NDA 219694
Yovo (atropine sulfate ophthalmic solution) 0.01%

FDA Presentation

Dermatologic and Ophthalmic Drugs Advisory Committee

October 30, 2026

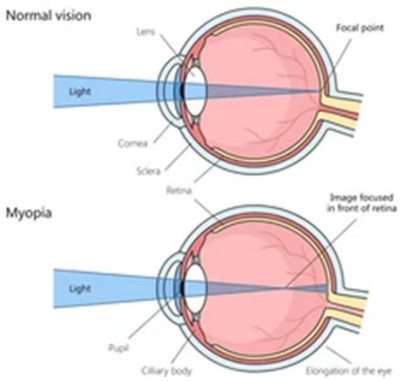
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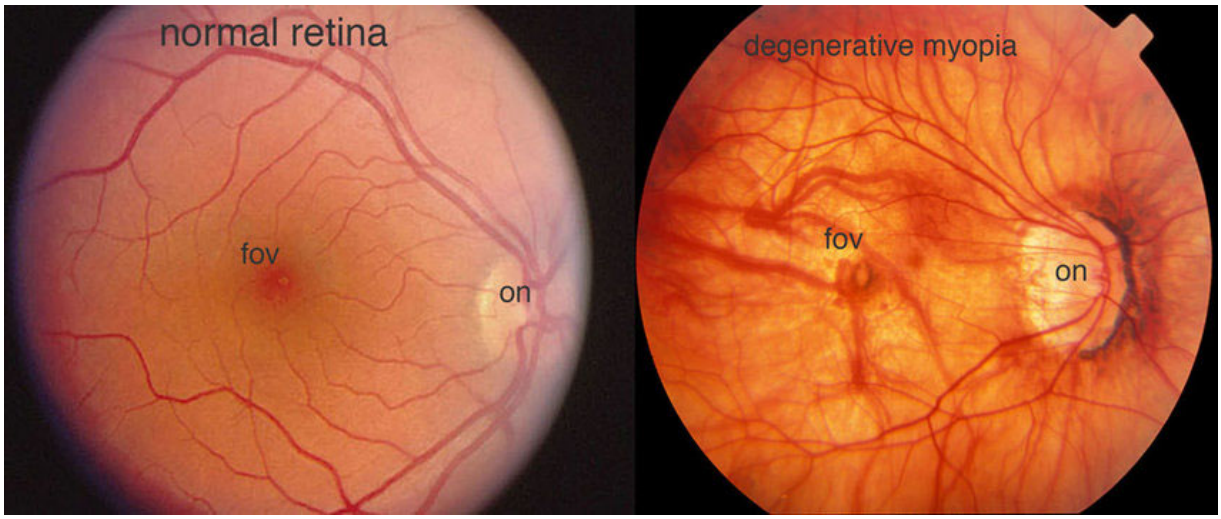
Outline

- Disease Background
- Mechanism of Action
- SYD-101-001 Design and Results
- Key Clinical Issues
- Statistical Considerations
- Substantial Evidence of Effectiveness
- Approved Treatments
- Considerations for Committee and Discussion Topics

Disease Background: Myopia

- Myopia or nearsightedness is an ocular condition in which the optical power of the eye is too strong for the corresponding axial length (AL), causing light rays entering the eye to focus anterior to the retina.
- Multifactorial: genetic, ocular, and behavioral
- Pathologic or high myopia (spherical equivalent [SE] ≤ -6 diopters or axial length > 26.5 mm) is seen in 5% of myopes, presents in early childhood, and has an increased risk of complications.

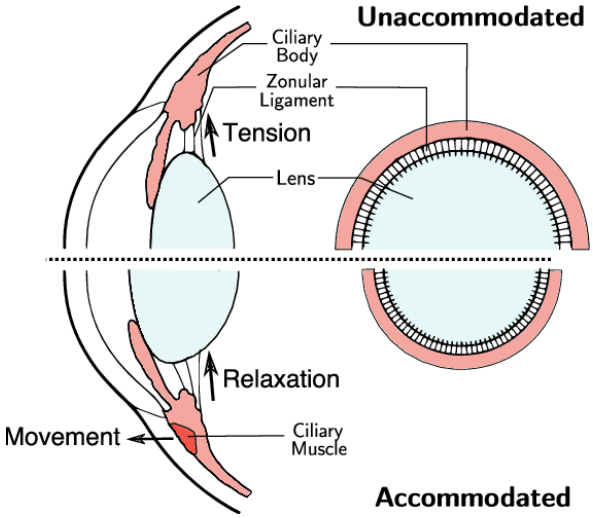




Credit: James Gilman, Moran Eye Center ophthalmic photography department.

Mechanism of Action: Atropine

- Atropine is a nonselective muscarinic antagonist that blocks the contraction of the pupillary sphincter muscle of the iris, resulting in mydriasis (dilation), and paralyzes the ciliary muscle which induces cycloplegia and inhibits accommodation (focusing with the lens).
- It is not fully understood how atropine impacts myopia progression.



