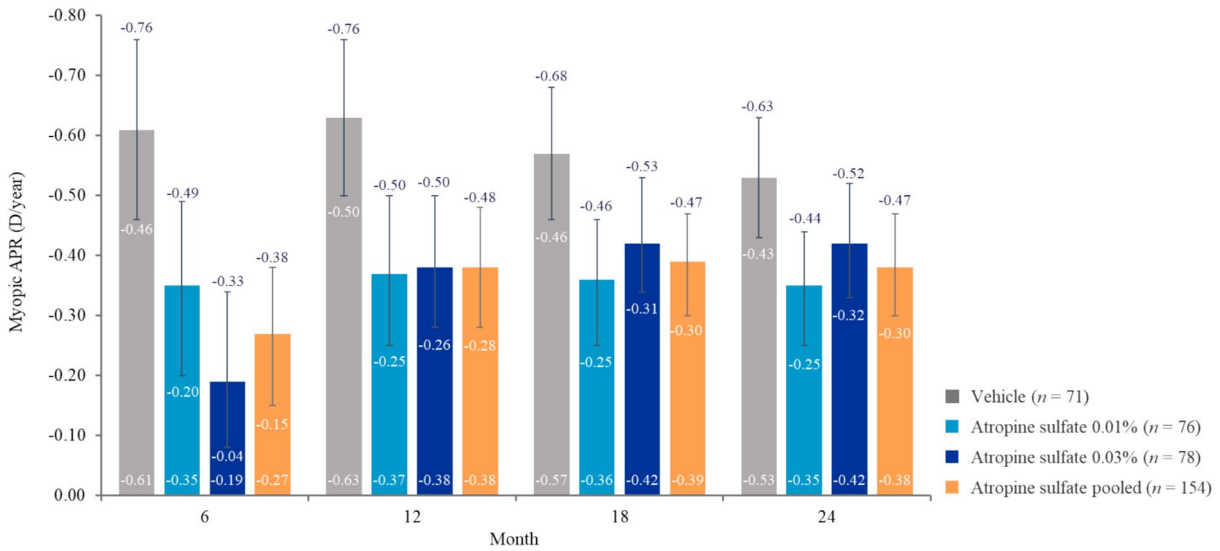

Fig. 4 Annual progression rate of myopia at month 24 in Fast Progressor Subgroup 2 (progression − 0.75 D/year or worse at baseline). *APR* annual progression rate, *D* diopters

vision (8.2% vehicle, 10.3% atropine sulfate 0.01%, 18.0% atropine sulfate 0.03%). Most ocular TEAEs were of mild intensity: 27.7% (vehicle), 28.4% (atropine sulfate 0.01%), and 33.9% (atropine sulfate 0.03%). One serious ocular TEAE was reported by a single participant in each treatment group, none of which were considered as related to the study treatment.

Corneal staining assessment showed no clinically significant differences between groups. Most participants had no staining at baseline through 24 months. Most participants had no corneal staining, and when staining was reported it was mild. No severe staining was reported (Table 5).

Table 3 Overall summary of treatment-emergent adverse events through month 24: safety analysis set

AE	Vehicle ($n = 282$), n (%)	Atropine sulfate 0.01% ($n = 282$), n (%)	Atropine sulfate 0.03% ($n = 283$), n (%)
Any TEAE	183 (64.9)	173 (61.3)	198 (70.0)
Non-ocular TEAEs	134 (47.5)	111 (39.4)	127 (44.9)
Ocular TEAEs	113 (40.1)	121 (42.9)	157 (55.5)
TEAEs related to study drug	93 (33.0)	101 (35.8)	133 (47.0)
Serious TEAEs	5 (1.8)	4 (1.4)	8 (2.8)
TEAEs leading to study drug discontinuation	2 (0.7)	2 (0.7)	7 (2.5)

TEAEs leading to treatment discontinuation are identified as AEs where the action taken with study drug is "Drug withdrawn" or "Caused treatment discontinuation" field is marked "Yes". If the relationship to study drug for an AE is missing, the AE is reported as "Related". At each level of summarization, a participant is counted once if the participant reported one or more events. Events are summarized based on treatment received at the time of event. *n* represents the number of participants at each level of summarization. AEs were coded using MedDRA v26.0

