FDA Briefing Document

NDA# 219694
Drug name: Atropine 0.01%
Applicant: Sydnexis, Inc.

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

10/30/2026

Division of Ophthalmology/Office of Specialty Medicine

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Glossary

AA	accommodative amplitude
AC	Advisory Committee
AE	adverse event
AL	axial length
ATOM	Atropine for the Treatment of Myopia
BRF	Benefit-Risk Framework
CMH	Cochran-Mantel-Haenszel
D	diopters
DODAC	Dermatologic and Ophthalmic Drugs Advisory Committee
FAS	full analysis set
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug and Cosmetic Act
ICE	intercurrent event
ICH	International Council for Harmonisation
LAMP	Low-Concentration Atropine for Myopia Progression
MAR	missing at random
MOSAIC	Myopia Outcome Study of Atropine in Children
NDA	New Drug Application
SD	standard deviation
SE	spherical equivalent
SEE	substantial evidence of effectiveness
SER	spherical equivalent refraction
TEAE	treatment-emergent adverse events
WA-ATOM	Western Australia Atropine for the Treatment of Myopia

1 Executive Summary/Points for Consideration by the Advisory Committee

The Food and Drug Administration is convening this meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee to discuss New Drug Application 219694, submitted by Sydnexis, Inc. The applicant is seeking approval for Sydnexis' SYD-101, an investigational atropine sulfate ophthalmic solution, 0.01% (0.01% atropine), for the proposed indication of slowing the progression of myopia in pediatric patients aged 3 years and older under Section 505 of the Federal Food, Drug and Cosmetic Act (FD&C Act). The primary objective of this advisory committee meeting is to deliberate whether a clinically meaningful benefit has been established for this product, based predominantly on the efficacy and safety results derived from the pivotal clinical trial, Study SYD-101-001. The agency also seeks the committee's expert input on several significant uncertainties identified during the statistical and clinical review of the application, particularly regarding the robustness of the primary efficacy results, the impact of substantial missing data, inconsistencies in the treatment effect over time, the interpretation of exploratory subgroup analyses, and inconsistent evidence in non-Asians from the published literature.

MYOPIA

Myopia, commonly known as nearsightedness, is a highly prevalent refractive error in which the eye focuses light in front of the retina instead of directly on it, causing distant objects to appear blurry while close objects remain clear. It is the most common refractive error globally and currently affects approximately 40% of children in the United States. Early-onset myopia, typically emerging between the ages of 3 and 10 years, is strongly associated with a faster rate of disease progression and a significantly higher ultimate severity of the condition. Myopia, particularly high myopia defined as a spherical equivalent refraction ≤ −6.00 diopters (D), is associated with an increased lifetime risk of serious, vision-threatening ocular complications. These long-term risks include retinal detachment, myopic maculopathy, glaucoma, and the early development of cataracts.

PHARMACOLOGIC TREATMENTS

Despite the significant public health burden of myopia and the severe long-term consequences of high myopia, there are currently no pharmacologic treatments approved by the Food and Drug Administration for this indication. In the absence of approved therapies, low-concentration atropine, specifically at the 0.01% concentration, has been utilized off-label through compounding pharmacies. It is important to note that compounded use of atropine does not constitute evidence of effectiveness as required under Section 505 of FD&C Act.

STUDY DESIGN AND ANALYSIS METHODS

To support the proposed indication, the applicant conducted Study SYD-101-001, a 48-month, multicenter, randomized, double-masked, vehicle-controlled clinical trial. The study was conducted across 47 clinical sites, with 41 of those sites located within the United States, ensuring the trial population is highly relevant to the U.S. demographic. The trial enrolled a total of 852 children between the ages of 3 and 14 years who had a baseline myopia ranging from −0.5 to −6.0 diopters (i.e., mild to moderate myopia). The study was structured into two distinct phases: Part 1 consisted of a primary

treatment period lasting 36 months, and Part 2 consisted of a randomized withdrawal period lasting 12 months.

In Part 1, eligible subjects in the trial were randomized in a 1:1:1 ratio to receive one of three treatments: SYD-101 at a concentration of 0.01% (0.01% atropine), at a concentration of 0.03% (0.03% atropine), or vehicle control. Randomization was stratified by baseline spherical equivalent and by age group to ensure balanced treatment arms. The primary efficacy outcome of interest was the spherical equivalent, measured in diopters by triplicate cycloplegic autorefraction. The primary efficacy endpoint was defined as the proportion of subjects experiencing confirmed myopic progression worse than 0.75 diopters at or before the Month 36 visit. To evaluate this, the primary estimand strategy employed a composite variable approach. Under this framework, subjects who required and received prohibited or escape medications, as well as subjects who discontinued the study drug due to adverse events, were automatically classified as having progressed, thereby counting as treatment failures. This approach is intended to reflect the clinical judgment that a subject who required escape medication or could not tolerate the study treatment has, in a clinically relevant sense, not achieved the desired therapeutic outcome.

The applicant conducted the primary efficacy analysis using a Cochran-Mantel-Haenszel test that adjusted for the stratifying variables. To manage the multiplicity arising from comparing two active dose arms against a single vehicle control, the applicant prespecified a truncated Hochberg procedure. Under this statistical approach, statistical significance would be achieved for both dose comparisons if both yielded 2-sided p-values less than 0.045. If one dose failed to meet this threshold, the other dose comparison was required to achieve a more stringent p-value of less than 0.025 to be deemed statistically significant (equivalently twice the p-value should be less than 0.05).

In Part 2, subjects randomized in Part 1 to 0.01% atropine and the 0.03% atropine arms were rerandomized to either continue their respective treatment or receive vehicle. Subjects in the vehicle arm were administered 0.03% atropine. All subjects were followed for an additional 12 months until Month 48. The objective of Part 2 of the study was to evaluate if there is faster myopia progression following treatment withdrawal (rebound effect).

EFFICACY

Based on this prespecified analysis plan, only the 0.01% atropine dose achieved statistical significance. Confirmed myopic progression at or before Month 36 occurred in 39.5% of subjects in the 0.01% atropine arm compared to 49.3% of subjects in the vehicle arm. This resulted in a treatment difference of −9.6%, with a 95% confidence interval ranging from −17.9% to −1.3%, and an adjusted two-sided p-value of 0.0452 (2*0.0226), which met the threshold of less than 0.05. Conversely, the higher concentration 0.03% atropine arm demonstrated a numerically favorable but statistically nonsignificant result, showing a −6.2% difference compared to the vehicle with a p-value of 0.1319, raising questions about the uncertainty of the dose-response relationship.

The key secondary efficacy endpoint, mean annual progression rate of myopia at 36 months, supported the primary finding for the lower dose; however, the magnitude of the treatment effect showed substantial attenuation over time. The treatment difference in the mean annual progression rate between 0.01% atropine and the vehicle was 0.079 diopters per year over three years (−0.30 D/year versus −0.38 D/year), representing approximately a 21% reduction in the progression rate at that

timepoint. This 0.079 D/year difference represents a marked 62% decline from the peak treatment effect of 0.21 D/year observed at Month 6, indicating progressive waning of efficacy across the study period. The sustained decline in treatment effect at Month 36 came despite three years of continuous treatment, raising concerns about the long-term sustainability and clinical meaningfulness of the observed treatment effect. Furthermore, the declining trajectory of the treatment difference, from 0.21 D/year (Month 6) to 0.13 D/year (Month 24) to 0.079 D/year (Month 36), suggests that the cumulative benefit does not continue to accrue proportionally over extended treatment duration.

In Part 2, the mean spherical equivalent change from Month 36 to Month 48 was −0.21 D for subjects who continued on 0.01% atropine compared to −0.24 D for those rerandomized to vehicle (mean difference: +0.034 D; 95% CI: −0.052, +0.119; nominal p =0.4396). Among participants originally treated with 0.03% atropine, the difference in mean spherical equivalent between those who continued on 0.03% atropine in Part 2 and those who were rerandomized to vehicle was +0.108 D (95% CI, +0.013, +0.203; nominal p=0.0258). These findings suggest that there was a potential rebound effect for the 0.03% atropine arm as treatment withdrawal resulted in a faster myopia progression.

STATISTICAL CONSIDERATIONS

While the primary endpoint was met for 0.01% atropine, the result is statistically borderline, and its interpretation depends critically on the validity of the assumptions underlying the primary analysis. A key assumption concerns the handling of missing data. At Month 36, approximately 26% of subjects in the 0.01% atropine arm, 23% in the vehicle arm, and 22% in the 0.03% atropine arm had missing primary outcome data, a substantial proportion for a primary endpoint. This is in addition to substantial intermittent missing data at earlier visits.

The primary analysis addressed this using multiple imputation under a missing at random (MAR) assumption, which cannot be verified from the observed data. Sensitivity analyses were conducted to evaluate the robustness of the primary result to variations in this assumption. While the sensitivity analyses generally provided directionally favorable results to the 0.01% atropine arm, the results were not persuasive. Specifically, a tipping point analysis showed that statistical significance for the primary endpoint was lost with a shift parameter of 0.02 D applied to the imputed values in the 0.01% atropine arm. This value represents one-fifth of the smallest shift parameter evaluated by the applicant, and a magnitude well within the measurement variability of cycloplegic autorefraction. Together, these analyses indicate that the primary result does not hold across the range of assumptions considered reasonable, raising questions about the robustness of the finding.

CLINICAL CONSIDERATIONS

Beyond the statistical uncertainty caused by missing data, the clinical review identified several inconsistencies in the efficacy profile that complicate the assessment of substantial evidence of effectiveness.

- First, the small reduction in the annual progression rate in the treatment group (0.079 D/year less myopic progression than the vehicle group) resulting in a total reduction in myopic progression of

0.21 D after 3 years of treatment is not clinically meaningful in that it does not likely improve how a patient functions or feels.

- Second, the data reveal a substantially declining treatment effect over time. Rather than a sustained or cumulative benefit, the treatment effect diminished, including an observed reversal of efficacy during the third year of the trial when the vehicle group's myopia progressed less than that of the treatment group's myopia.
- Third, the study failed to demonstrate a significant effect on axial length. Because axial elongation is the primary structural driver of progressive myopia and its associated long-term retinal complications, the absence of a corresponding reduction in axial length raises questions about the disease-modifying and risk reduction potential of the drug.
- Fourth, there is a distinct absence of a dose-response relationship. The lower 0.01% atropine concentration achieved statistical significance (albeit borderline), while the higher 0.03% atropine concentration failed to separate from the vehicle, a finding that lacks a clear pharmacological rationale and is inconsistent with findings in the literature.
- Finally, the agency notes that external evidence from other randomized controlled trials conducted in non-Asian Western populations has generally been unsupportive of the efficacy of 0.01% atropine, further contextualizing the borderline findings of the current application.

SUBGROUP ANALYSIS

In response to the borderline overall results, attention has been directed toward the results of subgroup analyses. Specifically, the subgroup of children aged 3 to ≤12 years, which comprised 78% of the full analysis set, showed a −16.2% treatment difference. Similarly, a subgroup of fast progressors, defined as those with a baseline progression of greater than or equal to −0.50 diopters per year, showed a −16.4% difference. The modest improvement in the younger age subgroup (subjects 3 to ≤12 years of age) could potentially be a result of real treatment heterogeneity or a chance finding as a mathematical artifact due to the exclusion of the less favorable older cohort. Notably, in the older cohort, which accounted for 22% of the study population, the treatment effect is in the wrong direction, numerically favoring the vehicle by +13.4% relative to 0.01% atropine and +17.0% relative to 0.03% atropine.

The agency emphasizes that these subgroup findings must be interpreted with caution and viewed through the appropriate regulatory lens. Although the subgroups were prespecified in the statistical analysis plan to assess heterogeneity of the treatment effect, they carry inherent limitations: observed variability may reflect true heterogeneity or may be attributable to chance alone. Because no pre-allocated significance levels or multiplicity adjustments were applied to these comparisons, the results can only be considered under nominal significance.

Consistent with International Council for Harmonisation (ICH) E9 guidance and established FDA precedent, subgroup analyses that lack prespecified type I error control and multiplicity adjustments are inherently exploratory and hypothesis-generating and cannot serve as the primary basis for regulatory approval. Accordingly, the agency maintains that these findings should be used solely to inform future study designs and cannot independently support approval of the current application.

CONCLUSIONS

For FDA to approve a drug under Section 505 of the FD&C Act, applicants must provide, among other things, substantial evidence of effectiveness (SEE) that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in labeling.[1] Substantial evidence can be evidence from more than one adequate and well-controlled investigation or from one adequate and well-controlled investigation and confirmatory evidence. As described in a recently published FDA guidance, when an applicant intends to demonstrate SEE from a single trial and confirmatory evidence, the strength of evidence needed to substantiate the findings from a single trial will depend on the quality of data, trial conduct, analysis plan, and statistical and clinical persuasiveness of the study results.[2] The agency seeks the committee's input on whether the current application meets this standard, given that Study SYD-101-001 is not highly persuasive on its own and the relevant literature for the US population does not provide robust confirmatory evidence.

To evaluate the strength of the clinical data under this framework, the advisory committee must deliberate on the robustness of Study SYD-101-001. Key considerations include the borderline statistical significance of the primary efficacy results, the sensitivity of these results to missing data, and the lack of a clinically meaningful benefit. Furthermore, the committee will discuss the declining treatment effect over time (including an observed reversal of efficacy in the third year), the lack of effect on axial length, the absence of a dose-response relationship, and the regulatory utility of the exploratory subgroup analyses. The committee will also consider whether the published literature provides meaningful confirmatory support for these findings, given the limited generalizability of predominantly East Asian study populations to the US demographic, the heterogeneity in study designs and treatment durations, the presence of a dose-response relationship across concentrations that was absent in the pivotal study, and conflicting evidence regarding accelerated myopia progression following treatment cessation. Ultimately, the committee will advise the agency on whether the provided data support the effectiveness of atropine 0.01% or if additional confirmatory clinical trials are necessary to resolve the outstanding uncertainties.

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) to discuss whether substantial evidence of effectiveness has been established for atropine sulfate ophthalmic solution, 0.01% for slowing the progression of myopia in pediatric patients aged 3 years and older, based primarily on results from the pivotal trial SYD-101-001.

1.2 Context for Issues to Be Discussed at the AC

Myopia is the most common refractive error affecting approximately 40% of US children. Early-onset myopia (ages 3-10) is associated with faster progression and higher ultimate severity. Myopia, particularly high myopia (SER ≤ –6.00 D), is associated with increased lifetime risk of serious ocular complications including retinal detachment, myopic maculopathy, glaucoma, and cataracts. There are currently no FDA-approved pharmacologic treatments for pediatric myopia, though the FDA has

[1] 21 U.S.C. § 355(d)

[2] FDA Draft Guidance for Industry, Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products (June 2026)

approved two devices, MiSight dual focus contact lenses and Essilor Stellest eyeglass lenses. Low-concentration (0.01%-0.05%) atropine is used off-label.

1.3 Brief Description of Issues for Discussion at the AC

While Study SYD-101-001 technically met its primary efficacy endpoint for the 0.01% atropine dose, the FDA has identified substantial uncertainties regarding the robustness, clinical interpretability, and regulatory acceptability of the data. The advisory committee will need to weigh a borderline statistically significant result against significant methodological vulnerabilities and clinical inconsistencies to determine if the statutory standard for substantial evidence of effectiveness has been met.

The most critical methodological issue for the committee to consider is the extreme fragility of the primary efficacy result in the context of substantial missing data. In addition to substantial intermittent missing data due to skipped visits of approximately 22%, approximately 26% of primary outcome data was missing in the 0.01% atropine arm at Month 36. The statistical significance of the primary endpoint is highly sensitive to the assumptions made regarding this missing data. While the Applicant's primary analysis, which assumed data were MAR, achieved statistical significance, a tipping point analysis demonstrated that this significance is entirely lost when a minimal shift parameter of only 0.02 diopters is applied to the imputed missing values in the 0.01% atropine arm. The committee must deliberate on whether a treatment effect that is so easily overturned by minor changes in missing data assumptions is sufficiently robust to support regulatory approval.