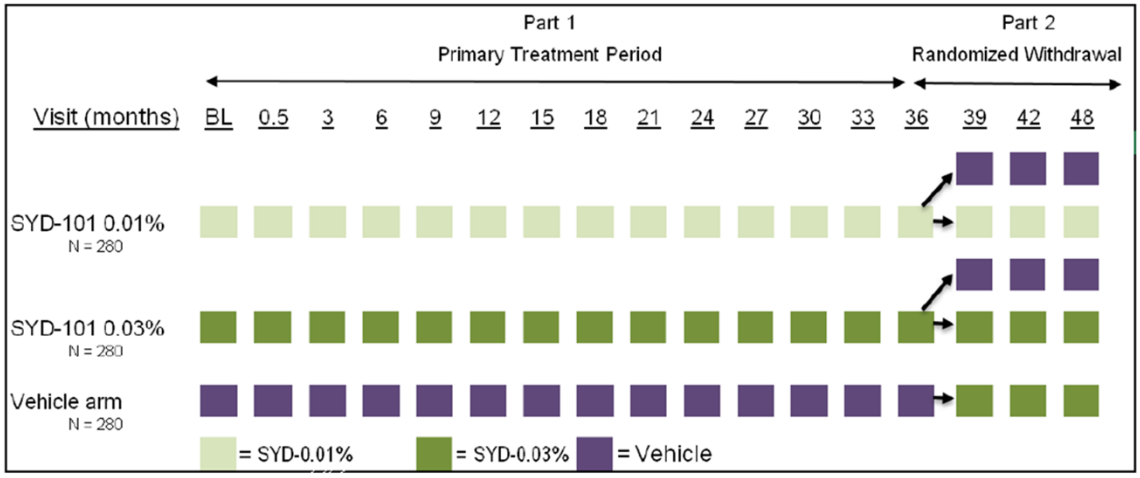
SYD-101-001 Design

- The Sponsor submitted a single adequate and well-controlled trial (SYD-101-001) and confirmatory literature evidence.
- This was a 48-month study conducted across 47 sites (41 in the U.S., 3 each in Austria and Slovakia).
- The objective of the study was to evaluate the efficacy, safety, and tolerability of two concentrations of Atropine Sulfate Ophthalmic Solution (0.01% and 0.03%) for slowing the progression of myopia in children over a 3-year treatment period.

SYD-101-001 Design

- The study had two parts: **Part 1** (Primary Treatment: 36 Months) and **Part 2** (Randomized Withdrawal: 12 Months).
  - **Part 1**: Eligible subjects were randomized in a 1:1:1 ratio to Vehicle (N=283), Atropine 0.01% (N=284) or Atropine 0.03% (N=285), and treated for 36 Months.
  - **Part 2:** Randomized withdrawal design**:**
    - Atropine 0.01%: re-randomized in a 1:1 ratio to receive Atropine 0.01% or Vehicle.
    - Atropine 0.03%: re-randomized in a 1:1 ratio to receive Atropine 0.03% or Vehicle.
    - Vehicle arm: received Atropine 0.03%.

SYD-101-001 Study Schema



SYD-101-001 Enrollment

- Total Enrollment: 852 children aged 3 to 14 years inclusive with myopia (spherical equivalent refraction [SER]) of at least -0.50 diopter (D) and no greater than -6.00 D in each eye.
- Over 91% of the subjects came from the U.S.
- Participants with a condition predisposing to degenerative myopia (e.g., Marfan or Stickler syndrome, DM, T21) excluded.

SYD-101-001 Endpoints

- Primary efficacy endpoint: Proportion of participants with myopic progression worse than 0.75 D at or before Month 36
- Secondary Efficacy Endpoints:
  - Mean annual progression rate of myopia through Month 36
  - Proportion of participants with annual myopia progression rate through Month 36 no worse than -0.50 D/year
  - Proportion of participants with annual myopia progression rate through Month 36 no worse than -0.25 D/year
  - Proportion of participants with an increase of myopia worse than -0.50 D at or before Month 36
  - Time to progression of myopia of worse than -0.75 D through Month 36
  - Mean change from baseline in axial length at Month 36 (at sites with the requisite equipment; at least 50% of study participants)

Study Results

Results: Demographic and Baseline Characteristics

- No significant baseline imbalances in age, gender, race, ethnicity, or iris color across treatment arms.
- Overall, the study enrolled:
  - Gender: Female (55.7%) and Male (44.3%)
  - Age distribution: 3 to <6 (3.1%), 6 to <9 (21.8%), 9 to <12 (39.1%), 12–14 (36.0%)
  - Race/Ethnicity: Most participants were White (68.5%) and non-Hispanic (73.3%).
- No major differences in baseline disease characteristics across treatment arms.

Results: Disposition

- **Substantial study discontinuation rates were observed across all treatment arms:**
  - Vehicle: 22% | Atropine 0.01%: 25% | Atropine 0.03%: 23%
- Primary reasons: withdrawal by subject/parent/guardian; lost to follow-up
- Substantial intermittent missed visits existed: attributed to COVID-19 disruptions
- **Escape medication (Atropine 0.03%) use:**
  - Vehicle arm: 19 (6.7%) subjects
  - Atropine 0.01% arm: 5 (1.8%) subjects

