CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217370
PDUFA Goal Date	May 30, 2025
Nexus TTT #	2024-9763
Reviewer Name	May L Chan-Liston, PharmD, MPH
Team Leader	Jacqueline Sheppard, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	May 28, 2025
Subject	Evaluation of Need for a REMS
Established Name	Acoltremon
Trade Name	TRYPTYR
Name of Applicant	Alcon Laboratories, Inc.
Therapeutic Class	Selective transient receptor potential melastatin 8 (TRPM8) Agonist
Formulation(s)	ophthalmic solution, 0.003%
Dosing Regimen	One drop twice daily in each eye

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tryptyr (acoltremon ophthalmic solution) 0.003%, for topical ophthalmic use is necessary to ensure the benefits outweigh its risks. Alcon Laboratories, Inc. submitted a New Drug Application (NDA) 217370 for Tryptyr (acoltremon) with the proposed indication for the treatment of the signs and symptoms of dry eye disease (DED).[1] This application is under review in the Division of Ophthalmology. The Applicant did not submit a proposed REMS or a risk management plan with this application.

2. Background

2.1. Product Information

Tryptyr (acoltremon), a new molecular entity, is an agonist of transient receptor potential melastatin 8 (TRPM8) thermoreceptors proposed for the treatment of the signs and symptoms of dry eye disease (DED). The exact mechanism of action for Tryptyr in DED increasing tear production is currently unknown. Tryptyr is an ophthalmic solution that will be supplied as a single-use, single dose vial. Tryptyr should be instilled one drop twice daily in each eye (approximately 12 hours apart). The single-use vials are to be used immediately after opening and can be used to dose both eyes.[1,2]

2.2. Regulatory History

The following is a summary of the regulatory history for Tryptyr (acoltremon) NDA 217370 relevant to this review:

- 05/30/2024: NDA 217370 submission for the treatment of signs and symptoms of dry eye disease.
- 11/14/2024: A Mid-Cycle meeting was held with the Applicant. The applicant was informed that based on the currently available data, no significant safety concerns had been identified to date.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Dry Eye Disease (DED) is a disease of the ocular surface with loss of homeostasis of the tear film resulting in ocular discomfort, visual disturbance, and potential damage to the ocular surface. Multiple factors contribute to the disease including tear film instability and hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities. DED is also known as keratoconjunctivitis sicca, dry eye syndrome, and dysfunctional tear syndrome.[3]

Symptoms in DED result from activation of sensory nerves of the ocular surface, either due to tear hyperosmolarity, the presence of inflammatory mediators, or hypersensitivity of the sensory nerves. Two general mechanisms are present in patients with DED. The first is related to decreased tear

production which creates a state of aqueous deficiency and the other is evaporative DED due to abnormal meibomian gland function. The meibomian glands are sebaceous glands of the eyelid margin that produce the outer lipid layer of the tear film. Chronic DED can cause severe pain, visual impairment, decreased tear production, tear film hyperosmolarity and instability.[4]

Based on data from the 2017 National Health and Wellness Survey, 6.8% of the United States adult population has been diagnosed with DED, with an increasing prevalence with older age and greater prevalence in women than men. In a 2022 meta-analysis of three United States studies, the prevalence ranged from 5.3 to 14.5 percent with an estimated pooled prevalence of 8.1 percent.[3]

3.2. Description of Current Treatment Options

The treatment of DED is focused on relieving the symptoms by: increasing or supplementing tear production, slowing tear evaporation, or reducing ocular surface inflammation. Initially, nonpharmacologic and over-the-counter treatment includes addressing modifiable factors or behaviors such as medications, contact lens use, smoking, and allergens. Using eye lubricants such as drops, gels, and ointments are also options.[3]

FDA Approved treatments are listed in the following table:

Table 1: Summary of Prescription Treatment Options Relevant to DED [5–9]				
Product Trade Name (Generic) Year of Approval	Indication	Dosing and Administration	Important Safety and Tolerability Issues	Risk Management Approaches
FDA Approved Treatments				
Restasis (Topical cyclosporine)[5] 2002	To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.	0.05% ophthalmic emulsion instilled as one drop twice a day in each eye	Ocular burning, conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).	
Xiidra (Topical lifitegrast)[6] 2016	For the treatment of the signs and symptoms of dry eye disease (DED)	5% Ophthalmic solution instilled as one drop twice daily in each eye	Eye irritation or discomfort, bad taste	Medication Guide
(b) (4) [7] 2021	For the treatment of the signs and symptoms of dry eye disease.	EQ 0.03MG BASE/ Nasal Spray, one spray in each nostril twice daily (approximately 12 hours apart).	Sneezing, cough, throat irritation, and instillation-site (nose) irritation.	Medication Guide
Miebo (Perfluorohexyloctane)[8] 2023	For the treatment of the signs and symptoms of dry eye disease.	Ophthalmic solution: 100% perfluorohexyloctane instilled four times daily to affected eye(s).	Blurred vision	
FML (fluorometholone)[9] Topical glucocorticoids 1972	Treatment of corticosteroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.	0.1% fluorometholone ophthalmic solution instilled 1 drop 4 times a day.	Elevation of intraocular pressure with possible development of glaucoma and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.	