Clinically, the efficacy profile presents several unexplained inconsistencies that complicate the clinical meaningfulness assessment and raise questions about the drug's true disease-modifying potential. First, there is a distinct lack of a dose-response relationship, as the higher 0.03% atropine concentration failed to demonstrate efficacy over the vehicle. Second, the small observed treatment effect was of questionable clinical meaningfulness and was not sustained; it declined substantially over the 36-month period, including a reversal of effect during the third year of the trial. Third, the drug failed to demonstrate a significant effect on axial length, which is the primary structural driver of progressive myopia and its associated long-term complications. The committee will be asked to discuss the clinical plausibility of these findings, particularly when viewed alongside unsupportive external evidence from other non-Asian Western randomized controlled trials evaluating 0.01% atropine.

1.4 Draft Points for Consideration

Please discuss:

- The robustness of the primary efficacy results from Study SYD-101-001, considering the borderline statistical significance and the impact of missing data on the reliability of the findings.
- The clinical meaningfulness of the observed efficacy profile, taking into account the magnitude of the treatment effect on spherical equivalent, the declining treatment trajectory over time, and the lack of a significant effect on axial length.
- How the descriptive and exploratory subgroup analyses (e.g., children aged 3 to ≤12 years and fast progressors) contribute to a determination of effectiveness.
- The utility of the external evidence in light of the borderline statistically significant result of SYD-101-001 and whether the published literature, taken as a whole, provides sufficient corroboration to satisfy the substantial evidence standard for approval.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Myopia results most commonly from pathological elongation of the ocular globe. US prevalence increased from ~25% in 1971 to 41.6% in 2004; the global affected population is projected to exceed 740 million by 2050. Progression is fastest in younger children: in the vehicle arm of SYD-101-001, mean annual rates ranged from −1.08 D/yr (ages 3 to <6) to −0.12 to −0.16 D/yr (ages 13-14). High myopia (worse than −6.00 D) significantly increases the risk of retinal detachment, choroidal neovascularization, glaucoma, cataract, and retinoschisis.

There are no FDA-approved pharmacological treatments for myopia progression in children. Whether the effect size in SYD-101-001 is sufficient to meaningfully reduce long-term complication risk is uncertain given the absence of a clinically and statistically significant axial length effect.

Two CDRH-approved medical devices demonstrate substantially larger effects on both spherical equivalent and axial elongation than atropine sulfate ophthalmic solution, 0.01%:

- MiSight (dual-focus contact lenses; ages 8-12): ~50% spherical equivalent reduction (0.67 D less) and 45% axial elongation reduction (0.28 mm less) over 36 months compared to control; no rebound on cessation.
- Essilor Stellest (aspheric spectacle lenses; ages 6-12): ~71% spherical equivalent reduction (0.64 D less) and 53% axial elongation reduction (0.24 mm less) over 24 months; no apparent rebound.

Neither device is indicated for children under 6 years of age.

2.2 Pertinent Drug Development and Regulatory History

- December 17, 2015 (Type B IND Meeting): FDA confirmed that a single Phase 3 study with supporting literature may be sufficient. FDA discussed that a change of less than 0.75 D of myopia progression over 5 years (including 1 year off treatment) could be clinically meaningful; a 50% reduction in the myopia progression rate was also discussed as an alternative threshold.
- September 24, 2018 (Type C Meeting): Agreement on Cochran-Mantel-Haenszel (CMH) test, 36-month primary timepoint, 0.03% atropine arm, escape medication criteria, and composite intercurrent events (ICEs) strategy.
- January 25, 2023: FDA recommended composite variable strategy for ICEs and vehicle-based imputation for key secondary endpoint.
- December 23, 2024: NDA 219694 submitted.
- October 22, 2025, Complete Response Letter: FDA cited small and not clinically meaningful treatment effect, lack of dose response, no significant axial length effect, and lack of US population efficacy evidence.
- February 19, 2026 (Type A Guidance Meeting): Discussion regarding the Complete Response. FDA described what it considered a clinically meaningful treatment effect in slowing the progression of myopia and recommended another clinical study in order to demonstrate durability and a clinically meaning treatment response; subgroup analysis of fast progressors and younger children was considered hypothesis generating.

- April 10, 2026: The Sponsor submitted a Formal Dispute Resolution Request to FDA to appeal the Complete Response.
- June 12, 2026: FDA informed the Sponsor that it was concluded that additional input in the form of an Advisory Committee was needed to reach a decision on the appeal.

3 Summary of Issues for the AC

The FDA review team has identified several critical efficacy issues that complicate the interpretation of Study SYD-101-001 and raise significant uncertainties regarding whether the statutory standard for substantial evidence of effectiveness has been met. These issues are summarized below:

3.1 Efficacy Issues

Key Efficacy Issue #1: Small Effect Size and Borderline Statistical Significance for the Primary Endpoint

While the trial technically met its primary endpoint for the 0.01% atropine arm, the result is highly fragile. The proportion of subjects with confirmed myopic progression worse than 0.75 D was 39.5% in the 0.01% atropine arm versus 49.3% in the vehicle arm, representing a treatment difference of −9.6% (95% CI: −17.9%, −1.3%). This magnitude of the effect is well short of the assumed effect size of 15% used in the sample size calculation. Under standard reporting, the adjusted two-sided p-value is 0.0452. While the difference is statistically significant under the prespecified truncated Hochberg procedure, the upper limit of the 95% confidence interval remains close to zero (−1.3%), underscoring the statistically borderline nature of the overall treatment effect.

Key Efficacy Issue #2: Extreme Sensitivity to Missing Data

The robustness of the primary efficacy result is severely compromised by a substantial amount of missing data, with approximately 26% of subjects in the 0.01% atropine arm missing primary outcome data at Month 36. Sensitivity analyses demonstrate that the primary finding is highly dependent on the missing-at-random assumption. For example, a tipping point analysis—which directly evaluates the robustness of the results against the primary missing data assumption—demonstrated that statistical significance is lost with a shift parameter of only 0.02 D (one-fifth of the smallest shift parameter the Applicant considered) in the 0.01% atropine arm. This clinically negligible margin indicates that even minor deviations in missing data assumptions overturn the trial's success. A highly persuasive trial is expected to demonstrate robustness of results to plausible violations in assumptions.

Key Efficacy Issue #3: Lack of Clinically Meaningful Effect on Myopia Progression

The 0.01% atropine group showed a reduction of 0.079 D (95% CI: 0.038, 0.120) in mean annual progression rate compared to vehicle. After 3 years of treatment, this amounted to 0.21 D less myopic progression in the treatment group. The FDA's guidance on substantial evidence of effectiveness makes clear that statistical significance alone is insufficient; a highly persuasive trial must also produce results that are clinically meaningful in magnitude. A treatment difference of less than a quarter diopter is not likely to have a meaningful impact on uncorrected vision or result in a significant reduction in the strength of the correction used for distance vision, if at all. The primary finding of SYD-101-001 therefore fails to meet the clinical meaningfulness requirement that the guidance identifies as necessary to a persuasive single-trial submission.

Key Efficacy Issue #4: Declining Treatment Effect Over Time

For a therapy that may be used chronically in the pediatric population, a sustained or cumulative benefit is expected for an effective treatment. However, the treatment difference in the mean annual progression rate declined substantially over the course of the study: from +0.21 D/year at Month 6 to +0.079 D/year at Month 36. This represents a decline of approximately 62% from the peak effect, and a 39% decline from Month 24 to Month 36 alone. Most concerning is an interval-specific reversal during Year 3 (Months 24–36), which favored the vehicle arm by approximately −0.02 D. During this third year, the vehicle arm decelerated approximately six times faster than the treated arm; an asymmetric pattern that is inconsistent with the known, symmetric natural history of myopia progression. A treatment effect that erodes over time and reverses in the final year of observation further undermines confidence that SYD-101-001 constitutes persuasive evidence of a genuine treatment effect.

Key Efficacy Issue #5: Lack of Effect on Axial Length and Biological Plausibility

Axial elongation is the primary structural driver of progressive myopia and its associated long-term, vision-threatening retinal complications (e.g., myopic maculopathy, retinal detachment). In this study, the observed treatment difference for axial length was only −0.01 mm (95% CI: −0.11, 0.08; p=0.7934) for 0.01% atropine and −0.04 (95% CI: −0.13, 0.06; p=0.4452) for 0.03% atropine, providing no directional signal of benefit. The absence of an effect on axial length undermines the biological plausibility of the spherical equivalent-based primary findings. The FDA's guidance contemplates that early-phase mechanistic data and the drug's known biological activity be considered when evaluating the persuasiveness of a single trial's results. Here, the null axial length finding directly contradicts the mechanistic premise on which a positive spherical equivalent-based result would rest, raising significant clinical concerns that 0.01% atropine may merely be altering ciliary muscle tone or lens accommodation: masking the refractive symptom rather than modifying the underlying structural progression of the disease. This lack of structural efficacy was central to the Complete Response Letter issued on October 22, 2025.

Key Efficacy Issue #6: Absence of a Dose-Response Relationship

The study failed to demonstrate a pharmacological dose-response relationship. The higher 0.03% atropine dose failed to achieve statistical significance for the primary endpoint (p=0.1319) and showed numerically lower efficacy result over the 0.01% dose at Month 36. This internal inconsistency casts doubt on the validity of the 0.01% finding. Conversely, published literature (e.g., the LAMP[3] and ATOM2[4] studies) consistently demonstrates a dose-response relationship for atropine in Asian populations, noting that, 0.01% is actually the least effective concentration studied.

Key Efficacy Issue #7: Unsupportive External Evidence and Generalizability

The FDA's guidance provides that all relevant trials should be considered in evaluating a drug's effectiveness. In particular, a single adequate and well-controlled trial, when combined with a source of strong confirmatory evidence, may be sufficient to demonstrate substantial evidence of effectiveness. A

[3] Yam JC et al. (2019). LAMP Study Phase 1. Ophthalmology. 126(1):113-124.
[4] Chia A et al. (2012). ATOM2 Phase 1. Ophthalmology. 119(2):347-354.

key question for this application is whether the broader external literature provides that level of corroboration for the borderline positive result of SYD-101-001. While some studies conducted in Asian populations have demonstrated treatment effects with 0.01% atropine, the extent to which these findings are generalizable to Western or U.S. demographics is uncertain, given the well-documented differences in myopia epidemiology, progression rates, and treatment response across populations. Additionally, many of these studies are of shorter duration, raising questions about whether they adequately characterize the sustained treatment effect necessary to support a regulatory conclusion. Studies conducted in the United States, the European Union, and Australia have generally demonstrated modest effects that frequently do not achieve statistical significance. An FDA meta-analysis[5] of four non-Asian randomized controlled trials evaluating 0.01% atropine at 24 months yielded a combined treatment difference of only 0.13 D. Notably, the only exclusively U.S.-based randomized, controlled trial (MTS1[6]) showed no significant treatment effect (p=0.83). Taken as a whole, the external literature does not provide sufficient corroboration in the generalizability and replicability of the pivotal trial's findings.

Key Efficacy Issue #8: Reliance on Exploratory Subgroup Analyses

To mitigate the borderline overall results, the Applicant relies heavily on numerically larger treatment effects observed in specific subgroups, such as children aged 3 to ≤12 years (−16.2% difference) and "fast progressors" of all ages (−16.4% difference). However, the apparent positive finding in the younger cohort is either potentially driven by the exclusion of the 13 to 14-year-old group (22% of the study population), where a treatment effect favoring the vehicle (+13.4%) is observed or is also possibly a chance finding. Consistent with ICH E9 guidance, the FDA considers these findings strictly exploratory and hypothesis-generating.

3.1.1 Sources of Data for Efficacy

The Applicant submitted this New Drug Application (NDA) pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, relying in part on the FDA's finding of safety for the listed drug, atropine sulfate ophthalmic solution 1% (NDA 206289). The proposed product, SYD-101, is formulated as an atropine sulfate 0.01% ophthalmic solution to be dosed as one drop instilled in each eye nightly. Notably, the SYD-101 formulation utilizes deuterium oxide (D_2O) as a solvent. This novel vehicle is designed to lower the pH of the solution to enhance stability and extend the room-temperature shelf life to over two years.

To establish SEE for the proposed indication, the Applicant relies primarily on a single pivotal clinical trial (Study SYD-101-001), supported by a synthesis of published literature evaluating various concentrations of atropine for myopia control. The key data sources are summarized in Table 1 below.

[5] Eshete A. Statistical Review and Evaluation, NDA 219694. CDER/OTS/OB/DBIV, 2025.
[6] Repka MX et al. (2023). MTS1. JAMA Ophthalmol. 141(8):756-765.

Table 1. Summary of Key Efficacy Data Sources

Data Source	Study Design	Population	Treatment Groups	Key Endpoints/ Limitations
Pivotal trial: SYD-101-001	Phase 3, multicenter, randomized (1:1:1), double-masked, vehicle-controlled, 48-month trial (36-month primary treatment period).	N=852, ages 3 to 14 years. Mild-to-moderate myopia (−0.5 D to −6.0 D). Predominantly U.S. sites.	1. 0.01% atropine 2. 0.03% atropine 3. vehicle	Primary: Proportion with confirmed myopic progression worse than 0.75 D at Month 36. Secondary: Mean annual progression rate; mean change in axial length.
External literature: Asian cohorts (e.g., ATOM, LAMP)	Randomized, controlled trials and observational studies.	Ages 4 to 12 years. Predominantly East Asian populations (e.g., China, Singapore, Japan).	Atropine 0.01%, 0.025%, 0.05%, 0.1%, 0.5%, 1.0% vs. control.	Limitations: High efficacy observed may not be generalizable to the diverse U.S. population due to differing genetic and environmental drivers of myopia.
External literature: Western cohorts (e.g., MTS1, EU/AUS studies)	Randomized, placebo-controlled trials.	Ages 5 to 15 years. U.S., European, and Australian populations.	Atropine 0.01% vs. placebo.	Limitations: Generally shorter duration (1–2 years). Results frequently fail to demonstrate statistically significant efficacy for the 0.01% concentration.

Source: Reviewer summary
Abbreviations: ATOM, Atropine for the Treatment of Myopia; D, diopters; LAMP, Low-Concentration Atropine for Myopia Progression; N, number of subjects

Pivotal Study SYD-101-001

The primary basis for the efficacy evaluation is Study SYD-101-001, a multicenter, randomized, double-masked, vehicle-controlled, two-part clinical trial. The trial enrolled 852 pediatric subjects aged 3 to 14 years with mild-to-moderate myopia (baseline spherical equivalent ranging from −0.5 D to −6.0 D). The study was conducted across 47 sites, 41 of which were located in the United States.

The trial consisted of a 36-month primary treatment period (Part 1) followed by a 12-month randomized withdrawal period (Part 2). During Part 1, eligible subjects were randomized in a 1:1:1 ratio to receive one drop of 0.01% atropine, 0.03% atropine, or vehicle in both eyes at bedtime. The primary efficacy endpoint was the proportion of subjects with confirmed myopic progression worse than 0.75 diopters (D) at or before Month 36, assessed via cycloplegic autorefraction. Key secondary efficacy endpoints included the mean annual progression rate of myopia through Month 36 and the mean change from baseline in axial length at Month 36. Axial length was assessed at a subset of study sites equipped with the requisite optical biometry instrumentation.

Published Literature and External Data Limitations

In addition to the pivotal trial, the Applicant submitted a comprehensive summary of published literature evaluating low-concentration atropine (0.01% to 1.0%) for myopia progression as a supportive data source. While these external randomized controlled trials provide context regarding the pharmacological class, they possess several important limitations that restrict their utility in establishing substantial evidence of effectiveness. Specifically, the vast majority of the supportive studies were conducted in East Asian populations, raising significant concerns about generalizability given that the sparse data from Western and U.S.-based cohorts are generally unsupportive. Furthermore, most published trials were limited to 12 to 24 months of follow-up, precluding an assessment of long-term efficacy or the Year 3 reversal of efficacy observed in the pivotal trial. Finally, the external literature demonstrates a dose-response relationship—which was notably absent in the Applicant's pivotal study—and provides conflicting evidence regarding post-treatment rebound effects.