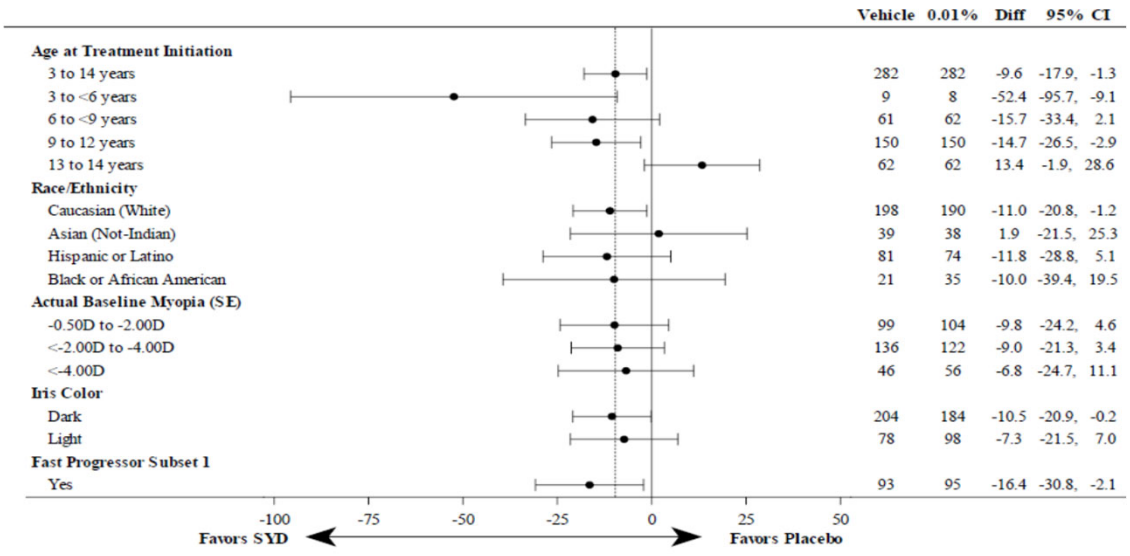
Efficacy Results: Primary Endpoint

- **Proportion of subjects with confirmed myopia progression >0.75 D by M36:**
  - Vehicle: 49.3% | Atropine 0.01%: 39.5% | Atropine 0.03%: 43.1%
- **Treatment difference vs. Vehicle:**
  - Atropine 0.03%: −6.2% (95% CI: −14.2%, 1.9%); → Not significant
  - Atropine 0.01%: −9.6% (97.5% CI: −19.1%, −0.08%); → borderline statistically significant compared to the allocated two-sided **alpha of 0.025**.

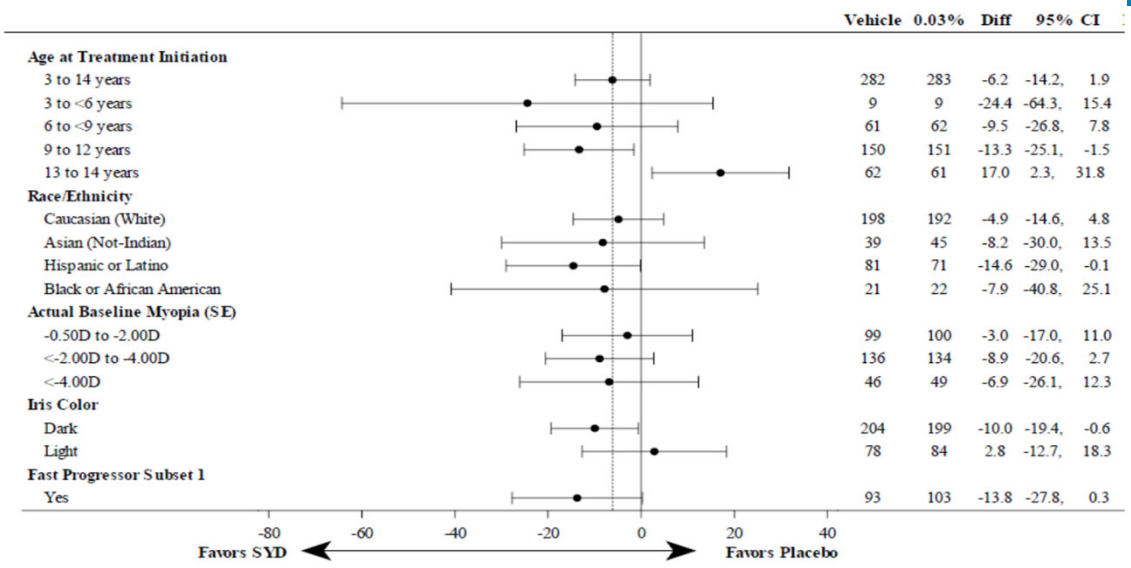
Exploratory Subgroup Analyses – Atropine 0.01%

- Results were broadly consistent with the primary analysis across most subgroups.
- **Notable exceptions:**
  - Fast progressors (subjects with a history of ≥ 0.5 D/year progression) showed a more favorable efficacy outcome for Atropine 0.01%.
  - Children aged 13–14 years showed results favoring the Vehicle arm (+13% against 0.01% atropine).
    - Re-grouping of the 12-year-olds to the older group masks the magnitude of the unfavorable results (only +0.8% favoring vehicle against 0.01% atropine)
    - This highlights the challenge in the interpretation of the age subgroups.
- Favorable results in subgroups may reflect random variation rather than true treatment effect.
- Per ICH E9, subgroup analyses are exploratory in nature and should be interpreted as such.

Subgroup Analysis – Atropine 0.01%



Subgroup Analysis – Atropine 0.03%



Efficacy Results: Key Secondary Endpoint

- **Key secondary endpoint: Mean annual myopia progression rate at 36 months.**
- Defined as: negative change in SER from baseline, divided by days since baseline, multiplied by 365.25.
- Results were favorable to both Atropine arms.
- The difference between 0.01% and vehicle is 0.08 D/yr (95% CI: 0.04, 0.12).

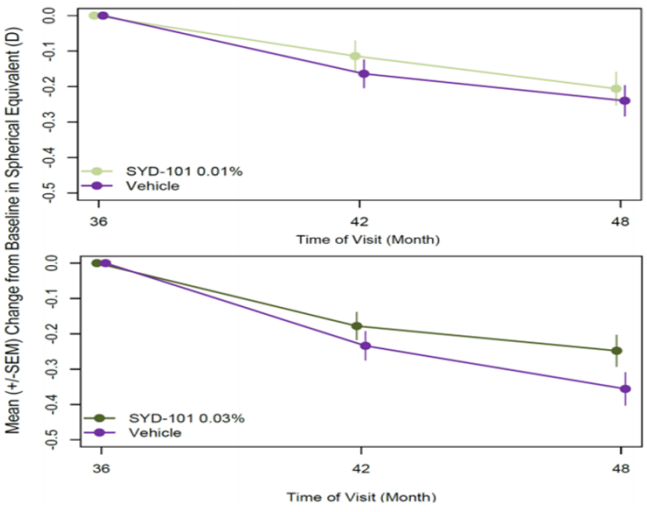
Visit	Vehicle (D/yr)	0.01% (D/yr)	Diff (95% CI)
Month 6	-0.48	-0.27	+0.21 (+0.10, +0.32)
Month 12	-0.49	-0.29	+0.20 (+0.13, +0.27
Month 24	-0.44	-0.31	+0.13 (+0.08, +0.20)
Month 36	-0.38	-0.30	+0.08 (+0.04, +0.12)