AE adverse event, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

Visual Function at 24 Months

At month 24, the mean (SD) change from baseline in binocular accommodative amplitude showed a dose-dependent effect: −0.43 D ±9.65 (vehicle), −1.03 D ±9.67 (atropine sulfate 0.01%), and −1.28 D ±9.80 (atropine sulfate 0.03%). Change in pupil diameter also showed a dose-dependent effect: +0.04 mm ± 1.28 (vehicle), +0.41 mm ± 1.30 (atropine sulfate 0.01%), and +0.82 mm ± 1.38 (atropine sulfate 0.03%). These changes in accommodative amplitude and pupil size were unremarkable and did not result in visual complaints.

DISCUSSION

Summary of Key Findings

The STAR study demonstrated that atropine sulfate at concentrations of 0.01% and 0.03% significantly reduced myopia progression in children aged 3–14 years over 24 months compared with vehicle. Treatment effects were evident by month 6 and sustained through month 24 for both concentrations. Primary and key secondary endpoints for 0.01% were met at month 24, with the exception of mean change in AL in the full population, which showed numerical but nonsignificant effects. At month 24, atropine sulfate 0.01% and 0.03% reduced the mean APR compared with vehicle by 0.13 D and 0.12 D, respectively. Both concentrations showed similar efficacy in the overall population but prespecified subgroup analyses revealed greater treatment effects in participants with progression of −0.50/−0.75 D/year or worse at baseline, and those with a higher baseline SE (0.03% only). These findings underscore the importance of early identification and initiation of therapy in children with progressive myopia.

Among children with high risk of progression (−0.50 D/year or worse based on historical refraction), atropine sulfate 0.01% significantly reduced APR in both predefined fast-progressor strata, supporting its use in eligible populations at risk for rapid progression. In Fast Progressor Subgroup 1 (progression −0.50 D/year or worse at baseline), differences versus vehicle were 0.18 D in the pooled active groups ($p < 0.0001$),

Table 4 Summary of frequent ocular treatment-emergent adverse events with 2% or greater incidence through month 24: safety analysis set

AE	Vehicle ($n=282$), *n* (%) [E]	Atropine sulfate 0.01% ($n=282$), *n* (%) [E]	Atropine sulfate 0.03% ($n=283$), *n* (%) [E]
Number of participants with at least one TEAE	113 (40.1) [215]	121 (42.9) [225]	157 (55.5) [314]
Eye disorders	77 (27.3) [127]	93 (33.0) [146]	121 (42.8) [217]
Eye irritation	10 (3.5) [12]	8 (2.8) [8]	6 (2.1) [6]
Eye pain	14 (5.0) [17]	8 (2.8) [10]	11 (3.9) [11]
Foreign body sensation in eyes	17 (6.0) [20]	18 (6.4) [19]	17 (6.0) [18]
Mydriasis	1 (0.4) [1]	5 (1.8) [6]	20 (7.1) [22]
Photophobia	47 (16.7) [52]	68 (24.1) [72]	86 (30.4) [101]
Vision blurred	23 (8.2) [25]	29 (10.3) [31]	51 (18.0) [59]
General disorders and administration-site conditions	29 (10.3) [33]	26 (9.2) [27]	28 (9.9) [31]
Instillation-site irritation	17 (6.0) [20]	19 (6.7) [20]	18 (6.4) [21]
Instillation-site pain	12 (4.3) [13]	7 (2.5) [7]	10 (3.5) [10]

The total number of AEs counts all TEAEs for participants. At each level of participant summarization, a participant was counted once if the participant reported one or more events. Only TEAEs that occurred in ≥ 2.0% of the safety set are included in this summary. Events are summarized based on treatment received at the time of event. [E] represents the number of events at each level of summarization. AEs were coded using MedDRA v26.0

AE adverse event, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

0.21 D (nominal $p<0.0001$) for atropine sulfate 0.01% and 0.15 D (nominal $p=0.0023$) for atropine sulfate 0.03%. In Fast Progressor Subgroup 2 (progression −0.75 D/year or worse at baseline), differences versus vehicle were 0.15 D in the pooled active groups ($p=0.0018$), 0.19 D (nominal $p=0.0008$) for atropine sulfate 0.01% and 0.11 D (nominal $p=0.0397$) for atropine sulfate 0.03%.