3.1.2 Efficacy Summary

Under Section 505(d) of the Federal Food, Drug, and Cosmetic Act, the FDA shall not approve a New Drug Application unless there is "substantial evidence" that the drug will have the effect it purports or is represented to have. Under FDA's Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (originally issued December 2019; revised June 2026), which represents FDA's current thinking, a single adequate and well-controlled clinical investigation, together with confirmatory evidence, may satisfy this statutory standard. Confirmatory evidence is always required when relying on a single investigation; the strength of that evidence depends on the persuasiveness of the single trial. Given the absence of a second adequate and well-controlled trial to substantiate findings, FDA would generally expect that strong confirmatory evidence would come from related adequate and well-controlled trial data in related diseases or conditions or for related products. In the absence of such data, a highly persuasive adequate and well-controlled trial supported by early phase confirmatory evidence may be sufficient to demonstrate SEE. A single highly persuasive trial would typically include: a design that provides information that is generalizable and relevant to clinical practice in the United States; a design and analysis plan intended to provide clinically and statistically highly persuasive results; the ability to generate primary analysis results that are clinically and statistically highly persuasive based on the clinical meaningfulness of the estimated magnitude of the benefit, the associated uncertainty, and the p-value; and the ability to demonstrate high-quality conduct, including comprehensive follow-up and minimal missing data, and demonstrate robustness of results to plausible violations in assumption. The efficacy summary below evaluates why the data from the pivotal trial, SYD-101-001, alongside external literature, does not meet this statutory threshold.

3.1.2.1 Pivotal Study: Design of the Study; Demographic Characteristics and Patient Disposition

Study SYD-101-001 was a multicenter, randomized, double-masked, vehicle-controlled trial enrolling 852 pediatric subjects aged 3 to 14 years with mild-to-moderate myopia (baseline spherical equivalent ranging from −0.5 D to −6.0 D). The trial consisted of a 36-month primary treatment period where subjects were randomized 1:1:1 to receive 0.01% atropine, 0.03% atropine, or vehicle.

Baseline demographic and clinical characteristics were well-balanced across treatment arms. The mean age was 10.3 years, with 36.0% of the population aged 12 to 14 years. The study population was predominantly White (68.5%), with 17.5% Asian and 9.2% Black or African American subjects. The vast

majority of subjects (91.7%) were enrolled at United States sites. The mean baseline spherical equivalent (SE) was −2.69 D, and the mean baseline axial length was 24.44 mm.

Table 2. Demographic and Baseline Characteristics

Characteristic	Vehicle N=282	0.01% Atropine N=282	0.03% Atropine 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 category 3 to <6 n (%)	9 (3.2)	8 (2.8)	9 (3.2)	26 (3.1)
Age category 6 to <9 n (%)	61 (21.6)	62 (22.0)	62 (21.9)	185 (21.8)
Age category 9 to <12 n (%)	110 (39.0)	110 (39.0)	111 (39.2)	331 (39.1)
Age category 12 to 14 n (%)	102 (36.2)	102 (36.2)	101 (35.7)	305 (36.0)
Sex male n (%)	133 (47.2)	115 (40.8)	127 (44.9)	375 (44.3)
Sex female n (%)	149 (52.8)	167 (59.2)	156 (55.1)	472 (55.7)
Race White n (%)	198 (70.2)	190 (67.4)	192 (67.8)	580 (68.5)
Race Black or African American n (%)	21 (7.4)	35 (12.4)	22 (7.8)	78 (9.2)
Race Asian n (%)	47 (16.7)	46 (16.3)	55 (19.4)	148 (17.5)
Ethnicity Hispanic or Latino n (%)	81 (28.7)	74 (26.2)	71 (25.1)	226 (26.7)
Ethnicity Not Hispanic or Latino n (%)	201 (71.3)	208 (73.8)	212 (74.9)	621 (73.3)
Region United States n (%)	258 (91.5)	263 (93.3)	256 (90.5)	777 (91.7)
Baseline SE mean (SD)	−2.70 (1.267)	−2.73 (1.375)	−2.65 (1.286)	−2.69 (1.309)
Axial length (mm) mean (SD)	24.49 (0.886)	24.51 (0.953)	24.33 (0.927)	24.44 (0.924)

Source: SYD-101-001 36-Month CSR, Table 9
Abbreviations: N, number of subjects; SD, standard deviation

Premature study discontinuation occurred in 24.3% of subjects in the 0.01% atropine arm compared to 21.2% in the vehicle arm. While the primary reasons provided for discontinuation were "withdrawal by subject/parent/guardian" and "loss to follow-up," the FDA review identified a potential confounding factor. Among subjects whose reason for discontinuation was listed as withdrawal by subject or parent, several had ongoing adverse events (AEs) at the time of withdrawal (7 in the vehicle arm, 7 in the 0.01% atropine arm, and 15 in the 0.03% atropine arm). This raises the possibility that some of these withdrawals were actually AE-related, which could impact the interpretation of the results under the primary estimand's composite variable strategy, which automatically classifies AE-related discontinuations as treatment failures. Overall, 6.7% of subjects in the vehicle arm received open-label 0.03% atropine as escape medication compared to 1.8% of subjects in the 0.01% atropine arm.

Table 3. Patient Disposition

Category	Vehicle n (%)	0.01% Atropine n (%)	0.03% Atropine n (%)	Total n (%)
Informed consent				1035
Screen failure				181
Randomized	283	284	285	852
Dosed	282	282	283	847
Completed Month 36	221 (78.1)	210 (73.9)	219 (76.8)	650 (76.3)
Received escape medication	19 (6.7)	5 (1.8)	11 (3.9)	35 (4.1)
Discontinued study	60 (21.2)	69 (24.3)	61 (21.4)	190 (22.3)
Discontinued study treatment	65 (23.0)	72 (25.4)	62 (21.8)	199 (23.4)
Primary reason for study discontinuation				
Adverse event	1 (0.4)	0	5 (1.8)	6 (0.7)
Withdrawal by subject	20 (7.1)	21 (7.4)	14 (4.9)	55 (6.5)
Withdrawal by parent/guardian	14 (4.9)	19 (6.7)	19 (6.7)	52 (6.1)
Lost to follow-up	21 (7.4)	27 (9.5)	21 (7.4)	69 (8.1)

Category	Vehicle n (%)	0.01% Atropine n (%)	0.03% Atropine n (%)	Total n (%)
Noncompliance with study drug	0	1 (0.4)	0	1 (0.1)
Physician decision	1 (0.4)	0	0	1 (0.1)
Other	3 (1.1)	1 (0.4)	2 (0.7)	6 (0.7)

Source: SYD-101-001 36-Month CSR, Table 6
Abbreviations: n, number of subjects with given characteristic

3.1.2.2 Statistical Methods and Multiplicity Adjustment

The primary efficacy analysis compared each SYD-101 arm against the vehicle using a CMH test, stratified by baseline spherical equivalent and age group. The primary analysis was conducted on the Full Analysis Set (FAS), which included all randomized subjects who received at least one dose of the study medication.

To evaluate the primary estimand, the Applicant employed a composite variable strategy to handle ICEs. Under this approach, subjects who received prohibited medications, required escape medications, or discontinued the study drug due to an adverse event were automatically classified as having progressed (i.e., treatment failures). Note, none of the subjects received prohibited medications. Missing data due to other reasons were handled using a multiple imputation approach (50 imputations) under a MAR assumption.

A critical component of the statistical analysis plan was the control of the overall Type I error rate (α =0.05) across the two dose comparisons (0.01% and 0.03% atropine versus vehicle). The Applicant prespecified a truncated Hochberg procedure (γ=0.80) to adjust for this multiplicity. Under this specific procedure:

If both dose comparisons yielded a p-value<0.045, both would be considered statistically significant. If one dose comparison failed to meet this threshold, the remaining dose comparison was required to achieve a more stringent p-value of <0.025 ($\alpha/2$) to be declared statistically significant. Prior to pooling the multiple imputations, the CMH statistics were transformed via the Wilson-Hilferty cube-root transformation.

The key secondary endpoint (mean annual progression rate) is assessed using a prespecified hierarchical gatekeeping procedure, with the testing rules determined by the outcome at the primary level.

If both dose comparisons (0.01% and 0.03% atropine versus vehicle) are statistically significant at the primary level, both are carried forward and tested for the key secondary endpoint using the same truncated Hochberg procedure (γ =0.80) at the full α =0.05. Specifically, both doses are considered statistically significant if both p-values are <0.045 [$\alpha \times (1+\gamma)/2$]; if one p-value is ≥0.045, the remaining dose comparison must achieve p<0.025 [$\alpha/2$] to be declared statistically significant.

If only one dose comparison achieves statistical significance at the primary level, only that dose is carried forward into the formal testing hierarchy. The key secondary endpoint for that dose is assessed at a more stringent threshold of p<0.005 [$\alpha \times (1-\gamma)/2$], while the nonsignificant dose is considered descriptive/nominal for the key secondary and all subsequent endpoints. All subsequent secondary endpoints for the dose remaining in the formal testing hierarchy are likewise assessed at this more stringent threshold.

Understanding this multiplicity adjustment is essential for interpreting the primary endpoint results. Because the 0.03% atropine dose failed to achieve significance (p=0.1319), the 0.01% dose was required

to meet the stricter <2-sided 0.025 threshold to ensure the overall type I error rate is controlled at a two-sided level of 0.05. The transformed CMH test for the 0.01% arm yielded a p-value of 0.0226, thereby technically satisfying the prespecified statistical requirement for success. However, for direct comparability with the 95% confidence intervals, the standard two-sided p-value of 0.0452 is reported throughout this document. The proximity of this value to the 0.05 significance level underscores the borderline nature of the trial's success.

3.1.2.3 Primary Efficacy Endpoint Results

The primary efficacy endpoint was the proportion of subjects with confirmed myopic progression worse than 0.75 D at or before Month 36. The primary endpoint was met for 0.01% atropine under the prespecified truncated Hochberg testing procedure. Confirmed progression occurred in 39.5% of subjects in the 0.01% arm versus 49.3% in the vehicle arm, representing a treatment difference of −9.6% (95% CI: −17.9%, −1.3%).

However, the two-sided p-value of 0.0452 lies just below the 0.05 threshold, and the upper limit of the 95% confidence interval is only −1.3%, underscoring the borderline nature of the statistical result. The 0.03% atropine dose failed to achieve statistical significance (p=0.1319), demonstrating a lack of a dose-response relationship.

Table 4. Primary Efficacy Analysis

Measure	Vehicle N=282	0.01% Atropine N=282	0.03% Atropine N=283
Participants with progression*	139 (49.3%)	111 (39.5%)	122 (43.1%)
Difference vs. vehicle	Reference	-9.6%	-6.2%
95% CI for difference		(−17.9%, −1.3%)	(−14.2%, +1.9%)
CMH p-value (adjusted two-sided)		0.0452	0.1319
Significant at alpha =0.05		Yes	No

Source: SYD-101-001 36-Month CSR, Table 12

*Based on average across 50 multiple imputations. The p-value from the Hochberg procedure after transformation of the CMH test is 0.0226 which should be compared to 0.025. Here, the adjusted p-value (0.0452<0.05) for the comparison of 0.01% atropine to Vehicle is reported for direct comparability with 95% CIs.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; N, number of subjects

3.1.2.4 Secondary Efficacy Endpoints

The key secondary endpoint evaluated the mean annual progression rate of myopia. The annual myopic progression rate is defined as the negative change in spherical equivalent from baseline divided by the number of days since baseline, multiplied by 365.25. At Month 36, the least squares mean change from baseline in spherical equivalent was −0.92 D in the vehicle group, −0.71 D in the 0.01% atropine group, and −0.76 D in the 0.03% atropine group. The mean annual progression rate was −0.30 D/year in the 0.01% atropine group and −0.32 D/year in the 0.03% atropine group, compared to −0.38 D/year in the vehicle group.

While there was a statistically significant difference between the 0.01% arm and the vehicle overall, the treatment difference was small and declined substantially over time. The difference dropped from +0.21 D/year at Month 6 to +0.079 D/year at Month 36—a 62% reduction from the peak effect. Most concerning is the interval-specific progression rate during Year 3 (Months 24 to 36), where treated subjects actually progressed slightly faster than vehicle subjects (~0.22 D versus ~0.20 D). During this third year, the vehicle arm decelerated approximately six times faster than the treated arm, an asymmetric pattern inconsistent with the known natural history of myopia (Table 5).

Table 5. Mean Annual Progression Rate

Visit	Vehicle	0.01% Atropine	0.03% Atropine	Diff: 0.01% Atropine vs. Vehicle (95% CI)	Diff: 0.03% Atropine vs. Vehicle (95% CI)
BL to Month 6	−0.48	−0.27	−0.16	+0.21	+0.32
BL to Month 12	−0.49	−0.29	−0.27	+0.20	+0.22
BL to Month 24	−0.44	−0.31	−0.31	+0.13 (+0.08, +0.18)	+0.13 (+0.08, +0.18)
BL to Month 36	−0.38	−0.30	−0.32	+0.08 (+0.04, +0.12)	+0.07 (+0.03, +0.11)

Source: Reviewer analysis
Abbreviation: Bl, Baseline; CI, confidence interval

Table 6. Interval Specific Mean Progression Rate

Period	Vehicle SE Change	0.01% SE Change	Interval Contribution
Year 1 (Month 0-12)	~−0.42 D	~−0.23 D	~+0.19 D (favors 0.01%)
Year 2 (Month 12-24)	~−0.30 D	~−0.26 D	~+0.04 D (favors 0.01%)
Year 3 (Month 24-36)	~−0.20 D	~−0.22 D	~−0.02 D (favors Vehicle)

Source: Reviewer analysis
Abbreviations: D, diopters; SE, spherical equivalent

Table 7. Asymmetric Deceleration

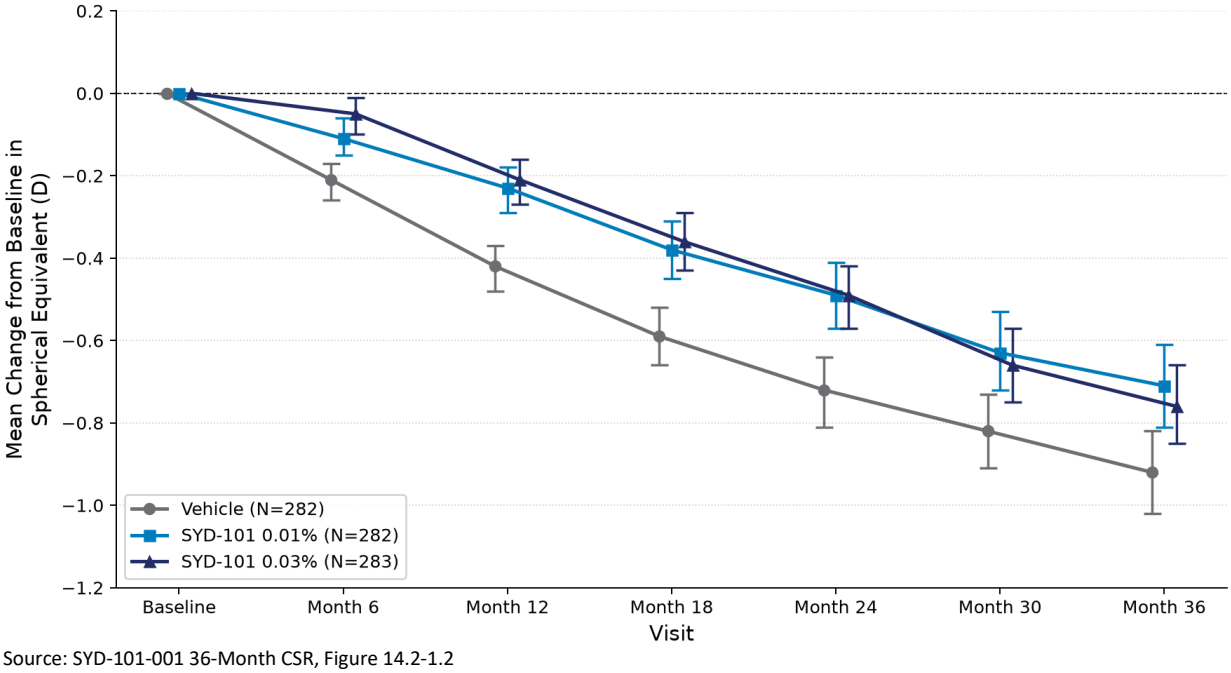
Group	APR at Month 24 (D/yr)	APR at Month 36 (D/yr)	Year 2 to 3 Deceleration
Vehicle	−0.44	−0.38	0.06 D/yr
0.01% Atropine	−0.31	−0.30	0.01 D/yr

Source: Reviewer analysis
Abbreviations: APR, annual progression rate; D, diopters

Another important secondary efficacy endpoint is the change in axial length. Crucially, the study failed to demonstrate a significant effect on this parameter. Axial length was assessed in a subset comprising nearly 50% of the randomized population. At Month 36, the treatment difference in mean change from baseline in axial length was a clinically negligible −0.01 mm for the 0.01% arm (p=0.7934) and −0.04 mm for the 0.03% atropine arm (p=0.4452). Because axial elongation is the primary structural driver of myopia, the absence of an effect on this parameter in a large subset of subjects raises significant questions about the drug's disease-modifying capabilities.