Lack of Efficacy in Axial Length

- Axial length was measured only at sites with requisite equipment (subset of the full analysis set [FAS]).
- At Month 36, measurements were available for 127, 128, and 128 participants in the Vehicle, atropine 0.01%, and atropine 0.03% groups, respectively (FAS: 282, 282, 283).
- Lower axial length change (i.e., less elongation) is a favorable outcome.
- **Mean change from baseline in axial length at Month 36:**
  - Vehicle: 0.40 mm | Atropine 0.01%: 0.39 mm | Atropine 0.03%: 0.37 mm
  - The treatment differences were small and statistically not significant.
    - 0.01% atropine : -0.01 (-0.11, 0.08; nominal p=0.7934)
    - 0.03% atropine: -0.04 (-0.13, 0.06; nominal p= 0.4452)

Efficacy Results: Withdrawal Period

- In total, 583 Part 2 participants (94.0%) completed the Month 48 study visit.
- Among participants originally treated with atropine 0.01%:
  - Continued 0.01%: mean SE change of −0.21 D from M36 to M48
  - Switched to vehicle: mean SE change of -0.24 D from M36 to M48
- The mean difference between groups: +0.033 D (95% CI: -0.052, +0.119); p = 0.4396



Key Clinical Issues

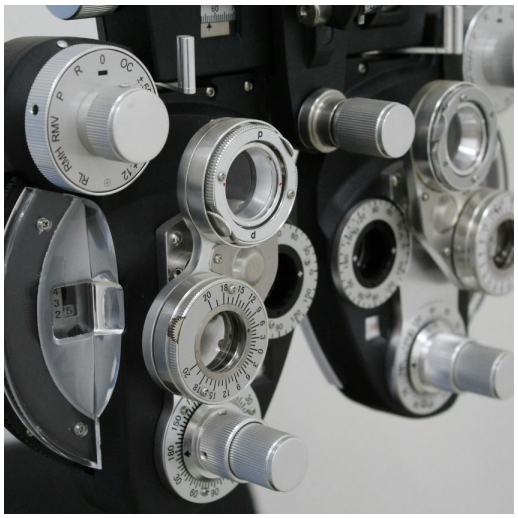
- Lack of clinically meaningful effect on myopia progression
- Declining treatment effect over time
- Lack of effect on axial length and biological plausibility
- Absence of a dose-response relationship
- Inadequate confirmatory evidence

Key Clinical Issues

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Magnitude of Effect in SER

- A mean difference of 0.21 D after 3 years of treatment with atropine 0.01% is less than one unit on the phoropter used to prescribe glasses.
- Treatment with atropine 0.01% for 3 years may result in the same glasses prescription as if you had not received treatment.



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Declining Treatment Effect Over Time

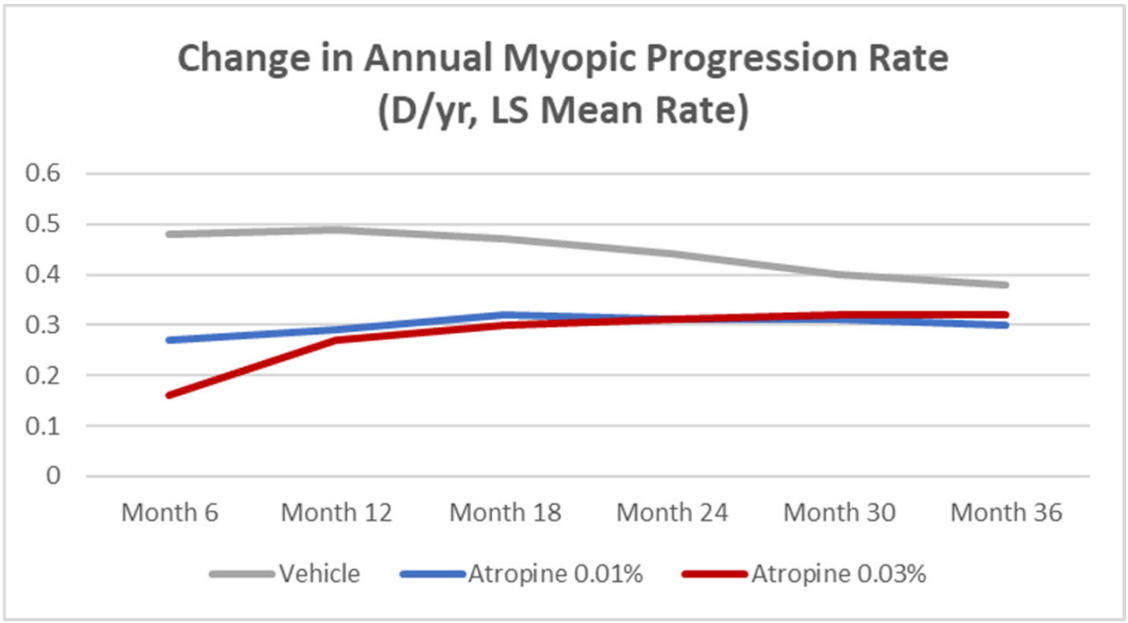
- There is a diminishing treatment effect in mean annual myopia progression rate (APR) over 36 months, including reversal in Year 3.

Timepoint	Vehicle APR	0.01% APR	Difference
Baseline → Month 6	−0.48 D/yr	−0.27 D/yr	+0.21 D/yr
Baseline → Month 36	−0.38 D/yr	−0.30 D/yr	+0.079 D/yr
Year 1 interval only	−0.42 D	−0.23 D	+0.19 D
Year 2 interval only	−0.30 D	−0.26 D	+0.04 D
Year 3 interval only	−0.20 D	−0.22 D	−0.02 D (reversal)

- 62% decline in annual treatment effect from Month 12 to Month 36 — insufficient durability for a chronic pediatric therapy.

