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RESEARCH**

APPLICATION NUMBER:

217370Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217370
Priority or standard	STANDARD
Submit date(s)	5/30/2024
Received date(s)	5/30/2024
PDUFA goal date	5/30/2025
Division/office	Division of Ophthalmology (DO)
Review completion date	5/15/2025
Established/proper name	acoltremon
(Proposed) proprietary name	Tryptyr (acoltremon) ophthalmic solution 0.003%
Pharmacologic class	Click or tap to enter class.
Other product name(s)	AR-15512
Applicant	ALCON LABORATORIES INC
Dosage form(s)/formulation(s)	0.003% Ophthalmic solution
Dosing regimen	Instill one drop twice daily in each eye (approximately 12 hours apart).
Applicant-proposed indication(s)/ population(s)	For the signs and symptoms of dry eye disease (DED)
SNOMED CT code for proposed indication disease term(s)^a	46152009 Tear film insufficiency (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Instill one drop in each eye twice daily (approximately 12 hours apart).
Approved indication(s)/ population(s) (if applicable)	TRYPTYR is a TRPM8 thermoreceptor agonist indicated for the treatment of the signs and symptoms of dry eye disease.
SNOMED CT code for approved indication disease term(s)^a	46152009 Tear film insufficiency (disorder)

^a For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AE	adverse event
ANCOVA	analysis of covariance
BCVA	best-corrected visual acuity
BID	twice daily
CAE	controlled adverse environment
C _{max}	maximum plasma concentration
CVA	corrected visual acuity
DED	dry eye disease
EC ₅₀	half maximal effective concentration
ECC	endothelial cell count
GLP	good laboratory practice
GRAS	generally recognized as safe
HEK	Human Embryonic Kidney
ICH	International Council for Harmonisation
IND	investigational new drug
IOP	intraocular pressure
IP	investigational product
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
IRT	interactive response technology
ISS	integrated summary of safety
ITT	intent-to-treat
LLOQ	lower limit of quantification
LS	least squares
NDA	new drug application
NOAEL	no observed adverse effect level
ODS	ocular discomfort score
OU	both eyes
PI	Prescribing Information
PK	pharmacokinetics
PP	per-protocol
PT	preferred term
RHOD	recommended human ocular dose
SANDE	Symptoms Assessment iN Dry Eye
SEE	substantial evidence of effectiveness
TEAE	treatment-emergent adverse event
TID	three times a day
TRP	transient receptor potential
TRPM8	transient receptor potential melastatin 8
VAS	visual analog scale

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

This new drug application (NDA), 217370 for Tryptyr (acoltremon ophthalmic solution) 0.003%, was submitted in accordance with Section 505(b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50 of the U.S. Code of Federal Regulations, by Alcon Laboratories, Inc. (Alcon), for the treatment of the signs and symptom of dry eye disease (DED) in adults when dosed twice daily in each eye.

The Applicant submitted three studies supporting the efficacy of Tryptyr (acoltremon ophthalmic solution) 0.003% (one Phase 2b and two Phase 3 pivotal studies). Each of these studies was prospective, randomized, and double-masked. Initial eligibility was assessed at the Screening visit, based on signs and symptoms of DED (anesthetized Schirmer test score, total corneal fluorescein staining score, global Symptoms Assessment iN Dry Eye [SANDE] score, and ocular discomfort score [ODS]). Subjects also had to demonstrate an increase in signs and symptoms of DED following exposure to a controlled adverse environment (CAE) at Screening. All qualified subjects at the Screening visit entered a 2-week run-in period with the vehicle. Following requalification of subjects based on signs and symptoms of DED, all eligible subjects were randomized to twice daily (BID) treatment in both eyes (OU) with acoltremon ophthalmic solution or vehicle for up to 3 months.

Both Phase 3 studies, COMET-2 and COMET-3, demonstrated safety and efficacy for the treatment of dry eye disease for the primary efficacy endpoint, percentage of subjects achieving a 10-mm increase or more in Schirmer's tear test scores. NDA 217370 was reviewed by a multidisciplinary team as a Standard Review and was not presented at an advisory committee.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

Phase 3 studies COMET-2 and COMET-3 demonstrated safety and efficacy for the treatment of dry eye disease for the primary efficacy endpoint, percentage of subjects achieving a 10-mm increase or more in Schirmer's tear test scores.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Dry eye disease (DED) is a multifactorial, age-related, chronic progressive disease of the ocular surface. • Chronic DED can cause severe pain, visual impairment, decreased tear production, and tear film hyperosmolarity and instability. – Patients with corneal staining are more susceptible than others to eye infections and damage to the surface of the eye (cornea).	Tryptyr (acoltremon ophthalmic solution) 0.003% is a TRPM8 agonist. The mechanism of action by which it may increase tear production is uncertain. The drug effect is negligible under topical anesthesia, so it appears to stimulate tear production through the afferent pathway.
Current treatment options	• Restasis (cyclosporine ophthalmic emulsion) 0.05% • Xiidra (lifitegrast ophthalmic solution) 0.05% • Cequa (cyclosporine ophthalmic solution) 0.09% • (b) (4) (varenicline tartrate (b) (4)) • Miebo (perfluorohexyloctane ophthalmic solution) • Vevye (Cyclosporine ophthalmic solution) 0.1% – OTC Monograph eye drops	Tryptyr (acoltremon ophthalmic solution) 0.003% would provide an alternative product for the treatment of DED by increasing tear production.
Benefit	• Tryptyr (acoltremon ophthalmic solution) 0.003% demonstrated a statistically significant increase in Schirmer tear score, improvement in tear production in two (COMET-2 and COMET-3) randomized, double-masked, vehicle-controlled multisite clinical studies in subjects with a diagnosis of dry eyes. • Uncertainties: The duration of action of Tryptyr is unknown. Successful tear production endpoints all began Schirmer Tear Tests at three minutes postdrop. This provides no data to evaluate tear production through the remainder of the nearly 12 hours before the next drop.	The increase in tear production by 10 mm on a Schirmer tear test is considered a clinically significant change on its own. The amount of change in tearing has been associated with a change in clinical symptoms.

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The most common adverse event experienced with Tryptyr (acoltremon ophthalmic solution) 0.003% was instillation site pain, at rate of 49.7% in the integrated safety population. • There were no deaths and no serious complications related to the study drug. • Urinary tract infections, COVID-19 infections, and sinusitis were the only nonocular TEAEs reported in $\geq 1\%$ of the 0.003% acoltremon arm in the safety population (2.1%, 1.0%, and 1.0%, respectively, compared to 1.7%, 1.3%, and 0.6% in the corresponding vehicle control. • In the PK substudy of COMET-4, systemic exposure to 0.003% acoltremon was evaluated in a subset of subjects. Overall, the plasma concentrations of acoltremon in most (22 of 25) subjects was below the limit of quantitation, indicating that systemic exposure via the topical ocular route is negligible.	Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

Abbreviations: OTC, over-the-counter; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; TRPM8, transient receptor potential melastatin 8

2.2. Conclusions Regarding Benefit-Risk

Studies COMET-2 and COMET-3 demonstrated that Tryptyr (acoltremon ophthalmic solution) 0.003% dosed twice daily in each eye was statistically superior to vehicle in the proportion of subjects experiencing a ≥ 10 -mm increase in Schirmer score on Day 14. These were identical, randomized, double-masked, vehicle-controlled studies evaluated in adult subjects with dry eye disease.

The primary efficacy endpoint, the proportion of subjects achieving a ≥ 10 -mm increase in Schirmer's tear test scores, is considered a clinically significant change without a corresponding symptom change. The amount of change in tearing has been associated with a change in clinical symptoms.

The safety of Tryptyr (acoltremon ophthalmic solution) 0.003% was assessed in over 766 subjects dosed twice a day. The mean for treatment exposure was 141.3 days; the median was 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 (acoltremon ophthalmic solution) 0.003% group and 4.1% in the vehicle group. The majority of instillation site pain (burning or stinging) events were mild in severity: 97.6% of these events were mild in the Tryptyr (acoltremon ophthalmic solution) 0.003% group, and 96.4% in the vehicle group.

II. Interdisciplinary Assessment

3. Introduction

The original NDA submission was reviewed by the interdisciplinary review team. The submitted studies supporting the efficacy of Tryptyr (acoltremon ophthalmic solution) 0.003% (one Phase 2b and two Phase 3 pivotal studies) were reviewed. Each of these studies were prospective, randomized, and double-masked. Initial eligibility was assessed at the Screening visit, based on signs and symptoms of DED (anesthetized Schirmer test score, total corneal fluorescein staining score, global SANDE score, and ODS). Subjects also had to demonstrate an increase in signs and symptoms of DED following exposure to a CAE at Screening. All qualified subjects at the Screening visit entered a 2-week run-in period with the vehicle. Following requalification of subjects based on signs and symptoms of DED, all eligible subjects were randomized to BID treatment in OU with acoltremon ophthalmic solution or vehicle for up to 3 months.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Uncertainty Regarding the Duration of the Treatment Effect

3.1.1.2. Clinical Significance of Corresponding Symptom Relief

3.1.2. Key Safety Review Issues

There are no key safety review issues.

3.2. Approach to the Clinical Review

The following studies were reviewed to assess the efficacy and safety of Tryptyr (acoltremon ophthalmic solution) 0.003%:

- Safety and efficacy study - COMET-2
- Safety and efficacy study - COMET-3
- Phase 2 dose ranging study - COMET-1
- Long-term safety study - COMET-4

3.3. Approach To Establishing Substantial Evidence of Effectiveness

(1) Verbatim indication:

Treatment of Dry Eye Disease

(2) SEE was established with

(a) Adequate and well-controlled clinical investigation(s):

- (i) Two or more adequate and well-controlled clinical investigations, **OR**
- (ii) One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

(b) One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

(c) Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

(3) Complete response, if applicable

- SEE was established
- SEE was not established

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations^a for Acoltremon

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized^b	Number of Centers and Countries
NCT04498182 AR-15512- CS201 (COMET-1)	Subjects 30 years of age and older with signs and symptoms of dry eye disease	<u>Control type:</u> Vehicle, concurrent <u>Randomization:</u> 1:1:1 standard randomization <u>Blinding:</u> Double-masked <u>Biomarkers:</u> No biomarkers <u>Innovative design features:</u> None	<u>Drug:</u> acoltremon <u>Dosage:</u> 0.0014% or 0.003% <u>Number treated:</u> 369 <u>Duration (quantity and units):</u> 84 days	<u>Coprimary efficacy endpoints:</u> • Change from baseline in pre-CAE ODS based on VAS at Day 28 • Change from baseline in pre-CAE anesthetized Schirmer score at Day 28 <u>Secondary:</u> None.	<u>Planned:</u> 360 <u>Randomized:</u> 369	15 sites in the United States
NCT05285644 AR-15512- CS301 (COMET-2)	Subjects 30 years of age and older with signs and symptoms of dry eye disease	<u>Control type:</u> Vehicle, concurrent <u>Randomization:</u> 1:1 standard randomization <u>Blinding:</u> Double-masked <u>Biomarkers:</u> No biomarkers <u>Innovative design features:</u> None	<u>Drug:</u> acoltremon 0.003% <u>Dosage:</u> One drop BID, both eyes <u>Number treated:</u> 465 <u>Duration (quantity and units):</u> 90 days	<u>Primary:</u> • Proportion of subjects with a ≥10-mm increase (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14 <u>Secondary:</u> • Change from baseline in global SANDE score on Day 28 • Change from baseline (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14 • Proportion of subjects with ≥10-mm increase (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1	<u>Planned:</u> 460 <u>Actual:</u> 465	23 sites in the United States (The same sites as in COMET-3.)

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 Tryptyr (acoltremon ophthalmic solution) 0.003%

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
NCT05360966 AR-15512- CS302- (COMET-3)	Subjects 30 years of age and older with signs and symptoms of dry eye disease	<u>Control type</u> : Vehicle, concurrent <u>Randomization</u> : 1:1:1 standard randomization <u>Blinding</u> : Quadruple-masked (subject, care provider, investigator, outcomes assessor) <u>Biomarkers</u> : No biomarkers <u>Innovative design features</u> : None	<u>Drug</u> : acoltremon 0.003% <u>Dosage</u> : One drop BID, both eyes <u>Number treated</u> : 467 <u>Duration (quantity and units)</u> : 90 days	- Change from baseline (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1 - Proportion of subjects with ≥10-mm increase (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90 - Change from baseline (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90 - Change from baseline in global SANDE score on Day 90 <u>Primary</u>: - Proportion of subjects with a ≥10-mm increase (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14 <u>Secondary</u>: - Change from baseline in SANDE score on Day 28 - Change from baseline (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14	<u>Planned</u> : 460 <u>Actual</u> : 467	23 sites in the United States (The same sites as in COMET-2.)

NDA 217370

Tryptyr (acoltremon ophthalmic solution) 0.003%

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
				• Proportion of subjects with ≥ 10-mm increase (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1 • Change from baseline (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1 • Proportion of subjects with ≥ 10-mm increase (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90 • Change from baseline (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90 • Change from baseline in global SANDE score on Day 90		

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
NCT05493111 AR-15512-LTSS COMET-4	Subjects with dry eye syndrome, clinician-diagnosed or patient-reported, who have used or desired to use artificial tears for DED symptoms within 3 months prior to the baseline visit. Median age 62.	<u>Control type:</u> Vehicle <u>Randomization:</u> 2:1 ratio <u>Blinding:</u> Double-masked <u>Biomarkers:</u> No <u>Innovative design features:</u> None	<u>Drug:</u> acoltremon 0.003% <u>Dosage:</u> One drop twice daily <u>Number treated:</u> 275 including 38 in a PK population <u>Duration:</u> 12 months	<u>Primary:</u> Safety evaluation <u>Secondary:</u> There were multiple exploratory endpoints which in many cases indicated subject preference toward vehicle over Tryptyr. An exploratory efficacy endpoint confirmed that Tryptyr was superior to vehicle in proportion of subjects with ≥10-mm increase in unanesthetized Schirmer score from predrop to postdrop	270 planned 275 randomized 274 in PP population	10 centers, all in the United States

Source: Reviewer.

^a Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

^b If no randomization, then replace with "Actual Enrolled."

Abbreviations: BID, twice daily; CAE, controlled adverse environment; DED, dry eye disease; LTSS, long-term safety study; NCT, national clinical trial; ODS, ocular discomfort score; PK, pharmacokinetics; PP, per-protocol; SANDE, Symptoms Assessment in Dry Eye; VAS, visual analog scale

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		Section 6
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The published literature established that acoltremon is a transient receptor potential melastatin 8 (TRPM8) agonist like menthol. TRPM8, a calcium-permeable cation channel, is a cold sensor in humans. The activation of TRPM8 opens the channel and allows influx of calcium ions into the cell, resulting in cold thermal transduction and pain detection, among other effects. The

Applicant verified some of these activities in vitro using cells transfected with rat TRPM8, ex vivo, and in vivo on Guinea pig corneas:

- In vitro, acoltremon increased cytosolic calcium influx in TRPM8 transfected cells at a half maximal effective concentration (EC₅₀) as low as 1 μ M (289 pg/mL).
- Ex vivo, acoltremon activated the corneal cold thermoreceptor (TRPM8) nerve endings in the Guinea pig with an EC₅₀ of 47.7 μ M (13,805 pg/mL).
- A single topical ocular (10- μ L) application of acoltremon in the Guinea pig increased blink and possibly tear rates, compared to vehicle with an EC₅₀ of 9.1 μ M (2,634 pg/mL or 0.026 μ g/eye).

5.2. Clinical Pharmacology/Pharmacokinetics

Tryptyr (acoltremon ophthalmic solution) 0.003% is proposed for topical ophthalmic use and the site of action is the eye. Acoltremon systemic exposure was evaluated in a subset of subjects with DED in the ongoing long-term safety study COMET-4, in which subjects received acoltremon ophthalmic solution 0.003% or vehicle one drop in each eye twice daily for 12 months. Plasma samples were collected on Days 1, 14, and 90 from 25 subjects dosed with acoltremon ophthalmic solution 0.003%. Acoltremon was detected in 6 samples from 3 subjects with plasma concentrations ranging from 22.8 pg/mL to 213 pg/mL but was below the limit of quantification (lower limit of quantification [LLOQ] of 20 pg/mL) in all other samples (refer to Section 14 for more details). Given the negligible systemic exposure of acoltremon following topical ocular administration, the impact of intrinsic and extrinsic factors on acoltremon pharmacokinetics (PK) has not been assessed.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	<i>Pharmacologic Activity</i>
EPC	TRPM8 thermoreceptor agonist
Mechanism of action	Acoltremon is a TRPM8 thermoreceptor ion channel agonist.
Active moieties	The active moiety is acoltremon
QT prolongation	Not applicable

Characteristic	Drug Information
	General Information
Bioanalysis	Acoltremon plasma concentrations were determined using a fully validated LC-MS/MS assay with the LLOQ of 20 pg/mL.
Healthy subjects versus patients	Not applicable
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Following topical ocular administration of acoltremon ophthalmic solution (0.003%) at the proposed dosing regimen, the systemic exposure of acoltremon is negligible. Since acoltremon ophthalmic solution (0.003%) is for topical ophthalmic use and the site of action is eye, the systematic exposure is not expected to affect treatment effect.
Range of effective dose(s) or exposure	Not applicable
Maximally tolerated dose or exposure	Not applicable
Dose proportionality	Not applicable
Accumulation	Not applicable
Time to achieve steady state	Not applicable
Bridge between to-be-marketed and clinical trial/study formulations	The formulation of Tryptyr (acoltremon ophthalmic solution) 0.003% was unchanged throughout Phase 2b and 3 clinical development and is same as the to-be-marketed formulation.
	Absorption
Bioavailability	Not applicable
T _{max}	Not applicable
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	Not applicable
Plasma protein binding	The protein binding of acoltremon in human plasma is 94%.
Drug as substrate of transporters	Not applicable
	Elimination
Mass balance results	Mass balance study was not conducted.
Clearance	Not assessed
Half-life	Not assessed
Metabolic pathway(s)	Not assessed
Primary excretion pathways (% dose)	Not assessed
	Intrinsic Factors and Specific Populations
Body weight	Not applicable
Age	Not applicable
Renal impairment	Not applicable
Hepatic impairment	Not applicable
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Not applicable
Inhibition/induction of transporter systems	Not applicable

Source: Module 2.7.2 Summary of Clinical Pharmacology Studies

Abbreviations: EPC, established pharmacologic class; LC-MS/MS, liquid chromatography/tandem mass spectrometry; LLOQ, lower limit of quantification; T_{max}, time to maximum concentration; TRPM8, transient receptor potential melastatin 8

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Based on nonclinical studies, the high protein binding of acoltremon, and negligible systemic (plasma) exposure following the clinically intended route of administration (topical ocular), there is limited potential for clinically significant systemic effect levels with topical ocular dosing. A systemic pharmacokinetic evaluation was incorporated in the long-term safety study (Phase 3, COMET-4). Results from this study are included in Module 2.7.2 and the final analysis reported included in Module 5.3.5.4.

Initial dose finding and dosing frequency were evaluated in the Phase 1/2a study conducted by the prior sponsor (AVX012-CT-001). Results demonstrated that both 0.0007% and 0.0014% acoltremon administered as a topical ophthalmic solution three times a day (TID), had an acceptable safety profile. Additionally, after 28 days of either BID or TID administration of 0.0014% acoltremon ophthalmic solution, both DED symptoms (SANDE score) and signs (tear production) were improved. Review of the totality of efficacy data concluded that TID administration provided no additional treatment benefit relative to BID, and BID dosing was chosen to maximize subject compliance.

The concentration of acoltremon ophthalmic solution 0.003% used in the final formulation was based on results from the Phase 2b study (COMET-1), which evaluated 0.0014% and 0.003% acoltremon. In this study, the 0.003% concentration yielded the most consistent and robust treatment effects across multiple signs and symptoms. This included a dose dependent increase in tear production on Days 1 and 14 based on unanesthetized Schirmer scores (Day 1: least squares [LS] mean difference from vehicle in change from baseline: 12.2 and 6.1 mm for 0.003% and 0.0014%, respectively; Day 14: LS mean difference from vehicle in change from baseline: 13.4 and 9.2 mm for 0.003% and 0.0014%, respectively) (COMET-1 clinical study report Table 14.2.3.10.1), and reduction in global SANDE scores on Days 28 and 84 (Day 28: LS mean difference from vehicle in change from baseline: -7.9 and -4.3 mm for 0.003% and 0.0014%, respectively; Day 84: LS mean difference from vehicle in change from baseline: -8.9 and -1.1 mm for 0.003% and 0.0014%, respectively).

Overall, evidence from preclinical safety and clinical studies support the concentration and dosing frequency of acoltremon chosen for Phase 3 development studies. The recommended dosage for Tryptyr (acoltremon ophthalmic solution) 0.003% is one drop in each eye, twice daily.