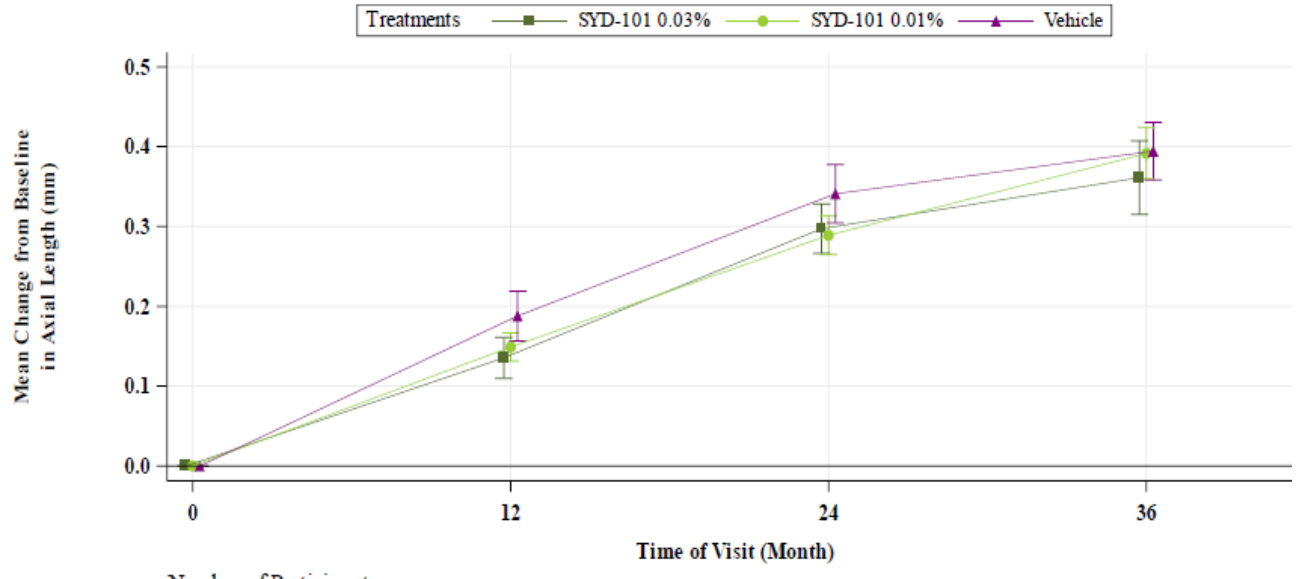
Concerns regarding a declining treatment effect are visually corroborated by the longitudinal data for both endpoints. As demonstrated in Figure 1 (spherical equivalent) and Figure 2 (Axial length), atropine exhibits a promising early efficacy signal during the first two years of therapy. By the third year, however, the treatment effect wanes to the point where there is very little discernible separation between the active treatment and vehicle groups. Given the chronic nature of the planned treatment, this diminishing efficacy is a major clinical concern. If this trajectory continues, subjects receiving atropine could potentially experience worse long-term outcomes than those receiving the vehicle.

Figure 1. Mean Change From Baseline in Spherical Equivalent



Source: SYD-101-001 36-Month CSR, Figure 14.2-1.2
Abbreviation: D, diopter

Figure 2. Mean Change From Baseline in Axial Length



Number of Participants				
SYD-101 0.03%	159	142	130	122
SYD-101 0.01%	156	143	134	123
Vehicle	164	151	138	124

Source: SYD-101-001 36-Month CSR, Figure 14.2-3b

3.1.2.5 Sensitivity Analyses: Missing Data

Substantial missing data were observed, with 26% of subjects in the 0.01% arm missing primary outcome data at Month 36 compared to 23% in the vehicle arm. In addition, there were several subjects with intermittent missing data due to skipped study visits. Please note that, because subjects who

received escape medication and those who discontinued treatment due to adverse events were classified as progressed, they were not counted towards the missing data rate.

Sensitivity analyses showed that the primary finding is highly fragile and dependent on the missing-at-random assumption. Most notably, a tipping point analysis, which directly challenges the missing-at-random assumption under which the primary analysis was conducted, showed that statistical significance is lost for a small shift parameter of −0.02 D added to the imputed values in the 0.01% atropine arm while the imputation for subjects in the vehicle arm remained similar to the primary analysis. This is a small perturbation that falls well within the measurement noise of cycloplegic autorefraction, indicating that the trial's success can be overturned by negligible deviations in missing data assumptions. The treatment difference becomes favorable to the vehicle arm if the imputed values are shifted by more than 0.8 D in the 0.01% atropine arm. Because the primary analysis for the 0.03% atropine arm was not statistically significant, the tipping point analysis for this arm is only intended to show the shift parameter that would lead to a favorable outcome for the vehicle arm (0.6 D).

Table 8. Tipping Point Analyses With the Primary Estimand Strategy

Treatment Comparison	Shift Parameter	Difference (SYD-101 Minus Vehicle)	95% CI	p-Value
0.01% Atropine vs. vehicle	0	−9.6	−17.9, −1.3	0.0226
	0.01	−9.5	−17.9, −0.0	0.0244
	0.02	−9.4	−17.7, −0.0	0.0254
	0.03	−9.3	−17.7, −0.0	0.0275
	0.04	−9.2	−17.6, −0.0	0.0296
	0.05	−9.1	−17.4, −0.0	0.0317
	0.1	−8.6	−16.9, −0.2	0.0413
	0.2	−7.3	−15.6, 1.0	0.0801
	0.3	−5.9	−14.3, 2.5	0.1631
	0.4	−4.7	−12.9, 3.6	0.2663
	0.5	−3.4	−11.7, 4.9	0.4254
	0.6	−2.3	−10.5, 6.0	0.5851
	0.7	−1.0	−9.2, 7.2	0.7342
	0.8	0.1	−8.2, 8.4	0.7780
	0.9	1.1	−7.2, 9.3	0.7386
	1.0	2.1	−6.2, 10.3	0.6162
0.03% Atropine vs. vehicle	0	−6.2	−14.2, 1.9	0.1319
	0.1	−5.9	−13.3, 3.0	0.2130
	0.2	−3.9	−12.1, 4.2	0.3458
	0.3	−2.8	−10.9, 5.4	0.5083
	0.4	−1.6	−9.8, 6.6	0.6601
	0.5	−0.4	−8.6, 7.8	0.7523
	0.6	0.7	−7.4, 8.8	0.7461
	0.7	1.6	−6.6, 9.8	0.6538
	0.8	2.4	−5.7, 10.6	0.5491
	0.9	3.2	−5.0, 11.3	0.4501
	1.0	3.8	−4.4, 11.9	0.3706

Source: Reviewer analysis

Note: All numeric values (except p-values) rounded to one decimal place. Negative signs preserved for values rounding to 0.0. For example, for the shift parameter 0.02, the upper limit of the 95% CI is −0.01.

Abbreviation: CI, confidence interval

3.1.2.6 Supplemental Analyses: Intercurrent Events and Analysis Population

The primary estimand applied a composite variable strategy for the intercurrent events of receipt of escape medication and treatment discontinuation due to adverse events. Under this strategy, subjects who received escape medication or discontinued treatment due to an adverse event were classified as progressors, regardless of their observed clinical status at the time of the intercurrent events. This approach reflects the clinical judgment that both intercurrent events represent meaningful treatment failures: a subject who required escape medication or could not tolerate the study treatment has, in a clinically relevant sense, not achieved the desired therapeutic outcome. Please note, because subjects are eligible for escape medication if they have shown a change from baseline in spherical equivalent of −2 D or worse, they would have been considered progressors, even with their observed outcomes. The primary estimand answers the question: what is the treatment effect on the proportion of progressors, where both escape medication use and treatment discontinuation due to adverse events are themselves considered evidence of progression?

Additional supplemental estimands using different intercurrent event strategies were evaluated to further contextualize the drug effect. Because each of these strategies define a fundamentally different estimand and therefore answer a different clinical question, the resulting treatment effect estimates are not directly comparable across analyses. Differences in point estimates or statistical significance across strategies should be interpreted as reflecting differences in the underlying question being posed, not as inconsistencies in the data. Taken together, the analyses provide a complementary characterization of the treatment effect across a range of clinically meaningful scenarios. Across all estimands evaluated, the direction of effect consistently favors atropine over vehicle; however, the magnitude of the observed treatment differences across all analyses warrants careful consideration in assessing clinical meaningfulness.

Expanded Composite Strategy

An estimand based on a composite variable strategy applied for escape medication and treatment discontinuation regardless of reported reason provided treatment differences versus vehicle of −6.3% (95% CI: −14.2%, +1.6%) for 0.01% atropine and −5.9% (95% CI: −13.6%, +1.8%) for 0.03% atropine. These effects are attenuated relative to the primary analysis, which applied the composite strategy selectively for treatment discontinuation due to adverse events only. The total number of subjects who discontinued study treatment was 64 (22.6%), 70 (24.8%), and 60 (21.3%) in the vehicle, 0.01% atropine, and 0.03% atropine arms, respectively. Of these, only 3 subjects, each in the vehicle and 0.03% atropine groups discontinued due to a reported adverse event, with none in the 0.01% atropine arm. The attenuation in treatment difference under this strategy is therefore expected, as more subjects in the 0.01% atropine arm reported to have discontinued for reasons unrelated to adverse events and were classified as progressors under this expanded definition. It should be noted, however, that this expanded composite strategy classifies all discontinuations, and could introduce a systematic imbalance against the active arm if nonadverse event discontinuations are unrelated to treatment.

Treatment Policy Strategy + Composite Strategy

This supplemental estimand applied a treatment policy strategy for escape medication, using all observed data including data collected after escape medication receipt, while retaining the composite variable strategy for treatment discontinuation due to adverse events. The clinical question answered by

this estimand is: what is the effect of randomization assignment on the proportion of progressors, where treatment discontinuation due to an adverse event is considered a treatment failure, but the use of escape medication is not, and any benefit or harm associated with escape medication is reflected in the observed outcomes? The treatment difference between 0.01% atropine and vehicle was −10.0% (95% CI: −18.3%, −1.7%), and the corresponding difference between 0.03% atropine and vehicle was −6.2% (95% CI: −14.6%, +1.9%), the latter of which includes zero. The only structural difference between this estimand and the primary analysis is in how subjects who received escape medication are handled. In this study, 12 of the 19 vehicle subjects who received escape medication had observed data post-escape, compared with only 1 of the 5 subjects in the 0.01% atropine arm.

Complete Treatment Policy Strategy

In this supplemental estimand, a treatment policy strategy was applied for both escape medication and treatment discontinuation. Under this strategy, all observed data were used irrespective of escape medication use or treatment discontinuation, and no special handling was applied to post-intercurrent observations. This supplemental estimand addressed a different question: what is the effect of randomization assignment on the proportion of progressors, regardless of whether subjects received escape medication or discontinued treatment due to adverse events? Because the number of subjects with observed data post-escape and post-treatment discontinuation was small, the analysis involved imputation of the missing data using the same missing data method employed in the primary analysis. Consequently, the results are driven primarily by the missing data methodology and are therefore comparable to the primary analysis results [−10.0% (95% CI: −18.1%, −1.6%) for 0.01% atropine and −6.9% (95% CI: −14.9%, +1.1%) for 0.03% atropine].

Per Protocol Analysis

In addition to the supplemental analyses employing different intercurrent event strategies, the primary efficacy endpoint was also evaluated in the per-protocol population, which excluded all subjects with major protocol violations. The per-protocol population excluded a total of 78 subjects [24 (vehicle), 29 (0.01% atropine), and 25 (0.03% atropine)]: 32 due to a major protocol deviation and 46 due to missing post-baseline efficacy assessments.

The treatment differences versus vehicle in the per-protocol population were −7.1% (95% CI: −15.5%, +1.2%) for 0.01% atropine and −5.1% (95% CI: −13.4%, +3.1%) for 0.03% atropine. For comparison, the primary efficacy analysis based on the full analysis set provided treatment differences of −9.6% (95% CI: −17.9%, −1.3%) for the 0.01% atropine arm and −6.2% (95% CI: −14.2%, +1.9%) for the 0.03% atropine arm. The direction of effect is consistent between the two populations for both doses. The per-protocol analysis results should be interpreted in the context of the potential for selection bias inherent in per-protocol analyses, as the exclusion of subjects with major protocol violations or missing assessments may not be independent of treatment assignment or outcome.

3.1.2.7 Subgroup Analyses

The subgroup analyses conducted using the same methodology as the primary efficacy endpoint, yielded results that are generally consistent with the primary findings across both the 0.01% and 0.03% atropine treatment arms.

While treatment differences were numerically favorable to SYD-101 across most subgroups, distinct patterns were observed in two specific cohorts. Notably, numerically larger treatment differences were observed in 'fast progressors' of all ages (−16.4% and −13.8% for the 0.01% and 0.03% atropine arms, respectively). In contrast, in the 13- to 14-year-old group, which comprised 22% of the study population, a treatment effect was observed in the wrong direction, favoring the vehicle (+13.4% relative to 0.01% atropine and +17.0% relative to 0.03% atropine).

Analyses restricted to children aged 3 to ≤12 years yielded numerically favorable results for both arms (−16.2% and −12.7% for the 0.01% and 0.03% atropine arms, respectively); however, this could represent a numerical artifact of excluding the 13- to 14-year-old group or simply a chance finding. Further complicating interpretation, the Applicant's post hoc regrouping of 12-year-olds into the older cohort attenuated the unfavorable result observed in the 13- to 14-year-old group (+0.8% and +0.5% for the 0.01% and 0.03% arms, respectively), illustrating the sensitivity of subgroup findings to age boundary definitions. In addition, because these subgroup analyses were conducted without pre-allocated statistical significance levels or multiplicity adjustments, they remain inherently exploratory, and these observed patterns would need to be validated using additional data. The results for the key secondary endpoint of mean annual progression rate followed a similar pattern.

Table 9. Subgroup Analysis: Primary Efficacy Endpoint

Subgroup	N (Vehicle/0.01% Atropine/0.03% Atropine)	Diff 0.01% Atropine vs. Vehicle (95% CI)	Diff 0.03% Atropine vs. Vehicle (95% CI)
Full analysis set	282/282/283	−9.6% (−17.9%, −1.3%)	−6.2% (−14.2%, 1.9%)
3 to <6 years	9/9/9	−45.8% (−95.7%, −9.1%)	−24.4% (−64.3%, +15.4%)
6 to <9 years	61/61/62	−15.7% (−33.4%, 2.1%)	−9.5% (−26.8%, +7.8%)
9 to ≤12 years	150/150/151	−14.7% (−26.5%, −2.9%)	−13.3% (−25.1%, −1.5%)
13 to 14 years	62/62/61	+13.4% (−1.9%, +28.6%)*	+17.0% (+2.3%, +31.8%)*
3 to ≤12 years	220/220/222	−16.2% (−25.9%, −6.5%)	−12.7% (−22.1%, −3.4%)
Fast progressors (≥0.50 D/yr)	93/95/96	−16.4% (−30.8%, −2.1%)	−13.8% (−27.8%, +0.3%)

Source: SYD-101-001 36-Month CSR, adapted from Figure 3
*Favors vehicle
Abbreviations: CI, confidence interval; D, diopters; N, number of subjects

Table 10. Subgroup Analysis: Primary Efficacy Endpoint

Subgroup	N (Vehicle/0.01% Atropine/0.03% Atropine)	Diff 0.01% Atropine vs. Vehicle (95% CI)	Diff 0.03% Atropine vs. Vehicle (95% CI)
Full analysis set	282/282/283	-9.6% (−17.9%, 1.3%)	-6.2% (−14.2%, 1.9%)
3 to <12 years	181/180/182	-15.4% (−26.2%, −4.7%)	-9.9% (−20.3%, +0.5%)
12 to 14 years	101/102/101	+0.8% (−11.8%, +13.4%)*	+0.5% (−11.7%, +12.7%)*

Source: SYD-101-001 36-Month CSR, Table 13
*Favors vehicle
Abbreviations: CI, confidence interval; N, number of subjects

Consistent with the primary efficacy endpoint, axial length, an important secondary endpoint, was also examined in the 3 to ≤12-year subgroup and regrouping the 12-year-olds to the older cohort. As axial length was measured only at a subset of study sites, the analysis includes fewer participants than the primary efficacy endpoint (N=380 versus N=847). In the 3 to <12-year subgroup, the difference in mean axial length change from baseline between 0.01% atropine and vehicle was −0.02 mm (95% CI −0.16,

+0.11), and between 0.03% atropine and vehicle was −0.05 mm (95% CI −0.19, +0.09). A similar result was observed when 12-year-olds were included in this subgroup.