SYD-101-001: Summary of Analysis of Annual Progression Rate of Myopia at Month 36 (FAS)

	Vehicle (N=282)	SYD-101 0.01% (N=282)	SYD-101 0.03% (N=283)
Annual Myopic Progression Rate (D/yr, LS Mean Rate)			
Baseline to Month 6	-0.48	-0.27	-0.16
Baseline to Month 12	-0.49	-0.29	-0.27
Baseline to Month 18	-0.47	-0.32	-0.30
Baseline to Month 24	-0.44	-0.31	-0.31
Baseline to Month 30	-0.40	-0.31	-0.32
Baseline to Month 36	-0.38	-0.30	-0.32
Difference to Vehicle (D/yr, LS Mean Rate)			
Baseline to Month 6		0.21	0.32
Baseline to Month 12		0.20	0.22
Baseline to Month 18		0.15	0.17
Baseline to Month 24		0.13	0.13
Baseline to Month 30		0.09	0.08
Baseline to Month 36		0.08	0.07



Long-term Effect: Atropine Treatment Long-Term Assessment (ATLAS) Study (Singapore)

- Prospective, double-masked observational study of ATOM1 and ATOM2 randomized clinical trials; included adults reviewed in 2021-22 from:
  - ATOM1 study (atropine 1% vs placebo; 1999 through 2003)
  - ATOM2 study (atropine 0.01% vs 0.1% vs 0.5%; 2006 through 2012)
- Efficacy finding: use of short-term topical atropine eye drops (0.01% to 1.0%) for a duration of 2 to 4 years during childhood was not associated with differences in final refractive errors 10 to 20 years after treatment.
  - Greater myopia progression post-cessation of treatment was associated with eyes that were treated at a younger age.
- Safety finding: no increased incidence of treatment or myopia-related ocular complications in the 1% atropine group vs. the placebo group.

Key Clinical Issues

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Lack of Effect on Axial Length

- Axial elongation is the primary structural driver of myopia-related complications (e.g., maculopathy, retinal detachment).
- Atropine 0.01% did not reduce axial elongation at 36 months compared to vehicle (−0.01 mm treatment difference, p=0.793).
- Suggests that small effect on spherical equivalent is the result of anterior globe changes rather than posterior globe effects.
- This data suggests that treatment with atropine 0.01% would not reduce the risk of myopia-related complications.

Key Clinical Issues

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Absence of Dose-Response Relationship

- 0.01% dose: statistically significant
- 0.03% dose: NOT significant (p=0.1319)
- Higher concentration performed numerically worse than lower — no pharmacological rationale.
- Published literature (LAMP, ATOM2) consistently shows robust, concentration-dependent atropine effects in Asian populations.
- Internal inconsistency casts significant doubt on whether the 0.01% finding reflects a true pharmacological effect.

Key Clinical Issues

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Inadequate Confirmatory Evidence

- Efficacy for atropine 0.01% is consistently demonstrated in East Asian populations (ATOM2, LAMP, AMIXT) — not generalizable to diverse U.S. population
- MTS1 (Repka et al., 2023) — the only exclusively U.S.-based RCT: treatment difference −0.02 D, (non-significant p-value=0.83).
- WA-ATOM (Australia) and MOSAIC (Europe): modest, non-significant effects at 24 months.
- FDA meta-analysis of 4 non-Asian Western RCTs: pooled SE difference +0.13 D — barely statistically significant.
- WA-ATOM washout data (Year 3): 0.01% arm progressed faster than placebo post-cessation, suggesting a rebound effect.
- External literature does not provide confirmatory evidence for the borderline SYD-101-001 findings in a U.S. demographic.

Summary of Clinical Issues

- Lack of clinically meaningful effect on myopia progression
- Declining treatment effect over time
- Lack of effect on axial length and biological plausibility
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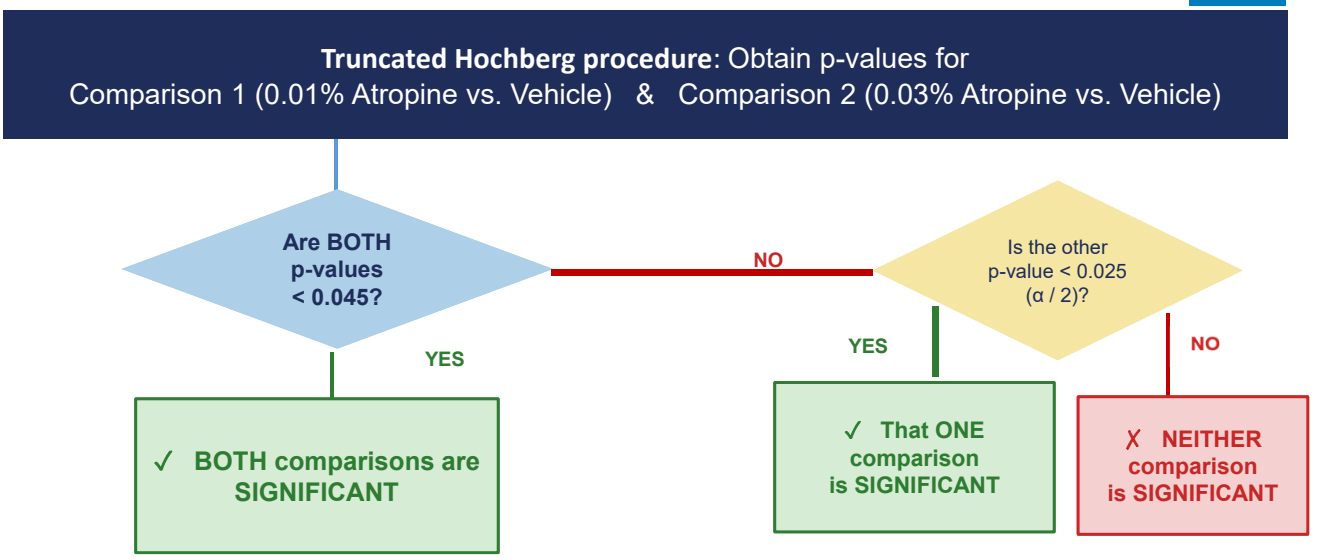
Statistical Considerations