6.1.1. Proposed Dosage Regimen

The proposed dosage regimen is Tryptyr (acoltremon ophthalmic solution) 0.003% one drop instilled twice daily in each eye (approximately 12 hours apart). This dosing regimen was tested in two independent Phase 3 studies (COMET-2 and COMET-3) as well as a Phase 2 study and a long-term safety study.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

Three randomized, double-masked, vehicle-controlled studies were conducted to support the efficacy of repeat dosing of Tryptyr (acotremone ophthalmic solution) 0.003% for up to 90 days in subjects of either sex and of any race with DED who met all other eligibility criteria.

All three efficacy studies were prospective, randomized, double-masked, vehicle-controlled, parallel group, multicenter studies. The Phase 3 studies COMET-2 and COMET-3 are intended to demonstrate efficacy for the treatment of dry eye disease. Refer to Section 15 for a detailed description of the study design and endpoints.

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 as outlined below, and were requalified at Baseline (Day 1) following a 14-day vehicle run-in.

Both of the following signs of DED in the same eye:

- Total corneal fluorescein staining score of ≥ 2 and ≤ 15 (modified National Eye Institute), and no region > 3 at Screening only
- Anesthetized Schirmer test score ≥ 2 and < 10 mm at 5 min at both Screening and Baseline visits
- ODS- visual analog scale (VAS) and global SANDE ≥ 50 at both Screening and Baseline
- Increased signs and symptoms of DED based on CAE exposure at Screening

Subjects were prohibited from wearing contact lenses, from using lid hygiene or lid heating therapies, and from using concomitant artificial tears, topical ocular anti-inflammatories, steroids, or other ophthalmic medications for DED. Short term use of some medications was allowed within a specified period relative to study visits. No rescue medication was provided or allowed in any study. Overall, any use of medications likely to bias the study results was minimized.

Eligible subjects were randomized at baseline to administer acotremone ophthalmic solution 0.003% or vehicle as one drop BID OU in the morning and evening. Treatment compliance was measured by count of used and unused vials with subjects deemed noncompliant entered as protocol deviations.

Design differences between Phase 2b and pivotal Phase 3 studies included additional exposure to CAE on Days 1, 28, and 84; omission of Day 7 and Day 60 (dispense only) study visits; and a total study duration of 84 days (instead of 90 days) for the Phase 2b study. Both Phase 3 studies had identical design and visit schedules.

Study Endpoints

Efficacy measures and endpoint differences between the Phase 2b and both pivotal Phase 3 studies were considered substantive and impacted the overall pooling strategy for primary efficacy evaluation based on tear production. The anesthetized Schirmer test was used in the Phase 2b study, whereas the pivotal Phase 3 studies utilized the unanesthetized Schirmer test. This difference alone was substantive, as anesthetic was shown to adversely impact accurate quantification of tear production following acoltremon ophthalmic solution administration (21-110-A). In addition, the postdrop unanesthetized Schirmer test used in the Phase 2b study was conducted 1 minute following drop instillation, as compared to 3 minutes following drop instillation in the pivotal Phase 3 studies. Lastly, different primary endpoints and timepoints were used between the Phase 2b and pivotal Phase 3 studies ([Table 6](#)).

DED symptoms based on the global SANDE scores were assessed in the Phase 2b and pivotal Phase 3 studies, however, the pooling strategy (only Phase 3 studies pooled) was done at the study level for consistency of the strategy across all endpoints.

Table 6. Primary and Select Secondary Endpoints, Studies COMET-1, COMET-2, and COMET-3

	AR-15512-CS201	AR-15512-CS301/ AR-15512-CS302
Primary Endpoint(s)	Change from Baseline in pre-CAE ODS - VAS on Day 28 Change from Baseline in pre-CAE anesthetized Schirmer Score on Day 28	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
Methodology for Unanesthetized Schirmer Testing	The post-drop unanesthetized Schirmer test was conducted 1 minute after randomized drop instillation (exploratory data)	The post-drop unanesthetized Schirmer test was conducted 3 minutes after randomized drop instillation
Secondary Endpoint	Change from Baseline in pre-CAE global SANDE on Day 28 ^a	(First [key] secondary) Change from Baseline in global SANDE score on Day 28

Source: summary-clin-efficacy 2.7.3 Summary of Clinical Efficacy Table 3.3 pg. 23 of 88, Results of Pooled Analyses, Studies/Trials AR-15512-CS301 (COMET-2,) and AR-15512-CS302 (COMET-3)

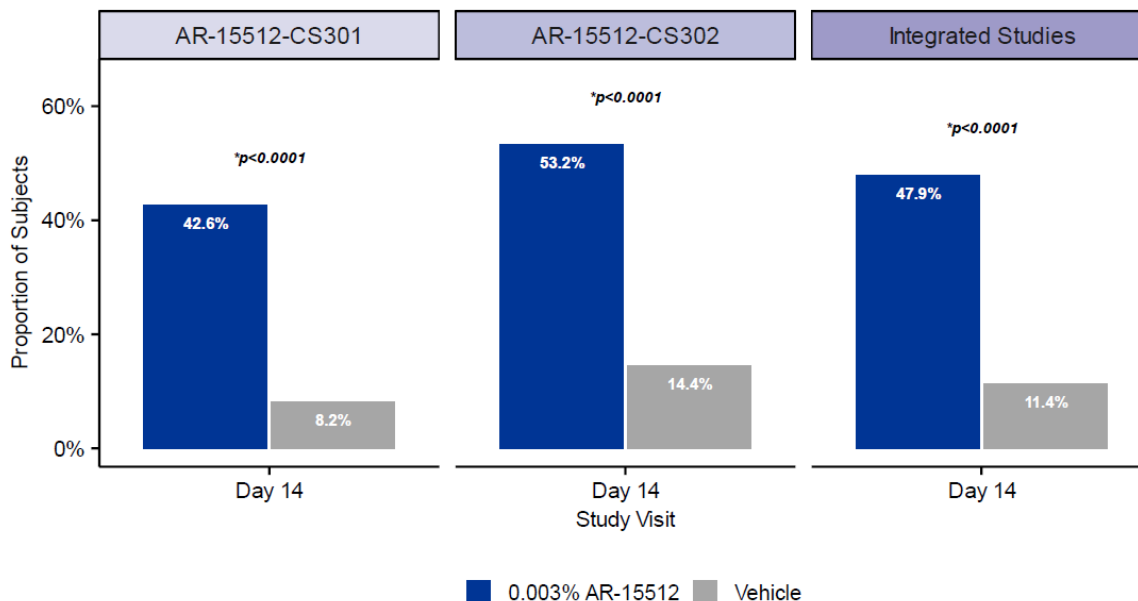
^a #15 on the list of secondary endpoints in the statistical analysis plan

Abbreviations: CAE, controlled adverse environment; ODS, ocular discomfort score; SANDE, Symptoms Assessment in Dry Eye; VAS, visual analogue scale

Two studies, COMET-2 and COMET-3, were submitted in support of the treatment of dry eye disease. These studies had the same study design and efficacy endpoints.

The primary efficacy endpoint was the comparison of 0.003% acoltremon to vehicle in the proportion of subjects with a ≥ 10 mm increase in unanesthetized Schirmer score on Day 14.

Figure 1. Proportion of Subjects With a ≥ 10 -mm Increase From Predrop at Baseline to Postdrop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1) (ITT 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

Source: AR-15512-CS301 Table 14.2.1.1; AR-15512-CS302 Table 14.2.1.1; ISE Table 14.2.1.1

Abbreviations: AR-15512, acoltremon; AR-15512-CS301, COMET-2; AR-15512-CS302, COMET-3; ISE, integrated summary of effectiveness; ITT, intent-to-treat

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 comparing baseline pre drop unanesthetized Schirmer test result to postdrop unanesthetized Schirmer test at Day 14. The postdrop Schirmer tear tests were initiated three minutes after instilling the randomized eye drop.

Secondary efficacy endpoints included the following key endpoint in the COMET-2 and COMET-3 study.

- Change from baseline in global SANDE score on Day 28 - first (key) secondary endpoint

The key secondary endpoint, change from baseline in global SANDE score compared to vehicle on Day 28, reached statistical significance, in favor of 0.003% acoltremon compared to vehicle in the COMET-2 study. The same secondary endpoint did not reach statistical significance in the COMET-3 study.

6.2.1. Study COMET-2

Study Name / Title

COMET-2 (Study AR-15512-CS301) A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease

6.2.1.1. Design, Study COMET-2

Study COMET-2 was a Phase 3, multicenter (23 sites in the United States), vehicle-controlled, double-masked, randomized study. All subjects were exposed to the CAE at the Screening visit only to assess eligibility. All qualified subjects at Screening instilled vehicle OU BID for approximately 14 days during the vehicle run-in period. Subjects who requalified at the Baseline visit were randomized in a 1:1 ratio to receive 0.003% acoltremon or vehicle instilled OU BID for 90 days. Efficacy was assessed at Baseline (Day 1) and Days 7, 14, 28, and 90. Safety assessments were conducted at each study visit.

Refer to Section [15](#) for a detailed description of the study design and endpoints.

6.2.1.2. Eligibility Criteria, Study COMET-2

Refer to Section [15](#) for a detailed description of the eligibility criteria.

6.2.1.3. Statistical Analysis Plan, Study COMET-2

Two studies, COMET-2 and COMET-3, were submitted in support of the treatment of dry eye disease. These studies had the same study design and efficacy endpoints and analyses.

The primary null and alternative hypotheses for the comparison of acoltremon ophthalmic solution 0.003% to vehicle with respect to the primary efficacy endpoint is:

- Hypothesis Testing: $H_0: p_T - p_V = 0$, $H_1: p_T - p_V \neq 0$. Where p_T is the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14=0 and whose eyes treated with acoltremon ophthalmic solution 0.003% and p_V is the proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14=0 and whose eyes treated with vehicle control.
- Type I error Control. The study-wise Type I Error rate is controlled at a two-sided significance level of 5% for testing the superiority of acoltremon ophthalmic solution 0.003% to vehicle in the primary and secondary efficacy endpoints.
- Per the protocol, superiority in the secondary efficacy endpoints was tested hierarchically if superiority in the primary efficacy endpoint was established.

- Analysis Populations: The analysis populations were defined as follows:
 - Intent-to-treat (ITT) population includes all randomized subjects. The primary efficacy analysis was performed on the ITT population.
 - Per-protocol (PP) population includes all randomized subjects who do not have a significant protocol deviation likely to seriously affect the primary outcome of the study and who complete the study through Day 90.
 - Safety population includes all randomized subjects who received at least one dose of the investigational product.
- Analysis of the primary endpoint: The comparison between acoltremon ophthalmic solution 0.003% and vehicle in the ITT population. Testing of the difference in proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14 used Pearson's Chi-square test. The differences in proportions along with corresponding two-sided 95% CIs and p-values from Pearson's Chi-square test were presented. Multiple imputations assuming missing not at random, using vehicle treatment group regardless of randomized treatment group, was used to impute missing due to withdrawal due to lack of efficacy, adverse events (AEs), or disallowed concurrent treatment. For missing data from other reasons listed above, multiple imputations using randomized treatment were used assuming missing at random.
- Supportive and sensitivity analysis of the primary endpoint: A logistic regression analysis with fixed effects of treatment, predrop measure at baseline, and treatment center was conducted and the adjusted odds ratios, along with corresponding two-sided 95% CIs and p-values, were presented.
- Analysis of secondary endpoints: Recall that the key secondary endpoint in both studies was change from baseline in global SANDE score on Day 28. Using the ITT population, the key secondary endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms for baseline value, treatment, and analysis center. LS means for each treatment group and for the difference between treatment groups were presented from the model, together with two-sided p-values and 95% CIs.
- Exploratory endpoints: The exploratory efficacy endpoints were analyzed using the ITT population with available data only. Quantitative exploratory efficacy variables were summarized using continuous descriptive statistics and analyzed using ANCOVA at each scheduled visit for change from baseline. Least squares means for each treatment group and for the difference between treatment groups were presented from the model, together with two-sided p-values and 95% CIs. Two-sample t-tests and Wilcoxon rank sum tests were also presented where appropriate as sensitivity analyses. Dichotomous exploratory efficacy variables were summarized descriptively (frequency and percentage) and analyzed at each measured visit similarly to the primary endpoint of proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14.

6.2.1.4. Results of Analyses, Study COMET-2

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of Tryptyr in treating the signs and symptoms of dry eye disease.

Disposition

Table 7. Summary of Subject Disposition (All Subjects), Study COMET-2

Study Disposition	0.003% Acoltremon BID		Vehicle BID	All Subjects
	n	%	n	n %
Total screened ^a				1578
Screen failures ^a				1113
Entered run-in period ^a				729
Number of randomized subjects ^a	230		235	465
Analysis populations ^b				
ITT	230	(100.0)	235	465 (100.0)
PP	193	(83.9)	200	393 (84.5)
Safety	230	(100.0)	235	465 (100.0)
Study completion				
Completed	210	(91.3)	213	423 (91.0)
Discontinued from study	20	(8.7)	22	42 (9.0)
Reasons for discontinuation				
Adverse event	3	(1.3)	3	6 (1.3)
Withdrawal of consent	2	(0.9)	5	7 (1.5)
Noncompliance	0		4	4 (0.9)
Lost to follow-up	4	(1.7)	6	10 (2.2)
Disallowed concurrent medication	1	(0.4)	1	2 (0.4)
Pregnancy	0		0	0
Lack of efficacy	0		0	0
Investigator decision	2	(0.9)	0	2 (0.4)
Protocol deviation	1	(0.4)	0	1 (0.2)
Death	0		0	0
Other	7	(3.0)	3	10 (2.2)
Protocol deviations ^c				
Any protocol deviations	192	(83.5)	198	390 (83.9)
Major deviations	66	(28.7)	55	121 (26.0)
Minor deviations	184	(80.0)	190	374 (80.4)
Protocol deviations related to Covid-19	1	(0.4)	3	4 (0.9)

Source: Clinical Study Report: COMET-2 Table 14.1.1 p 59 of 153

Note: Percentages are based on the number of randomized subjects in the treatment group unless otherwise specified.

^a A subject was allowed to be rescreened once and the subject was only counted once based on final enrollment status (screen failure or randomized). Entered run-in period subjects are those who had at least one run-in medication.

^b ITT subjects are reported as randomized; PP and Safety subjects are reported as treated.

^c Severities of the deviations were assigned by the Applicant before database lock.

Abbreviations: BID, twice daily; ITT, intent-to-treat; PP, per-protocol

A similar percentage of subjects in each treatment arm failed to complete the study 8.7% in the acoltremon arm and 9.4% in the vehicle arm.

Baseline Demographics

Table 8. Demographics and Baseline Characteristics (ITT Population), Study COMET-2

Category / Characteristic	0.003% Acoltremon BID		Vehicle BID	All Subjects
	N=230	N=235		N=465
Sex, n (%)				
Male	57	(24.8)	55	112 (24.1)
Female	173	(75.2)	180	353 (75.9)

Category / Characteristic	0.003% Acoltremon BID N=230	Vehicle BID N=235	All Subjects N=465
Race, n (%)			
American Indian / Alaska Native	0	1 (0.4)	1 (0.2)
Asian	24 (10.4)	21 (8.9)	45 (9.7)
Black / African American	35 (15.2)	32 (13.6)	67 (14.4)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
White	168 (73.0)	179 (76.2)	347 (74.6)
Multiracial	2 (0.9)	1 (0.4)	3 (0.6)
Other	0	1 (0.4)	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	31 (13.5)	34 (14.5)	65 (14.0)
Not Hispanic or Latino	199 (86.5)	201 (85.5)	400 (86.0)
Age, years (SD)			
Mean (SD)	59.5 (13.04)	59.6 (13.43)	59.6 (13.23)
Median	62.0	61.0	62.0
Min, max	31, 88	31, 88	31, 88
Age category (years), n (%)			
30-45	40 (17.4)	41 (17.4)	81 (17.4)
46-60	64 (27.8)	68 (28.9)	132 (28.4)
61-75	107 (46.5)	102 (43.4)	209 (44.9)
>75	19 (8.3)	24 (10.2)	43 (9.2)
Iris color - study eye, n (%)			
Black	5 (2.2)	5 (2.1)	10 (2.2)
Blue	50 (21.7)	62 (26.4)	112 (24.1)
Brown	122 (53.0)	113 (48.1)	235 (50.5)
Grey	1 (0.4)	2 (0.9)	3 (0.6)
Green	21 (9.1)	26 (11.1)	47 (10.1)
Hazel	31 (13.5)	27 (11.5)	58 (12.5)
Ocular Discomfort Score - VAS at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	74.4 (12.67)	73.4 (12.11)	73.9 (12.39)
Median	76.0	74.0	75.0
Min, max	50, 100	50, 100	50, 100
Eye Dryness Score - VAS at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	72.8 (14.77)	71.5 (13.54)	72.2 (14.16)
Median	75.0	74.0	75.0
Min, max	20, 100	23, 100	20, 100
Ocular Pain Score - VAS at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	45.8 (27.97)	44.6 (29.89)	45.2 (28.93)
Median	51.0	53.0	52.0
Min, max	0, 100	0, 100	0, 100
Anesthetized Schirmer Score at Baseline (Day 1) - Study Eye (mm)			
n	230	235	465
Mean (SD)	5.2 (2.23)	5.4 (2.20)	5.3 (2.22)
Median	5.0	5.0	5.0
Min, max	2, 9	2, 9	2, 9

Category / Characteristic	0.003% Acoltremon BID N=230	Vehicle BID N=235	All Subjects N=465
Unanesthetized Schirmer Test Predrop Score at Baseline (Day 1) - Study Eye (mm)			
n	230	235	465
Mean (SD)	6.2 (5.49)	5.9 (5.41)	6.1 (5.45)
Median	5.0	5.0	5.0
Min, max	0, 35	0, 35	0, 35
Global SANDE Score at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	72.7 (12.16)	72.7 (11.74)	72.7 (11.94)
Median	71.5	72.0	72.0
Min, max	50, 100	50, 100	50, 100
SANDE Frequency Score at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	75.2 (13.77)	75.0 (13.74)	75.1 (13.74)
Median	75.0	74.0	75.0
Min, max	43, 100	44, 100	43, 100
SANDE Severity Score at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	71.1 (13.28)	71.3 (12.64)	71.2 (12.95)
Median	71.0	71.0	71.0
Min, max	39, 100	42, 100	39, 100
Quality of Life - VAS at Baseline (Day 1) (mm)			
n	230	235	465
Mean (SD)	49.5 (26.11)	51.0 (25.49)	50.3 (25.78)
Median	55.0	55.0	55.0
Min, max	0, 100	0, 100	0, 100
Total Corneal Fluorescein Staining Score (Modified NEI Scale) at Baseline (Day 1) - Study Eye			
n	230	235	465
Mean (SD)	7.4 (3.18)	7.4 (3.14)	7.4 (3.16)
Median	7.0	7.0	7.0
Min, max	1, 19	1, 18	1, 19
Total Conjunctival Lissamine Green Staining Score (Modified NEI Scale) at Baseline (Day 1) - Study Eye			
n	230	235	465
Mean (SD)	5.4 (3.61)	5.5 (3.69)	5.4 (3.65)
Median	5.0	5.0	5.0
Min, max	0, 16	0, 20	0, 20
Total Staining Score (Modified NEI Scale) at Baseline (Day 1) - Study Eye			
n	230	235	465
Mean (SD)	12.8 (5.74)	12.8 (5.92)	12.8 (5.82)
Median	12.0	12.0	12.0
Min, max	1, 27	1, 31	1, 31
Average Tear Film Break-up Time at Baseline (Day 1) - Study Eye (sec)			
n	230	235	465
Mean (SD)	3.022 (1.1705)	2.931 (0.8765)	2.976 (1.0323)
Median	2.875	2.870	2.870
Min, max	1.08, 13.67	1.10, 6.49	1.08, 13.67

Category / Characteristic	0.003% Acoltremon BID N=230	Vehicle BID N=235	All Subjects N=465
Conjunctival Redness Score at Baseline (Day 1) - Study Eye			
n	230	235	465
Mean (SD)	1.09 (0.688)	1.07 (0.732)	1.08 (0.710)
Median	1.00	1.00	1.00
Min, max	0.0, 3.0	0.0, 3.5	0.0, 3.5

Source: Table 14.1.2.1

Note: Percentages are based on the number of subjects in the respective treatment group for the population being analyzed.

Abbreviations: BID, twice daily; ITT, intent-to-treat; NEI, National Eye Institute; max, maximum; min, minimum; SANDE, Symptoms Assessment in Dry Eye; SD, Standard Deviation; VAS, visual analog scale.

Overall, the study population was composed of mostly female (75.9%), white (74.6%), and non-Hispanic or Latino (86.0%) subjects, with a median age of 62.0 years. There were no significant differences across treatment groups in terms of the baseline characteristics.

Clinical Characteristics

Overall, the baseline ocular medical history was balanced between treatment groups. The most frequently reported baseline ocular condition was dry eye (99.8%), followed by cataract (41.7%). The treatment groups were comparable.

Overall, the most common ($\geq 20\%$) baseline medical conditions were postmenopause (56.1%), hypercholesterolemia (31.2%), drug hypersensitivity (31.6%), and hypertension (36.8%) system organ classes.

Analysis of Efficacy

Primary efficacy analyses were performed using the ITT population as the primary population.