Table 11. Subgroup Analysis: Axial Length

Subgroup	N (Vehicle/0.01% Atropine/0.03% Atropine)	Diff 0.01% Atropine vs. Vehicle (95% CI)	Diff 0.03% Atropine vs. Vehicle (95% CI)
Full analysis set	125/127/128	−0.01 (−0.11, +0.08)	−0.04 (−0.13, +0.06)
3 to <12 years	75/85/79	−0.02 (−0.16, +0.11)	−0.05 (−0.19, +0.09)
3 to ≤12 years	95/100/99	−0.02 (−0.14, +0.09)	−0.06 (−0.18, +0.06)

Source: SYD-101-001 36-Month CSR, adapted from Table 14.2-5.1.x and Table 14.2-5.1.y
Abbreviations: CI, confidence interval; N, number of subjects

3.1.2.8 Summary: Randomized Withdrawal Period (Part 2)

Part 2 of the SYD-101-001 trial was a 12-month exploratory extension designed to evaluate the effects of abrupt treatment withdrawal, continued treatment, and delayed treatment initiation following 36 months of initial therapy. A total of 620 participants (97.3% of the active cohort) were rerandomized at Month 36 (redefined as "Baseline 2"); with 583 participants (94.0%) completing the Month 48 visit.

At the original study baseline (Day 1), the mean age was 10.5 years, increasing to approximately 13.5 years by the start of Part 2. The population was 55.3% female and 68.5% White, with a mean original baseline spherical equivalent of −2.70 D. Because rerandomization at Month 36 was unstratified, all key analyses in Part 2 assessed the change in progression from Baseline 2 (Month 36) to normalize the post-randomization starting point.

3.1.2.8.1 Efficacy Overview: Part 2

The primary objective of Part 2 was to determine if discontinuing treatment triggered a "rebound" effect (defined as myopia progression that exceeds both the on-treatment trajectory and the original, pretreatment rate).

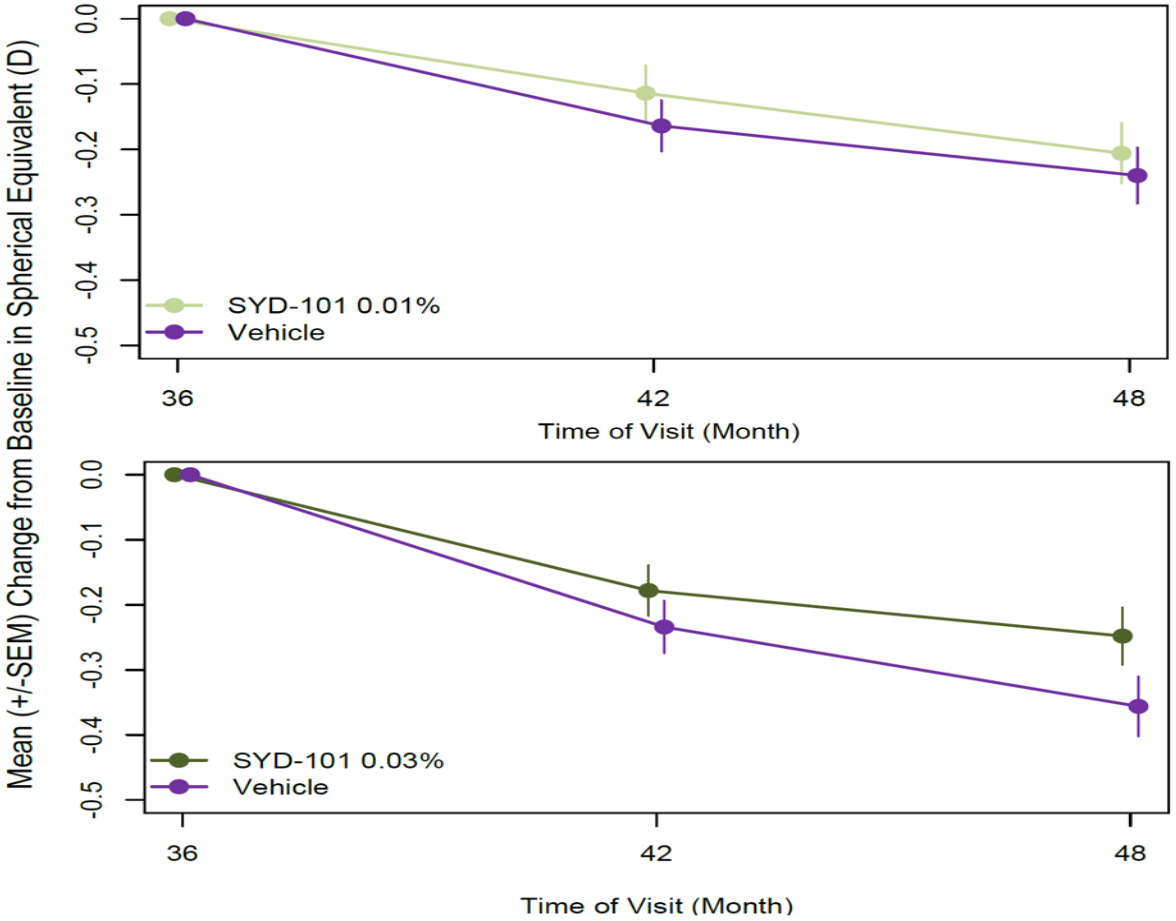
- **0.01% Atropine Cohort**: Discontinuation of 0.01% atropine after three years of treatment did not result in a rebound effect. Refractive outcomes, including change in spherical equivalent (−0.21 D versus −0.24 D) and Annual Progression Rate (−0.22 D/year versus −0.25 D/year), were nearly identical between participants who continued treatment with 0.01% atropine and those who were switched to the vehicle.
- **0.03% Atropine Cohort**: Withdrawal of 0.03% atropine was associated with a nominally statistically significant increase in myopia progression (−0.25 D versus −0.36 D spherical equivalent change) compared to those who continued treatment with 0.03% atropine. However, this post-withdrawal progression did not exceed pretreatment trajectories.
- **Delayed Initiation**: Participants originally on the vehicle who initiated 0.03% atropine at Month 36 demonstrated mean change in spherical equivalent of −0.015 D.

Table 12. Summary of Key Efficacy Outcomes Following Rerandomization (Baseline 2 to Month 48)

Efficacy Endpoint	Continued SYD-101	Switched to Vehicle	LS Mean Difference (95% CI) [p-Value]
0.01% atropine cohort (n=102 cont., n=103 w/d)			
Mean change in SE (D)	−0.21	−0.24	+0.033 (−0.052, +0.119)
Mean APR (D/year)	−0.22	−0.25	+0.03 (−0.06, +0.11)
0.03% atropine cohort (n=105 cont., n=105 w/d)			
Mean change in SE (D)	−0.25	−0.36	+0.108 (+0.013, +0.203)
Mean APR (D/year)	−0.33	−0.44	+0.11 (+0.02, +0.21)

Source: 1.11.3 Clinical Information Amendment, Figure 3, Table 14.2-6.4a.48, and Table 14.2-1.7.1.48
Note: LS Mean Difference represents the difference between continued treatment versus switched to vehicle.
Abbreviations: SE, spherical equivalent; APR, annual progression rate

Figure 3. Mean Change From Baseline 2 in SE Through Month 48



Source: 1.11.3 Clinical Information Amendment, Figure 3
Abbreviations: D, diopters; SE, spherical equivalent

3.1.2.8.2 Safety Overview: Part 2

The safety profile during the 12-month extension remained consistent with the primary 36-month treatment period, and no new safety signals were identified. The most common ocular treatment-emergent adverse events (TEAEs) were photophobia, blurred vision, and mydriasis. Notably, these ocular events occurred predominantly in participants who were newly initiated on the 0.03% atropine dose at Month 36 (the delayed treatment group), rather than in those continuing or withdrawing from

therapy. Only one serious adverse event was reported during Part 2 (a 15-year-old male who sustained severe injuries in an all-terrain vehicle accident). This event was assessed by both the investigator and the sponsor as entirely unrelated to the study drug.

3.1.2.9 Confirmatory Evidence

The Applicant submitted literature summaries evaluating the use of low-concentration atropine for myopia progression as confirmatory evidence to support the findings from a single pivotal trial. While this literature provides important context regarding the pharmacological class, the FDA review team notes several critical limitations regarding its utility in establishing substantial evidence of effectiveness for this specific NDA.

First, the published literature demonstrates significant population-specific variation in the efficacy of 0.01% atropine. The vast majority of the literature submitted by the Applicant is derived from studies conducted in East Asia (primarily China, Singapore, and Japan). While these studies reported favorable outcomes in those specific cohorts, the incidence, progression rate, and underlying genetic and environmental drivers of myopia might differ significantly between East Asian and Western populations.[7] Consequently, these findings have limited generalizability to the more diverse U.S. pediatric population and do not serve as strong confirmatory evidence for this application. External evidence derived from Western populations is sparse and generally unsupportive. Studies conducted in the United States, the European Union, and Australia demonstrate modest effects that often fail to achieve statistical significance. Notably, of the four randomized controlled trials conducted primarily in the United States, the only one conducted exclusively in the U.S. (the MTS1 study by Repka et al., 2023) failed to demonstrate a clinically meaningful treatment effect for 0.01% atropine. Therefore, the external data do not provide confirmatory evidence to support the borderline efficacy findings of SYD-101-001 in a U.S. demographic.

Second, the published studies evaluated a wide range of atropine concentrations (from 0.01% up to 1.0%) and enrolled children across varying age ranges (typically 4 to 16 years). Furthermore, the majority of these randomized controlled trials had a primary treatment duration of only 12 to 24 months. Studies with shorter follow-up consistently report somewhat larger effect sizes than those observed at 36 months, which is consistent with a declining treatment trajectory. Because most published studies did not evaluate Year 3 outcomes, they cannot determine whether the Year 3 reversal of efficacy observed in Study SYD-101-001 is generalizable. This short duration represents a material limitation in evaluating the long-term efficacy and potential tachyphylaxis of low-dose atropine.

Third, the published literature demonstrates a dose-response relationship across varying concentrations of atropine. This fundamental pharmacological characteristic was notably absent in the Applicant's pivotal study, further complicating the interpretation of the NDA's efficacy results.

Finally, the published studies provide conflicting evidence regarding a potential rebound effect following treatment cessation. While some literature shows no rebound after stopping 0.01% atropine, other studies demonstrate accelerated myopia progression. For example, in an Australian study[8] (Lee et al.,

[7] Biswas, S., Lanca, C., Kynman-Sprinks, D., & Grzybowski, A. (2026). Ethnic and dose-dependent differences in atropine efficacy for myopia control: a systematic review and meta-analysis. *The British journal of ophthalmology*, *110*(5), 483–491.

[8] Lee SS et al. (2024). WA-ATOM Cessation Analysis. Clin Exp Ophthalmol. 52(5):507-515.

2024b), subjects initially treated with 0.01% atropine for two years exhibited faster myopia progression during a one-year washout period compared to placebo-treated subjects.

3.1.3 Efficacy Issues in Detail

The FDA review team has determined that Study SYD-101-001, as a single adequate and well-controlled investigation, is not sufficiently persuasive to support approval, particularly in the absence of strong confirmatory evidence. The following subsections detail the critical efficacy issues, methodological vulnerabilities, and clinical inconsistencies that preclude a determination of substantial evidence of effectiveness.

Lack of Structural Efficacy and Biological Plausibility (Axial Length)

A significant clinical deficiency in the SYD-101-001 data is the complete absence of treatment effect on axial length. Myopia is fundamentally a structural disease characterized by the abnormal elongation of the eyeball. It is this axial elongation that stretches the retina and sclera, directly driving the severe, long-term, vision-threatening complications of the disease, including myopic maculopathy, retinal detachment, and glaucoma.

In this trial, the observed treatment difference between 0.01% and vehicle for axial length was a negligible −0.01 mm (p=0.7934). The failure to reduce axial elongation severely undermines the biological plausibility of the primary endpoint finding, which was based solely on spherical equivalent (refractive error). If a drug improves refractive error without slowing the physical growth of the eye, it strongly suggests that the drug is merely altering ciliary muscle tone or lens accommodation—effectively masking the refractive symptom without modifying the underlying structural progression of the disease. Consequently, the retina continues to stretch, and the patient remains at high risk for long-term sequelae. The Sponsor’s argument that treatment with 0.01% atropine could reduce future complications of myopia is not supported by the axial length data. This lack of structural efficacy was central to the Complete Response Letter issued by the FDA in October 2025.

Statistical Fragility and Extreme Sensitivity to Missing Data

The statistical significance of the primary endpoint is fragile. The two-sided p-value of 0.0452 and a 95% confidence interval upper bound of −1.3% provide a very narrow margin of success. This fragility is compounded by an unacceptably high rate of missing data (26% in the 0.01% arm at Month 36).

The FDA's tipping point analysis illustrates the severity of this issue. Statistical significance is entirely lost when a shift parameter of merely 0.02 D is applied to the imputed missing values. To contextualize this, 0.02 D is a fraction of the standard 0.25 D increment used in clinical refraction and falls well within the standard error of measurement for cycloplegic autorefraction. The fact that the trial's success hinges on a margin smaller than the noise of the measurement instrument itself indicates that the primary result is not robust, and therefore, the data cannot be considered highly persuasive.

Inconsistent Pharmacological Profile: Declining Efficacy and Lack of Dose-Response

A chronic therapy intended to modify a pediatric disease must demonstrate a sustained, durable effect. SYD-101 fails to demonstrate this durability. The treatment difference in the mean annual progression rate declined by 62% from Month 6 to Month 36. Most alarmingly, during Year 3 of the trial, the

treatment effect reversed, with subjects in the 0.01% arm progressing slightly faster than those in the vehicle arm. This asymmetric deceleration is inconsistent with the natural history of myopia and suggests the onset of tachyphylaxis (tolerance) to the medication.

Furthermore, the trial failed to demonstrate a pharmacological dose-response relationship, as the higher 0.03% atropine concentration failed to separate from the vehicle. In established literature (such as the LAMP and ATOM2 studies), atropine consistently demonstrates a robust, concentration-dependent effect. The internal inconsistency of the 0.01% dose succeeding while the 0.03% atropine dose fails casts significant doubt on whether the 0.01% atropine finding represents a true pharmacological effect or a statistical anomaly.

Regulatory Unacceptability of Exploratory Subgroup Analyses

In the setting of a borderline overall result, the Applicant has heavily emphasized numerically larger treatment effects observed in specific subgroups, particularly children aged 3 to ≤12 years. The FDA fundamentally disagrees with affording these findings evidentiary weight.

The apparent positive findings in the younger cohort are potentially a true treatment heterogeneity, or a chance finding as a mathematical artifact driven by the exclusion of the 13 to 14-year-old group, which comprised over 22% of the study population and where a treatment effect favoring the vehicle is observed. More importantly, while the subgroups themselves were prespecified, the comparative statistical analyses were descriptive and assessed without prespecified type I error control or multiplicity adjustments. Consistent with ICH E9 guidance, such analyses are strictly exploratory and hypothesis-generating.