Both atropine sulfate concentrations significantly reduced the proportion of children experiencing myopia progression worse than −0.75 D at 24 months: 25.6% of children in the atropine sulfate 0.01% group versus 35.7% in the vehicle group ($p=0.0091$), and 22.4% of the children in the atropine sulfate 0.03% group versus 35.7% in the vehicle group ($p=0.0005$). This reduction is particularly important given that each additional 1 D of myopia increases the risk of complications in later life, such as myopic maculopathy (by 58%), open-angle glaucoma (by 20%), posterior subcapsular cataract (by 21%), and retinal detachment (by 30%) [9].

The 0.01% atropine group was found to have a mean reduction of myopia progression of 0.13 D per year and, after 1 year of treatment, 0.05 mm less mean AL elongation when compared with the vehicle group. In the 0.03% treatment group, a mean reduction of myopia progression of 0.12 D per year and 0.06 mm less mean AL elongation was observed when compared with the vehicle group. The adult-based Gullstrand model eye predicts approximately 3.00 D change in SE per 1.0 mm change in AL, referenced to an average adult AL of 23.5 mm [33, 34]. While pediatric ocular dimensions differ from adult eyes and the model may therefore be less precise in children, applying this relationship to the present study yields internally

Table 5 Shift from baseline in corneal staining scores through month 24: safety analysis set

	Vehicle ($n = 282$) Baseline					Atropine sulfate 0.01% ($n = 282$) Baseline					Atropine sulfate 0.03% ($n = 283$) Baseline				
Maximum post-baseline value	0	0.5	1	2	3	0	0.5	1	2	3	0	0.5	1	2	3
0—none	223	3	0	0	0	223	4	0	0	0	225	1	0	0	0
0.5—trace	30	5	0	0	0	27	4	0	0	0	28	5	0	0	0
1—mild	6	1	0	0	0	6	5	0	0	0	9	3	1	0	0
2—moderate	2	0	0	0	0	1	0	0	0	0	1	0	0	0	0
3—severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	261	9	0	0	0	257	13	0	0	0	263	9	1	0	0
Most recent post-baseline value	0	0.5	1	2	3	0	0.5	1	2	3	0	0.5	1	2	3
0—none	251	3	0	0	0	245	9	0	0	0	249	3	0	0	0
0.5—trace	8	5	0	0	0	10	1	0	0	0	10	4	1	0	0
1—mild	3	0	0	0	0	1	3	0	0	0	4	2	0	0	0
2—moderate	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
3—severe	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	262	8	0	0	0	257	13	0	0	0	263	9	1	0	0

Data are summarized for worse eye, defined as the eye with the higher grade at summarized visit. Counts represent participants with a baseline value in addition to having a value at any post-baseline visit

Baseline is the last non-missing assessment prior to dosing

consistent estimates: the mean AL differences at 12 months (−0.05 mm with atropine sulfate 0.01%; −0.06 mm with atropine sulfate 0.03%) correspond to predicted reductions in myopic progression of ~0.15 D and ~0.18 D, aligning closely with the observed APR changes (0.13 D and 0.12 D per year, respectively). Although AL data were only available for a subset of participants, the concordance between predicted and observed SE supports a plausible treatment effect mediated by reduced axial elongation.