Primary Estimand

- **Outcome**: Average spherical equivalent refraction (SE) across both eyes.
- **Primary Endpoint**: Proportion of subjects with confirmed myopic progression worse than −0.75 D at or before Month 36.
- **Population**: Children aged 3–14 years with myopia.
- **Treatment**: Atropine 0.01%, Atropine 0.03%, and Vehicle.
- **Intercurrent Events (ICEs): Composite Variable Strategy (classified as progressed):**
  - Prohibited medication use (no subjects received prohibited medication)
  - Treatment discontinuation due to an adverse event (AE)
  - Use of escape medication (Atropine 0.03%)

Primary Analysis

- **Statistical Method**: Cochran-Mantel-Haenszel (CMH) test, adjusting for stratifying variables (baseline SE age categories).
- **Missing Data**: Multiple imputation under the missing at random (MAR) assumption. Subjects who discontinued due to an AE were classified as progressed.
- **Multiplicity: Truncated Hochberg procedure.**
  - Both comparisons significant if both p-values < 0.045.
  - If one p-value ≥ 0.045, the other must be < 0.025 [α/2] to be significant
  - The test for the key secondary endpoint will follow the same truncated procedure
  - The other secondary endpoints will be evaluated using a fixed-sequence hierarchical approach.



Major Statistical Issue #1: Missing Data

- Substantial and moderately unbalanced missing data rates at Month 36:
  - Vehicle: 23% | Atropine 0.01%: 26% | atropine 0.03%: 22%
- Additional notable missing data due to missed earlier visits (e.g., ~22% of the 0.01% arm and 25% of the vehicle arm had missing data at Month 24).
- The primary analysis was conducted under the MAR assumption.
- While this is a reasonable starting assumption, deviation from this assumption could lead to biased results.
- The following sensitivity analyses will highlight the lack of robust finding.

Sensitivity Analysis

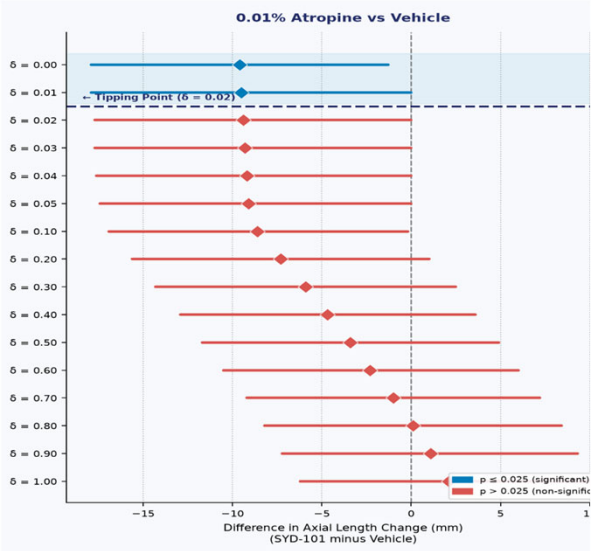
- Results were directionally favorable for Atropine 0.01%; however, the magnitude of treatment differences was generally smaller, and none achieved nominal significance.
- **Selected examples**:
  - Withdrawal of consent / lost-to-follow-up as progressed: −6.2% (−14.2%, +1.9%)
  - Missing data at Month 36 for any reason as progressed: −7.0% (−14.9%, +0.9%)
  - Any missing data for any reason as progressed: −4.9% (−12.7%, +2.8%)
- Tipping point analysis: See following slide.

Sensitivity Analysis: Tipping Point Analysis

- **Method**: The tipping point analysis is conducted as follows:
  - Shift parameters, starting with 0.01 D, were subtracted from multiply imputed spherical equivalent outcomes in the Atropine arms.
  - Progression status was then re-determined based on the updated data.
  - Subjects with AE discontinuations or escape medication use were set as progressed regardless of imputed values.
  - The primary analysis was conducted after each shift parameter is added using the primary analysis method.

Efficacy Results: Tipping Point Analysis

- **Key findings**: Statistical significance was lost with a shift parameter of only -0.02D is Spherical equivalent change.
  - A value we would expect from normal measurement variability is sufficient to overturn the primary finding entirely.
  - This tells us that the primary result is highly sensitive to the assumptions underlying the multiple imputation.
  - The primary analysis result is not robust to departures from the MAR assumption underlying the multiple imputation.



Supplemental Analyses

- **Supplemental analyses under different intercurrent event strategies were conducted**:
  - Treatment policy for escape medication (use all observed data) and composite variable strategy for treatment discontinuation due to AE (progressed): -10.0% (95% CI: -18.3%, -1.7%).
  - Treatment policy for both escape medication and treatment discontinuation due to AE: -10.0% (95% CI: -18.1%, -1.6%).
    - Data post escape and treatment discontinuation was limited.
    - The treatment policy-based results are expected to be comparable to the primary analysis results.
  - Expanded composite variable strategy (all treatment discontinuation progressed): -6.3% (95% CI: -14.2%, +1.6%).
  - Expanded composite strategy #2 (if only 10% of treatment discontinuation in the 0.01% atropine treated as progressed): -8.3% (-16.7%, +0.06%).