Lack of Clinical Meaningfulness

Ultimately, the efficacy results demonstrate a treatment effect of low clinical magnitude. The observed treatment difference in the mean change from baseline in spherical equivalent at Month 36 was only 0.21 D. Over a three-year treatment period, a difference of one-fifth of a diopter is clinically negligible; it will not result in a meaningful reduction in a child's corrective lens prescription, nor will it provide any noticeable improvement in daily visual function. When viewed alongside the lack of structural protection (axial length), the declining treatment trajectory, and long-term external data (e.g., the ATLAS study[9]) showing no significant difference in outcomes 20 years post-treatment, the FDA concludes that the modest refractive difference observed in SYD-101-001 does not translate to a compelling or durable clinical benefit.

3.2 Safety Issues

The safety profile of 0.01% atropine appears generally favorable and is consistent with the known pharmacological effects of topical low-concentration anticholinergic agents. The FDA review team did not identify any severe or life-threatening safety signals that would preclude approval. However, there

[9] Li, Y. et al. (2024). Topical Atropine for Childhood Myopia Control: The Atropine Treatment Long-Term Assessment Study. JAMA Ophthalmology, 142(1), 15–23.

are two minor safety-related issues that warrant the committee's awareness, particularly as they intersect with the trial's tolerability and missing data:

- **Key Safety Issue #1**: Local Anticholinergic Effects: As expected with topical atropine, the most common adverse events are local ocular effects, including photophobia (light sensitivity), mydriasis (pupil dilation), and blurred near vision secondary to reduced accommodative amplitude (AA). While these are generally mild at the 0.01% concentration, they represent a chronic tolerability burden for pediatric patients.
- **Key Safety Issue #2**: Potential Underreporting of AE-Related Discontinuations: While the Applicant reported zero study discontinuations due to adverse events in the 0.01% atropine arm, FDA analysis revealed that several subjects who officially discontinued due to "withdrawal by subject/parent" had ongoing adverse events at the time of withdrawal. This suggests the true rate of AE-related intolerance may be slightly higher than formally reported.

3.2.1 Sources of Data for Safety

The primary source of safety data is the 36-month primary treatment period (Part 1) of the pivotal Phase 3 trial, SYD-101-001. The safety population includes all 847 randomized subjects who received at least one dose of the study drug (282 in the vehicle arm, 282 in the 0.01% atropine arm, and 283 in the 0.03% atropine arm). This database is considered adequate in size and duration to characterize the safety profile of a low-concentration topical ophthalmic product. Supportive safety data were also derived from the Applicant's submitted literature review of external randomized controlled trials (e.g., ATOM1, ATOM2, and LAMP), which evaluated the safety of atropine concentrations ranging from 0.01% to 1.0% in pediatric populations.

3.2.2 Safety Summary

Overall, 0.01% atropine was well-tolerated over the 36-month treatment period. The incidence of TEAEs was comparable between the 0.01% atropine arm and the vehicle arm. The vast majority of TEAEs were mild to moderate in severity and resolved without sequelae.

Because atropine is a nonselective muscarinic antagonist, systemic absorption can theoretically lead to systemic anticholinergic toxicity (e.g., dry mouth, tachycardia, flushing, hyperthermia, and altered mental status). However, at the highly dilute 0.01% concentration, systemic exposure is minimal. No cases of systemic anticholinergic toxicity were reported in the 0.01% atropine arm during the pivotal trial. The safety profile was dominated by local ocular events, primarily allergic conjunctivitis, photophobia, and instillation site pain or irritation. Serious adverse events were rare, distributed evenly across treatment arms, and were generally assessed by the investigators as unrelated to the study drug (e.g., appendicitis, limb fractures).

3.2.3 Safety Issues in Detail

Local Ocular Tolerability and Visual Function

The primary safety consideration for topical atropine is its effect on the ciliary muscle and iris sphincter, leading to cycloplegia (loss of accommodation) and mydriasis (pupil dilation). In historical studies using higher concentrations of atropine (e.g., 0.5% or 1.0%), these effects caused significant visual disability, requiring children to wear bifocals and photochromic lenses.

In Study SYD-101-001, the 0.01% concentration successfully minimized these visual side effects. Changes in AA and resting pupil diameter in the 0.01% arm were clinically negligible and significantly lower than those observed in the 0.03% atropine arm. Consequently, the incidence of photophobia and blurred near vision was low. However, because this therapy is intended for nightly use over several years during critical periods of visual and educational development, the committee should consider the chronic, cumulative tolerability burden of even mild photophobia or accommodative lag on a child's daily activities.

Study Discontinuations and Conflicting Reporting of Adverse Events

According to the Applicant's formal disposition data, the rate of discontinuation due to an adverse event was 0.4% (1 subject) in the vehicle arm, 0% in the 0.01% atropine arm, and 1.8% (5 subjects) in the 0.03% atropine arm.

However, the FDA review team identified a discrepancy when cross-referencing the reasons for dropout with the adverse event datasets. A substantial number of subjects discontinued the study under the broad categories of "Withdrawal by Subject" or "Withdrawal by Parent/Guardian" (12.0% in vehicle, 14.1% in 0.01% atropine, and 11.6% in 0.03% atropine). Upon closer inspection, 7 subjects in the vehicle arm, 7 subjects in the 0.01% atropine arm, and 15 subjects in the 0.03% atropine arm had ongoing, unresolved adverse events at the exact time they withdrew consent. While this does not raise severe safety alarm—as the events were generally mild ocular irritations—it indicates that the true rate of drug intolerance is likely higher than 0%.

4 Appendix

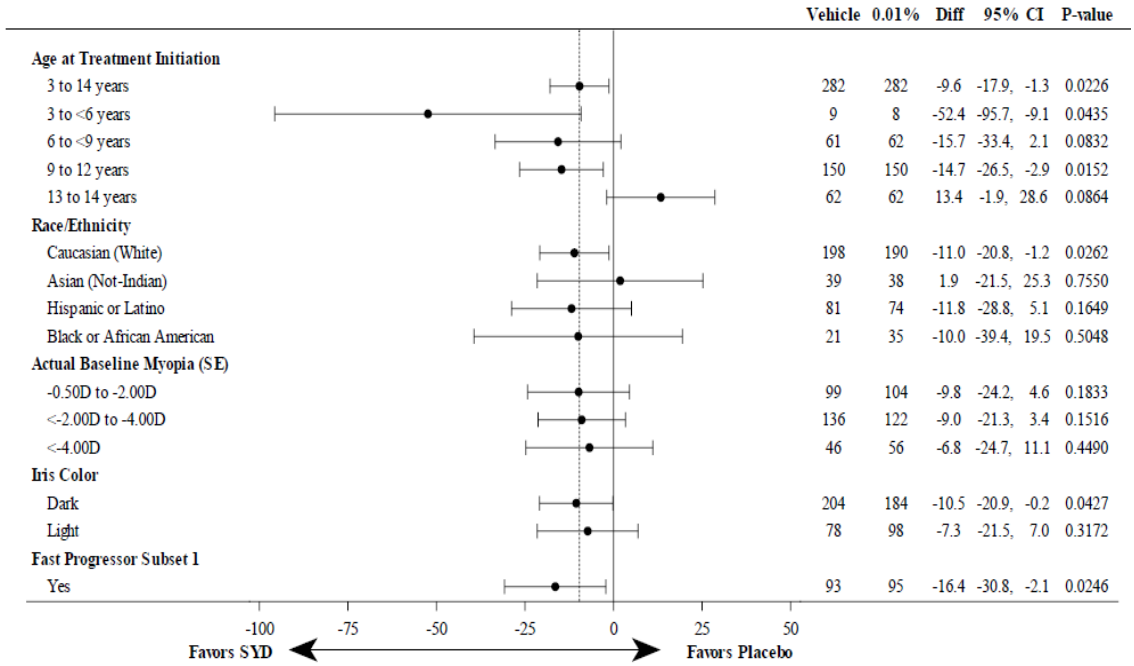
4.1 Appendix A: Selected Efficacy Outcomes

Table 13. Subgroup: Clinical Meaningfulness Threshold (Per 2015 Pre-IND)

Population	Vehicle (D/yr)	0.01% Atropine (D/yr)	Percent Reduction	Meets 50% Threshold?
Full analysis set	−0.38	−0.30	~21%	No
Ages 3 to <12 years	~−0.45	~−0.33	~27%	No
Fast progressors (≥0.50 D/yr)	~−0.53	~−0.39	~26%	No

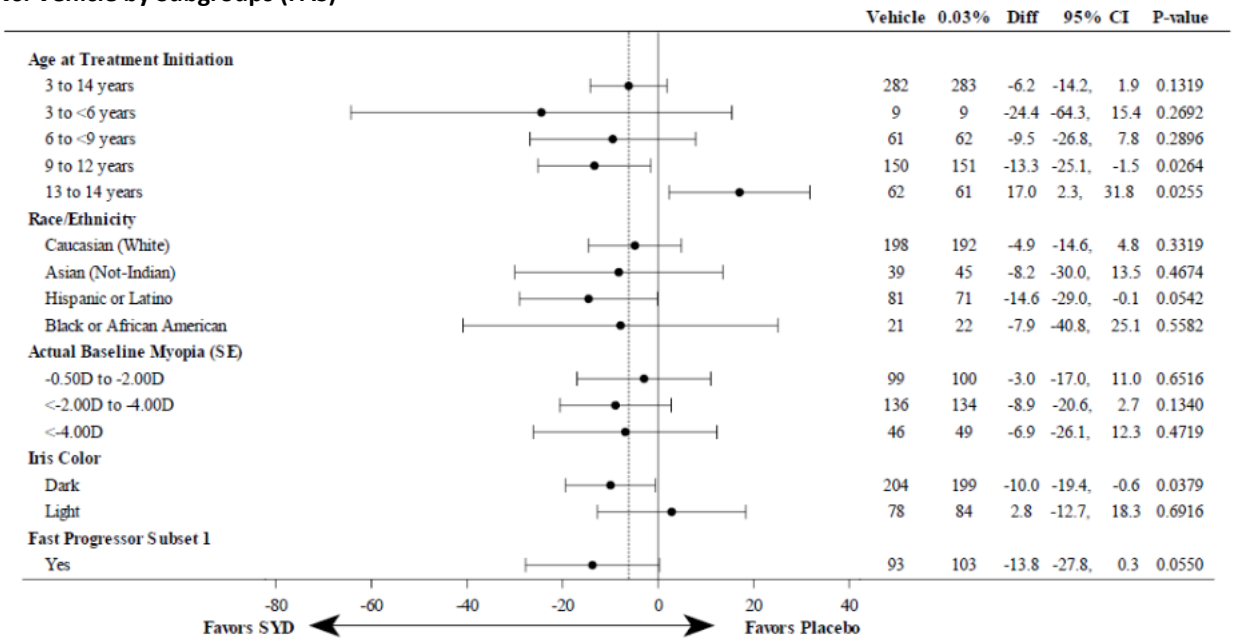
Source: Reviewer analysis
Abbreviations: D, diopters; IND, investigational new drug

Figure 4. Forest Plot of the Proportion of Subjects With Confirmed Progression at Month 36 for 0.01% Atropine vs. Vehicle by Subgroups (FAS)



Abbreviations: AE = Adverse Event; CI = Confidence Interval; D = Diopter; LS = Least Square; MAR = Missing At Random; SE = Spherical Equivalent.
Note: The difference in percentages and 95% confidence interval for the difference are displayed (solid horizontal line). Solid vertical line at zero represents no difference in treatment percentages. Vertical dashed reference line is the percentage with confirmed progression at Month 36 for the SYD treatment group. Confirmed myopia progression is defined as a progression worse than -0.75 D (averaged over both eyes) at or before 36 months. Intermittent missing observations was multiply imputed assuming MAR. Observations after use of escape/prohibited medications or treatments were multiply imputed as having
Source: SYD-101-001 36-Month CSR, Figure 3

Figure 5. Forest Plot of the Proportion of Subjects With Confirmed Progression at Month 36 for 0.03% Atropine vs. Vehicle by Subgroups (FAS)



Abbreviations: AE = Adverse Event; CI = Confidence Interval; D = Diopter; LS = Least Square; MAR = Missing At Random; SE = Spherical Equivalent.
Note: The difference in percentages and 95% confidence interval for the difference are displayed (solid horizontal line). Solid vertical line at zero represents no difference in treatment percentages. Vertical dashed reference line is the percentage with confirmed progression at Month 36 for the SYD treatment group. Confirmed myopia progression is defined as a progression worse than -0.75 D (averaged over both eyes) at or before 36 months. Intermittent missing observations was multiply imputed assuming MAR. Observations after use of escape/prohibited medications or treatments were multiply imputed as having

Source: SYD-101-001 36-Month CSR, Figure 4

4.2 Appendix B: Literature Summary

4.2.1 Overview

This appendix provides an overview of selected published clinical trials assessing low-dose atropine for myopia management. While these studies offer valuable class-level context, their ability to independently substantiate effectiveness is constrained by several critical limitations:

- **Limited Generalizability**: The bulk of the published data originates from East Asian cohorts. In contrast, the limited data available from U.S. and Western populations generally fail to corroborate these efficacy findings, raising questions about the applicability of the results to a broader demographic.
- **Inadequate Follow-Up Duration**: Most external trials evaluate outcomes over a truncated 12- to 24-month period. This time frame is insufficient to assess long-term durability and fails to capture the concerning Year 3 loss of efficacy identified in the Applicant's pivotal trial.
- **Inconsistent Dose-Response Profile**: Unlike the Applicant's pivotal data—which lacked a discernible dose-response gradient—the broader literature consistently demonstrates a clear dose-dependent treatment effect.
- **Unresolved Rebound Risks**: The external studies present mixed and contradictory findings regarding the risk of accelerated myopia progression (rebound) following the cessation of therapy.

4.2.2 Publications: Asian Populations

LAMP Study; Yam et al., 2019

The Low-Concentration Atropine for Myopia Progression (LAMP) study[10] was a single-center, randomized, double-masked, placebo-controlled trial conducted in China to evaluate the efficacy and safety of 0.05%, 0.025%, and 0.01% atropine eye drops. The study enrolled 438 children aged 4 to 12 years, randomized in a 1:1:1:1 ratio to one of the three active treatment arms or placebo, administered once nightly in both eyes. Randomization was stratified by sex and age group. The primary outcome was myopia progression, defined as the change in spherical equivalent (SE) over one year. Secondary outcomes included changes in axial length (AL) and various safety parameters (e.g., AA, pupil size, and visual acuity). Data were analyzed using an intention-to-treat approach with a generalized estimating equation to adjust for the correlation between eyes.

At Year 1, all three atropine concentrations demonstrated a dose-dependent reduction in SE progression compared to placebo. The mean difference favoring atropine versus placebo was +0.54 D for 0.05% and +0.35 D for 0.025% (both p<0.001). While the 0.01% dose also showed a statistically significant reduction in SE progression compared to placebo (+0.22 D, p<0.001), it failed to demonstrate a statistically significant difference in AL change (p=0.18). The authors reported that all concentrations were well tolerated with no treatment-related adverse events. The Year 1 efficacy results are summarized below.

Table 14. Efficacy Results From the LAMP Study: Year 1

Efficacy Parameter	0.05% Atropine N=109	0.025% Atropine N=108	0.01% Atropine N=110	Placebo N=111
Mean SE change (D) ± SD	−0.27±0.61	−0.46±0.45	−0.59±0.61	−0.81±0.53
Mean AL change (mm) ± SD	0.20±0.25	0.29±0.20	0.36±0.29	0.41±0.22
Progression <0.5 D (%)	69.6%	51.6%	43.8%	24.2%
Progression ≥1.0 D (%)	15.2%	12.6%	27.8%	37.1%

Source: Adapted from Yam et al., 2019

Abbreviations: AL, axial length; D, diopters; LAMP, Low-Concentration Atropine for Myopia Progression; N, number of subjects; SD, standard deviation; SE, spherical equivalent

LAMP Phase 2; Yam et al., 2020

Phase 2 of the LAMP study[11] evaluated the two-year efficacy and safety of 0.05%, 0.025%, and 0.01% atropine eye drops. Subjects originally randomized to placebo in Phase 1 were switched to 0.05% atropine for Phase 2 (the "switchover" group).