Both concentrations of atropine sulfate exhibited favorable safety profiles. TEAEs occurred at similar rates across treatment groups, with no serious drug-related events reported. The most common non-ocular TEAE was headache, while photophobia was the most frequent ocular TEAE, occurring in 16.7% of the vehicle group, 24.1% of the atropine sulfate 0.01% group, and 30.4% of the atropine sulfate 0.03% group. Despite these events, discontinuation rates remained low across all groups. Given comparable efficacy on APR across doses and a higher frequency of ocular TEAEs with 0.03% (notably photophobia and vision blurred), 0.01% offered a favorable benefit–risk profile for routine use. Observed changes in accommodative amplitude and pupil size were non-remarkable and did not result in visual complaints.

Comparison with Existing Literature

Our findings align with results from previous studies of low-dose atropine in pediatric myopia. The efficacy observed with atropine sulfate

0.01% and 0.03% in the STAR study is comparable with that reported in the ATOM2 study for the 0.01% concentration [23]. Direct comparisons between findings from the STAR study and other low-dose atropine studies should be interpreted cautiously because of variations in study populations, methodological designs, outcome measures, and formulation characteristics that may confound cross-trial efficacy comparative assessments.

The STAR study significantly expands the evidence supporting the use of low-dose atropine in children with myopia by demonstrating efficacy in a predominantly white population (68.5%), as previous pivotal studies such as ATOM1, ATOM2, and LAMP were conducted primarily in Asian populations [22, 23, 25]. This addresses an important knowledge gap, as genetic factors and environmental influences on myopia progression likely vary across ethnicities [35].

While the study medication's effect of reducing myopic SE progression was statistically significant, the reduction in elongation of the AL showed a numerical but not statistically significant effect. This pattern has been observed in other studies [36] and may reflect measurement limitations, as AL was assessed only in a subset of sites with appropriate equipment. The COVID-19 pandemic further impacted the ability to collect these measurements during in-person visits, resulting in fewer participants with AL data than was originally anticipated.

Clinical Significance

The clinical significance of these findings should be considered in the context of myopia as a progressive condition with potential long-term complications. Even modest reductions in myopia progression, such as the observed differences in the proportion of participants with myopia progression worse than −0.75 D, may significantly lower lifetime risk of sight-threatening complications [9]. These categorical outcomes reinforce the clinical relevance of early intervention to reduce the likelihood of clinically meaningful progression events in susceptible children.

Our results support early intervention, particularly in children with established fast progression. The benefits observed across age groups provide clinicians with flexibility in treatment initiation. It should be noted, however, that our study included relatively few children in the youngest age category (3.1% of participants were aged 3 to <6 years), and the age groups were not equally represented in the study population. While there was a trend toward greater efficacy in younger children, these findings should be interpreted with caution given the sample size limitations in the youngest age groups.

Low-dose atropine formulations are known to be intrinsically unstable, especially in aqueous solutions, where they readily hydrolyze. It is well established that the stability is enhanced if maintained at low pH values [30, 37]. The novel excipient D_2O was included in the atropine sulfate formulation, instead of purified water, to stabilize the product by reducing its degradation by hydrolysis and result in a system that is closer to the physiological pH of the precorneal tear film. The use of D_2O in this formulation offers enhanced chemical stability, extended shelf life, and increased optimal ophthalmic bioavailability [30, 32].

Despite the presence of BAK, corneal staining assessments showed no clinically significant differences between treatment groups, with most participants exhibiting no staining at 24 months. Across arms, corneal fluorescein staining remained predominantly none/trace, with only rare moderate shifts (two in vehicle, one in atropine sulfate 0.01%, one in atropine sulfate 0.03%). The low dropout rates due to AEs and sustained high compliance rates support a favorable tolerability profile, a conclusion reinforced by the finding that corneal staining assessments showed no clinically significant differences across treatment arms and no severe staining was reported in any participant despite the presence of BAK. As all STAR arms contained BAK, the study did not isolate BAK-specific effects. Furthermore, the pharmaceutical-grade formulation used in this study is differentiated from compounded atropine preparations, which often have varying stability, quality, pH, and

consistency [29]. This makes a low-dose atropine formulation an effective myopia control option for children who may be poor candidates for optical interventions, including orthokeratology or multifocal contact lenses, due to age, ocular surface conditions, or compliance challenges [38].