Sensitivity Analyses Summary

- Collectively, the sensitivity analyses demonstrate that the primary result lacks statistical robustness.
  - While alternative models remained directionally positive, they yielded attenuated effect sizes that failed to achieve nominal significance.
  - Crucially, the primary finding is highly sensitive to model assumptions, reaching a tipping point where a minor analytical shift completely alters the conclusion.
- Furthermore, supplemental analyses using the expanded composite variable strategy yielded consistently smaller effect sizes that failed to corroborate the magnitude of the primary finding.

Major Statistical Issue #2: Limitation of Confirmatory Evidence

- **Asian Studies**: The literature is predominantly from studies conducted in Asia (China, Hong Kong, and Singapore).
  - Study durations ranged from 12 to 24 months; various age groups and doses were evaluated. Limiting their application to the US population.
- **US, Europe and Australian Studies:**
  - Few studies were conducted primarily in the U.S.
  - Additional studies conducted in Europe and Australia were also reviewed.
  - The following slides provide a highlight of the studies conducted in the US, Europe and Australia.

Limitation of Confirmatory Evidence

- **CHAMP**: This study was a randomized double-blind study evaluating two concentrations of Atropine (0.01% and 0.02%) in subjects 3-16 year in the US and Europe (N=576)
  - The primary analysis was based on subjects 6-10 years (modified ITT, N=489)
  - The two doses were compared against vehicle hierarchically, with the 0.02% tested first. The 0.02% concentration was not statistically significant (0.1 D; p=0.1); the results for the 0.01% (0.22 D) are considered exploratory.
  - There were also several methodological issues including large missing data, problems with accounting for correlations between eyes.
- **MTS1:** This was a 24-month, randomized double-blind vehicle-controlled conducted exclusively in the US enrolling 5–12-year-olds (N=187).
  - This study compared 0.01% atropine with vehicle with respect to change in spherical equivalent at Month 24.
  - The treatment difference in spherical equivalent at Month 24 was only 0.02 D.
  - NB: The study population in this study is comparable to the subgroup that is highlighted by the Applicant.

Limitation of Confirmatory Evidence

- **APP**: This study was a 24-Month randomized placebo-controlled study in Danish children 6-12 years of age (N=97) to investigate the macular choroidal thickness changes.
  - The study used different inclusion criteria (≤ -1 D for ages 6-9 and ≤ -2 D for ages 9-12).
  - The treatment difference at Month 24 between 0.01% and placebo was 0.26 D.
  - This was a relatively small study of only 24-month duration that used age-dependent inclusion criteria.
- **MOSAIC:** This was a 24-month, randomized double-blind placebo-controlled study conducted in Irish children 5–12 years of age (N=250).
  - This study compared 0.01% atropine with vehicle with respect to change in spherical equivalent at Month 24.
  - The difference in spherical equivalent at Month 24 was only 0.1D which is a slight improvement from 0.03 D observed at Month 12.

Limitation of Confirmatory Evidence

- **Diaz-Llopis**: This was a 60-Month study in Spanish children 9-12 years of age (N=200).
  - The study used a no-treatment control and was not blinded.
  - The treatment difference in spherical equivalent difference was not reported.
  - This study is highly susceptible to bias given no blinding is used.
- **Moriche-Carretero:** This was a 60-month study in Spanish children (N=361).
  - The study used a no-treatment control and was not blinded; and the age range is not provided.
  - The study excluded subjects based on post-baseline factors introducing potential bias in favor of the treatment arm.
  - The treatment difference in spherical equivalent at Month 60 is only 0.29 D a 49% decline from the 0.57 D difference observed at Month 36.

Limitation of Confirmatory Evidence

- **WA-ATOM**: This was a 24-Month randomized placebo-controlled study in Australian children 6-16 years of age (N=153).
  - The treatment difference between 0.01% and Vehicle in spherical equivalent at Month 24 was only 0.14 D, a 39% decline from 0.23D observed at Month 12.
  - This study also provided some evidence of a rebound effect following treatment cessation.
  - Children of Asian ancestry residing in Australia had an effect that is half of what is observed in Asian studies.

Efficacy Results: Published Literature (U.S., Europe, and Australia)

Study: Location	Population	Sample size	Duration	Spherical Equivalent: Difference (95% CI)
MTS1: US	Ages 5-12	187	24 Month	0.02 D (-0.15, +0.19)
WA-ATOM: Australia	Ages 6-16	153	24 Month	0.14 D (-0.03, +0.29)
MOSAIC: Europe	Ages 6-16	256	24 Month	0.1 D (-0.02, +0.21)
CHAMP: US and Europe	Ages 3-16 (Primary: ages 6-10)	576 (489)	36 Month	0.25 D (+0.13, +0.38) 0.24 D (+0.11, +0.37)
SYD-101-001: US and Rest of the World	Ages 3-14	852	36 Month	0.21 D (+0.08, +0.35)

Limitation of Confirmatory Evidence

- **Meta- Analysis :** A meta-analysis of four studies (CHAMP, MTS1, MOSAIC, WA-ATOM) was conducted.
  - The meta-analysis included children aged 5 years or older.
  - The analysis resulted in a very modest effect of 0.13 D (95% CI: 0.05, 0.20 D) over a 24-month period. The lower bound of 0.05 D is nearly zero, which is smaller than the typical measurement variability of cycloplegic autorefraction.
  - Beyond the modest effect size, the meta-analysis carries caveats that limit its value as confirmatory evidence:
    - Studies enrolled children with different age ranges and substantially different racial and ethnic compositions, limiting the generalizability of the pooled estimate to the intended US population.
    - None of the individual studies included in the meta-analysis — including CHAMP — met the pre-specified success criterion on their own.
    - The results do not offer evidence of long-term efficacy beyond 24 months — a critical gap given the declining treatment effect observed in the pivotal trial from Month 24 to Month 36.

Limitation of Confirmatory Evidence

- **Conclusion**: The available literature does not provide the substantial corroborative evidence necessary to support a pivotal study that lacks persuasive efficacy data. Relevant individual studies failed to meet their primary endpoints, and meta-analytic synthesis yielded only a modest effect size whose lower bound is clinically negligible.