At the end of Year 2, the 0.05% dose remained the most effective concentration, demonstrating a cumulative mean spherical equivalent (SE) change of −0.55 D, compared to −0.85 D for the 0.025% group and −1.12 D for the 0.01% group. The differences between the groups were statistically significant. The authors noted that the efficacy of 0.05% atropine in slowing SE progression over two

[10] Yam, J. C. et al. (2019). Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control. Ophthalmology, 126(1), 113–124.

[11] Yam JC et al. (2020). LAMP Study Phase 2. Ophthalmology. 127(7):910-919.

years was double that observed with 0.01% atropine. A secondary age-effect analysis[12] demonstrated that younger children (ages 4–12) required the higher 0.05% concentration to achieve similar treatment efficacy as older children.

Regarding safety, all concentrations were well tolerated with no apparent adverse effects on vision-related quality of life. While more subjects reported photophobia at the end of the second year if not wearing photochromic glasses, the occurrence of allergic conjunctivitis was similar across groups. Seventeen subjects experienced severe adverse events requiring hospitalization over the two-year period, but none were deemed related to the topical atropine therapy. The Year 2 efficacy results are summarized below.

Table 15. Cumulative Efficacy Results From the LAMP Study: Year 2

Efficacy Parameter	0.05% Atropine	0.025% Atropine	0.01% Atropine	Switchover Group (Placebo to 0.05%)
Cumulative mean SE change (D) ± SD	−0.55±0.86	−0.85±0.73	−1.12±0.85	Not reported
Cumulative mean AL change (mm) ± SD	0.39±0.35	0.50±0.33	0.59±0.38	Not reported
Progression <0.5 D (%)	52.7%	32.0%	22.0%	27.5%
Progression ≥2.0 D (%)	9.1%	7.0%	19.2%	12.5%

Source: Adapted from Yam et al., 2020
Abbreviations: AL, axial length; D, diopters; LAMP, Low-Concentration Atropine for Myopia Progression; SD, standard deviation; SE, spherical equivalent

AMIXT Trial

The AMIXT Trial[13] was a single-center, randomized, double-masked, placebo-controlled clinical trial conducted in China to evaluate the efficacy and safety of 0.01% atropine in children with both myopia and basic-type intermittent exotropia. The study enrolled 300 children aged 6 to 12 years with baseline myopia ranging from −0.50 to −6.00 D. Subjects were randomized in a 2:1 ratio to receive either 0.01% atropine or placebo eye drops, administered once nightly in both eyes for 12 months. The primary outcome was the change in cycloplegic spherical equivalent (SE) from baseline at 1 year. Secondary outcomes included changes in AL, AA, exotropia conditions, and binocular vision. Data were analyzed using an intention-to-treat approach with generalized estimating equations to account for intereye correlation.

At Year 1, the 0.01% atropine group demonstrated a statistically significant reduction in SE progression compared to placebo (treatment difference: +0.24 D, $p<0.001$). The atropine group also showed significantly less AL elongation compared to placebo (treatment difference: −0.11 mm, $p<0.001$).

However, the atropine group experienced a notable decrease in AA compared to placebo (treatment difference: −3.18 D, $p<0.001$). The authors reported that 0.01% atropine did not negatively interfere with exotropia conditions or binocular vision, and the incidence of photophobia and blurred near vision

[12] Li FF, Yam JC et al. Age Effect on LAMP Study Responses (Secondary analysis).
[13] Wang, Z et al. (2024). 0.01% Atropine Eye Drops in Children With Myopia and Intermittent Exotropia: The AMIXT Randomized Clinical Trial. JAMA Ophthalmology, 142(8), 722–730.

was similar between the treatment and placebo groups. Year 1 efficacy and safety results are summarized below.

Table 16. Efficacy and Safety Results From the AMIXT Trial

Parameter	0.01% Atropine N=200	Placebo N=100	Treatment Difference (95% CI)
Mean SE change (D)	−0.51	−0.75	+0.24 (0.11, 0.37)
Mean AL change (mm)	0.31	0.42	−0.11 (−0.17, −0.06)
Mean AA change (D)	−3.06	0.12	−3.18 (−3.92, −2.44)
Photophobia (%)	6.0%	8.0%	−2.0% (−9.4%, 3.7%)
Blurred near vision (%)	6.0%	7.0%	−1.0% (−8.2%, 4.5%)

Source: Adapted from Wang et al., 2023

Abbreviations: AA, accommodative amplitude; AL, axial length; CI, confidence interval; SE, spherical equivalent

Chai et al: ATOM 2

The Atropine for the Treatment of Myopia 2 (ATOM 2) study[14] was a single-center, double-masked, randomized clinical trial designed to compare the efficacy and safety of three lower doses of atropine (0.5%, 0.1%, and 0.01%). Conducted in Singapore, the study enrolled 400 children aged 6 to 12 years with baseline myopia of at least −2.0 D. Subjects were randomized in a 2:2:1 ratio to receive 0.5%, 0.1%, or 0.01% atropine, administered once nightly in both eyes for two years. Please note that this study did not have a concurrent control. Each arm was compared to a historical control. The primary objective was to evaluate myopia progression (spherical equivalent) and axial length elongation, alongside visual side effects such as cycloplegia and mydriasis. Data were analyzed using an intention-to-treat approach, with Huber-White robust standard errors used to account for intereye correlation.

At Year 2, all three concentrations demonstrated efficacy in reducing myopia progression. The mean myopia progression was −0.30 D, −0.38 D, and −0.49 D in the 0.5%, 0.1%, and 0.01% groups, respectively. While the 0.5% group showed statistically significantly less progression than the 0.01% group (p=0.02), the authors noted that the absolute clinical differences in myopia progression (0.19 D) and axial length change (0.14 mm) between the highest and lowest doses were small and clinically insignificant.

Crucially, the 0.01% concentration demonstrated a vastly superior safety profile. It had a negligible effect on accommodation and pupil size, no effect on near visual acuity, and zero reported cases of allergic conjunctivitis or dermatitis (compared to 16 cases in the higher-dose groups). The authors concluded that 0.01% atropine is a safe and effective regimen for slowing myopia progression with minimal impact on visual function. The Year 2 efficacy results are summarized below.

Table 17. Efficacy Results From the ATOM 2 Study

Efficacy Parameter	0.5% Atropine	0.1% Atropine	0.01% Atropine
Mean myopia progression (D) ± SD	−0.30±0.60	−0.38±0.60	−0.49±0.63
Mean axial length change (mm) ± SD	0.27±0.25	0.28±0.28	0.41±0.32

Source: Adapted from Chia, et al, 2012

Abbreviations: ATOM, Atropine for the Treatment of Myopia; D, diopters; SD, standard deviation

[14] Chia, A. et al (2012). Atropine for the treatment of childhood myopia: Safety and efficacy of 0.5%, 0.1%, and 0.01% atropine (Atropine for the Treatment of Myopia 2). Ophthalmology, 119(2), 347–354.

Remark: This study did not have concurrent control. The results were compared against historical control. Therefore, the results need to be interpreted with caution. Besides, the Authors stated that no multiplicity adjustment was used.

LAMP; Li et al.: Age Effect on Treatment Responses to Low-Concentration Atropine

This article[15] summarizes a secondary analysis of the LAMP study, which evaluated the efficacy of 0.05%, 0.025%, and 0.01% atropine versus placebo in children aged 4 to 12 years over a two-year period. While the primary LAMP study demonstrated a concentration-dependent reduction in spherical equivalent (SE) progression (67%, 43%, and 27% reductions for the 0.05%, 0.025%, and 0.01% doses, respectively, at Year 1), the authors noted wide variability in individual treatment responses, with some children progressing quickly despite treatment.

The primary objective of this secondary analysis was to identify factors associated with SE and AL changes over two years. The authors evaluated seven potential predictors: age at treatment, sex, baseline SE, baseline outdoor time, baseline near work time, parental myopia level, and treatment compliance. Data were analyzed using generalized estimating equations to adjust for intereye correlation, with a significance threshold set at $p<0.01$ to account for multiple comparisons.

The analysis revealed a clear age-dependent effect on treatment response. Among the factors evaluated, younger age was the only significant risk factor for a poor treatment response across all three atropine concentrations. While a concentration-dependent response (higher concentration yielding better efficacy) was maintained within each age cohort, the data demonstrated that younger children required the highest concentration (0.05%) to achieve similar treatment efficacy as older children receiving lower doses. Because all concentrations were well tolerated across the 4 to 12-year age range, the authors concluded that 0.05% atropine should be the preferred concentration administered to younger children to optimize myopia control.

Hieda et al. 2021: Efficacy and Safety of 0.01% Atropine for Prevention of Childhood Myopia in a 2-Year Randomized Placebo-Controlled Study

This article[16] summarizes results from a multicenter, randomized, double-masked, placebo-controlled, parallel-arm study that was conducted at 7 university hospitals in Japan from December 2014 through September 2019. The study enrolled 171 Japanese school children aged 6 to 12 years, with progressive myopia, spherical equivalence (SE) of −1.00 to −6.00 D, and astigmatism of ≤1.5 D.

Eligible subjects were randomized to receive either 0.01% atropine eye drops or atropine-matched placebo eye drops in 1:1 ratio. The study investigators, as well as the children and their legal guardians, were masked to the specific study drug assigned throughout the study period. In all subjects, 1 drop of a randomly allocated drug was instilled in each eye once per night for 24 months.

The primary efficacy endpoint was myopia progression, defined as the change in objective SE from baseline to after 24-months continuous administration of the study drug. The secondary efficacy endpoints were the changes in AL from baseline to after 24 months of atropine therapy, as well as the

[15] Li, F. F. et al. (2021). Age Effect on Treatment Responses to 0.05%, 0.025%, and 0.01% Atropine: Low-Concentration Atropine for Myopia Progression Study. Ophthalmology, 128(8), 1180–1187.
[16] Hieda O et al. (2021). J-ATOM 2-year RCT. Jpn J Ophthalmol. 65(3):315-325.

changes in objective SE and AL from baseline to each follow-up time-point. Safety endpoints were incidence of TEAEs and study drug-related TEAEs, abnormal findings on the ocular surface, cornea, retina and accessory visual structures, accommodative function, intraocular pressure measured by non-contact tonometers, and pupil diameter throughout the 24-month treatment period.

Per the authors, all data were analyzed based on the intention-to-treatment principle. The primary analysis was performed in the FAS, and robustness of the results was explored through sensitivity analysis in the per-protocol set. The repeated-measure endpoints were analyzed with linear mixed models that included intervention, dummy variables for time, intervention-by-time interactions as covariates, and the subjects as a random effect. The covariance structure was a completely general (i.e., unstructured) covariance matrix. The results were reported as the least squares means with 95% CI at each time-point.

Per the reported results, there was no major difference between arms in terms of baseline and disease characteristics. The authors reported that in this study, 0.01% atropine eye drops slowed down the progression of myopia at the end of 2 years (i.e., a reduction of 0.22 D for SE and −0.14 mm for AL compared with the placebo eye drops). They further state that, although the findings in this multicenter clinical trial verify that 0.01% atropine eye drops are effective for childhood myopia progression in relation to Japanese lifestyles and habits, they also illustrate that it takes as long as 2 years to receive the beneficial effects of atropine.

Based on the findings, the authors concluded that the findings in this present study show that 0.01% atropine eye drops can safely and effectively attenuate the progression of myopia in Japanese school age children, however, long-term administration is necessary for a beneficial outcome. Further study is needed to determine the optimal atropine concentration, and if 0.01% is adequate for populations with a small pupil size.

Remark: This study also established the efficacy and safety of 0.01% atropine in Japanese school children. The authors state that long term treatment might be needed to maintain efficacy.

4.2.3 Publications: Non-Asian/Western Populations

MTS1 (Repka et al., 2023)

This article[17] summarizes the results of the MTS1 study, a randomized, double-masked, placebo-controlled clinical trial conducted across 12 community- and institution-based practices in the United States from June 2018 to September 2022. The study enrolled 187 children aged 5 to 12 years with low to moderate bilateral myopia (−1.00 D to −6.00 D spherical equivalent refractive error [SER]).

Eligible subjects were randomized in a 2:1 ratio to receive either 0.01% atropine (n=125) or placebo (n=62) eye drops, administered once nightly for 24 months, followed by a 6-month observation period off-treatment. Baseline and demographic characteristics were well-balanced between the treatment arms. Retention rates were high, with 95% of the atropine group and 94% of the placebo group completing the 24-month primary outcome visit.

[17] Repka MX et al. (2023). MTS1. JAMA Ophthalmol. 141(8):756-765.

Data were analyzed using an intention-to-treat approach. The primary analysis compared the mean change in SER from baseline to 24 months using a longitudinal discrete-time mixed model, adjusting for baseline SER, age, iris color, and race (East Asian versus non-East Asian).

At the 24-month primary outcome visit, there was no statistically significant difference in myopia progression between the two groups. The adjusted mean change in SER from baseline was −0.82 D in the atropine group and −0.80 D in the placebo group (adjusted difference: −0.02 D; p=0.83). Similarly, there was no significant difference in AL elongation at 24 months (adjusted difference: −0.002 mm). These null findings persisted at the 30-month visit (after 6 months off-treatment), with an adjusted SER difference of −0.04 D and an adjusted AL difference of +0.009 mm.

Based on these results, the authors concluded that nightly administration of 0.01% atropine did not slow myopia progression or axial elongation compared to placebo, and that these findings do not support the use of 0.01% atropine for myopia control in U.S. children. The efficacy results are summarized below.

Table 18. Efficacy Results From the MTS1 Study

Efficacy Parameter	0.01% Atropine N=125	Placebo N=62	Adjusted Treatment Difference (95% CI)
Mean SER change at 24 Months (D)	−0.82	−0.80	−0.02 (−0.19, +0.15) *
Mean AL change at 24 Months (mm)	0.44	0.45	−0.002 (−0.106, +0.102)
Mean SER change at 30 Months (D)	NR	NR	−0.04 (−0.25, +0.17)
Mean AL change at 30 Months (mm)	NR	NR	+0.009 (−0.115, +0.134)

Source: Adapted from Repka et al, 2023

* p =0.83

Abbreviations: AL, axial length; CI, confidence interval; D, diopters; N, number of subjects; NR, not reported; SER, spherical equivalent refraction

Remark: In this exclusively U.S.-based study, the authors concluded that there is no statistically significant treatment difference between 0.01% atropine and placebo, failing to demonstrate any clinically meaningful efficacy for the proposed concentration in a U.S. demographic.

MOSAIC

The Myopia Outcome Study of Atropine in Children (MOSAIC)[18] was an investigator-led, double-masked, randomized controlled trial designed to evaluate the efficacy and safety of 0.01% atropine in a predominantly White European population. The study included two Phases: a 24-month randomized treatment period (Phase 1) and a washout period of 12 months (Phase 2). During Phase 1, the study enrolled 250 children aged 6 to 16 years with myopia. Subjects were randomized in a 2:1 ratio to receive either 0.01% atropine or placebo eye drops, administered once nightly in both eyes for two years. The primary and secondary efficacy outcomes were the change in spherical equivalent (SE) and AL at 24 months, respectively.

Data were analyzed using an intention-to-treat approach. The authors noted that the preplanned mixed-measures ANOVA was abandoned in favor of linear mixed models due to unequal visit spacing caused by the COVID-19 pandemic, violations of variance assumptions, and the need to better handle missing data. Missing data were treated as MAR, and multiple imputation was not performed because dropout rates and progression profiles were similar between groups. Of the 250 enrolled subjects, 204 (81.6%) completed the 24-month visit.

[18] Loughman J et al. (2023). MOSAIC. Acta Ophthalmol. 102:e245-e256.

At 24 months, the change in SE was not statistically significantly different between the 0.01% atropine and placebo groups (treatment difference: +0.10 D, p=0.07). However, AL elongation was significantly lower in the atropine group compared to placebo (treatment difference: −0.07 mm, p=0.007). Subgroup analyses suggested that significant treatment effects on both SE and AL were observed in White children, but not in non-White children. Additionally, the authors reported a larger treatment effect among subjects who were least affected by COVID-19 restrictions (Table 19).