4. Benefit Assessment

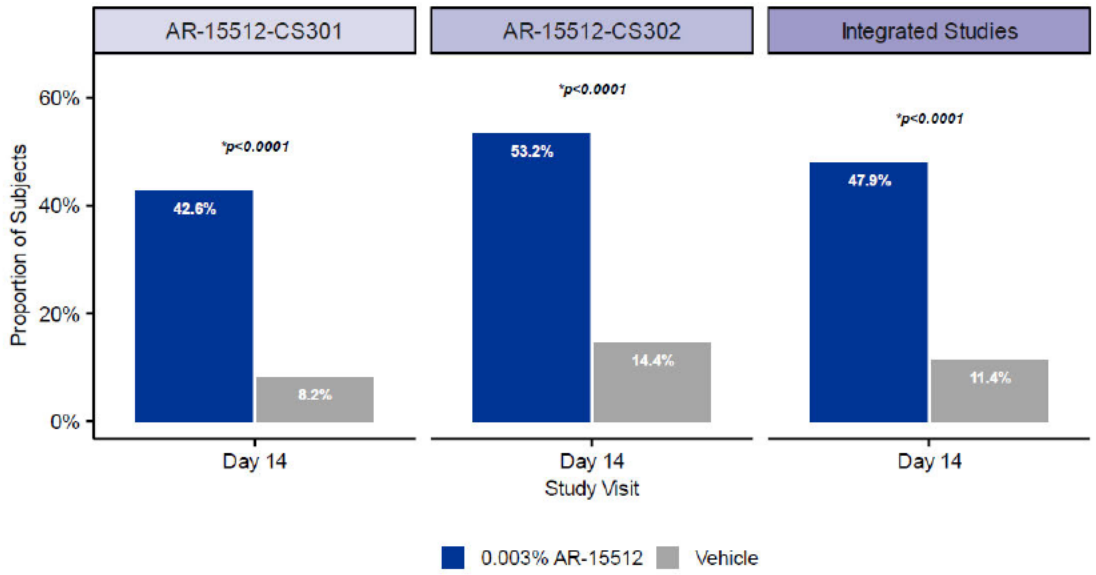
One Phase 2b and two pivotal Phase 3 clinical studies were used to support the efficacy of Tryptyr (acoltremon). All three efficacy studies were prospective, randomized, double-masked, vehicle-controlled, parallel group, multicenter studies. Subject inclusion and exclusion criteria were the same among all studies. Subjects 30 years and older with a history of artificial tear use for DED were qualified based on signs and symptoms of DED at screening and were requalified at baseline (Day 1) following a 14-day vehicle run-in.[4]

The multicenter, vehicle-controlled, double-masked, randomized Phase 2b study AR-15512-CS201 (COMET-1) (NCT04498182) (n = 369) was conducted to evaluate the safety and efficacy of two concentrations of Tryptyr (acoltremon) ophthalmic solution (0.0014% and 0.003%). The coprimary endpoints was change from baseline in pre-CAE (Controlled Adverse Environment) anesthetized

Schirmer Score[a] on Day 28. Results indicate that the coprimary endpoints were not met, however efficacy was demonstrated across multiple prespecified secondary and exploratory endpoints, in particularly for the 0.003% strength compared to vehicle.[2,4]

The AR-15512-CS301 (COMET-2) (NCT05285644) and AR-15512-CS302 (COMET-3) (NCT05360966) Phase 3, multicenter, vehicle-controlled, double-masked, randomized studies included the primary endpoint of the comparison of 0.003% Tryptyr (AR-15512) to Vehicle in the proportion of subjects with a ≥ 10 mm increase (post-drop on Day 14 vs pre-drop at baseline) in unanesthetized Schirmer score on Day 14. The post-drop Schirmer Tear Tests were initiated three minutes after instilling the randomized eye drop. The results for the primary endpoint for the Phase 3 studies are shown in the figure below:

Figure **Proportion of Subjects with a ≥ 10 mm Increase from Pre-drop at Baseline to Post-drop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1) - Intent-to-Treat Population (Individual Phase 3 and Integrated Studies)**



*Person's Chi-squared test
Source: AR-15512-CS301 Table 14.2.1.1; AR-15512-CS302 Table 14.2.1.1; ISE Table 14.2.1.1

The clinical reviewer concluded that the COMET-2, COMET-3 and Pooled results of COMET-2 and COMET-3 each demonstrated a statistically significant increase in percentage of subjects whose 5 minute unanesthetized Schirmer Tear Test score increased by ≥ 10 mm when comparing the baseline pre drop unanesthetized Schirmer test result to the post-drop unanesthetized Schirmer Test at day 14 (see Figure above). Demonstration of a 10mm or greater improvement from baseline in Schirmer Tear Test results has been the basis of other drug approvals for dry eye.[4] Additionally, the statistical reviewer

[a] The Schirmer test is the quantification of the number of tears produced by each eye. Small strips of filter paper are placed in the lower eyelids of each eye, either with or without prior instillation of anesthetic eye drops. Results are measured in millimeters of tears collected over a five-minute time period. This test is often used in the clinical setting but provides extremely variable results.[3]

concluded that COMET-2 showed statistically significant efficacy to meet the secondary endpoint, change from baseline in global SANDE (Symptom Assessment Questionnaire iN Dry Eye) score on Day 28, representing evidence of clinically meaningful improvement in reducing symptoms of dry eye disease. This key secondary endpoint was not met in the COMET- 3 study.

