



NDA 217711

COMPLETE RESPONSE

Vyluma, Inc.
c/o Nevakar Injectables, Inc.
Attention: Nithila Duraisamy
Vice President, Head of Regulatory Affairs
1019 US Highway 202/206, Building K
NJ Center of Excellence
Bridgewater, New Jersey 08807

Dear Nithila Duraisamy:

Please refer to your new drug application (NDA) (b) (4)

for atropine sulphate ophthalmic solution, 0.01%.

We acknowledge receipt of your amendment dated (b) (4), which constituted a complete response to our (b) (4), action letter. We also acknowledge receipt of your major amendment dated (b) (4), which extended the goal date by three months.

CLINICAL

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. 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 studies contained in this submission do not support the effectiveness of atropine sulfate ophthalmic solution, 0.01% for the treatment of myopia in children.

The CHAMP study¹ includes multiple critical statistical deficiencies. First, the study failed its pre-specified hierarchical testing procedure. In that sequential testing hierarchy, efficacy regarding the 0.01% strength would only proceed to formal statistical testing if efficacy for the 0.02% strength was established for the primary and first key secondary efficacy endpoints. However, the required 0.02% vs. placebo comparisons failed on both the primary and first key secondary endpoints [primary: OR 1.774,

¹ Zadnik K, Schulman E, Flitcroft I, Fogt J, Blumenfeld L, Fong T, Lang E, Hemmati H, Chandler S; et al. Efficacy and Safety of 0.01% and 0.02% Atropine for the Treatment of Pediatric Myopia Progression Over 3 Years: A Randomized Clinical Trial [CHAMP]. JAMA Ophthalmol. 2023;141(10):990-999.

$p=0.373$; key secondary: mean difference 0.099, $p=0.101$], thereby rendering any 0.01% efficacy analyses exploratory only and precluding formal statistical inference.

Second, the study suffered from substantial and imbalanced missing data that creates a significant potential for bias, with the 0.01% arm exhibiting 25% missing data at the primary endpoint compared to 11% in the placebo arm and 14% in the 0.02% arm. This 2-fold higher missing data rate in the 0.01% arm raises concerns that the data are not missing at random, and extensive sensitivity analyses that both you and FDA conducted could not adequately address these concerns.

Third, although you continued comparisons between the 0.01% strength and placebo outside of pre-specified formal statistical testing, there were significant flaws in your analyses regarding a treatment effect. Specifically, your correlation structure failed to properly account for within-eye and between-eye correlations that varied over time. When appropriate correlation models were applied, the treatment effect for the 0.01% arm diminished substantially from OR 4.540 to OR 1.72 (95% CI [1.05, 2.84]).

Additionally, tipping point analyses showed that when only 25% of subjects with missing data in the atropine 0.01% arm were assumed to be treatment failures, even nominal statistical significance was eliminated.

You conducted post-hoc analyses to support effectiveness of the 0.01% strength. Such analyses were not statistically controlled, and they cannot overcome the fundamental failure of the pre-specified analyses. These post-hoc analyses increase the risk of a type 1 error and thus increase the risk of finding a treatment effect when one does not exist.

The additional studies and published literature^{2, 3, 4, 5} you submitted as supportive evidence of effectiveness and safety are insufficient to overcome the deficiencies in the CHAMP study. Moreover, the studies and published literature do not provide supportive evidence of effectiveness and safety in the United States intended use population. Overall, most of the studies, including the studies conducted by your Chinese

² Loughman, J, Lingham, G, Nkansah, E, Kobia-Acquah, E, Filtcroft, DI. Efficacy and Safety of Different Atropine Regimens for the Treatment of Myopia in Children: Three-Year Results of the MOSAIC Randomized Clinical Trial. *JAMA Ophthalmol.* 2025 Feb 1;143(2):134-144.

³ Hvid-Hansen, A, Jacobsen, N, Flemming, M, Bek, T, Ozenne, B, Kessel, L. Myopia Control with Low-Dose Atropine in European Children: Six-Month Results from a Randomized, Double-Masked, Placebo-Controlled, Multicenter Study. *J. Pers. Med.* 2023, 13, 325.

⁴ Lee, SS, Lingham, G, Blaszkowska, M, Sanfilippo, P, Koay, A, Franchina, M, et al. Low-concentration atropine eyedrops for myopia control in a multi-racial cohort of Australian children: A randomized trial. *Clin Experiment Ophthalmol.* 2022; 50: 1001-12.

⁵ Li, Y., Yip, M, Ning, Y, Chung, J., Toh, A., et al. Topical Atropine for Childhood Myopia Control: The Atropine Treatment Long-Term Assessment Study *JAMA Ophthalmol.* 2024;142(1):15-23.

development partner and others described in published literature, were of insufficient duration (1-2) years and/or were conducted in populations (generally Asian populations) with different genetics, environments, and healthcare settings that limits generalizability to United States children. Studies conducted in non-Asian populations reflected in published literature failed to demonstrate a statistically significant treatment effect. Most critically, one of those studies, the MTS1 study⁶, tested your atropine 0.01% product in 187 children in the United States and failed to demonstrate efficacy at 24 months.

FACILITY INSPECTIONS

Following a CGMP inspection of (b) (4), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA Form 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a Pre-Approval Inspection (PAI) of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to an approval of the application.

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 Resources⁷ and Pregnancy and Lactation Labeling Final Rule⁸ 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.

⁶ Repka, M. X, Weise, K. K, Chandler, D. L., Wu, R., Melia, B. M., et al. Low-Dose 0.01% Atropine Eye Drops vs Placebo for Myopia Control, A Randomized Clinical Trial. JAMA Ophthalmol. 2023; 2023 Aug 1;141(8):756-765.

⁷ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

⁸ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

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 product 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.

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*.

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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