The primary efficacy endpoint of the study, proportion of subjects with ≥ 10 -mm increase from baseline in unanesthetized Schirmer score on Day 14, was met with a p-value < 0.0001 (42.6% of 0.003% acoltremon BID subjects versus 8.2% of vehicle BID subjects). The difference of proportions between 0.003% acoltremon BID versus vehicle BID was 34.4% (95% CI 26.9, 42.0).

The study met its primary efficacy endpoint.

Table 9. Proportion of Subjects Who Achieved ≥ 10 mm Increase From Predrop at Baseline to Postdrop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1) (ITT Population), Study COMET-2

Parameter	0.003% Acoltremon BID N=230	Vehicle BID N=235
Proportion (%) ^a	42.6	8.2
Proportion difference (acoltremon -vehicle) ^a	34.4	
95% CI for difference ^a	26.9, 42.0	
p-value ^b	< 0.0001	

Parameter	0.003% Acoltremon BID N=230	Vehicle BID N=235
Odds ratio (acoltremon/vehicle) ^c	9.61	
95% CI for odds ratio	5.35, 17.27	
p-value	<0.0001	

Source: Table 14.2.1.1

Note: Baseline is the predrop measurement at baseline. Estimand 1 uses multiple imputation methodology.

^a Combined inferential statistics are from multiple imputation methodology where inferential statistics are based on asymptotic normal approximation.^b Combined p-value is based on multiple imputation methodology and analyzed with Pearson's Chi-squared test.^c Combined inferential statistics are from multiple imputation methodology and analyzed with logistic regression analysis with effect treatment, baseline value, and analysis center.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat

Key Secondary Efficacy Analysis

Secondary analyses were performed using the ITT population as the primary population.

The first (key) secondary endpoint of the study, change from baseline in global SANDE score on Day 28, was met with p-value=0.0138 (0.003% acoltremon BID LS mean -19.7 [SE 1.61] versus vehicle BID LS mean -14.7 [SE 1.58]). The LS mean difference between 0.003% acoltremon BID and vehicle BID was -5.1 (SE 2.06; 95% CI -9.1, -1.0).

SANDE Score

Table 10. Actual and Change From Baseline in Global SANDE Score (mm) at Day 28 (Estimand 1) (ITT Population), Study COMET-2

SANDE Score Parameter	0.003% Acoltremon BID N=230	Vehicle BID N=235
Baseline (Day 1)		
n*	230	235
Mean (SD)*	72.7 (12.16)	72.7 (11.74)
Median*	71.5	72.0
Min, max*	50, 100	50, 100
Day 28		
n*	218	221
Mean (SD)*	53.4 (23.79)	58.8 (23.72)
Median*	56.5	63.0
Min, max*	0, 99	0, 100
Change from baseline Day 28		
LS mean (SE) ^a	-19.7 (1.61)	-14.7 (1.58)
LS mean difference (SE) ^a	-5.1 (2.06)	
95% CI for LS mean difference ^a	-9.1, -1.0	
p-value –ANCOVA ^a	0.0138	
p-value –WRS test ^b	0.0326	
p-value –2-sample t-test ^c	0.0153	

Source: Table 14.2.2.1.1 and Table 14.2.2.1.4

* = (available data)

Note: N is the number of subjects in the respective treatment group for the population being analyzed. Baseline is the measurement at baseline. Higher SANDE scores indicate greater frequency or severity of symptoms of dryness and/or irritation. Estimand 1 is using multiple imputation methodology.

^a Based on ANCOVA models with effects of treatment, baseline, and analysis center.^b Based on WRS tests for comparing each acoltremon with vehicle.^c Based on 2-sample t-tests for comparing acoltremon with vehicle.

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; LS, least squares; max, maximum; min, minimum; SANDE, Symptoms Assessment in Dry Eye; SE, Standard Error; WRS, Wilcoxon rank sum

In addition to the key secondary endpoint, the following additional secondary endpoints were also met in hierarchical order:

- Change from baseline in unanesthetized Schirmer score on Day 14, 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$).
- Proportion of subjects with ≥ 10 mm increase from baseline in unanesthetized Schirmer score on Day 1, 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$).
- Change from baseline in unanesthetized Schirmer score on Day 1, 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$).
- Proportion of subjects with ≥ 10 mm increase from baseline in unanesthetized Schirmer score on Day 90, 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$).
- Change from baseline in unanesthetized Schirmer score on Day 90, 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$).
- The symptom secondary endpoints on Day 90 were not met.

Numerous exploratory analyses yielded data with numerical differences in favor of 0.003% acoltremon BID compared to vehicle BID including:

- Change from baseline in unanesthetized Schirmer score on Days 7 ($p < 0.0001$) and 28 ($p < 0.0001$).
- Proportion of subjects with ≥ 10 mm increase from baseline in unanesthetized Schirmer score on Days 7 ($p < 0.0001$) and 28 ($p < 0.0001$).

Reviewer's comment: *The first key secondary endpoint, change from baseline in global SANDE score on Day 28, was also statistically significant. Other endpoints that were met, proportion of subjects with ≥ 10 -mm increase from baseline in unanesthetized Schirmer score on Day 1, and on Day 90 0.003% acoltremon BID versus vehicle BID ($p < 0.0001$), indicate that the study drug is more effective at increasing tear production than vehicle beginning with the first dose and will continue to temporarily stimulate tearing after 90 days of use.*

The symptom-related secondary endpoints at Day 90 were not met, while the Schirmer-test-based endpoints at Day 90 were met. Thus, there was a lack of correlation between symptoms and the Schirmer test results at Day 90.

The duration of the treatment effect was not assessed in the study. Without measurements of postdrop Schirmer tests at different intervals postdrop, there is no evidence from the COMET-1, 2, or 3 studies to inform the duration of effect and slope of fall-off of tear production between 8 minutes $\pm$ 45 seconds postdrop and the next dose scheduled 12 hours later.

The first key secondary endpoint of the COMET-2 study, change from baseline in global SANDE score on Day 28, reached a clinically significant reduction in symptoms of dry eye disease, Tryptyr versus vehicle. This key secondary endpoint in the COMET-3 study, designed to replicate the COMET-2 study, did not demonstrate statistical significance in change from baseline in global SANDE score on Day 28.

The statistical reviewer noted that for DED signs, an evaluation of change in Schirmer score from predrop at baseline to pretreatment instillation at each visit did not show a statistically significant difference at each of the 5 visits and in both COMET-2 and COMET-3 studies. This may be an indication that acoltremon does not have a long-term treatment effect and should be taken continuously.

Table 11. Actual and Change From Predrop at Baseline to Predrop Unanesthetized Schirmer Score (mm) in Study Eye by Visit (Available Data) (ITT Population), Study COMET-2

Schirmer Score Parameter	0.003% Acoltremon BID N=230	Vehicle BID N=235
Baseline (Day 1), predrop		
n*	230	235
Mean (SD)*	6.2(5.48)	5.8(5.42)
Median*	5.0	5.0
Min, max*	0, 35	0, 30
Day 7, predrop		
n*	222	220
Mean (SD)*	6.5 (5.46)	6.5 (6.63)
Median*	5.0	5.0
Min, max*	0, 35	0, 35
Change from baseline Day 1 to predrop Day 7		
n	222	220
Mean (SD)	0.5(6.13)	0.7(6.70)
Median	0.0	0.0
Min, max	-31, 32	-25, 27
LS mean (SE)	0.4 (0.41)	0.6 (0.42)
LS mean difference (SE)	-0.2 (0.54)	
95% CI for LS mean difference	-1.3, 0.8	
p-value –ANCOVA	0.7064	
p-value –WRS test	0.394	
p-value –2-sample t-test	0.673	
Day 14, predrop		
n*	218	222
Mean (SD)*	6.5 (.56)	6.5 (5.84)
Median*	5.0	5.0
Min, max*	0, 35	0, 35
Change from baseline Day 1 to predrop Day 14		
n	218	222
Mean (SD)	0.4(6.95)	0.6(6.73)
Median	0.0	0.0
Min, max	-33, 31	-24, 35
LS mean (SE)	0.4 (0.44)	0.4 (0.42)
LS mean difference (SE)	0.0 (0.56)	
95% CI for LS mean difference	-1.1, 1.1	
p-value –ANCOVA	0.9597	
p-value –WRS test	0.2254	
p-value –2-sample t-test	0.7198	
Day 28, predrop		
n*	218	221
Mean (SD)*	6.3(5.47)	6.6(6.22)
Median*	5.0	5.0
Min, max*	0, 30	0, 35

Schirmer Score Parameter	0.003% Acoltremon BID N=230	Vehicle BID N=235
Change from baseline Day 1 to predrop Day 28		
n	218	221
Mean (SD)	0.2(6.19)	0.7(6.90)
Median	0.0	0.0
Min, max	-32, 26	-21, 34
LS mean (SE)	0.0 (0.42)	0.4 (0.41)
LS mean difference (SE)	-0.4 (0.53)	
95% CI for LS mean difference	-1.4, 0.7	
p-value –ANCOVA	0.483	
p-value –WRS test	0.648	
p-value –2-sample t-test	0.376	
Day 90, predrop		
n*	208	213
Mean (SD)*	6.6(6.00)	6.7(6.74)
Median*	5.0	5.0
Min, max*	0, 35	0, 34
Change from baseline Day 1 to predrop Day 90		
n	208	213
Mean (SD)	0.5(6.98)	0.9(7.54)
Median	0.0	0.0
Min, max	-25, 31	-21, 34
LS mean (SE)	0.3 (0.46)	0.6 (0.46)
LS mean difference (SE)	-0.2 (0.59)	
95% CI for LS mean difference	-1.4, 0.9	
p-value –ANCOVA	0.683	
p-value –WRS test	0.431	
p-value –2-sample t-test	0.501	

Source: Table 14.2.2.2.1, Table 14.2.2.2.4.1,
* = available data

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; ITT, intent-to-treat; LS, least squares; max, maximum; min, minimum; SANDE, Symptoms Assessment iN Dry Eye; SE, Standard Error; WRS, Wilcoxon rank sum

6.2.2. Study COMET-3

6.2.2.1. Design, Study COMET-3

Refer to Section [15](#) for a detailed description of the study design and endpoints.

6.2.2.2. Eligibility Criteria, Study COMET-3

Refer to Section [15](#) for a detailed description of the study eligibility criteria.

6.2.2.3. Statistical Analysis Plan, Study COMET-3

Two studies, COMET-2 and COMET-3, were submitted in support of the treatment of dry eye disease. These studies had the same study design and efficacy endpoints and analyses.

The primary null and alternative hypotheses for the comparison of acoltremon ophthalmic solution 0.003% to vehicle with respect to the primary efficacy endpoint are:

- Hypothesis testing: $H_0: p_T - p_V = 0$, $H_1: p_T - p_V \neq 0$. Where p_T is the proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14=0 and whose eyes were treated with acoltremon ophthalmic solution 0.003%, and p_V is the proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14=0 and whose eyes were treated with vehicle control.
- Type I error control. The study-wise Type I error rate is controlled at a two-sided significance level of 5% for testing the superiority of acoltremon ophthalmic solution 0.003% to vehicle in the primary and secondary efficacy endpoints.
- Per the protocol, superiority in the secondary efficacy endpoints was tested hierarchically if superiority in the primary efficacy endpoint was established.
- Analysis populations: The analysis populations were defined as follows:
 - ITT population includes all randomized subjects. The primary efficacy analysis was performed on the ITT population.
 - PP population includes all randomized subjects who do not have a significant protocol deviation likely to seriously affect the primary outcome of the study and who complete the study through Day 90.
 - Safety population includes all randomized subjects who received at least one dose of the investigational product.
- Analysis of the primary endpoint: The comparison between acoltremon ophthalmic solution 0.003% and vehicle in the ITT population. Testing of the difference in proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14 used Pearson's Chi-square test. The differences in proportions, along with corresponding two-sided 95% CIs and p-values from Pearson's Chi-square test, were presented. Multiple imputations assuming missing not at random, using vehicle treatment group regardless of randomized treatment group, was used to impute missing due to withdrawal due to lack of efficacy, AEs, or disallowed concurrent treatment. For missing data from other reasons listed above, multiple imputations using randomized treatment is used assuming missing at random.
- Supportive and sensitivity analysis of the primary endpoint: A logistic regression analysis with fixed effects of treatment, predrop measure at baseline, and treatment center was conducted and the adjusted odds ratios along with corresponding two-sided 95% CIs and p-values were presented.
- Analysis of secondary endpoints: Recall that the key secondary endpoint in both studies was change from baseline in global SANDE score on Day 28. Using ITT population, the key secondary endpoint was analyzed using an ANCOVA model with terms for baseline value, treatment, and analysis center. LS mean for each treatment group and for the difference between treatment groups were presented from the model, together with two-sided p-values and 95% CIs.

- Exploratory endpoints: The exploratory efficacy endpoints were analyzed using the ITT population with available data only. Quantitative exploratory efficacy variables were summarized using continuous descriptive statistics and analyzed using ANCOVA at each scheduled visit for change from baseline. Least-squares means for each treatment group and for the difference between treatment groups were presented from the model, together with two-sided p-values and 95% CIs. Two-sample t-tests and Wilcoxon rank sum tests were also presented where appropriate as sensitivity analyses. Dichotomous exploratory efficacy variables were summarized descriptively (frequency and percentage) and analyzed at each measured visit, similarly to the primary endpoint of proportion of subjects with ≥ 10 mm increase in unanesthetized Schirmer score on Day 14.

6.2.2.4. Results of Analyses, Study COMET-3

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary and key secondary efficacy results to support the efficacy of Tryptyr in treating the signs and symptoms of dry eye disease.

Disposition

Table 12. Summary of Subject Disposition (All Subjects), Study COMET-3

	0.003% AR-15512 BID	Vehicle BID	All Subjects
	n %	n %	n %
Total Screened			1606
Screen Failures			1139
Entered Run-In Period			753
Number of Randomized Subjects ^[1]	232	235	467
Analysis Populations ^[2]			
ITT	232 (100.0)	234 (99.6)	466 (99.8)
PP	192 (82.8)	203 (86.4)	395 (84.6)
Safety	232 (100.0)	234 (99.6)	466 (99.8)
Study Completion			
Completed	215 (92.7)	219 (93.2)	434 (92.9)
Discontinued from Study	17 (7.3)	16 (6.8)	33 (7.1)
Adverse Event	5 (2.2)	5 (2.1)	10 (2.1)
Withdrawal of Consent	5 (2.2)	3 (1.3)	8 (1.7)
Non-Compliance	2 (0.9)	1 (0.4)	3 (0.6)
Lost to Follow-Up	2 (0.9)	3 (1.3)	5 (1.1)
Protocol Deviation	2 (0.9)	1 (0.4)	3 (0.6)
Other	1 (0.4)	3 (1.3)	4 (0.9)
Any Protocol Deviations ^[3]			
Major Deviations	51 (22.0)	47 (20.0)	98 (21.0)
Minor Deviations	185 (79.7)	191 (81.3)	376 (80.5)
Protocol deviations Related to Covid-19	1 (0.4)	3 (1.3)	4 (0.9)

Source Table 14.1.1 Clinical Study Report COMET-3 Pg 56 of 155

Note: Percentages are based on the number of randomized subjects in the treatment group unless otherwise specified.

^a A subject was allowed to be rescreened once and the subject was only counted once based on final enrollment status (screen failure or randomized). Entered run-in period subjects are those who had at least one run-in medication.

^b ITT subjects are reported as randomized; PP and Safety subjects are reported as treated.

^c Severities of the deviations were assigned by the Applicant before database lock.

Abbreviations: AR-15512, acoltremon; BID, twice daily; ITT, intent-to-treat; PP, per-protocol

A similar percentage of subjects in each treatment arm failed to complete the study: 7.3% in the acoltremon arm and 6.8% in the vehicle arm.

Demographics and Baseline Characteristics**Table 13. Baseline Demographics and Clinical Characteristics (ITT Population), Study COMET-3**

Characteristic	0.003% Acoltremon BID N=232	Vehicle BID N=234	All Subjects N=466
Sex, n (%)			
Male	55 (23.7)	68 (29.1)	123 (26.4)
Female	177 (76.3)	166 (70.9)	343 (73.6)
Race, n (%)			
American Indian / Alaska Native	2 (0.9)	1 (0.4)	3 (0.6)
Asian	16 (6.9)	17 (7.3)	33 (7.1)
Black / African American	35 (15.1)	27 (11.5)	62 (13.3)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.4)
White	174 (75.0)	186 (79.5)	360 (77.3)
Multiracial	4 (1.7)	2 (0.9)	6 (1.3)
Ethnicity, n (%)			
Hispanic or Latino	16 (6.9)	28 (12.0)	44 (9.4)
Not Hispanic or Latino	216 (93.1)	206 (88.0)	422 (90.6)
Age, years (SD)			
Mean (SD)	63.1 (12.23)	62.1 (12.19)	62.6 (12.21)
Median	64.0	63.0	64.0
Min, max	32, 93	30, 87	30, 93
Age category (years), n (%)			
30-45	21 (9.1)	23 (9.8)	44 (9.4)
46-60	70 (30.2)	77 (32.9)	147 (31.5)
61-75	110 (47.4)	104 (44.4)	214 (45.9)
>75	31 (13.4)	30 (12.8)	61 (13.1)
Iris color - study eye, n (%)			
Black	5 (2.2)	7 (3.0)	12 (2.6)
Blue	46 (19.8)	59 (25.2)	105 (22.5)
Brown	123 (53.0)	101 (43.2)	224 (48.1)
Grey	0	4 (1.7)	4 (0.9)
Green	25 (10.8)	30 (12.8)	55 (11.8)
Hazel	33 (14.2)	33 (14.1)	66 (14.2)
Ocular discomfort score - VAS at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	74.5 (12.64)	73.2 (13.34)	73.9 (13.00)
Median	73.0	73.0	73.0
Min, max	50, 100	50, 100	50, 100
Eye dryness score - VAS at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	71.6 (14.32)	70.6 (17.69)	71.1 (16.09)
Median	72.0	72.0	72.0
Min, max	30, 100	5, 100	5, 100
Ocular pain score - VAS at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	43.0 (32.03)	43.2 (29.96)	43.1 (30.97)
Median	49.5	50.0	50.0
Min, max	0, 100	0, 100	0, 100

Characteristic	0.003% Acoltremon BID N=232	Vehicle BID N=234	All Subjects N=466
Anesthetized Schirmer score at Baseline (Day 1) - Study Eye (mm)			
n	232	234	466
Mean (SD)	5.4 (2.25)	5.5 (2.38)	5.4 (2.31)
Median	5.0	5.0	5.0
Min, max	2.9	2.10	2.10
Unanesthetized Schirmer test predrop score at baseline (Day 1) - study Eye (mm)			
n	232	234	466
Mean (SD)	6.8 (6.28)	6.4 (5.47)	6.6 (5.88)
Median	5.0	5.0	5.0
Min, max	0, 35	0, 30	0, 35
Global SANDE score at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	73.4 (11.99)	73.9 (12.65)	73.6 (12.32)
Median	73.0	73.0	73.0
Min, max	50, 100	50, 100	50, 100
SANDE frequency score at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	76.6 (13.98)	76.8 (14.13)	76.7 (14.04)
Median	76.0	76.0	76.0
Min, max	45, 100	45, 100	45, 100
SANDE severity score at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	71.2 (13.59)	71.8 (13.94)	71.5 (13.76)
Median	71.0	72.5	72.0
Min, max	31, 100	37, 100	31, 100
Quality of life - VAS at Baseline (Day 1) (mm)			
n	232	234	466
Mean (SD)	47.2 (28.49)	49.8 (27.91)	48.5 (28.20)
Median	53.0	54.0	53.0
Min, max	0, 100	0, 100	0, 100
Total corneal fluorescein staining score (modified NEI scale) at Baseline (Day 1) - study eye			
n	232	234	466
Mean (SD)	7.6 (3.48)	7.4 (3.44)	7.5 (3.45)
Median	7.0	7.0	7.0
Min, max	2, 18	1, 19	1, 19
Total conjunctival lissamine green staining score (modified NEI scale) at Baseline (Day 1) - study eye			
n	232	234	466
Mean (SD)	6.0 (4.55)	5.9 (4.20)	5.9 (4.37)
Median	6.0	6.0	6.0
Min, max	0, 23	0, 18	0, 23
Total staining score (Modified NEI Scale) at Baseline (Day 1) - study eye			
n	232	234	466
Mean (SD)	13.6 (6.59)	13.3 (6.47)	13.5 (6.53)
Median	13.0	13.0	13.0
Min, max	2, 41	1, 33	1, 41
Average tear film break-up time at Baseline (Day 1) - study eye (sec)			
n	232	234	466
Mean (SD)	3.028 (1.0868)	2.851 (1.0478)	2.939 (1.0699)
Median	2.762	2.652	2.705
Min, max	1.01, 7.71	0.98, 7.87	0.98, 7.87

Characteristic	0.003% Acoltremon BID N=232	Vehicle BID N=234	All Subjects N=466
Conjunctival redness score at Baseline (Day 1) - study eye			
n	232	234	466
Mean (SD)	1.51 (0.733)	1.48 (0.807)	1.49 (0.770)
Median	1.50	1.50	1.50
Min, max	0.0, 4.0	0.0, 4.0	0.0, 4.0

Source: Table 14.1.2.1

Note: Percentages are based on the number of subjects in the respective treatment group for the population being analyzed.