Limitations and Future Directions

There are several limitations in this study that should be acknowledged. As previously mentioned, AL measurements were available for only a subset of participants as a result of equipment limitations at some study sites and disruptions from the COVID-19 pandemic. This may have limited the statistical power to detect significant AL differences despite favorable numerical dioptric trends.

The inclusion criteria restricted enrollment to children with myopia between −0.50 D and −6.00 D, limiting generalizability to those with more severe myopia. The youngest age group (3 to <6 years) was only 3.1% of the study population, which may slightly underrepresent this age band as a result of the requirement for cooperation with the testing. Additionally, the study employed a vehicle control rather than an active comparator, reflecting the absence of approved standard treatments at study initiation but preventing direct comparison with other myopia control options, such as orthokeratology or multifocal contact lenses.

Environmental confounding factors, including seasonal effects, variations in outdoor time, and near-work or digital device use, cannot be fully controlled; however, we found no interaction between these and outcomes. The study also provided limited data on potential rebound effects after treatment cessation—an important consideration that will be addressed in the upcoming 48-month results from the randomized withdrawal phase. Furthermore, the fixed treatment assignment throughout the study period did not allow for patients to be moved from the 0.03% to the 0.01% concentration when good myopia control was achieved, potentially failing to reflect optimal clinical practice where dose adjustments might be based on individual response and tolerability. Lastly, the multicenter design with different examiners may have introduced measurement variability despite standardized protocols, though this inherent limitation of large clinical trials was mitigated by the randomized design and consistent findings across multiple endpoints.

At the time of writing, these 24-month results of the STAR study have prompted the EMA to approve this formulation of atropine sulfate at a dose of 0.01% for slowing the progression of pediatric myopia in children aged 3–14 years with a progression rate of 0.5 D or more per year and a severity of −0.50 D to −6.00 D at treatment initiation. Future research directions should include investigation of long-term safety and efficacy beyond 24 months, including results from the 36- and 48-month STAR study analyses. Studies of combination therapy with optical interventions such as orthokeratology and multifocal lenses would help determine optimal comprehensive treatment strategies. Development of treatment algorithms for optimal patient selection would allow more personalized approaches to myopia management. Additionally, studies focused on higher degrees of myopia and different age groups would address current gaps in our understanding of atropine's efficacy across the spectrum of myopia severity and developmental stages.

CONCLUSION

In this phase 3 study, atropine sulfate 0.01% and 0.03% demonstrated statistically significant efficacy in slowing myopia progression at 24 months in children aged 3–14 years. Both atropine sulfate concentrations slowed myopia progression versus vehicle through 24 months, with effects evident by month 6 and sustained thereafter. Furthermore, atropine sulfate significantly decreased the proportion of children experiencing myopia progression worse than −0.75 D versus vehicle. The greatest benefits were observed in children with a history of fast progression, particularly in Fast Progressor

Subgroup 1 (progression ≤ −0.50 D/year at baseline). Both concentrations were well tolerated with manageable AEs and low discontinuation rates. Future research should focus on combination therapies with optical interventions, personalized treatment algorithms, and longer-term outcomes to optimize myopia management across different degrees of myopia severity and age groups.

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Data Availability. Vehicle data are available upon reasonable request. The full protocol and statistical analysis plan are available at ClinicalTrials.gov.

Declarations

Conflict of Interest. Michael Korenfeld, MD, is a paid consultant for Santen Inc and Sydnexis. Maria Hurcikova: no conflicts of interest. Kay Tatsuoka is an employee of Santen Inc. Dana Tomciková: no conflicts of interest. Janet Cheetham is a consultant for Sydnexis, and owns stock in AbbVie, Merck, and Johnson & Johnson. Marek Kacerik: no conflicts of interest.

Ethical Approval. The protocol and informed consents/assents were approved by the required institutional review boards or ethics committees, and the study was conducted in accordance with Good Clinical Practice guidelines and tenets of the Declaration of Helsinki. Before any protocol-required procedure, written informed consent was obtained from parents or legal guardians; participants 6 years and above provided self-assent.

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