Regarding safety, 0.01% atropine was well tolerated. Adverse event rates were similar between the atropine (16.9%) and placebo (13.2%) groups (p=0.38). Seven adverse events were deemed possibly or probably related to the study medication (e.g., eye discomfort, temporary blurred near vision, temporary pupil dilation, and eyelid rash). One serious adverse event (hospitalization for abdominal surgery) occurred but was unrelated to the study drug. The authors concluded that 0.01% atropine was safe, well-tolerated, and effective in slowing axial elongation in this European population. The efficacy results are summarized below.

Table 19. Efficacy Results From the MOSAIC Study

Efficacy Parameter	Treatment Difference (0.01% Atropine vs. Placebo)	95% CI
Month 24		
Overall mean SE change (D)	+0.10	(−0.04, +0.24)
Overall mean AL change (mm)	−0.07	(−0.13, −0.002)
Month 36*		
Overall mean SE change (D)	+0.04	(−0.13, +0.20)
Overall mean AL change (mm)	−0.05	(−0.12, +0.02)
Subgroup		
SE change in White cohort (D)	+0.14	
AL change in White cohort (mm)	−0.11	
SE change in Non-White cohort (D)	+0.05	
AL change in Non-White cohort (mm)	+0.008	

Source: Adapted from Loughman et al, 2023

*The month 36 results are following a one-year washout period and are presented in a subsequent publication.

Abbreviations: AL, axial length; D, diopters; MOSAIC, Myopia Outcome Study of Atropine in Children; N, number of subjects; SE, spherical equivalent

Remark: The treatment effect observed in this study is very low and failed to achieve statistical significance for the primary endpoint (SE change). Furthermore, the study design and statistical analysis methods were altered after the trial commenced. While the authors attribute the modest effects to COVID-19 disruptions, the overall findings do not provide robust confirmatory evidence of efficacy.

WA-ATOM: Lee et al. 2022b: Low-Concentration Atropine Eyedrops for Myopia Control in a Multi-Racial Cohort of Australian Children: A Randomized Clinical Trial (WA-ATOM)

This article[19] summarizes the results of the WA-ATOM (Western Australia Atropine for the Treatment of Myopia) study, a single-center, randomized, double-masked, placebo-controlled clinical trial conducted at the Lions Eye Institute, University of Western Australia. Baseline visits were completed between June 2017 and December 2019. The study enrolled 153 children aged 6 to 16 years with documented myopia progression of at least 0.50 D/year and spherical equivalent of −1.50 D or worse.

[19] Lee SS et al. (2022). WA-ATOM 24-month results. Clin Exp Ophthalmol. 50(9):1001-1012.

Eligible subjects were randomized in a 2:1 ratio to receive either 0.01% atropine (n=104) or placebo (n=49) eyedrops, administered once nightly for 24 months. The cohort was notably multiracial, comprising approximately 49% European, 22% South Asian, 18% East Asian, and 12% other/mixed ancestry. While most baseline characteristics were balanced between arms, the placebo group was on average one year older than the atropine group, a difference that was statistically significant and was accounted for by including baseline age as a covariate in all models. Retention was higher in the atropine group, with 90.4% completing the 24-month visit compared to 75.5% in the placebo group, a difference that became statistically significant at 18 and 24 months.

Data were analyzed using an intention-to-treat approach. The primary analysis evaluated mean change in spherical equivalent (SphE) and AL from baseline using linear mixed models, adjusting for baseline age and baseline ocular measures.

At earlier time points, the atropine group showed statistically significantly slower myopia progression than the placebo group. At 12 months, the mean SphE change from baseline was −0.31 D in the atropine group versus −0.53 D in the placebo group (difference: +0.23 D; p=0.004), and AL elongation was 0.16 mm versus 0.25 mm, respectively (difference: −0.08 mm; p=0.006).

At 18 months, the treatment difference in SphE remained statistically significant (+0.25 D; p=0.002). However, at the 24-month primary endpoint, the group difference in SphE change (−0.64 D atropine versus −0.78 D placebo; difference: +0.14 D) and AL elongation (0.34 mm versus 0.38 mm; difference: −0.05 mm) were no longer statistically significant (p=0.09 and p=0.10, respectively).

The authors attributed the loss of significance at 24 months primarily to a slowing of progression in the placebo group during the final 6 months of the treatment period, likely driven by differential dropout: subjects who withdrew tended to be faster progressors, particularly in the placebo arm, introducing attrition bias that may have inflated the apparent placebo response at 24 months.

Subgroup analyses revealed a significant treatment-by-ancestry interaction. Participants of European or other/mixed ancestry showed a greater response to 0.01% atropine, with statistically significant effects observed up to 18 months, while no significant treatment effect was observed in children of East Asian or South Asian ancestry at any time point.

As expected with atropine use, the atropine group showed significantly reduced AA (by 2.0-2.7 D from baseline across visits) and altered pupillary light responses compared to the placebo group. However, these pharmacological effects were not associated with clinically meaningful complaints of photophobia or blurred near vision, and no significant between-group differences in best-corrected visual acuity or stereoacuity were observed. The overall adverse event rate was low and not significantly different between groups (8.7% atropine versus 2.1% placebo; p=0.17), and no severe adverse events were reported.

Based on these results, the authors concluded that 0.01% atropine eyedrops had a **modest myopia** control effect in multiracial Australian children, with statistically significant benefits observed at earlier time points but not at the 24-month primary endpoint. The authors noted that the apparent decrease in efficacy at 24 months was likely driven by attrition bias in the placebo group rather than a true loss of drug effect. They further concluded that 0.01% atropine did not appear effective for myopia control in children of East or South Asian ancestry living in Australia and called for larger multiracial trials and investigation of higher atropine concentrations in non-Asian populations.

Table 20. Summary of Primary Efficacy Results: WA-TOM

Visit	Placebo N=49	0.01% Atropine N=104	Diff (95% CI)
6 months	−0.36 (−0.49, −0.24)	−0.13 (−0.21, −0.04)	+0.24 (+0.08, +0.40)
12 months	−0.53 (−0.66, −0.40)	−0.31 (−0.39, −0.22)	+0.23 (+0.07, +0.39)
18 months	−0.74 (−0.87, −0.61)	−0.49 (−0.58, −0.41)	+0.25 (+0.10, +0.42)
24 months	−0.78 (−0.91, −0.65)	−0.64 (−0.73, −0.56)	+0.14 (−0.03, +0.29)
Axial length (mm)			
6 months	+0.16 (+0.11, +0.20)	+0.07 (+0.04, +0.11)	−0.08 (−0.14, −0.02)
12 months	+0.25 (+0.20, +0.30)	+0.16 (+0.13, +0.20)	−0.08 (−0.14, −0.02)
18 months	+0.35 (+0.30, +0.39)	+0.25 (+0.22, +0.28)	−0.10 (−0.16, −0.04)
24 months	+0.38 (+0.33, +0.43)	+0.34 (+0.30, +0.37)	−0.05 (−0.11, +0.01)

Source: Adapted from Lee at all, 2022

Abbreviations: CI, confidence interval; N, number of subjects; WA-ATOM, Western Australia Atropine for the Treatment of Myopia

Remark: This study was conducted in Australia where nearly 40% of the study subjects were of Asian origin. Overall, the 0.01% atropine only showed a modest effect, and the effect was not statistically significant at Month 24. Besides, the study results showed that for children of Asian descent living in Australia, the magnitude of difference in SE between the placebo and atropine groups was only about half that found in the other studies. Note, this same phenomenon was observed in the pivotal study reviewed under this submission. A subgroup analysis shows that, the treatment effect for the children of Asian descent was small and appears to be favorable to the placebo arm. Note however, the sample size for the Asian population in this study was relatively small.

CHAMP Trial (Zadnik et al., 2023)

The CHAMP Trial[20] was a phase 3, multicenter, randomized, double-masked, placebo-controlled clinical trial conducted across 27 sites in North America and 5 countries in Europe to evaluate the efficacy and safety of low-dose atropine in treating myopia progression.

The study enrolled 576 children aged 3 to 16 years with baseline myopia (spherical equivalent refractive error [SER]) ranging from −0.50 D to −6.00 D. Subjects were randomized in a 2:2:3 ratio to receive once-daily drops of placebo, 0.01% atropine, or 0.02% atropine in each eye for 36 months.

The primary and secondary efficacy endpoints were evaluated in a modified intention-to-treat (mITT) population of 489 children who were aged 6 to 10 years at baseline. The primary efficacy endpoint was a responder analysis (proportion of eyes with <0.50 D myopia progression at 36 months). Secondary endpoints included the mean change from baseline in SER and AL. Safety was evaluated in all 573 participants who received at least one dose of the trial medication.

At Month 36, the 0.02% atropine group failed to demonstrate a statistically significant difference from placebo in the primary responder analysis or in the mean progression of SER, though it did show a significant reduction in AL elongation. Conversely, the 0.01% atropine group demonstrated statistically significant improvements across all three main endpoints compared to placebo. Atropine 0.01% increased the proportion of responders (28.5% versus 17.5%), reduced mean SER progression (treatment difference: 0.24 D), and reduced mean AL elongation (treatment difference: −0.13 mm).

Both atropine concentrations were well tolerated with no serious ocular adverse events. The incidence of common ocular adverse events, such as photophobia and blurred vision, was low and generally

[20] Zadnik K et al. (2023). CHAMP Study. JAMA Ophthalmol. 141(10):990-999.

comparable to placebo. Month 36 efficacy outcomes for both the 0.01% and 0.02% doses compared to placebo are summarized below.

Table 21. Month 36 Efficacy Results From the CHAMP Trial (mITT Set)

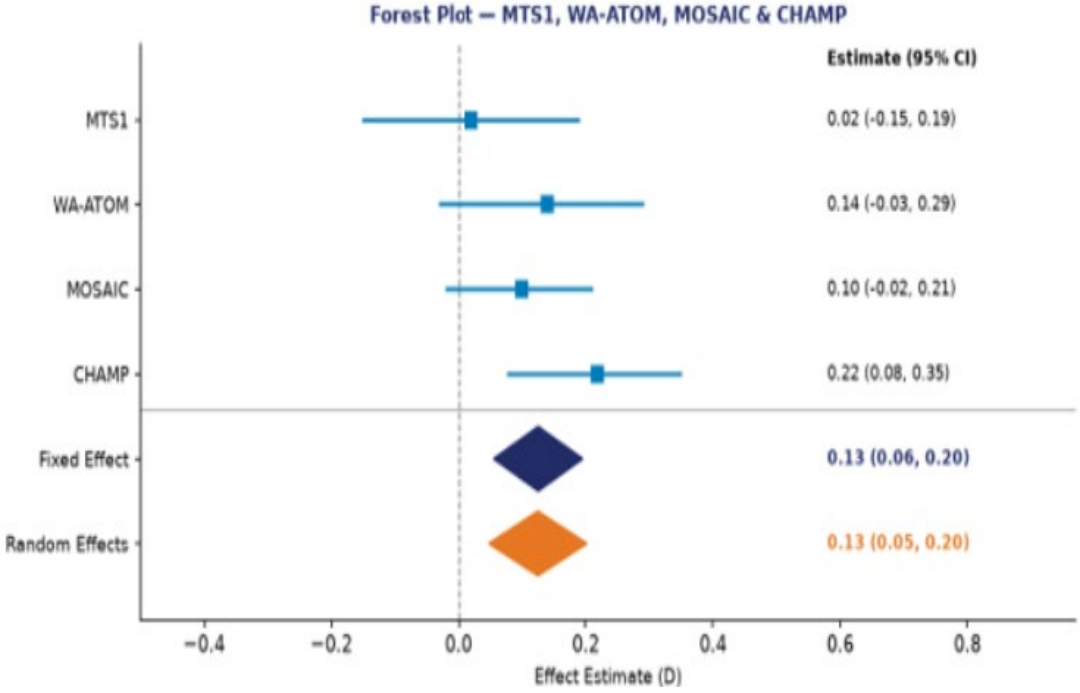
Parameter	0.01% Atropine N=133	0.02% Atropine N=212	Placebo N=144	0.01% vs. Placebo Diff (95% CI)	0.02% vs. Placebo Diff (95% CI)
Responders (<0.50 D progression) (%)	28.5%	22.1%	17.5%	OR: 4.54 (1.15, 17.96)	OR: 1.77 (0.50, 6.26)
Mean SE change (D)	−1.04	−1.18	−1.28	0.24 (0.11, 0.37)	0.10 (−0.02, 0.22)
Mean AL change (mm)	0.68	0.73	0.81	−0.13 (−0.19, −0.07)	−0.08 (−0.13, −0.02)

Source: Adapted from Zadnik at al, 2023
Note: Evaluated in the mITT population (children aged 6–10 years at baseline). Number of eyes: Placebo (n=252); 0.01% Atropine (n=200).
Abbreviation: AL, axial length; CI, confidence interval; D, diopters; N, number of subjects; OR, odds ratio; SE, spherical equivalent

Meta-Analysis

An FDA-conducted random-effects meta-analysis[21] of these studies yielded an overall mean SE treatment difference of only +0.13 D favoring 0.01% atropine at Month 24 (Figure 6). The inclusion of the SYD-101-001 shifts the pooled effect slightly (0.15 D) (Figure 7).

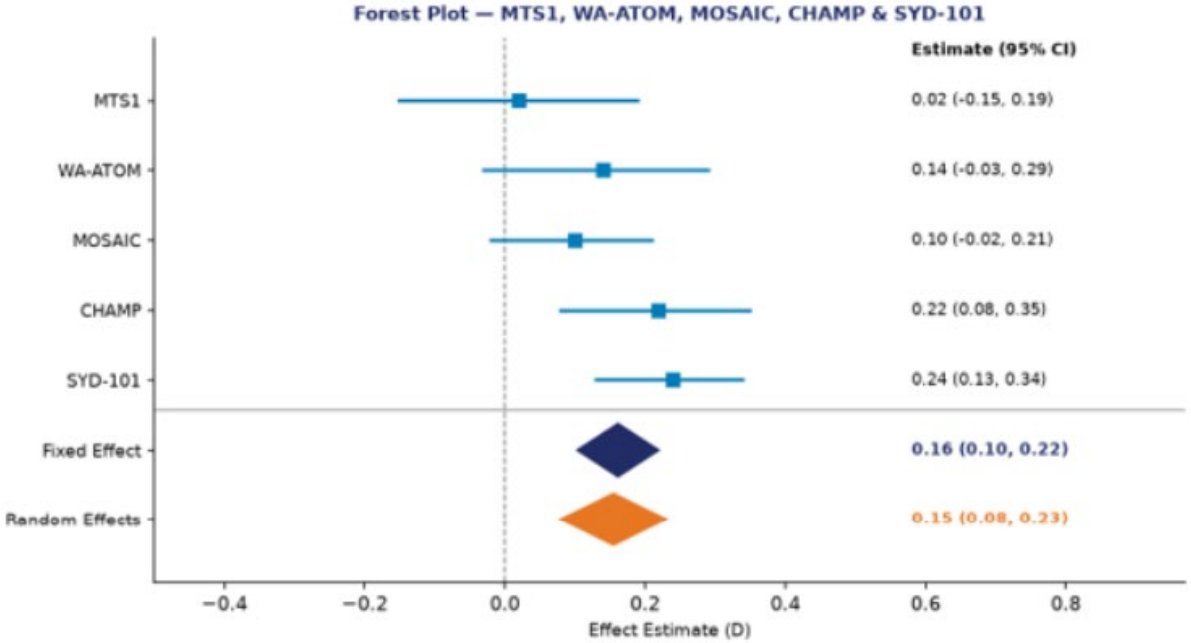
Figure 6. Meta-Analysis: U.S. and Western Studies (Month 24)



Source: Reviewer analysis
Abbreviations: CI, confidence interval; D, diopters; MOSAIC, Myopia Outcome Study of Atropine in Children; WA-ATOM, Western Australia Atropine for the Treatment of Myopia

[21] DerSimonian R, Laird N. (1986). Meta-analysis in clinical trials. Control Clin Trials. 7(3):177-188.

Figure 7. Meta-Analysis: U.S. and Western Studies Including SYD-101-001 (Month 24)



Source: Reviewer analysis
Abbreviations: CI, confidence interval; D, diopters; MOSAIC, Myopia Outcome Study of Atropine in Children; WA-ATOM, Western Australia Atropine for the Treatment of Myopia