Abbreviations: BID, twice daily; ITT, intent-to-treat; max, maximum; min, minimum; NEI, National Eye Institute; SANDE, Symptoms Assessment in Dry Eye; SD, standard deviation; VAS, visual analog scale

The demographic and baseline characteristics for the ITT population present an acceptable representation of the American population which is likely to be seeking treatment for tear film dysfunction, dry eyes. The baseline characteristics were similar across both treatment groups for the 466 subjects.

Efficacy Results and Tabulations of Individual Subject Data

Primary Efficacy Analysis

Primary efficacy analyses were performed using the ITT population as the primary population.

The primary efficacy endpoint of the study, proportion of subjects with ≥ 10 -mm increase from baseline in unanesthetized Schirmer score on Day 14, was met with a p-value < 0.0001 (53.2% of 0.003% acoltremon BID subjects versus 14.4% of vehicle BID subjects). The difference of proportions between 0.003% acoltremon BID and vehicle BID was 38.8% (95% CI 30.8, 46.8), [Table 14](#) and [Figure 2](#).

Table 14. Proportion of Subjects Who Achieved ≥ 10 mm Increase From Predrop at Baseline to Postdrop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1) (ITT Population), Study COMET-3

Parameter	0.003% Acoltremon BID N=232	Vehicle BID N=234
Proportion (%) ^a	53.2	14.4
Proportion difference (acoltremon - vehicle) ^a	38.8	
95% CI for difference ^a	30.8, 46.8	
p-value ^b	< 0.0001	
Odds ratio (acoltremon / vehicle) ^c	7.85	
95% CI for odds ratio	4.86, 12.69	
p-value	< 0.0001	

Source: Table 14.2.1.1

Note: Baseline is the predrop measurement at baseline. Estimand 1 used multiple imputation methodology.

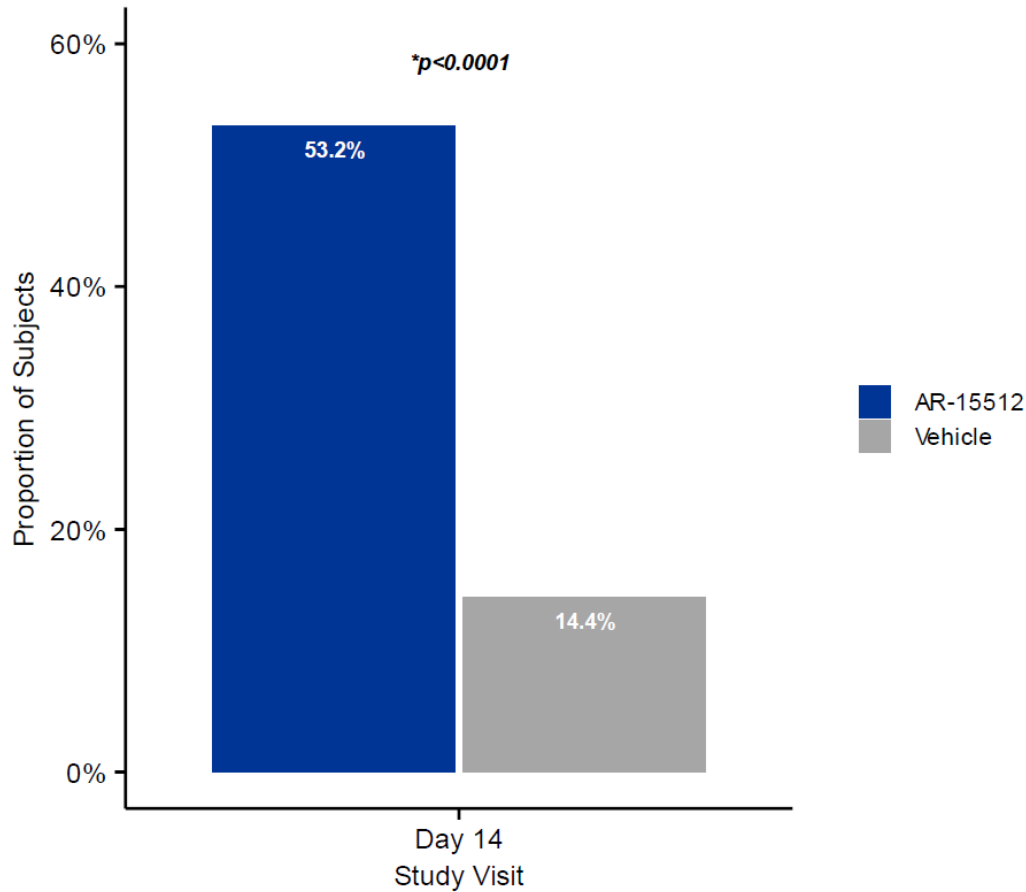
^a Combined inferential statistics are from multiple imputation methodology where inferential statistics are based on asymptotic normal approximation.

^b Combined p-value is based on multiple imputation methodology and analyzed with Pearson's Chi-squared test.

^c Combined inferential statistics are from multiple imputation methodology and analyzed with logistic regression analysis with effect treatment, baseline value, and analysis center.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat

Figure 2. Proportion of Subjects Who Achieved ≥ 10 -mm Increase From Predrop at Baseline to Postdrop on Day 14 in Study Eye Unanesthetized Schirmer Score (Estimand 1) (ITT Population), Study COMET-3



Source: Table 14.2.1.1

Note: Results from Estimand 2 and 3 analyses were similar to Estimand 1, Figure 11-2, Tables 14.2.1.2, 14.2.1.3, 14.2.2.3.1, 15.2.2.3.2, and 14.2.2.3.3. Analysis using trimmed means also yielded similar results (Tables 14.2.1.4 and 14.2.2.3.4), as did analysis of all available data, Figure 11-2, Table 14.2.1.5, and 14.2.2.3.5.1. The results in the PP population were also similar, Table 14.2.1.6 and 14.2.2.3.6.

Abbreviations: AR-15512, acoltremon; ITT, intent-to-treat; PP, per-protocol

The primary efficacy endpoint of the study, proportion of subjects with ≥ 10 -mm increase from baseline in unanesthetized Schirmer score on Day 14, was met with a p -value < 0.0001 (53.2% of 0.003% acoltremon BID subjects versus 4.4% of vehicle BID 1subjects). The difference of proportions between 0.003% acoltremon BID versus vehicle BID was 38.8% (95% CI 30.8, 46.8).

Key Secondary Efficacy Analysis

Secondary analyses were performed using the ITT population as the primary population.

Table 15. Actual and Change From Baseline in Global SANDE Score (mm) at Day 28 (Estimand 1) (ITT Population), Study COMET-3

Parameter	0.003% Acoltremon BID N=232	Vehicle BID N=234
Baseline (Day 1)		
n*	232	234
Mean (SD)*	73.4 (11.99)	73.9 (12.65)
Median*	73.0	73.0
Min, max*	50, 100	50, 100
Day 28		
n*	219	229
Mean (SD)*	53.4 (24.75)	57.0 (25.51)
Median*	56.0	61.0
Min, max*	0, 100	0, 100
Change from baseline Day 28		
LS mean (SE) ^a	-22.3 (1.66)	-19.1 (1.64)
LS mean difference (SE) ^a	-3.1 (2.08)	
95% CI for LS mean difference ^a	-7.2, 0.9	
p-value –ANCOVA ^a	0.1321	
p-value –WRS test ^b	0.1011	
p-value –2-sample t-test ^c	0.1422	

Source: Table 14.2.2.1.1 and Table 14.2.2.1.4

* = (available data)

Note: N is the number of subjects in the respective treatment group for the population being analyzed. Baseline is the measurement at baseline. Higher SANDE scores indicate greater frequency or severity of symptoms of dryness and / or irritation. Estimand 1 is using multiple imputation methodology.

(a) Based on analysis of covariance (ANCOVA) models with effects of treatment, baseline, and analysis center.

(b) Based on Wilcoxon rank sum (WRS) tests for comparing each AR-15512 with Vehicle.

(c) Based on 2-sample t-tests for comparing AR-15512 with Vehicle.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; LS, least squares; SANDE, Symptoms Assessment in Dry Eye; SE, standard error

The first (key) secondary endpoint of the study, change from baseline in global SANDE score on Day 28, did not achieve statistical significance.

The statistical reviewer noted that for DED signs, an evaluation of change in Schirmer score from predrop at baseline to predrop at each visit did not show a statistically significant difference at any of the 5 visits and in both COMET-2 and COMET-3 studies. This may suggest that twice a day dosing regimen of acoltremon is not sufficient to maintain the treatment effect.

Table 16. Actual and Change from Pre-drop at Baseline to Post-drop Unanesthetized Schirmer Score (mm) in Study Eye by Visit (Estimand 1) (ITT Population)

Parameter	Acoltremon BID 0.003% N=232	Vehicle BID N=234
Baseline (Day 1), predrop		
n*	232	234
Mean (SD)*	6.8(6.28)	6.4(5.47)
Median*	5.0	5.0
Min, max*	0, 35	0, 30

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Parameter	Acoltremon BID 0.003% N=232	Vehicle BID N=234
Day 7, predrop		
n*	222	226
Mean (SD)*	7.0 (6.66)	7.2 (6.31)
Median*	5.0	5.0
Min, max*	0, 35	0, 35
Change from Baseline Day 1 to predrop Day 7		
n	222	226
Mean (SD)	0.2(6.43)	0.7(5.70)
Median	0.0	1.0
Min, max	-23, 22	-20, 29
LS mean (SE)	0.2 (0.41)	0.5 (0.41)
LS mean difference (SE)	-0.3 (0.52)	
95% CI for LS mean difference	-1.3, -0.7	
p-value –ANCOVA	0.544	
p-value –WRS test	0.0384	
p-value –2-sample t-test	0.473	
Day 14, predrop		
n*	221	228
Mean (SD)*	6.2 (5.46)	7.0 (6.68)
Median*	5.0	5.0
Min, max*	0, 34	0, 35
Change from Baseline Day 1 to predrop Day 14		
n	221	228
Mean (SD)	-0.6(6.45)	0.5(6.83)
Median	-1.0	0.0
Min, max	-31, 24	-23, 31
LS mean (SE)	-0.6 (0.42)	0.4 (0.42)
LS mean difference (SE)	-1.0 (0.53)	
95% CI for LS mean difference	-2.0, 0.0	
p-value –ANCOVA	0.0583	
p-value –WRS test	0.215	
p-value –2-sample t-test	0.0683	
Day 28, predrop		
n*	219	229
Mean (SD)*	7.0(6.77)	6.9(6.58)
Median*	5.0	5.0
Min, max*	0, 35	0, 35
Change from Baseline Day 1 to predrop Day 28		
n	229	229
Mean (SD)	0.2(7.27)	0.4(6.35)
Median	0.0	0.0
Min, max	-34, 33	-19, 23
LS mean (SE)	0.0 (0.46)	0.1 (0.45)
LS mean difference (SE)	-0.1 (0.56)	
95% CI for LS mean difference	-1.2, 1.0	
p-value –ANCOVA	0.836	
p-value –WRS test	0.918	
p-value –2-sample t-test	0.765	

Parameter	Acoltremon BID 0.003% N=232	Vehicle BID N=234
Day 90, predrop		
n*	215	218
Mean (SD)*	6.8(6.03)	7.5(6.40)
Median*	5.0	6.0
Min, max*	0, 35	0, 34
Change from Baseline Day 1 to predrop Day 90		
n	215	218
Mean (SD)	0.0(6.48)	0.8(6.20)
Median	0.0	1.0
Min, max	-25, 25	-23, 26
LS mean (SE)	-0.3 (0.42)	0.5 (0.41)
LS mean difference (SE)	-0.7 (0.52)	
95% CI for LS mean difference	-1.8, 0.3	
p-value –ANCOVA	0.1583	
p-value –WRS test	0.318	
p-value –2-sample t-test	0.165	

Source: Statistical reviewer's analysis

* = available data

Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; LS, least squares; max, maximum; min, minimum; SANDE, Symptoms Assessment in Dry Eye; SE, Standard Error; WRS, Wilcoxon rank sum

6.3. Key Efficacy Review Issues

6.3.1. Uncertainty Regarding the Duration of the Treatment Effect

Issue

The duration of the treatment effect was not assessed.

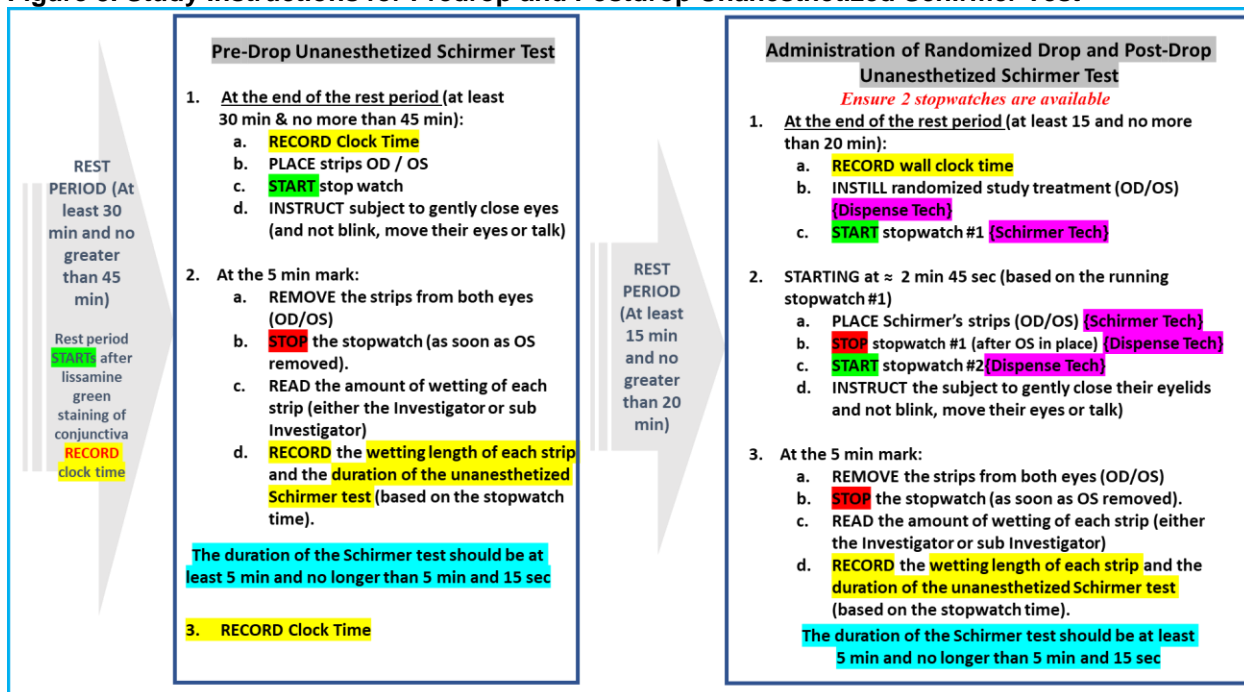
Background

The primary endpoint was met in two randomized, double-masked, well-controlled studies. The FDA has previously accepted drugs for the treatment of signs and symptoms of dry eye disease with two replicated studies that succeeded in demonstrating a statistically significant difference between the percentage of subjects achieving a 10-mm increase or more in Schirmer scores, without requiring a demonstration of symptom relief. Because this magnitude of increased tear production has been associated with a reduction in symptoms, the Division has accepted this primary efficacy endpoint without a corresponding symptom endpoint to support a demonstration of safety and efficacy.

Assessment

The postdrop Schirmer tests were all initiated at 2 minutes and 45 seconds postdrop for the first eye and 3 minutes postdrop for the second eye. The Schirmer test strips were removed 5 minutes later, then evaluated and compared to baseline predrop Schirmer. See the study instructions for predrop and postdrop unanesthetized Schirmer test below.

Figure 3. Study Instructions for Predrop and Postdrop Unanesthetized Schirmer Test



Source: COMET-3 Manual of Procedures, Version 1.0, Appendix 2
Abbreviations: OD, right eye; OS, left eye

The data obtained using this methodology provides an 8-minute sampling to assess the benefit in tear production in a drug seeking every 12 hours dosing.

The only tear production measurements that were measured at an interval exceeding 8 minutes were the predrop unanesthetized Schirmer tear tests performed at every visit in the COMET-2, COMET-3, and COMET-4 studies. Predrop unanesthetized Schirmer tear tests when performed at each visit, in both Tryptyr and vehicle groups when compared to Day 1 predrop unanesthetized Schirmer tear tests demonstrated <1 mm mean change from baseline in every study. These post Day 1 predrop Schirmer tests do tell us that any increase in tear production that had been present after taking the second drop on the previous day was no longer inducing increased tear production at the time of the testing visit. We do not know the time of the most recent drop prior to the testing visit so we don't have information to provide a degradation curve between the first 8 minutes of increased tear production and the unknown interval that led to the <1-mm increase the following day.

At each visit, the postdrop Schirmer tear test showed a higher proportion of Tryptyr subjects than vehicle subjects with a ≥ 10 -mm mean increase postdrop on day of visit versus predrop at baseline. This data demonstrates that Tryptyr provides a convincing repeated increase in tear production after each drop in a 90-day period, with the effect of each drop lasting at least 8 minutes. The window of time between 8 minutes and 12 hours postdrop is not assessed.

The FDA has previously accepted drugs for the treatment of signs and symptoms of dry eye disease with two replicated studies that succeeded in demonstrating a statistically significant difference between the percentage of subjects achieving a 10-mm increase or more in Schirmer scores, without requiring a demonstration of symptom relief.

This study demonstrated a lack of correlation between meeting the primary endpoint and meaningful benefit to the patient. The lack of statistical evidence of reduction of symptoms from baseline on all but one day of one study while the primary Schirmer test endpoint was replicated consistently, casts doubt upon the clinical relevance of the Schirmer test as performed in this study. The study provides little or no evidence that Tryptyr, dosed twice daily, improves the way dry eye patients feel or function.

The statistical reviewer noted that for DED signs, an evaluation of change in Schirmer score from predrop at baseline to pretreatment instillation at each visit, did not show a statistically significant difference at any of the 5 visits in both COMET-2 and COMET-3 studies. This may suggest that the twice daily dosing regimen of acotremon is not sufficient to maintain the treatment effect. Evidence is sufficient to recommend approval of Tryptyr [REDACTED] (b) (4)

Conclusion

The treatment group effect in the proportion of subjects who achieve a ≥ 10 -mm increase in Schirmer test score on Day 14 is considered a clinically significant endpoint without a corresponding symptom endpoint.

6.3.2. Clinical Significance of Corresponding Symptom Relief

Issue

Is evidence of symptom relief clinically significant?

Background

A statistically significant treatment group difference in the change from baseline in SANDE symptom score was only demonstrated in COMET-2. The Phase 2 study, COMET-1, failed its primary endpoint; thus, the secondary endpoints including change from baseline in SANDE score cannot be evaluated. In COMET-3, the change from baseline in SANDE score at Day 28 was not statistically significant. Clinically significant symptom relief was not demonstrated in clinical studies.

Assessment

Evidence of symptom relief represented by the global SANDE score was not demonstrated to be statistically superior to vehicle in relief of symptoms in replicated studies.

Conclusion

A separate demonstration of safety with a symptom endpoint was not demonstrated in replicated studies. However, the sign endpoint, the proportion of subjects who achieved a ≥ 10 -mm increase in Schirmer test score, is considered a clinically significant endpoint without a corresponding symptom endpoint.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

None identified.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Not applicable.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. Acoltremon ophthalmic solution has not been previously marketed.

7.3.1. Adverse Events Identified in Postmarket Experiences

Not applicable. Acoltremon ophthalmic solution has not been previously marketed.

7.3.2. Expectations on Safety

The active substance of Tryptyr (acoltremon ophthalmic solution) 0.003%, acoltremon, is composed of the chemical compound (1R,2S,5R)-N-(4-methoxyphenyl)-5-methyl-2-(1-methylethyl) cyclohexanecarboxamide, which is designated as generally recognized as safe (GRAS) (No. 4681) and used as a flavoring agent in food products (U.S. FDA/FEMA). Furthermore, acoltremon is structurally related to menthol and has been thoroughly evaluated by the European Food Safety Authority (Fl no. 16.123) without safety concerns ([European Food Safety Authority 2014](#)). This background, along with evidence from the nonclinical program for Tryptyr (acoltremon ophthalmic solution) 0.003% as presented within this NDA submission, fully support the overall safety of the product for topical ocular use.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

The clinical safety review focused on the safety database from COMET-2, COMET-3, and COMET-4. The COMET-1 study evaluated two different concentrations of acoltremon. The other studies all evaluated 0.003% acoltremon compared to placebo. These studies were reviewed to assess the safety of acoltremon ophthalmic solution.