5. Risk Assessment & Safe-Use Conditions

The clinical safety review focused on the safety database with data from AR-15512-CS201 (COMET 1), AR-15512-CS301 (COMET 2), AR-15512-CS302 (COMET 3), and AR-15512-LTSS (COMET 4, long term safety study study).[2,4]

The safety of Tryptyr 0.003% was assessed in over 766 subjects dosed twice a day. The mean for treatment exposure was 141.3 days with the median exposure of 92 days. The safety profile of Tryptyr is acceptable. The most common treatment emergent adverse event experienced during the clinical studies was instillation site pain (burning or stinging) events, 49.7% in the Tryptyr group and 4.1% in the Vehicle group. The majority of instillation site pain (burning or stinging) events were mild in severity (97.6%) and less than 1% of patients discontinued therapy due to burning or stinging. The majority of subjects reported sensations resolved within a few seconds or within 30 seconds. There were no deaths and no serious complications related to the study drug.

Serious TEAEs were mostly nonocular in nature, were reported at a rate of 3.2% or less in any treatment group, were not unexpected considering the age of the study population and length of studies and were assessed as not related to treatment. Urinary tract infections, Covid-19 infections and sinusitis were the only non-ocular TEAEs reported in ≥ 1% of the 0.003% Tryptyr arm in the safety population.[2,4]

6. Expected Postmarket Use

This product will likely be prescribed by ophthalmologists and other health care providers such as primary care HCPs familiar with treating DED. These prescribers should be knowledgeable about the risks of instillation site pain commonly associated with eye drops used to treat DED. It is expected that Tryptyr will be self-administered by the patient in the outpatient setting.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Tryptyr (acoltremon) beyond routine pharmacovigilance and labeling. Product information and directions regarding product administration are proposed to be available in the Instructions for Use (IFU) and labelling on the carton and foil pouch.[1]

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of Tryptyr (acoltremon) for the treatment of the signs and symptoms of dry eye disease (DED).

DED is a disease of the ocular surface with loss of homeostasis of the tear film resulting in ocular discomfort, visual disturbance, and potential damage to the ocular surface. The benefit of treatment with acoltremon was demonstrated by a statistically significant increase in percentage of subjects whose

5 minute unanesthetized Schirmer Tear Test score increased by ≥ 10 mm when comparing the baseline pre drop unanesthetized Schirmer test result to the post-drop unanesthetized Schirmer Test in the COMET-2, COMET-3 and Pooled results of COMET-2 and COMET-3.

DRM and DO agree that a REMS is not necessary to ensure the benefits outweigh the risks of acoltremon. Likely prescribers are familiar with treating DED and the safety profile with acoltremon is similar to other ophthalmic solutions for this indication. Routine pharmacovigilance is expected to adequately monitor for potential new adverse reactions. If approved, Tryptyr will include Instructions for Use (IFU) detailing use instructions and adverse events are described in Section 6 of labeling. Labeling also includes a warning and precaution instructing the user to avoid the potential for eye injury and contamination they should not touch the vial tip to the eye or other surfaces.

9. Conclusion & Recommendations

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of Tryptyr (acoltremon) for the for the treatment of the signs and symptoms of dry eye disease (DED) without a REMS to ensure the benefits outweigh the risks.

10. Appendices

10.1. References

1. Alcon Laboratories, Inc. Proposed Tryptyr (acoltremon) Prescribing Information. NDA 217370. May 30, 2024.
2. Alcon Laboratories, Inc. Summary of Clinical Efficacy for Tryptyr (acoltremon) NDA 217370. May 30, 2024.
3. Shtein, RM. Dry eye disease. In:UpToDate, Jacobs DS and Li H (Eds), UpToDate, Waltham, MA August 2024.
4. Food and Drug Administration. Integrated Review for Tryptyr (acoltremon) NDA 217370. Draft. March 11, 2025.
5. Allergan, Inc. Restasis (cyclosporine ophthalmic emulsion) 0.05% Prescribing Information. 2002.
6. Novartis Pharmaceuticals Corporation. Xiidra (lifitegrast ophthalmic solution) 5% Prescribing Information. 2016.
7. Oyster Point Pharma, Inc. (b) (4) (varenicline solution) nasal spray Prescribing Information. 2024.
8. Bausch & Lomb, Inc. Miebo (perfluorohexyloctane ophthalmic solution) Prescribing Information. 2023.
9. Allergan, Inc. FML (fluorometholone ophthalmic suspension, USP) 0.1% Prescribing Information. 2003.

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