U.S. FOOD & DRUG ADMINISTRATION

NDA 219694

COMPLETE RESPONSE

SYDNEXIS Inc.
Attention: Caryn Peterson
Regulatory Advisor
445 Marine View Ave, Suite 200
Del Mar, CA 92014-3951

Dear Caryn Peterson:

Please refer to your new drug application (NDA) (b) (4) for atropine sulfate ophthalmic solution, 0.01%.

We also acknowledge receipt of your amendment dated (b) (4), which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the clinical study contained and the referenced literature in this submission do not support the effectiveness of atropine sulfate ophthalmic solution, 0.01% for the treatment of myopia in children.

In Study SYD-101-001, the atropine 0.01% dose but not the atropine 0.03% dose met the primary endpoint. Both concentrations of atropine showed a diminishing effect on the rate of myopia progression over time. By 36 months, the small treatment group difference compared to vehicle in the rate of myopic progression from baseline is nearing zero for both concentrations (0.079 D/yr for 0.01% and 0.067 D/yr for 0.03%). This small difference in spherical equivalent is not clinically meaningful and would not result in a change in glasses prescription. The chronic use of a daily eye drop in the pediatric population for such a minimal improvement in refractive error is not justified and does not confer any benefit to the child who would continue to need corrective lenses. If the rate of myopic progression while on atropine continued on this trajectory

over the course of 4 or 5 years and diminished to the rate observed with vehicle, then chronic use of atropine would have no clinical effect.

While it is known that a higher level of myopia is a risk factor for retinal complications such as retinal detachments, the effect of atropine on reducing this risk cannot be determined from your clinical program. The small and diminishing magnitude of the reduction in myopia seen in this trial would be unlikely to reduce the future risk of retinal complications in any meaningful way, given that there was no difference in the change from baseline in axial length between the treatment and placebo group.

Lastly, the additional studies and published literature [1,2,3,4,5] you submitted as supportive evidence of effectiveness and safety are insufficient to overcome the deficiencies in the SYD-101-001 study. Moreover, the studies and published literature do not provide supportive evidence of effectiveness and safety for the intended use population in the United States. Overall, most of the studies were of insufficient duration (1-2) years and/or were conducted in populations (generally Asian populations) with different genetics, environments, and healthcare settings that limit generalizability to children in

[1] Yam JC, Jiang Y, Tang SM, Law AKP, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP. 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. 2019 Jan;126(1):113-124.
[2] Yam JC, Li FF, Zhang X, Tang SM, Yip BHK, Kam KW, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP. Two-Year Clinical Trial of the Low-Concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report. Ophthalmology. 2020 Jul;127(7):910-919.
[3] Yam JC, Zhang XJ, Zhang Y, Yip BHK, Tang F, Wong ES, Bui CHT, Kam KW, Ng MPH, Ko ST, Yip WWK, Young AL, Tham CC, Chen LJ, Pang CP. Effect of Low-Concentration Atropine Eyedrops vs Placebo on Myopia Incidence in Children: The LAMP2 Randomized Clinical Trial. JAMA. 2023 Feb 14;329(6):472-481.
[4] Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). Ophthalmology. 2012 Feb;119(2):347-54.
[5]Chia A, Ngo C, Choudry N, Yamakawa Y, Tan D. Atropine Ophthalmic Solution to Reduce Myopia Progression in Pediatric Subjects: The Randomized, Double-Blind Multicenter Phase II APPLE Study. Asia Pac J Ophthalmol (Phila). 2023 Jul-Aug 01;12(4):370-376.

the United States. Notably, studies conducted in non-Asian populations reflected in published literature[6,7,8,9] failed to demonstrate a statistically significant treatment effect.

While Study SYD-101-001 achieved its prespecified primary endpoint, multiple factors raise significant concerns regarding the robustness and clinical meaningfulness of the observed treatment effect:

(1) Magnitude of Treatment Effect: The treatment effect is modest (<10%) with the upper limit of the 95% confidence interval for the treatment difference (atropine 0.01% vs. Vehicle) at -1.28%, indicating limited clinical benefit. This effect is even more notably small when the summary measure is the mean change from baseline spherical equivalent at Month 36 [only 0.21 D (95% CI: 0.08, 0.35)].

(2) Missing Data Impact: Substantial missing primary outcome data occurred across all treatment arms (approximately 26% for atropine 0.01%, 22% for atropine 0.03%, and 23% for Vehicle). Sensitivity analyses revealed the primary result lacks robustness. Tipping point analysis demonstrated that statistical significance was lost with a shift parameter of only 0.03 D applied to imputed missing values—representing one-third of the smallest shift parameter evaluated by you.

(3) Declining Efficacy Over Time: The treatment difference in mean change from baseline spherical equivalent decreased from 0.24D at Month 12 to 0.21D at Month 36, representing a 12.5% decline in efficacy and raising concerns about long-term sustainability.

(4) Treatment Withdrawal Analysis: No treatment difference was observed between subjects who continued atropine 0.01% treatment versus those for whom treatment was withdrawn, questioning the necessity of continued therapy.

(5) Generalizability Concerns: While Asian studies show robust treatment effects, studies conducted in the United States, European Union, and Australia

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[6]Repka MX, Weise KK, Chandler DL, Wu R, Melia BM, Manny RE, Kehler LAF, Jordan CO, Raghuram A, Summers AI, Lee KA, Petersen DB, Erzurum SA, Pang Y, Lenhart PD, Ticho BH, Beck RW, Kraker RT, Holmes JM, Cotter SA; Pediatric Eye Disease Investigator Group. Low-Dose 0.01% Atropine Eye Drops vs Placebo for Myopia Control: A Randomized Clinical Trial. JAMA Ophthalmol. 2023 Aug 1;141(8):756-765.

[7] Lee SS, Lingham G, Blaszkowska M, Sanfilippo PG, Koay A, Franchina M, Chia A, Loughman J, Flitcroft DI, Hammond CJ, Azuara-Blanco A, Crewe JM, Clark A, Mackey DA. Low-concentration atropine eyedrops for myopia control in a multi-racial cohort of Australian children: A randomised clinical trial. Clin Exp Ophthalmol. 2022 Dec;50(9):1001-1012.

[8] Loughman J, Kobia-Acquah E, Lingham G, Butler J, Loskutova E, Mackey DA, Lee SSY, Flitcroft DI. Myopia outcome study of atropine in children: Two-year result of daily 0.01% atropine in a European population. Acta Ophthalmol. 2024 May;102(3):e245-e256.

[9] Zadnik K, Schulman E, Flitcroft I, Fogt JS, Blumenfeld LC, Fong TM, Lang E, Hemmati HD, Chandler SP; CHAMP Trial Group Investigators. Efficacy and Safety of 0.01% and 0.02% Atropine for the Treatment of Pediatric Myopia Progression Over 3 Years: A Randomized Clinical Trial. JAMA Ophthalmol. 2023 Oct 1;141(10):990-999.

demonstrate modest effects that often fail to achieve statistical significance. This population-specific variation raises questions about the generalizability of atropine 0.01% efficacy to diverse populations, particularly in the United States where the intended patient population includes significant non-Asian demographics.

These findings collectively suggest limited to no clinical benefit with questionable durability and robustness of the treatment effect.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[10] and Pregnancy and Lactation Labeling Final Rule[11] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4) which addresses the proposed proprietary name, (b) (4) This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

[10] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[11] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

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