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to the Medical Dictionary for Regulatory Activities (Version 25.0) preferred terms for the events reported in COMET-2, COMET-3, and COMET-4 were reviewed and found to be acceptable. Treatment-emergent adverse events (TEAEs) were protocol-defined as any event that occurred or worsened on or after the day that randomized study intervention was initiated. Percentages are based on the total number of subjects in the respective treatment for the population being analyzed.

For the presentation of the overall summary of TEAEs, TEAEs related to study intervention included possibly related or related TEAEs. TEAEs were also classified by strongest relationship to study intervention (not related, unlikely related, possibly related, or related). The relationship of each AE was determined by the investigator. TEAEs were also classified by maximum severity (mild, moderate, or severe). Severity was defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to them by the subject.

In addition, burning or stinging TEAEs that occurred upon study intervention instillation were identified by preferred term (PT) and/or reported AETERM (i.e., PT was "Instillation site pain" and AETERM contained "burning" or "stinging"). The number of subjects with burning or stinging upon study intervention instillation TEAEs, burning upon study intervention instillation TEAEs, and stinging upon study intervention instillation TEAEs were summarized separately in the same table using counts and percentages by maximum severity for each treatment group. The subjects who had a TEAE reporting both burning and stinging symptoms were counted once toward burning upon study intervention instillation TEAEs and once toward stinging upon study intervention instillation TEAEs.

7.5. Adequacy of the Clinical Safety Database

Data contributing to the overall safety evaluation of 0.003% acoltremon were collected within the Phase 2b and all Phase 3 clinical studies. The clinical safety database from the submitted studies sufficiently represented the population expected to use acoltremon ophthalmic solution, 0.003% so that its safety could be assessed.

Safety assessments included AEs, corrected visual acuity (CVA), slit lamp biomicroscopy parameters, dilated fundus examination, and intraocular pressure (IOP) for all studies. The two pivotal Phase 3 efficacy studies and the long-term safety study (LTSS) also evaluated subjects' vital signs and clinical labs for safety (hematology, chemistry, and urinalysis). In addition, the Phase 3 LTSS included assessments for best-corrected visual acuity (BCVA), endothelial cell count (ECC), and total ocular staining.

Integrated analysis of all safety parameters among studies was not supported due to differences in exposure to the CAE and timing of safety assessments in relation to study drug dosing. Specifically, IOP and dilated fundus examinations were conducted post-CAE at Screening (Baseline) and at Day 84/Exit in COMET-1 and were not collected on Day 1. This differed from the Phase 3 studies, which conducted IOP and dilated fundus assessments post-CAE (pivotal Phase 3 studies) or without CAE exposure (LTSS) at Screening (Baseline), and at follow-up visits without CAE exposure. Furthermore, while CVA and slit lamp examination were

conducted prior to CAE exposure in COMET-1, the follow-up timepoints differed, with no Day 7 evaluation within the study. Therefore, to accurately reflect the safety profile of 0.003% acoltremon, integration of ocular safety assessments was conducted according to the pooling strategy outlined in Module 2.7.4, Section 2.1.2.

Table 17. Treatment Exposure Safety Population (Integrated Safety Population)

Parameter	0.0014% Acoltremon		0.003% Acoltremon	
	(N=121)	(N=766)	(N=766)	Vehicle (N=688)
Treatment exposure (days)				
n	121	766	766	688
Mean (SD)	81.0 (14.47)	141.3 (112.83)	141.3 (112.83)	116.8 (90.48)
Median	85.0	92.0	92.0	92.0
Min, max	14, 100	1, 411	1, 411	1, 379
Categorical summary, n (%)				
1-15 days	2 (1.7)	29 (3.8)	29 (3.8)	22 (3.2)
16-30 days	3 (2.5)	10 (1.3)	10 (1.3)	16 (2.3)
31-60 days	2 (1.7)	7 (0.9)	7 (0.9)	13 (1.9)
61-90 days	113 (93.4)	180 (23.5)	180 (23.5)	170 (24.7)
91-180 days	1 (0.8)	383 (50.0)	383 (50.0)	387 (56.3)
181-365 days	0	110 (14.4)	110 (14.4)	50 (7.3)
>365 days	0	47 (6.1)	47 (6.1)	30 (4.4)

Source: ISS Table 14.1.5. Module 2.7.4 Summary of Clinical Safety Table 2-5

Note: N is the number of subjects in the respective treatment group for the population being analyzed. Treatment Exposure (days) = Date of Last Dose – Date of First Dose + 1.

Abbreviations: ISS, integrated summary of safety; SD, standard deviation

The overall exposure to the proposed Tryptyr (acoltremon ophthalmic solution) 0.003%, dosed BID, was adequate to assess safety for the full 12-month treatment period.

The safety population is representative of the population that Tryptyr is intended to treat. The safety database is adequate with respect to size, duration of exposure, duration of treatment, subject demographics, and disease characteristics.

Table 18. Demographics (Integrated Safety Population)

Characteristic	0.0014% Acoltremon		0.003% Acoltremon		Vehicle (N=688)	All Subjects (N=1575)
	(N=121)	(N=766)	(N=766)	(N=766)		
Age (years)						
n	121	766	766	766	688	1575
Mean (SD)	65.5 (10.89)	61.5 (13.21)	61.5 (13.21)	61.5 (13.21)	61.0 (13.10)	61.6 (13.04)
Median	67.0	63.0	63.0	63.0	63.0	63.0
Min, max	31, 85	24, 93	24, 93	24, 93	23, 90	23, 93
Age category (years), n (%)						
18-64	48 (39.7)	415 (54.2)	415 (54.2)	415 (54.2)	376 (54.7)	839 (53.3)
≥65	73 (60.3)	351 (45.8)	351 (45.8)	351 (45.8)	312 (45.3)	736 (46.7)
Sex, n (%)						
Male	39 (32.2)	194 (25.3)	194 (25.3)	194 (25.3)	185 (26.9)	418 (26.5)
Female	82 (67.8)	572 (74.7)	572 (74.7)	572 (74.7)	503 (73.1)	1157 (73.5)

Characteristic	0.0014% Acoltremon (N=121)	0.003% Acoltremon (N=766)	Vehicle (N=688)	All Subjects (N=1575)
Race, n (%)				
American Indian or Alaska Native	0	4 (0.5)	4 (0.6)	8 (0.5)
Asian	8 (6.6)	67 (8.7)	55 (8.0)	130 (8.3)
Black or African American	15 (12.4)	111 (14.5)	91 (13.2)	217 (13.8)
Native Hawaiian or Other Pacific Islander	0	4 (0.5)	1 (0.1)	5 (0.3)
White	97 (80.2)	572 (74.7)	531 (77.2)	1200 (76.2)
Multiracial	0	6 (0.8)	3 (0.4)	9 (0.6)
Other	1 (0.8)	2 (0.3)	3 (0.4)	6 (0.4)
Ethnicity, n (%)				
Hispanic or Latino	4 (3.3)	90 (11.7)	93 (13.5)	187 (11.9)
Not Hispanic or Latino	117 (96.7)	676 (88.3)	595 (86.5)	1388 (88.1)
Iris color – right eye, n (%)				
Black	2 (1.7)	19 (2.5)	15 (2.2)	36 (2.3)
Blue	33 (27.3)	164 (21.4)	169 (24.6)	366 (23.2)
Brown	50 (41.3)	395 (51.6)	329 (47.8)	774 (49.1)
Grey	1 (0.8)	2 (0.3)	6 (0.9)	9 (0.6)
Green	13 (10.7)	80 (10.4)	83 (12.1)	176 (11.2)
Hazel	22 (18.2)	106 (13.8)	86 (12.5)	214 (13.6)
Other	0	0	0	0
Iris color -left eye, n (%)				
Black	2 (1.7)	17 (2.2)	15 (2.2)	34 (2.2)
Blue	33 (27.3)	167 (21.8)	169 (24.6)	369 (23.4)
Brown	50 (41.3)	395 (51.6)	329 (47.8)	774 (49.1)
Grey	1 (0.8)	1 (0.1)	6 (0.9)	8 (0.5)
Green	13 (10.7)	80 (10.4)	83 (12.1)	176 (11.2)
Hazel	22 (18.2)	106 (13.8)	86 (12.5)	214 (13.6)
Other	0	0	0	0
Iris color group, n (%)				
Black/brown	52 (43.0)	411 (53.7)	344 (50.0)	807 (51.2)
Blue/grey/green	47 (38.8)	245 (32.0)	258 (37.5)	550 (34.9)
Hazel	22 (18.2)	106 (13.8)	86 (12.5)	214 (13.6)
Heterochromia	0	4 (0.5)	0	4 (0.3)

Source: ISS Table 14.1.2. Module 2.7.4 Summary of Clinical Safety, Table 2-6

Note: Percentages are based on the number of subjects (N) in the respective treatment group for the population being analyzed. Subjects who record more than one race are grouped into the single category denoted as Multiracial. The age in years is the age at the time of signing the informed consent form.

Abbreviations: ISS, integrated summary of safety; SD, standard deviation

Reviewer's comment: *The integrated safety population was 73.5% female, the mean age of the subjects 61.5 years. This population is representative of the U.S. population that will be likely to seek treatment for the symptoms of dry eye disease.*

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

AEs were elicited by the investigator during interviews of study subjects and from observations made by the study investigators. AEs were also collected for any new medical diagnosis or worsening in preexisting (prestudy) intercurrent illnesses. Within the integrated studies, changes

in any safety parameters (CVA, slit lamp biomicroscopy, dilated fundus examination, IOP, vital signs, and laboratory parameters, or BCVA, ECC, and total ocular staining in the LTSS) were assessed by the study investigator for potential AEs.

Table 19. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Adverse Event	0.0014% Acoltremon (N=121) n (%)	0.003% Acoltremon (N=766) n (%)	Vehicle (N=688) n (%)
Number of TEAEs	83	723	319
Number of subjects with at least one TEAE	57 (47.1)	456 (59.5)	202 (29.4)
Number of ocular TEAEs	63	491	109
Number of subjects with at least one ocular TEAE	51 (42.1)	409 (53.4)	83 (12.1)
Number of nonocular TEAEs	20	232	210
Number of subjects with at least one nonocular TEAE	18 (14.9)	154 (20.1)	136 (19.8)
Number of serious TEAEs	1	13	27
Number of subjects with at least one serious TEAE	1 (0.8)	12 (1.6)	22 (3.2)
Number of TEAEs related to study intervention ^a	53	441	56
Number of subjects with at least one TEAE related to study intervention ^a	46 (38.0)	392 (51.2)	46 (6.7)
Number of serious TEAEs related to study intervention ^a	0	0	0
Number of subjects with at least one serious TEAE related to study intervention ^a	0	0	0
Number of subjects with TEAEs by maximum severity ^b			
Mild	50 (41.3)	401 (52.3)	150 (21.8)
Moderate	5 (4.1)	46 (6.0)	35 (5.1)
Severe	2 (1.7)	9 (1.2)	17 (2.5)
Number of subjects with TEAEs by strongest relationship to study intervention ^b			
Not related	9 (7.4)	50 (6.5)	139 (20.2)
Unlikely related	2 (1.7)	14 (1.8)	17 (2.5)
Possibly related	8 (6.6)	41 (5.4)	16 (2.3)
Related	38 (31.4)	351 (45.8)	30 (4.4)
Number of TEAEs leading to study intervention discontinuation	3	28	23
Number of subjects with at least one TEAE leading to study intervention discontinuation	3 (2.5)	16 (2.1)	19 (2.8)
Number of TEAEs leading to death	0	0	0
Number of subjects with any TEAE leading to death	0	0	0

Source: ISS Table 14.3.1.1

Note: TEAEs are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated. Percentages are based on the total number of subjects (N) in the respective treatment group for the population being analyzed. TEAEs related to study intervention include TEAEs that are possibly related or related to study intervention.

If a subject experienced more than one adverse event, the subject is counted only once for the maximum severity or strongest relationship to study intervention.

Source: Module 2.7.4 Summary of Clinical Safety Table 3.1

Abbreviations: ISS, integrated summary of safety; TEAE, treatment-emergent adverse event

Table 20. Summary of Treatment-Emergent Adverse Events Reported in Clinical Studies by Subject (Integrated Safety Population), Studies COMET-1, COMET-2, COMET-3, and COMET-4

Adverse Event Type	COMET-1			COMET-2		COMET-3		COMET-4		Integrated ^a	
	0.0014% Acoltremon N=121	0.003% Acoltremon N=122	Vehicle N=126	0.003% Acoltremon n N=230	Vehicle N=235	0.003% Acoltremon n N=232	Vehicle N=234	0.003% Acoltremon n N=182	Vehicle N=93	0.003% Acoltremon n N=766	Vehicle N=688
Any treatment-emergent AE ^b	57 (47.1)	63 (51.6)	26 (20.6)	140 (60.9)	63 (26.8)	143 (61.6)	74 (31.6)	110 (60.4)	39 (41.9)	456 (59.5)	202 (29.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	1 (0.8)	1 (0.8)	2 (1.6)	1 (0.4)	6 (2.6)	3 (1.3)	6 (2.6)	7 (3.8)	8 (8.6)	12 (1.6)	22 (3.2)
Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DC study intervention due to an AE	3 (2.5)	2 (1.6)	4 (3.2)	4 (1.7)	4 (1.7)	5 (2.2)	6 (2.6)	5 (2.7)	5 (5.4)	16 (2.1)	19 (2.8)
Ocular	51 (42.1)	59 (48.4)	13 (10.3)	128 (55.7)	22 (9.4)	129 (55.6)	28 (12.0)	93 (51.1)	20 (21.5)	409 (53.4)	83 (12.1)
Related	46 (38.0)	54 (44.3)	7 (5.6)	126 (54.8)	13 (5.5)	122 (52.6)	14 (6.0)	88 (48.4)	12 (12.9)	390 (50.9)	46 (6.7)
Mild	49 (40.5)	56 (45.9)	12 (9.5)	125 (54.3)	20 (8.5)	124 (53.4)	25 (10.7)	88 (48.4)	17 (18.3)	393 (51.3)	74 (10.8)
Preferred terms >1% with acoltremon in any study											
Instillation site pain	45 (37.2)	53 (43.4)	4 (3.2)	120 (52.2)	10 (4.3)	118 (50.9)	7 (3.0)	90 (49.5)	7 (7.5)	381 (49.7)	28 (4.1)
Visual acuity reduced	2 (1.7)	2 (1.6)	2 (1.6)	2 (0.9)	1 (0.4)	3 (1.3)	1 (0.4)	1 (0.5)	1 (1.1)	8 (1.0)	5 (0.7)
Eye irritation	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.2)	2 (0.9)	0 (0.0)	0 (0.0)	5 (0.7)	2 (0.3)
Conjunctival haemorrhage	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.3)	1 (0.4)	2 (0.9)	1 (0.4)	2 (1.1)	1 (1.1)	7 (0.9)	4 (0.6)
Vision blurred	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.9)	1 (0.4)	2 (0.9)	3 (1.3)	3 (1.6)	0 (0.0)	8 (1.0)	5 (0.7)
Vitreous detachment	2 (1.7)	0 (0.0)	1 (0.8)	2 (0.9)	2 (0.9)	2 (0.9)	4 (1.7)	2 (1.1)	1 (1.1)	6 (0.8)	8 (1.2)
Swelling of eyelid	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)
Lacrimation increased	2 (1.7)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (1.1)	2 (0.3)	1 (0.1)
Eye pruritus	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.9)	2 (0.9)	2 (1.1)	3 (3.2)	5 (0.7)	5 (0.7)
Punctate keratitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.3)	0 (0.0)
Nonocular	18 (14.9)	9 (7.4)	16 (12.7)	43 (18.7)	44 (18.7)	47 (20.3)	50 (21.4)	55 (30.2)	26 (28.0)	154 (20.1)	136 (19.8)
Related	0	0	0	2 (0.9)	0	0	0	7 (3.8)	1 (1.1)	9 (1.2)	1 (0.1)
Mild	13 (10.7)	8 (6.6)	9 (7.1)	34 (14.8)	30 (12.8)	33 (14.2)	35 (15.0)	37 (20.3)	17 (18.3)	112 (14.6)	91 (13.2)

Adverse Event Type	COMET-1			COMET-2		COMET-3		COMET-4		Integrated ^a	
	0.0014% Acoltremon N=121	0.003% Acoltremon N=122	Vehicle N=126	0.003% Acoltremon n N=230	Vehicle N=235	0.003% Acoltremon n N=232	Vehicle N=234	0.003% Acoltremon n N=182	Vehicle N=93	0.003% Acoltremon n N=766	Vehicle N=688
Preferred terms >1% with acoltremon in any study											
Urinary tract infection	3 (2.5)	0	1 (0.8)	4 (1.7)	1 (0.4)	7 (3.0)	8 (3.4)	5 (2.7)	2 (2.2)	16 (2.1)	12 (1.7)
Headache	1 (0.8)	2 (1.6)	0	3 (1.3)	1 (0.4)	0	3 (1.3)	1 (0.5)	0	6 (0.8)	4 (0.6)
Dermatitis atopic	2 (1.7)	0	0	0	0	0	0	0	0	0	0
COVID-19	0	0	0	3 (1.3)	4 (1.7)	2 (0.9)	3 (1.3)	3 (1.6)	2 (2.2)	8 (1.0)	9 (1.3)
Sinusitis	1 (0.8)	0	0	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)	4 (2.2)	2 (2.2)	8 (1.0)	4 (0.6)
Blood alkaline phosphatase increased	0	0	0	1 (0.4)	1 (0.4)	3 (1.3)	0	2 (1.1)	0	6 (0.8)	1 (0.1)
Ear infection	0	0	0	1 (0.4)	0	1 (0.4)	0	2 (1.1)	0	4 (0.5)	0
Upper respiratory tract infection	0	0	0	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (1.1)	2 (2.2)	4 (0.5)	3 (0.4)
Alanine aminotransferase increased	0	0	0	2 (0.9)	1 (0.4)	0	1 (0.4)	3 (1.6)	0	5 (0.7)	2 (0.3)
Aspartate aminotransferase increased	0	0	0	2 (0.9)	1 (0.4)	2 (0.9)	1 (0.4)	3 (1.6)	0	7 (0.9)	2 (0.3)
White blood cell count increased	0	0	0	0	0	1 (0.4)	0	3 (1.6)	0	4 (0.5)	0
Red blood cells urine positive	0	0	0	0	0	0	0	2 (1.1)	0	2 (0.3)	0
Sciatica	0	0	0	1 (0.4)	0	0	1 (0.4)	2 (1.1)	1 (1.1)	3 (0.4)	2 (0.3)

Source: Module 2.5 Summary of Clinical Safety, Table 5.1

Integrated analysis presented only for 0.003% acoltremon and vehicle. Results for treatment 0.0014% acoltremon within the integrated analysis are identical to those within study COMET-1.

Any TEAE is reported by subject. Subjects who experienced multiple events (ocular and nonocular) are counted only once in the any TEAE category. Source: COMET-1 CSR Table 14.3.1.1.3, 14.3.1.1.1, 14.3.1.1.2, 14.3.1.2.1, 14.3.1.2.2, 14.3.1.7.1, 14.3.1.7.2

COMET-2 CSR Tables 14.3.1.1.1, 14.3.1.1.2, 14.3.1.1.3, 14.3.1.3.1; 14.3.1.3.2; 14.3.1.2.3; 14.3.1.2.2

COMET-3 CSR Tables 14.3.1.1.1, 14.3.1.1.2, 14.3.1.1.3, 14.3.1.3.1; 14.3.1.3.2; 14.3.1.2.3; 14.3.1.2.2

COMET-4 CSR Tables 14.3.1.1.1, 14.3.1.1.2, 14.3.1.1.3, 14.3.1.3.1, 14.3.1.3.2, 14.3.1.2.3, 14.3.1.2.2

ISS Tables 14.3.1.1, 14.3.1.3.1, 14.3.1.3.2, 14.3.1.7.1, 14.3.1.7.2, 14.3.1.8.1, 14.3.1.8.2

Note: Percentages are based on the total number of subjects (N) in the respective treatment group for the population being analyzed. TEAEs are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated.

Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

Abbreviations: AE, adverse event; CSR, clinical study report; DC, discontinued; ISS, integrated summary of safety; TEAE, treatment-emergent adverse event

Reviewer's comment: The most frequently reported ocular adverse reaction was instillation site pain, which occurred in 49.7% of treated subjects. The next most frequent adverse reactions, both occurring in 1% of subjects, were visual acuity reduced and vision blurred and should be included in labeling.

The most commonly reported nonocular adverse reaction was urinary tract infection, 2.1%.

7.6.1.1. Deaths, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

There were no treatment-emergent deaths reported in any studies.

7.6.1.2. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

All serious events were assessed as not related to treatment, were generally nonocular in nature, and occurred at a higher incidence in the vehicle (22 subjects, 3.2%) group compared to either 0.0014% acoltremon (1 subject, 0.8%) or 0.003% acoltremon (12 subjects, 1.6%) groups in the integrated safety population (ISS Table 14.3.1.1).