Regulatory Considerations

- FDA supports strategies to slow the progression of myopia and prevent long-term complications.
- When a single adequate and well-controlled trial is submitted, FDA generally expects that a demonstration of substantial evidence of effectiveness with this approach will involve a highly persuasive trial or a source of strong confirmatory evidence. [1]
- Ultimately, drug must meet criteria for approval
  - Demonstrate benefit that is clinically meaningful

[1]Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Comparison to Approved Treatments

	Comparator	PE Timepoint	Difference from comparator in SER change from BL	Difference from comparator in AL change from BL
MiSight CL	Single-vision CL	36 months	+0.67 D	-0.28 mm
Essilor Stellest	Single-vision spectacle lens	24 months	+0.64 D	-0.24 mm
Atropine 0.01%	Vehicle	36 months	+0.21 D	-0.01 mm

Substantial Evidence Of Effectiveness (SEE)

- Statutory Standard (21 U.S.C. § 355(d)): Approval requires substantial evidence of effectiveness from adequate and well-controlled investigations.
- Single Trial plus Confirmatory Evidence Pathway: Under the FDA's 2026 Substantial Evidence of Effectiveness (SEE) Guidance, the FDA expects a highly persuasive single trial (Pathway 1) or a single trial supported by strong confirmatory evidence (Pathway 2).
- Here we will outline how this statutory standard has not been met.

Substantial Evidence Of Effectiveness (SEE)

- Pathway 1: Clinical and Statistical Persuasiveness
- Without strong confirmatory evidence, a single pivotal trial should generate primary analysis results that are clinically and statistically highly persuasive, based on the magnitude of benefit, the associated uncertainty, and the p-value. (SEE 2026 Guidance, Section IV.A.2)
- **The Evidence Shows (Statistical Fragility):**
  - The primary efficacy endpoint only marginally met the significance threshold (p=0.0226 vs. 0.025).
- This result is highly fragile and not robust to missing data assumptions; a tipping point analysis shows that adding a very small value of −0.02D to imputed values in the treatment arm removes statistical significance.

Substantial Evidence Of Effectiveness (SEE)

Clinical Meaningfulness & Sustainability

- To establish substantial evidence, the treatment effect should be, in FDA's judgment, clinically meaningful and robust to violations in key analytical assumptions. (SEE 2026 Guidance, Section III.D)
- **The Evidence Shows (Lack of Clinical Meaningfulness & Sustainability):**
  - No Meaningful Reduction in Myopia Progression: After 3 years of treatment with daily atropine 0.01%, myopia progression in the treatment group was only 0.21 D less than in the vehicle group.
  - No Structural Disease Modification: The drug failed to demonstrate any effect on axial length (−0.01 mm; p=0.79), the primary driver of blinding myopia complications, indicating it masks refractive symptoms without modifying structural disease.
  - Efficacy Decay & Year 3 Reversal: The continuous treatment effect declined 62% from its Month 6 peak and actively reversed in Year 3.
  - Abnormal Physiology: The vehicle group naturally stabilized (decelerated) ~6× faster than the treated group, indicating the active drug may interfere with the eye's natural maturation.

Substantial Evidence Of Effectiveness (SEE)

- Pathway 2: Strength of Confirmatory Evidence & Generalizability
- Without a clinically and statistically persuasive study, FDA expects strong confirmation evidence, such as from related adequate and well-controlled trial data (SEE 2026 Guidance, Sections IV.A.1)
- **The Evidence Shows (Confirmatory Evidence Insufficient):**
  - US Data Contradiction: The only exclusively US-based RCT (MTS1) showed no significant treatment effect (p=0.83).
  - Weak pooled data: FDA's meta-analysis of four non-Asian Western RCTs yielded a pooled difference of only +0.13D at Month 24, failing to corroborate the borderline SYD-101-001 study results.
- **The Evidence Shows (Generalizability Failure):**
  - A concerning, unfavorable effect was observed in adolescents aged 13–14 (22% of the population), showing a 13.4 percentage point increase in progressors in the treatment arm. No confirmatory data resolves this signal.

Substantial Evidence Of Effectiveness (SEE)

- **Overall Assessment:** The three evidentiary deficiencies are cumulative and mutually reinforcing.
  - **Robustness:** A borderline, statistically fragile primary result (p=0.0452; tipping point: 0.02 D) that cannot withstand negligible deviations in missing data assumptions.
  - **Clinical Meaningfulness & Durability:** A total treatment benefit of 0.21 D over 3 years that declined 62% from its peak, reversed in Year 3, and was unaccompanied by structural disease modification (axial length: −0.01 mm; p=0.79).
  - **Confirmatory Evidence:** External literature fails to corroborate efficacy in Western populations (FDA meta-analysis: +0.13 D; MTS1: p=0.83) and leaves a population-specific signal in 13–14-year-olds (+13.4% favoring vehicle; 22% of the population) unresolved.
- Collectively, these deficiencies preclude a finding of substantial evidence of effectiveness under section 505 of the FD&C Act and the FDA Draft Guidance on SEE (June 2026).

Considerations for the Committee and Discussion Topics

Considerations for the Committee

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 and clinical meaningfulness of the result. We are seeking the Advisory Committee's opinion regarding the evidence for the effectiveness of 0.01% atropine.

Discussion Topic #1

FDA seeks input from the Committee on the following:

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.

Discussion Topic #2

FDA seeks input from the Committee on the following:

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.

Discussion Topic #3

FDA seeks input from the Committee on the following:

How the descriptive and exploratory subgroup analyses (e.g., children aged 3 to ≤12 years and fast progressors) contribute to a determination of effectiveness.

Discussion Topic #4

FDA seeks input from the Committee on the following:

Whether the published literature provides sufficient corroboration to satisfy the substantial evidence standard for approval.


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