7.6.1.3. Dropouts and/or Discontinuations Due to Adverse Events, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Table 21. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Preferred Term	0.0014% Acoltremon	0.003% Acoltremon	Vehicle
	(N=121) n (%)	(N=766) n (%)	(N=688) n (%)
Any ocular TEAE leading to study intervention discontinuation	3 (2.5)	11 (1.4)	7 (1.0)
Preferred terms			
Instillation site pain	2 (1.7)	5 (0.7)	1 (0.1)
Instillation site reaction	0	1 (0.1)	0
Vision blurred	0	2 (0.3)	0
Eye pain	0	1 (0.1)	2 (0.3)
Photophobia	0	1 (0.1)	0
Posterior capsule opacification	0	1 (0.1)	0
Visual acuity reduced	0	1 (0.1)	0
Blepharitis	0	0	1 (0.1)
Corneal epithelium defect	0	0	1 (0.1)
Eye pruritus	0	0	1 (0.1)
Eyelid margin crusting	0	0	1 (0.1)
Eyelid oedema	1 (0.8)	0	0
Eyelids pruritus	0	0	1 (0.1)
Foreign body sensation in eyes	0	0	1 (0.1)
Ocular hyperaemia	0	0	1 (0.1)
Periorbital cellulitis	0	1 (0.1)	0

Source: Module 2.5 Summary of Clinical Safety, Table 5.2 Reference: ISS Table 14.3.1.6.1

Abbreviations: ISS, integrated summary of safety; TEAE, treatment-emergent adverse event

Reviewer's comment: *Treatment discontinuations due to adverse events were similar between treatment groups and did not suggest a safety signal. The most common adverse event which led to treatment discontinuation which occurred with the acoltremon 0.003% was instillation site pain. No subjects discontinued due to nonocular treatment-emergent adverse events.*

Table 22. Instillation Site Pain Severity in Subjects Reporting Adverse Events for Instillation Site Pain (Integrated Safety Population), Studies COMET-1, COMET-2, COMET-3, and COMET-4

Severity	0.0014% Acoltremon	0.003% Acoltremon	Vehicle
	N=45 n (%)	N=381 n (%)	N=28 n (%)
Mild	44 (97.8)	372 (97.6)	27 (96.4)
Moderate	0 (0.0)	8 (2.1)	1 (3.6)
Severe	1 (2.2)	1 (0.3)	0 (0.0)

Source: ISS Table 14.3.1.7.1

Abbreviations: ISS, integrated summary of safety; N, number of subjects with ocular TEAEs within the treatment group; n, number of subjects with TEAEs in that category of severity; TEAE, treatment-emergent adverse event

Table 23. Nonocular Treatment-Emergent Adverse Events Reported in ≥1% of Subjects in the Acoltremon Groups by Clinical Study and Treatment Group (Safety Population), Studies COMET-1, COMET-2, COMET-3, and COMET-4

System Organ Class Preferred Term	COMET-1			COMET-2		COMET-3		COMET-4		All	
	0.0014% Acol- tremon N=121 n (%)	0.003% Acol- tremon N=122 n (%)	Vehicle N=126 n (%)	0.003% Acol- tremon N=230 n (%)	Vehicle N=235 n (%)	0.003% Acol- tremon N=232 n (%)	Vehicle N=234 n (%)	0.003% Acol- tremon N=182 n (%)	Vehicle N=93 n (%)	0.003% Acol- tremon N=766 n (%)	Vehicle N=688 n (%)
Infections and infestations											
Urinary tract infection	3 (2.5)	0 (0.0)	1 (0.8)	4 (1.7)	1 (0.4)	7 (3.0)	8 (3.4)	5 (2.7)	2 (2.2)	16 (2.1)	12 (1.7)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	4 (1.7)	2 (0.9)	3 (1.3)	3 (1.6)	2 (2.2)	8 (1.0)	9 (1.3)
Sinusitis	1 (0.8)	0 (0.0)	0 (0.0)	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)	4 (2.2)	2 (2.2)	8 (1.0)	4 (0.6)
Ear Infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.1)	0 (0.0)	4 (0.5)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)	2 (1.1)	2 (2.2)	4 (0.5)	3 (0.4)
Nervous system disorders											
Headache	1 (0.8)	2 (1.6)	0 (0.0)	3 (1.3)	1 (0.4)	0 (0.0)	3 (1.3)	1 (0.5)	0 (0.0)	6 (0.8)	4 (0.6)
Injury, poisoning and procedural complications											
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	4 (0.5)	0 (0.0)
Investigations											
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	3 (1.3)	0 (0.0)	2 (1.1)	0 (0.0)	6 (0.8)	1 (0.1)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	1 (0.4)	3 (1.6)	0 (0.0)	5 (0.7)	2 (0.3)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	2 (0.9)	1 (0.4)	3 (1.6)	0 (0.0)	7 (0.9)	2 (0.3)
Red blood cells urine positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.3)	0 (0.0)
White blood cell count increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.6)	0 (0.0)	4 (0.5)	0 (0.0)
Nervous system disorders											
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	2 (1.1)	0 (0.0)	3 (0.4)	2 (0.3)
Metabolism and nutrition disorders											
Type 2 diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.4)	1 (0.1)
Respiratory, thoracic and mediastinal disorders											
Nasal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.3)	0 (0.0)

System Organ Class Preferred Term	COMET-1			COMET-2		COMET-3		COMET-4		All	
	0.0014% Acol- tremon N=121 n (%)	0.003% Acol- tremon N=122 n (%)	Vehicle N=126 n (%)	0.003% Acol- tremon N=230 n (%)	Vehicle N=235 n (%)	0.003% Acol- tremon N=232 n (%)	Vehicle N=234 n (%)	0.003% Acol- tremon N=182 n (%)	Vehicle N=93 n (%)	0.003% Acol- tremon N=766 n (%)	Vehicle N=688 n (%)
Skin and subcutaneous tissue disorders											
Dermatitis atopic	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (0.8)	1 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.9)	2 (1.1)	0 (0.0)	4 (0.5)	3 (0.4)
Vascular disorders											
Hypertension	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.6)	0 (0.0)	4 (0.5)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)0											
Basal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (2.2)	2 (0.3)	2 (0.3)

Source: COMET-1 CSR Table 14.3.1.2.2, COMET-2 CSR Table 14.3.1.2.3, COMET-3 CSR Table 14.3.1.2.3, COMET-4 CSR Table 14.3.1.2.3, ISS Table 14.3.1.3.2

Note: Percentages are based on the total number of subjects (N) in the respective treatment group for the population being analyzed. TEAEs are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated.

Adverse events are coded using MedDRA Version 25.0. Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT. SOCs and PTs within each SOC are listed in order of descending frequency for 0.003% acoltremon.

Source Module 2.74 Summary of Clinical Safety, Table 3.5

Abbreviations: CSR, clinical study report; ISS, integrated summary of safety; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Reviewer's comment: Urinary tract infections, Covid-19 infections, and sinusitis were the only nonocular TEAEs reported in $\geq 1\%$ of the 0.003% acoltremon arm in the safety population, 2.1%, 1.0%, and 1.0% compared to 1.7%, 1.3%, and 0.6% in the corresponding vehicle control arm.

Increased blood alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase were TEAEs reported in $\geq 1\%$ of the 0.003% acoltremon arm in the long-term safety study (COMET-4), 1.1%, 1.6%, and 1.6% compared to zero in the corresponding vehicle control arm.

7.6.1.4. Laboratory Findings, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

The incidence of TEAEs reported due to changes in serum chemistry parameters was generally similar between 0.003% acoltremon and vehicle, and the events were not reported in more than seven subjects in either treatment group. Of the AEs reported for clinically significant changes in serum chemistry parameters, in the 0.003% acoltremon group, 2 subjects at 1 site had increases in liver function tests that were assessed as possibly related to study intervention (one subject had alanine aminotransferase and aspartate aminotransferase increase on Day 178 which resolved at Day 369, and one subject had an increase in aspartate aminotransferase, alanine aminotransferase, and blood alkaline phosphatase on Day 364) (Listing 16.2.7.1.2). Reported TEAEs for any other clinically significant chemistry findings were assessed as not related to treatment by the investigator (ISS Table 14.3.1.3.2 and ISS Table 14.3.1.8.2).

Reviewer's comment: These abnormalities occurred in $< 1\%$ of the integrated safety population. They were not considered a safety signal.

7.6.1.5. Vital Signs, Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Blood pressure and heart rate were measured in the Phase 2b and Phase 3 studies. However, the Phase 2b collected vital signs only at Screening; therefore, they were not considered for the evaluation of safety.

Vital signs were assessed on Day 1 (Baseline) and the Exit visit for all Phase 3 studies, and on Days 14, 90, 180, and 270 in the Phase 3 LTSS. Heart rate was measured manually or by automated methods, and blood pressure was measured using an appropriate sphygmomanometer after the subjects were at rest (seated) for a minimum of 5 minutes.

Overall, data from the integrated safety population showed that vital signs remained stable without significant changes throughout the treatment period. There were no identified safety concerns with 0.003% acoltremon treatment related to vital signs.

7.6.1.6. Subgroups, Pooled Analyses, Integrated Safety Population, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Ocular and nonocular AEs were analyzed using the following intrinsic factors as subgroups: age, sex, race, and iris color. The safety analyses did not show any clear or consistent differences between the treatment groups in any of the subgroups.

NDA 217370

Tryptyr (acoltremon ophthalmic solution) 0.003%

Overview of Serious Adverse Events by Demographic Subgroup, Integrated Safety Population

No serious treatment-related TEAEs were reported in the integrated safety population (ISS Table 14.3.1.1). Serious TEAEs were mostly nonocular in nature, were reported at a rate of 3.2% or less in any treatment group and were not unexpected considering the age of the study population and length of studies. The rate of serious TEAEs was higher in subjects receiving vehicle (3.2%) than either active treatment (0.8% for 0.0014% acoltremon and 1.6% for 0.003% acoltremon), but no clinically relevant differences in the types or incidences of serious events were observed among treatment groups (ISS Table 14.3.1.5).

Table 24. Overview of Adverse Events by Demographic Subgroup, Integrated Safety Population Incidence of TEAEs by Demographic Subgroups by SOC for SOCs With Incidence >2.0% in Any Treatment Group in the Overall Population (Integrated Safety Population), Studies COMET-1, COMET-2, COMET-3, and COMET-4

Treatment Group	Overall Population m/n (%)	Age		Sex		Race ^a			Iris Color		
		18-64 Years m/n (%)	≥65 Years m/n (%)	Male m/n (%)	Female m/n (%)	Asian m/n (%)	Black m/n (%)	White m/n (%)	Black /Brown m/n (%)	Blue/ Grey/ Green m/n (%)	Hazel m/n (%)
Any TEAE											
0.0014%	57/121 (47.1)	22/48 (45.8)	35/73 (47.9)	15/39 (38.5)	42/82 (51.2)	1/8 (12.5)	6/15 (40.0)	49/97 (50.5)	25/52 (48.1)	23/47 (48.9)	9/22 (40.9)
0.003%	456/766 (59.5)	221/415 (53.3)	235/351 (67.0)	96/194 (49.5)	360/572 (62.9)	15/67 (22.4)	51/111 (45.9)	385/572 (67.3)	211/411 (51.3)	171/245 (69.8)	72/106 (67.9)
Vehicle	202/688 (29.4)	96/376 (25.5)	106/312 (34.0)	41/185 (22.2)	161/503 (32.0)	10/55 (18.2)	21/91 (23.1)	168/531 (31.6)	96/344 (27.9)	79/258 (30.6)	27/86 (31.4)
General disorders and administration site conditions											
0.0014%	45/121 (37.2)	17/48 (35.4)	28/73 (38.4)	15/39 (38.5)	30/82 (36.6)	1/8 (12.5)	4/15 (26.7)	39/97 (40.2)	21/52 (40.4)	16/47 (34.0)	8/22 (36.4)
0.003%	385/766 (50.3)	184/415 (44.3)	201/351 (57.3)	79/194 (40.7)	306/572 (53.5)	8/67 (11.9)	38/111 (34.2)	335/572 (58.6)	166/411 (40.4)	154/245 (62.9)	63/106 (59.4)
Vehicle	34/688 (4.9)	15/376 (4.0)	19/312 (6.1)	8/185 (4.3)	26/503 (5.2)	0/55 (0.0)	3/91 (3.3)	30/531 (5.6)	13/344 (3.8)	15/258 (5.8)	6/86 (7.0)
Eye disorders											
0.0014%	12/121 (9.9)	7/48 (14.6)	5/73 (6.8)	2/39 (5.1)	10/82 (12.2)	1/8 (12.5)	2/15 (13.3)	9/97 (9.3)	5/52 (9.6)	5/47 (10.6)	2/22 (9.1)
0.003%	61/766 (8.0)	33/415 (8.0)	28/351 (8.0)	15/194 (7.7)	46/572 (8.0)	4/67 (6.0)	12/111 (10.8)	44/572 (7.7)	37/411 (9.0)	16/245 (6.5)	7/106 (6.6)
Vehicle	49/688 (7.1)	21/376 (5.6)	28/312 (9.0)	12/185 (6.5)	37/503 (7.4)	1/55 (1.8)	1/91 (1.1)	46/531 (8.7)	24/344 (7.0)	20/258 (7.8)	5/86 (5.8)
Infections and Infestations											
0.0014%	4/121 (3.3)	1/48 (2.1)	3/73 (4.1)	0/39 (0.0)	4/82 (4.9)	0/8 (0.0)	0/15 (0.0)	4/97 (4.1)	1/52 (1.9)	2/47 (4.3)	1/22 (4.5)
0.003%	59/766 (7.7)	30/415 (7.2)	29/351 (8.3)	6/194 (3.1)	53/572 (9.3)	3/67 (4.5)	5/111 (4.5)	51/572 (8.9)	31/411 (7.5)	16/245 (6.5)	11/106 (10.4)
Vehicle	52/688 (7.6)	23/376 (6.1)	29/312 (9.3)	10/185 (5.4)	42/503 (8.3)	3/55 (5.5)	6/91 (6.6)	43/531 (8.1)	24/344 (7.0)	21/258 (8.1)	7/86 (8.1)

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Overall Treatment Group	Population m/n (%)	Age		Sex		Race ^a			Iris Color		
		18-64 Years m/n (%)	≥65 Years m/n (%)	Male m/n (%)	Female m/n (%)	Asian m/n (%)	Black m/n (%)	White m/n (%)	Black /Brown m/n (%)	Blue/ Grey/ Green m/n (%)	Hazel m/n (%)
Investigations											
0.0014%	1/121 (0.8)	1/48 (2.1)	0/73 (0.0)	0/39 (0.0)	1/82 (1.2)	0/8 (0.0)	0/15 (0.0)	1/97 (1.0)	0/52 (0.0)	1/47 (2.1)	0/22 (0.0)
0.003%	27/766 (3.5)	16/415 (3.9)	11/351 (3.1)	9/194 (4.6)	18/572 (3.1)	3/67 (4.5)	5/111 (4.5)	18/572 (3.1)	18/411 (4.4)	7/245 (2.9)	2/106 (1.9)
Vehicle	16/688 (2.3)	10/376 (2.7)	6/312 (1.9)	7/185 (3.8)	9/503 (1.8)	3/55 (5.5)	3/91 (3.3)	10/531 (1.9)	10/344 (2.9)	4/258 (1.6)	2/86 (2.3)
Nervous system disorders											
0.0014%	2/121 (1.7)	1/48 (2.1)	1/73 (1.4)	1/39 (2.6)	1/82 (1.2)	0/8 (0.0)	0/15 (0.0)	2/97 (2.1)	0/52 (0.0)	2/47 (4.3)	0/22 (0.0)
0.003%	21/766 (2.7)	11/415 (2.7)	10/351 (2.8)	2/194 (1.0)	19/572 (3.3)	1/67 (1.5)	1/111 (0.9)	19/572 (3.3)	10/411 (2.4)	7/245 (2.9)	4/106 (3.8)
Vehicle	13/688 (1.9)	7/376 (1.9)	6/312 (1.9)	1/185 (0.5)	12/503 (2.4)	0/55 (0.0)	2/91 (2.2)	11/531 (2.1)	5/344 (1.5)	5/258 (1.9)	3/86 (3.5)
Injury, poisoning and procedural complications											
0.0014%	3/121 (2.5)	0/48 (0.0)	3/73 (4.1)	2/39 (5.1)	1/82 (1.2)	0/8 (0.0)	0/15 (0.0)	3/97 (3.1)	1/52 (1.9)	2/47 (4.3)	0/22 (0.0)
0.003%	15/766 (2.0)	3/415 (0.7)	12/351 (3.4)	2/194 (1.0)	13/572 (2.3)	0/67 (0.0)	0/111 (0.0)	15/572 (2.6)	4/411 (1.0)	10/245 (4.1)	1/106 (0.9)
Vehicle	20/688 (2.9)	9/376 (2.4)	11/312 (3.5)	4/185 (2.2)	16/503 (3.2)	0/55 (0.0)	2/91 (2.2)	17/531 (3.2)	6/344 (1.7)	9/258 (3.5)	5/86 (5.8)
Skin and subcutaneous tissue disorders											
0.0014%	4/121 (3.3)	1/48 (2.1)	3/73 (4.1)	0/39 (0.0)	4/82 (4.9)	0/8 (0.0)	0/15 (0.0)	4/97 (4.1)	3/52 (5.8)	1/47 (2.1)	0/22 (0.0)
0.003%	9/766 (1.2)	4/415 (1.0)	5/351 (1.4)	0/194 (0.0)	9/572 (1.6)	0/67 (0.0)	0/111 (0.0)	8/572 (1.4)	4/411 (1.0)	5/245 (2.0)	0/106 (0.0)
Vehicle	5/688 (0.7)	3/376 (0.8)	2/312 (0.6)	0/185 (0.0)	5/503 (1.0)	1/55 (1.8)	0/91 (0.0)	4/531 (0.8)	4/344 (1.2)	1/258 (0.4)	0/86 (0.0)

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Treatment Group	Overall Population m/n (%)	Age		Sex		Race ^a			Iris Color			
		18-64 Years m/n (%)	≥65 Years m/n (%)	Male m/n (%)	Female m/n (%)	Asian m/n (%)	Black m/n (%)	White m/n (%)	Black /Brown m/n (%)	Blue/ Grey/ Green m/n (%)	Hazel m/n (%)	
Metabolism and nutrition disorders												
0.0014%	1/121 (0.8)	0/48 (0.0)	1/73 (1.4)	0/39 (0.0)	1/82 (1.2)	0/8 (0.0)	0/15 (0.0)	1/97 (1.0)	0/52 (0.0)	1/47 (2.1)	0/22 (0.0)	
0.003%	8/766 (1.0)	4/415 (1.0)	4/351 (1.1)	1/194 (0.5)	7/572 (1.2)	0/67 (0.0)	5/111 (4.5)	3/572 (0.5)	5/411 (1.2)	3/245 (1.2)	0/106 (0.0)	
Vehicle	15/688 (2.2)	8/376 (2.1)	7/312 (2.2)	1/185 (0.5)	14/503 (2.8)	0/55 (0.0)	3/91 (3.3)	12/531 (2.3)	6/344 (1.7)	6/258 (2.3)	3/86 (3.5)	

Source: ISS Tables 14.3.1.2, ISS Table 14.3.1.9.1, ISS Table 14.3.1.9.2, ISS Table 14.3.1.9.3, ISS Table 14.3.1.9.4

^a For the race categories containing ≥8 subjects

Note: Percentages are based on the total number of subjects (N) in the respective treatment group for the population being analyzed. TEAEs are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated.

Adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. Subjects experiencing more than one TEAE within a given SOC are counted once within that SOC.

Abbreviations: ISS, integrated summary of safety; m, number of subjects with an event; n, number of subjects in the group; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 25. Related TEAEs by Demographic Subgroup for the Most Common SOC and PT (1% or More Incidence in Preferred Term in Any Treatment Group in the Overall Population) (Integrated Safety Population), Studies COMET-1, COMET-2, COMET-3, and COMET-4

Treatment Group	Overall Population m/n (%)	Age		Sex		Race ^a			Iris Color			
		18-64 Years m/n (%)	≥65 Years m/n (%)	Male m/n (%)	Female m/n (%)	Asian m/n (%)	Black m/n (%)	White m/n (%)	Brown /Black m/n (%)	Blue/ Grey/ Green m/n (%)	Hazel m/n (%)	
Any related TEAE												
0.0014%	46/121 (38.0)	17/48 (35.4)	29/73 (39.7)	14/39 (35.9)	32/82 (39.0)	1/8 (12.5)	4/15 (26.7)	40/97 (41.2)	20/52 (38.5)	18/47 (38.3)	8/22 (36.4)	
0.003%	392/766 (51.2)	190/415 (45.8)	202/351 (57.5)	82/194 (42.3)	310/572 (54.2)	8/67 (11.9)	43/111 (38.7)	338/572 (59.1)	171/411 (41.6)	155/245 (63.3)	64/106 (60.4)	
Vehicle	46/688 (6.7)	20/376 (5.3)	26/312 (8.3)	11/185 (5.9)	35/503 (7.0)	1/55 (1.8)	4/91 (4.4)	40/531 (7.5)	20/344 (5.8)	19/258 (7.4)	7/86 (8.1)	

Treatment Group	Overall Population m/n (%)	Age		Sex		Race ^a			Iris Color		
		18-64 Years m/n (%)	≥65 Years m/n (%)	Male m/n (%)	Female m/n (%)	Asian m/n (%)	Black m/n (%)	White m/n (%)	Brown /Black m/n (%)	Blue/ Grey/ Green m/n (%)	Hazel m/n (%)
SOC: General disorders and administration site conditions											
0.0014%	43/121 (35.5)	15/48 (31.3)	28/73 (38.4)	14/39 (35.9)	29/82 (35.4)	1/8 (12.5)	4/15 (26.7)	37/97 (38.1)	20/52 (38.5)	16/47 (34.0)	7/22 (31.8)
0.003%	379/766 (49.5)	181/415 (43.6)	198/351 (56.4)	79/194 (40.7)	300/572 (52.4)	8/67 (11.9)	38/111 (34.2)	331/572 (57.9)	162/411 (39.4)	153/245 (62.4)	62/106 (58.5)
Vehicle	31/688 (4.5)	14/376 (3.7)	17/312 (5.4)	8/185 (4.3)	23/503 (4.6)	0/55 (0.0)	3/91 (3.3)	27/531 (5.1)	13/344 (3.8)	13/258 (5.0)	5/86 (5.8)
PT: Instillation site pain											
0.0014%	43/121 (35.5)	15/48 (31.3)	28/73 (38.4)	14/39 (35.9)	29/82 (35.4)	1/8 (12.5)	4/15 (26.7)	37/97 (38.1)	20/52 (38.5)	16/47 (34.0)	7/22 (31.8)
0.003%	377/766 (49.2)	180/415 (43.4)	197/351 (56.1)	79/192 (40.7)	298/572 (52.1)	8/67 (11.9)	37/111 (33.3)	330/572 (57.7)	160/411 (38.9)	153/245 (62.4)	62/106 (58.5)
Vehicle	28/688 (4.1)	13/376 (3.5)	15/312 (4.8)	7/185 (3.8)	21/503 (4.2)	0/55 (0.0)	2/91 (2.2)	26/531 (4.9)	10/344 (2.9)	13/258 (5.0)	5/86 (5.8)

Source: ISS Table 14.3.1.9.1, ISS Table 14.3.1.9.2, ISS Table 14.3.1.9.3, ISS Table 14.3.1.9.4

^a For the race categories containing ≥8 subjects

Most common SOC and PT defined as those with ≥1% incidence in any treatment group. Events considered related to treatment included those possibly related or related.

Note: Percentages are based on the total number of subjects (N) in the respective treatment group for the population being analyzed. TEAEs are defined as any event that occurs or worsens on or after the day that randomized study intervention is initiated.

Adverse events are coded using MedDRA Version 25.0. Subjects experiencing more than one TEAE within a given SOC or PT are counted once within that SOC or PT.

Abbreviations: ISS, integrated summary of safety; m, number of subjects with an event; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects in the group;

PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

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Reviewer's comment: Overall, no conclusions could be drawn based on the relatively small numbers analyzed in most subgroup analyses.

7.6.1.7. Exposure-Adjusted Pooled Analyses, Studies COMET-1, COMET-2, COMET-3, and COMET-4

Not applicable.

7.6.2. Safety Results, Study COMET-4

Safety data from study COMET-4 which was either unique to the COMET-4 study or not pooled with the other pooled studies will be presented in this section.

IOP

There were no safety concerns following a review of the IOP.

Dilated Fundus Examination

Dilated fundus examination was comparable between the Tryptyr group and vehicle group.

BCVA

There were no safety concerns following review of visual acuity assessments.

ECC

There were no safety concerns following a review of endothelial cell count data. The percent of subjects with a $\geq 10\%$ decrease from baseline in endothelial cell density was $\leq 5.1\%$ and comparable between treatment groups.

The percent of subjects without polymegathism at baseline who had polymegathism at study exit was $\leq 1.4\%$ and comparable between treatment groups.

Total Ocular Staining (Oxford Grading)

Revealed no safety concerns.

PK Results

Systemic exposure to 0.003% acoltremon was evaluated in a subset of subjects. Overall, the lack of measurable plasma concentrations of acoltremon in most (22 of 25) subjects indicates that systemic exposure via the topical ocular route is negligible.

Extent of Exposure**Table 26. Treatment Exposure Duration (Safety Population), Study COMET-4**

Exposure Parameter	0.003% Acoltremon (N=182)	Vehicle (N=93)
Total exposure duration (days)		
n	182	93
Mean (SD)	319.4 (104.55)	316.8 (110.17)
Median	363.0	364.0
Min, max	1, 411	3,379

Source: Table 14.1.5.2

Note: N is the number of subjects in the respective treatment for the population being analyzed.

Note: Treatment Exposure Duration (days) = Date of Last Dose – Date of First Dose + 1. The Date of Last Dose is the latest nonmissing dosing date collected on the Study Exit eCRF page or the Study Drug Administration eCRF page, and the Date of First Dose is collected on the Study Drug Administration eCRF page.

Abbreviation: eCRF, electronic case report file

Exposure duration of study intervention was comparable between groups.

Table 27. Summary of Subject Disposition (Population: All Subjects), Study COMET-4

Disposition	0.003% Acoltremon n (%)	Vehicle n (%)	All Subjects n (%)
Total screened ^a			318
Screen failures ^a			43
Enrolled ^a			275
Randomized ^a	182	93	275
Analysis populations ^b			
mITT	182 (100.0)	93 (100.0)	275 (100.0)
Safety	182 (100.0)	93 (100.0)	275 (100.0)
PP	181 (99.5)	93 (100.0)	274 (99.6)
PK	25 (13.7)	13 (14.0)	38 (13.8)
Study completion			
Completed study	149 (81.9)	76 (81.7)	225 (81.8)
Discontinued from study	33 (18.1)	17 (18.3)	50 (18.2)
Reason for discontinuation			
Adverse event	3 (1.6)	4 (4.3)	7 (2.5)
Withdrawal of consent	19 (10.4)	10 (10.8)	29 (10.5)
Noncompliance	1 (0.5)	1 (1.1)	2 (0.7)
Lost to follow-up	8 (4.4)	1 (1.1)	9 (3.3)
Disallowed concurrent treatment	1 (0.5)	0	1 (0.4)
Pregnancy	0	0	0
Investigator decision	0	0	0
Protocol deviation	0	0	0
Death	0	0	0
Other	1 (0.5)	1 (1.1)	2 (0.7)
Protocol deviations ^c			
Any protocol deviations	154 (84.6)	73 (78.5)	227 (82.5)
Major protocol deviations	71 (39.0)	34 (36.6)	105 (38.2)
Minor protocol deviations	137 (75.3)	73 (78.5)	210 (76.4)
Protocol deviations related to COVID-19	0	0	0

Source: Table 14.1.1

Note: Percentages are based on the number of randomized subjects in the treatment group unless otherwise specified.

^a A subject could be rescreened once, and the subject was reported based on their final enrollment status (screen failure or randomized). Enrolled subjects were those who signed informed consent and met all eligibility criteria but may or may not have been randomized.^b mITT subjects were reported as randomized, Safety, PP, and PK subjects were reported as treated.^c Severities of the deviations were assigned by the Applicant before database lock.

Abbreviations: mITT, modified intent-to-treat; PK, pharmacokinetic; PP, per-protocol

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study COMET-4

Safety-related results of individual studies COMET-2 and COMET-3 are covered in the discussion of the Pooled Integrated Safety Population. Safety results from the COMET-4 study which were not pooled are discussed in Section [7.6.2](#), above. Pertinent elements of the design of Study COMET-3 can be found in Section [17](#).

7.7. Key Safety Review Issues

There are no key safety review issues.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable.

8.2. Extrinsic Factors

Tryptyr is not effective during topical ophthalmic anesthesia. No other drug interaction studies were performed.

8.3. Plans for Pediatric Drug Development

An Initial Pediatric Study Plan (iPSP), which included a request for a full waiver of required pediatric assessments for Acoltremon Ophthalmic Solution 0.003%, was submitted to the Agency (IND: 147005; seq0022) in February 2022. The agreed iPSP with additional edits, as suggested by the Agency, was also submitted in June 2022 (seq0024).

In this submission, Aerie requested a full waiver for the pediatric population from birth to 17 years. The pathophysiology of dry eye syndrome occurs, for the most part, only in adults. Dry eye syndrome is included in FDA's list of adult-related conditions that qualify for a waiver because studies are impossible or highly impracticable due to the low incidence of dry eye in the pediatric population.

There is no pending or agreed investigational plan for pediatric studies with the European Medicines Agency, Pharmaceuticals and Medical Device Agency, or any other regulatory authority.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Tryptyr has not been tested in pregnant or lactating women. Males of reproductive potential were not excluded from the study population. The intravenous administration of acoltremon to pregnant rats and rabbits during organogenesis did not produce embryo-fetal toxicity at

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approximately 806- and 2151-fold the recommended human ocular dose (RHOD) of acoltremon ophthalmic solution, 0.003% on a mg/m² basis.

Fertility and pre- and postnatal development animal studies have not been performed because there is negligible clinical systemic exposure at the RHOD and lack of systemic toxicity.

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 217370 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. The shelf life of 18 months for acoltremon ophthalmic solution is granted when stored at 2°C to 8°C.

9.1. Device or Combination Product Considerations

The product is regulated as a drug and device combination product per the Genus decision. The Center for Devices and Radiological Health confirmed that no Center for Devices and Radiological Health consult was necessary on June 6, 2024.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Independent Ethics Committee or Institutional Review Board

This study was conducted in accordance with Institutional Review Board (IRB) regulations (i.e., U.S. 21 CFR Part 56.103) and good clinical practice regulations. The investigators obtained appropriate approval from a properly constituted IRB/Independent Ethics Committee prior to initiating the study. A copy of a letter from the IRB/Independent Ethics Committee indicating approval of each investigator was received by the Sponsor prior to the investigator conducting any study-specific procedures.

The protocol, protocol amendments, informed consent form, and all documents that were provided to subjects (i.e., subject diary, subject dosing instructions) were submitted to the IRBs for review and approval.

Ethical Conduct of the Study

This study was conducted in accordance with current good clinical practice, the ethical principles that have their origin in the Declaration of Helsinki ([World Medical Association 2013](#)), Parts 50, 54, 56, and 312 of Title 21 of the CFR, International Conference on Harmonization (ICH)

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Guideline E6 R2, and the standard operating procedures of Aerie Pharmaceuticals[®], Inc. (Aerie), Statistics & Data Corporation, and other vendors participating in the conduct of the study.

Subject Information and Consent

The consent process occurred before any study-specific procedures were initiated.

All forms provided directly to the subject were approved by the Sponsor and IRB prior to their use. If such forms required revision, the investigator was responsible for ensuring that:

- The amended documents were reviewed and approved by the Sponsor prior to submission to the governing IRB.
- The revised consent form was read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study, if directed by the IRB.

Source: AR-15512 Ophthalmic Solution Clinical Study Report: COMET-2

11. Advisory Committee Summary

No advisory committee meeting was held for this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

Aerie Pharmaceuticals, Inc. submitted investigational new drug (IND) 147005 for acoltremon for the signs and symptoms of DED to the FDA on August 28, 2020. Tryptyr (acoltremon ophthalmic solution) 0.003% is a preservative-free ophthalmic formulation of acoltremon drug substance for topical ocular administration packaged in a single-use ophthalmic dispenser and was developed as a drug, in compliance with 21 CFR Part 312.

- June 12, 2020: Pre-IND meeting to discuss the nonclinical and chemistry, manufacturing, and controls information required to support the IND filing, the design of the proposed Phase 2b clinical study, and the nonclinical and clinical development plans.
- January 28, 2022: End of Phase 2 meeting to discuss development of the two Phase 3 studies, as well as inclusion of the PK clinical evaluation in the long-term safety study COMET-4.
- February 2022 An iPSP, which included a request for a full waiver of required pediatric assessments for acoltremon ophthalmic solution 0.003%, was submitted to the Agency.
- June 2022: The agreed iPSP with additional edits, as suggested by the Agency, was also submitted (Source Module 2.5 Clinical Overview Section 1.2.2 [Pediatric Waiver]).

“Alcon acknowledges and as stated in Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry July 2020 FDA guidance, that the Agency is not at liberty to make a formal decision about granting a waiver for pediatric assessments until the time of the approval of the NDA, and as such, request for full waiver for pediatric studies is included for final decision within this acoltremon ophthalmic solution 0.003% NDA submission (Section 1.9.1) “ ([July 2020](#))

- With the issuance of the FDA guidance for industry *Certain Ophthalmic Products: Policy Regarding Compliance with 21 CFR Part 4* ([March 2022](#)), Acoltremon ophthalmic solution 0.003% was reclassified as a drug-led combination product, thus requiring its compliance with 21 CFR Part 4 and 21 CFR Part 820.30. Procedures were developed to follow 21 CFR Part 4, and the proceeding development of acoltremon ophthalmic solution 0.003% was completed following Design Controls, which is summarized in Section 3.2.R.
- February 13, 2024: The agency accepted Alcon’s Use-Related Risk Analysis study results in lieu of a Human Factors validation study for Acoltremon ophthalmic solution 0.003%. After the reclassification to a drug-led combination product, Alcon Laboratories (Alcon) conducted a Use-Related Risk Analysis for acoltremon ophthalmic solution 0.003% to gain insight into any potential use errors and also review any relevant risk mitigation strategies to reduce the likelihood of harm from use errors. Subsequently, this risk analysis formed the basis for the justification to not conduct a Human Factors validation study for acoltremon ophthalmic solution 0.003%.

- March 4, 2024: Pre-NDA meeting to discuss the nonclinical, clinical, chemistry, manufacturing, and control information to support the NDA filing for acoltremon ophthalmic solution 0.003%

During the meeting, Alcon indicated it would be submitting data from one Phase 2b study (COMET-1) and two pivotal Phase 3 studies (COMET-2 and COMET-3) to adequately support an NDA submission for acoltremon ophthalmic solution 0.003% for the treatment of the signs and symptoms of dry eye disease. The Agency explained that adequacy of the data is a review issue and cannot be addressed until the NDA is submitted and reviewed. The submission of data for the long-term, 12-month safety study (COMET-4) was also discussed at the meeting, with Alcon presenting justification that based on the safe profile of the product to date, submission of the 12-month safety data could be submitted within the Day 120 Safety Update report window during NDA review. Although the Agency expressed it was not the current Division's recommendation that COMET-4 be submitted in the 120-Day Safety Update report, the approach was acceptable as previously discussed and agreed to with Dr. Wiley Chambers. The Agency requested that Alcon submit completed PK data from the long-term safety study (COMET-4) at the time of initial NDA submission, which was agreed to by Aerie.

Reviewer's comment: The FDA Form 1571 submitted with the Sponsor Minutes to the March 4, 2024, Pre-NDA meeting identified Aerie as the Sponsor. The minutes referenced Alcon as the meeting participants. The change in Sponsor identity was clarified in correspondence on July 3, 2024, see below.

- July 31, 2024, Alcon Laboratories, Inc. notified the FDA that the Sponsor name change had occurred through merger/acquisition and IND 147005 was included in the transfer.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Studies Reviewed

- TDOC-PHAR-00101: AVX-012 activity on TRPM8-Human Embryonic Kidney (HEK) cells
- TDOC-PHAR-00102: Effect of AVX-012 on the activity of corneal cold thermoreceptor nerve endings
- TDOC-PHAR-00103: Effect of AVX-012 on blinking and tearing in awake guinea pigs
- TDOC-PHAR-00104: Effect of AVX-012 formulations on the neural activity of corneal cold thermoreceptors recorded in vitro
- STF-AR-1512-IPK01: In vitro S9 metabolism of AR-15512
- STF-AR-1512-IPK01: In vitro binding of AR-15512 to rat, rabbit, dog, and human plasma

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- STF-G10986 AVX-012: 28-day repeat dose intravenous toxicity study in Sprague-Dawley rats with 14-day recovery period and toxicokinetics
- STF-G10985 AVX-012: 28-day repeat dose toxicity and local tolerance study in New Zealand White rabbits by the ocular route
- STF-474-0002-TX AVX-012: 28-day repeated dose toxicity ocular toxicity study in beagle dogs with a 14-day recovery period
- STF-AR-15512-AS01: 90-day study of AR-15512 by ocular administration in rabbits with a 14-day recovery period
- STF-AR-15512-AS02: 90-day study of AR-15512 by ocular administration in dogs with a 14-day recovery period
- STF-G10982 AVX-12: Bacterial reverse mutation test
- STF-G10983 AVX-012: In vitro mammalian chromosomal aberration test in human peripheral blood lymphocytes
- STF-G10984 AVX-012: Local lymph node assay in CBA/Ca mice
- STF-TDOC-TOX-0012: Toxicology 2. AVX-012 acute ocular irritation study in New Zealand rabbit
- STF-1741500 AVX-012: Cytotoxicity assay in vitro with BALB/c 3T3 cells: neutral red test during simultaneous irradiation with artificial sunlight
- STF-TDOC-TOX-00101: Toxicology 1. AVX-012 toxicity on HEK cells
- AR-15512-AS03: 6-month study of AR-15512 by ocular administration in rabbits with a 14-day recovery period
- AR-15512-AS04: 6-month study of AR-15512 by ocular administration in dogs with a 14-day recovery period
- 50662.01102: Evaluation of in vivo micronucleus frequency in female Sprague Dawley Rats administered AR-15512

Pharmacology

The published literature establishes that acoltremon (as WS-12) is a TRPM8 agonist like menthol. TRPM8, a calcium-permeable cation channel, is a cold sensor in humans. The activation of TRPM8 opens the channel and allows influx of calcium ions into the cell, resulting in cold thermal transduction and pain detection, among other effects ([Izquierdo et al. 2021](#)). The Applicant verified this activity in vitro (using cells transfected with rat TRPM8) and ex vivo

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(using guinea pig corneas). In vivo, topical ocular acoltremon increased blinking immediately after administration.

- Acoltremon activity compared to menthol was studied in vitro on rat TRPM8-transfected HEK cells. In this assay, acoltremon activated TRPM8 (increasing cytosolic calcium influx) with an EC_{50} of 0.9 to 26.0 μM (measured by microfluorometry) and 13.5 to 20.8 μM (measured by patch clamp electrophysiology).
 - **Reviewer's comment:** *The large range of EC_{50} s obtained in this assay may reflect the lack of solubility of the test compound in the cell medium.*
- Acoltremon toxicity was also studied in vitro on HEK cells. In this MTT assay to determine cell viability, no cytotoxicity was observed at 1 μM , whereas slight dose-dependent responses occurred at 10 μM (-4.0% cell viability) and 100 μM (-10.1% cell viability).
- Acoltremon activated the corneal cold thermoreceptor (TRPM8) nerve endings ex vivo in the Guinea pig with an EC_{50} of 47.7 μM (measured by nerve terminal impulse [NTI] activity in response to exposure to cold).
- A single topical ocular dose of acoltremon (10 $\mu\text{L}/\text{eye}/\text{OU}$ at 0, 10, 50, or 200 μM acoltremon into the lower conjunctival sac) increased blink rate in guinea pigs (measured over 5 minutes) and in parallel, a slight but not statistically significant increase in tear rate was measured compared to vehicle, with an EC_{50} of 9.1 μM .

The literature indicated that acoltremon is a specific agonist of TRPM8 without activity on other transient receptor potential (TRP) channels such as TRPV1, TRPV2, TRPV3, TRPV4 and TRPA1 ([Sherkheli et al. 2008](#)).

There was no evidence of test-article-related adverse effects on cardiovascular and central nervous system functions, when evaluated during the good laboratory practice (GLP) toxicity studies in the dog and the rat.

Reviewer's comment: *Taking into account the most conservative EC_{50} of approximately 1 μM (289 pg/mL) (range 1 to 50 μM) observed in pharmacology studies in vitro, and at least 90% protein binding in all species tested, and in the absence of observable systemic toxicity in all GLP ocular studies in the rabbit and the dog, this reviewer judged that the systemic exposure to the test article (free maximum plasma concentration [C_{max}]) can be considered negligible and hence, neither on- nor off-target activity of the test article could be expected other than locally in the ocular tissues.*

Pharmacokinetics/Absorption, Distribution, Metabolism, Excretion/Toxicokinetics

- At the end of the dosing period, in an ocular distribution study in the rabbit where animals received 3 µg/eye/day (1.67-fold the therapeutic dose) for 28 days, acoltremon was detected in the conjunctiva of 2 out of 8 eyes, while cornea, conjunctiva, aqueous humor, iris/ciliary body, vitreous humor, and retina were below the LLOQ of 5.05 ng/mL in all animals. Similarly, exposure in all blood samples was below the acoltremon LLOQ of 0.2 ng/mL.
- Acoltremon was 90 to 95% protein bound in all species studied in vitro (dog, rat, rabbit, human).
- No human specific metabolite was found in vitro.
- In ocular toxicity studies, the test article was detected in the blood at the end of a 6-month dosing period in the dog and the rabbit at a LLOQ of 20 pg/mL. On Days 178 to 180, at the ocular and systemic no observed adverse effect levels (NOAELs) of 4.793 µg/eye/day and 9.586 µg/animal/day in both species, mean acoltremon C_{max} was 78.8 pg/mL and AUC_{last} was 80.7 hr·pg/mL for male and female rabbits combined, while in the dogs, mean acoltremon C_{max} was 364 pg/mL and AUC_{last} was 235 hr·pg/mL for males and females combined.

Toxicity

- In a 28-day repeat-dose intravenous GLP toxicity study in the Sprague-Dawley rat with a 14-day recovery period, at the doses of 4, 12, and 36 µg/kg/day acoltremon, the highest dose tested was the NOAEL. Test-article-related, dose-dependent decreases in serum calcium levels were observed, possibly due to excess pharmacological activity of the test article causing calcium mobilization. Calcium levels recovered after a 2-week reversibility period and the finding was not considered adverse. There was about 97-fold clinical safety margin with the RHOD of 1.8 µg/eye/day, in mg/m² equivalent.
- In 6-month repeat dose ocular GLP toxicity studies in the beagle dog and the New Zealand White rabbit with 14-day recovery periods, at the doses of 0.868, 1.736, and 4.793 µg/eye/day/OU acoltremon, the highest dose tested was the NOAEL in both species. Test-article-related, reversible, nonadverse conjunctival redness and swelling (rabbit) and/or ocular discharge (dog) were observed. There were about 3-fold ocular safety margins with the RHOD compared to the rabbit and the dog ocular NOAELs and 29- and 9-fold systemic safety margins with the RHOD, in mg/m² equivalent, compared to the rabbit and the dog systemic NOAELs, respectively.

Table 28. Ocular Safety Margins Based on NOAELs in Pivotal Toxicology Studies

Species/ Duration	NOAEL	Total Dose µg/Eye/Day	Clinical Safety Margin (Based on Clinical Dose of 1.8 µg/Eye/Day)
Rabbit/6 months	0.004%/QID	4.793	2.7x
Dog/6 months	0.004%/QID	4.793	2.7x

Source: created by the reviewer from source data

Abbreviations: NOAEL, no observed adverse effect level; QID, four times daily

Table 29. Systemic Safety Margins Based on NOAELs in Pivotal Toxicology Studies

Species/ Duration	NOAEL ^a µg/kg/Day	HED µg/kg/Day	C _{max} pg/mL ^b AUC pg-h/mL ^b	Clinical Safety Margin (Based on Clinical Dose ^c of 0.06 µg/kg/Day)
Rat/28 days (IV)	36	5.0865	C _{max} =31100 AUC _{last} =10595	96x
Rabbit/6 months (ocular)	5.3256	1.7180	C _{max} =79 AUC _{last} =81	28x
Dog/6 months (ocular)	0.9586	0.5326	C _{max} =364 AUC _{last} =235	8.9x

Source: created by the reviewer from source data

^a Calculations based on a 1.8 kg rabbit and a 10 kg dog

^b Males and females combined

^c Calculation based on a 60-kg adult

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; HED, human equivalent dose; IV, intravenous; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

Genotoxicity

A standard battery of tests was performed according to GLP standards. All studies were valid and acoltremon was negative in the Ames test, an in vitro chromosomal aberration test in human peripheral blood lymphocytes, and an in vivo micronucleus assay in the rat.

Special Toxicology Studies

- In the neutral red uptake test with BALB/c 3T3 fibroblasts simultaneously irradiated with artificial sunlight, acoltremon at up to 15.6 µg/mL, the highest dose tested, showed no cytotoxicity (with or without irradiation).
- The product was not a sensitizer in the local lymph node assay performed with CBA/Ca mice at up to 50% acoltremon applied on the dorsal surface of both ears once daily (25 µL/dose) for 3 days consecutively.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Studies and Documents Reviewed

- Impurities and degradants
- Waiver request for carcinogenicity studies
- Waiver request for fertility/early embryonic development, and pre- and postnatal development studies
- AR15512-AS07: An Intravenous Slow Push Study of the Effects of AR-15512 on Embryo/Fetal Development in Rats
- AR15512-AS08: An Intravenous Slow Push Study of the Effects of AR-15512 on Embryo/Fetal Development in Rabbits

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Carcinogenicity

Carcinogenicity studies were not conducted with acoltremon. ICH S1A indicates that pharmaceuticals administered by the ocular route may not require carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure ([March 1996](#)).

Alcon consulted with the Agency at the pre-NDA meeting held on March 4, 2024, on supporting data required for rodent carcinogenicity study waiver requests. Based on the Agency feedback, the Applicant used the following integrated approach to assess potential carcinogenicity risk of acoltremon to request a waiver of the studies. This rationale was presented to the Executive Carcinogenicity Assessment Committee for review of the waiver request. The committee agreed with the Division that in the absence of systemic exposure for acoltremon ophthalmic solution, 0.003%, there is no need to conduct carcinogenicity studies.

Carcinogenicity Data for Another Compound in the Same Class

Acoltremon is also widely known as WS-12, a menthol derivative, and Flavor and Extract Manufacturers Association 4681. WS-12 is widely used as a food flavoring agent and is the most common agent used to create the “cool mint” flavor. WS-12 is GRAS for oral food exposure (refer to Pharmacology and Toxicology review of IND 147005 by Dr. McDougal).

The Applicant indicated the lack of test-article-related carcinogenicity findings in mouse and rat 2-year feeding studies conducted with the cooling agent dl-menthol by the National Toxicology Program ([National Toxicology Program 1979](#)).

In these studies, B6C3F1 mice (50/sex/group) were administered vehicle control (basal diet containing 2% corn oil) or 2000 or 4000 ppm mg/kg/day dl-menthol in the diet ad libitum 7 days per week for 104 weeks. Assuming a 0.03-kg mouse consumes 5 grams of food per day, these doses corresponded to 0, 334 and 667 mg/kg/day, respectively. Fischer 344 rats (50/sex/group) were administered vehicle control (basal diet containing 2% corn oil) or 3750 or 7500 ppm mg/kg/day dl-menthol in the diet ad libitum 7 days per week for 104 weeks; assuming a 0.4-kg rat consumes 20 grams of food per day, these doses corresponded to 0, 188 and 375 mg/kg/day, respectively. Animals were evaluated for mortality, clinical observations, masses, body weight, and food consumption, gross and microscopic pathology.

All animals survived to the scheduled necropsy and there were no test-article-related effects on clinical observations, body weight, food consumption, or gross pathology findings. There were no test-article-related preneoplastic or neoplastic findings up to and including the highest doses tested in mice (667 mg/kg/day) and rats (375 mg/kg/day).

Based on the available data, dl-menthol did not produce any evidence of a carcinogenic effect in B6C3F1 mice and Fischer 344 rats up to the highest tested doses (mice: 667 mg/kg/day; rats: 375 mg/kg/day).

Lack of Test Article-Related Cellular Proliferation in Repeated Dose Toxicity Studies

Alcon completed 6-month repeated dose ocular GLP toxicity studies in rabbits (Study AR-15512-AS03) and dogs (Study AR-15512-AS04) and 28-day repeated dose intravenous GLP toxicity studies in rats (Study STF-G10986 AVX-012). None of these studies suggested preneoplastic development based on organ weights, gross and microscopic findings.

Lack of Genotoxic Potential of Acoltremon

An Ames test (Study STF-G10982 AVX-12), an in vitro mammalian chromosomal aberration test in human peripheral blood lymphocytes (Study STF-G10983 AVX-012), and an in vivo micronucleus assay in rats (Study 50662.01102), all performed according to GLP standards, were valid and negative in the conditions of the studies.

Assessment of Hormonal Perturbation and Immune Modulation

Although there were no test-article-related gross or microscopic findings in the reproductive, endocrine, or lymphoid systems suggestive of altered hormone functions, no specific studies took place to study those functions (e.g., levels of estrogens, androgens, thyroid hormones, lymphocyte phenotypes, etc.). In addition, rabbits and dogs used for the 6-month toxicity studies were barely sexually mature, which could have changed the results if the test article had any effect on cell proliferation via hormone dysregulation.

Systemic Pharmacokinetics

In Preclinical Studies

Variable EC_{50} s from 1 to 50 μ M were derived from primary pharmacology studies in vitro and in vivo performed by the Applicant. At an EC_{50} of 1 μ M (289 pg/mL) found in calcium influx experiments on TRPM8-HEK 293 cells, acoltremon C_{max} at the NOAELs in the 6-month repeated ocular dose study in the rabbit (C_{max} = 79 pg/mL) and the dog (C_{max} = 364 pg/mL) represented approximately 4- to 1-fold lower concentrations relative to the most conservative EC_{50} . However, considering 90% protein binding in vitro in all species tested including dog, rabbit, and man, free C_{max} represented 37- and 8-fold lower concentrations relative to an EC_{50} of 1 μ M. No systemic findings were observed in the toxicity studies.

In Clinical Studies

The clinical PK summary (Module/Section 2.7.2) of the long-term safety clinical study COMET-4 for plasma samples from a total of thirty-eight (38) subjects (25 for Tryptyr [acoltremon ophthalmic solution] 0.003% and 13 for vehicle) collected at Baseline (Day 1) and Days 14 and 90 at predose, and postdose (15 min, 30 min, 1 hour, 4 hours, and 8 hours) indicated that all subjects exposed to vehicle were below the LLOQ of 20.0 pg/mL at all visits and timepoints. Among the 25 Tryptyr subjects exposed to drug product, only 3 had plasma concentrations of acoltremon above the LLOQ, while most of the subjects exposed to Tryptyr were below LLOQ at all visits and timepoints (22 of 25 subjects [88%] below LLOQ; 626 of 654 samples [95.7%] below LLOQ). Among the 28 plasma samples that were above the LLOQ, the range of values reported were 22.8 pg/mL to 213 pg/mL.

Overall, the lack of measurable plasma concentrations of acoltremon in most (22/25) subjects indicated that systemic exposure after the topical ocular route could be considered negligible. Given the limited number of subjects with measurable acoltremon systemic (plasma) exposure, noncompartmental analysis for PK parameter estimation was not conducted.

Reviewer's comment: While this reviewer agrees with the Applicant's overall justification for waiving rodent carcinogenicity studies, this reviewer has noted that the Applicant neglected to explore the published literature on the role of TRPM8 in cancer. This reviewer has found peer-reviewed articles pointing to a significant role for the receptor in the initiation and progression of a variety of tumors in humans ([Liu et al. 2016](#); [Samanta et al. 2018](#)).

Reproductive and Developmental Toxicity

In embryo-fetal toxicity studies in the rat and the rabbit, the NOAELs for maternal and embryo-fetal developmental toxicity were the highest doses tested, 300 µg/kg and 400 µg/kg, respectively. As a result, clinical safety margins at the maximum RHOD were 806-fold and 2151-fold with the rat and the rabbit NOAELs, respectively, in mg/m² equivalent.

In consultation with the Agency, fertility and pre- and postnatal development studies waiver requests were submitted by the Applicant and reviewed. In the absence of test-article-related systemic adverse findings and given negligible systemic exposure observed in toxicity studies, this reviewer judged that the rationale for waiving fertility and pre- and postnatal development studies was justified, considering that the clinical systemic exposure was judged to be negligible.

Reviewer's comment: The clinical pharmacology section of the labeling indicated that (b) (4) plasma concentrations (b) (4) 213 pg/mL (highest). (b) (4). (b) (4). Based on the data, this reviewer judges the clinical systemic exposure negligible.

Fertility and Early Embryonic Development

Study was not conducted based on justified waiver request.

Embryo-Fetal Development

Table 30. An Intravenous Slow Push Study of the Effects of Acoltremon on Embryo/Fetal Development in Rats

Study Features	Details
Study report location	SDN0001
Conducting laboratory and location	(b) (4)
Date of study initiation	1/19/2023
GLP compliance	Yes
QA statement	Yes
Drug, lot #, and % purity	Acoltremon, lot # 2140342, purity 99.9%

Source: Module 2.4 Nonclinical Overview
Abbreviations: GLP, good laboratory practice; QA, quality assurance

Key Study Findings

The administration of acoltremon by intravenous (slow push) injection to pregnant rats was well tolerated up to and including the highest dose tested, 300 µg/kg/day.

When the total malformations and developmental variations were evaluated on a proportional basis, no statistically significant differences from the control group were noted. Fetal malformations and developmental variations in the test-article-treated groups occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the (b) (4) historical control data ranges. Based on these data, no fetal malformations or developmental variations were attributed to the test article. Considering the lack of maternal and embryo-fetal effects, the NOAEL for maternal and embryo-fetal developmental toxicity was 300 µg/kg/day associated with a Gestation Day 17 C₀ and AUC_{0-24hr} of 351 ng/mL and 161 hr·ng/mL, respectively.

Table 31. Methods, Rat Embryo-Fetal Toxicity Study

Study Method	Description
Doses	30, 100, 300 µg/kg
Frequency of dosing	Once daily during Gestation Days 6-17
Dose volume	10 mL/kg
Route of administration	Intravenously
Formulation/vehicle	(b) (4) (w/v) Cremophor EL (b) (4) Na ₂ HPO ₄ ·2H ₂ O, (b) (4) NaCl in sterile water, pH 6.8-7.2
Species/strain	Rat/Sprague Dawley
Number/sex/group	22
Satellite groups	3-6 (TK groups)
Study design	See below
Deviation from study protocol	None of impact

Source: Study report AR15512-AS07

Abbreviations: TK, toxicokinetics

Table 32. Experimental Design, Rat Embryo-Fetal Toxicity Study

Group No.	Test Material	Dose Level ^a (µg/kg/day)	Dose Volume ^b (mL/kg)	Dose Concentration (µg/mL)	Number of Females	
					Main	TK
1	Vehicle	0	10	0	22	3
2	AR-15512	30	10	3	22	6
3	AR-15512	100	10	10	22	6
4	AR-15512	300	10	30	22	6

Source: Study report AR15512-AS07

^a Not corrected for salt, purity, and water content.

^b Based on the most recent body weight measurement.

Abbreviations: AR-15512, acoltremon; TK, toxicokinetics

Reviewer's comment: Historical Control Data for the conducting laboratory was provided in Appendix 14 of the study report:

- CD (Sprague Dawley rats)
- Studies included: 66
- Multiple routes of administration
- Study Type: Embryo-fetal development
- Full Litters included: 1,515
- Fetuses included: 9328
- Studies between February 1, 2019, and July 26, 2022

Results

Mortality

There was no mortality during the study.

Clinical Signs

One control animal and one animal at 100 µg/kg/day delivered early, on Gestation Day 21, and two animals at 30 µg/kg did not get pregnant.

Body Weight and Feed Consumption

Compared to control, mean maternal body weights, body weight gains, adjusted body weights, adjusted body weight gains, and gravid uterine weights at 30, 100, and 300 µg/kg/day groups were unaffected by the test article.

Feed consumption was not affected by the test article at any dose.

Toxicokinetics

Table 33. Bioanalytical Sample Collection, Rat Embryo-Fetal Toxicity Study

Group No.	No. of Animals	(Time Postdose) on GD 6 and 17						
		0 hrs ^a	0.17 hrs (10 min)	0.5 hrs	2 hrs	4 hrs	8 hrs	24 hrs
1	3	-	X	-	-	-	-	-
2	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-
3	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-
4	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-

Source: Study report AR15512-AS07
 Abbreviation: GD, gestation day

- Acoltremon was quantifiable up to 8 hours after the high dose on Gestation Day 6 and up to 24 hours after the high dose on Gestation Day 17, respectively.
- Time to maximum concentration and half-life were 0.17 hours (first blood collection time point) and 1 to 3 hours postdose, respectively.
- Acoltremon exposure (C_0 and AUC_{0-24hr}) increased approximately proportionally with increasing dose on Gestation Days 6 and 17.
- Acoltremon did not accumulate after multiple doses ([Table 34](#)).

Table 34. Summary of Toxicokinetic Parameters, Rat Embryo-Fetal Toxicity Study

Dose	$AUC_{(0-24hr)}$ (hr•ng/mL)		C_0 (ng/mL)		T_{last} (hr)		$t_{1/2}$ (hr)	
	GD 6	GD 17	GD 6	GD 17	GD 6	GD 17	GD 6	GD 17
30 µg/kg/day	15.0	17.0	34.1	41.4	4	8	0.801	1.77
100 µg/kg/day	46.3	60.4	77.1	93.1	8	8	1.71	1.64
300 µg/kg/day	132	161	296	351	8	24	1.92	3.09

Source: Study report AR15512-AS07, page 15

Abbreviations: AUC, area under the concentration-time curve; C_0 , _concentration at time 0_; GD, gestation day; T_{last} , time of last measurable concentration_; $t_{1/2}$, half-life

Dosing Solution Analysis

All formulations analyzed that were used for dosing had mean concentrations within or equal to the acceptance criteria of $\pm 10\%$ of their theoretical concentrations, with each individual concentration within $\pm 15\%$ ([Table 35](#)).

Table 35. Results of Concentration Analyses, Rat Embryo-Fetal Toxicity Study

Date of Preparation	Mean Concentration, µg/mL (% of Target)		
	Group 2 (3 µg/mL)	Group 3 (10 µg/mL)	Group 4 (30 µg/mL)
29 Jan 2023	2.84 (94.7)	9.74 (97.4)	29.82 (99.4)
08 Feb 2023	2.00 (66.8)	6.98 (69.8)	21.22 (70.7)
08 Feb 2023 Backup Samples	2.04 (68.1)	7.09 (70.9)	21.26 (70.9)
10 Feb 2023	2.77 (92.4)	9.88 (98.8)	31.14 (103.8)

Source: Study report AR15512-AS07, page 14

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Terminal Procedures

Table 36. Terminal Procedures, Rat Embryo-Fetal Toxicity Study

Main Study Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			
		Necropsy	Tissue Collection	Ovarian and Uterine Examination	Fetal Examination
1	GD 21	X	Gross Lesions and Injection Sites	X	X
2	GD 21	X	Gross Lesions and Injection Sites	X	X
3	GD 21	X	Gross Lesions and Injection Sites	X	X
4	GD 21	X	Gross Lesions and Injection Sites	X	X
Found dead or unscheduled euthanasia	-	X	Gross Lesions and Injection Sites	X	X ^a

X = Procedure to be conducted; - = Not applicable; GD = Gestation Day.

^a External examination only.

Toxicokinetic Animals

Group No.	Scheduled Euthanasia Day ^a	Necropsy Procedures		
		Necropsy	Tissue Collection	Ovarian and Uterine Examination
1	GD 18	-	-	X (limited) ^b
2	GD 18	-	-	X (limited) ^b
3	GD 18	-	-	X (limited) ^b
4	GD 18	-	-	X (limited) ^b
Toxicokinetic animals (found dead or unscheduled euthanasia)	-	-	-	X (limited) ^b

X = Procedure to be conducted; - = Not applicable; GD = Gestation Day.

^a Scheduled euthanasia following the last blood collection.

^b Pregnancy status only.

Source: Study report AR15512-AS07

Constructed Variables

Figure 4. Constructed Variables, Rat Embryo-Fetal Toxicity Study

Body Weight Gains	Calculated between each scheduled interval as well as between the following intervals: GD 6-18
Food Consumption	Calculated for each corresponding body weight interval
Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.	
The following parental indices and litter calculations will be included, where applicable:	
Pre-Implantation Loss	= $\frac{\text{No. of corpora lutea} - \text{no. of implants}}{\text{No. of corpora lutea}} \times 100$
Post-Implantation Loss	= $\frac{\text{No. of implants} - \text{no. of live fetuses}}{\text{No. of implants}} \times 100$
Sex Ratio (% males)	= $\frac{\text{No. of live male fetuses}}{\text{No. of live males} + \text{No. of live females}} \times 100$
Litter % of Fetuses with Abnormalities	= $\frac{\text{No. of fetuses in litter with a given finding}}{\text{No. of fetuses in litter examined}} \times 100$

Source: Study report AR15512-AS07
Abbreviation: GD, gestation day

Necropsy

There were no test-article-related macroscopic findings at the scheduled necropsy.

Cesarean Section Data

Compared to control, there was no effect of the test article on mean litter proportions of postimplantation loss, mean number of live fetuses, mean fetal body weights, fetal sex ratios, mean numbers of corpora lutea, mean numbers of implantation sites, and mean litter proportions of preimplantation loss.

Offspring

The numbers of fetuses (litters) available for morphological evaluation were 286 (22), 243 (20), 270 (22), and 275 (22) in the control, 30, 100, and 300 µg/kg/day groups, respectively. There were two late resorptions in the control group (which were excluded from the group mean calculation).

External Malformations and Variations

No test-article-related external developmental variations were observed in fetuses in this study.

Visceral Malformations and Variations

No test-article-related visceral malformations or variations were noted in fetuses at any dose level.

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Skeletal Malformations and Variations

No test-article-related skeletal malformations or variations were noted in fetuses at any dose level.

Rabbit Embryo-Fetal Toxicity Study

Table 37. An Intravenous Slow Push Study of the Effects of Acoltremon on Embryo/Fetal Development in Rabbits

Study Features	Details
Study no.	AR15512-AS08
Study report location	SDN0001
Conducting laboratory and location	(b) (4)
Date of study initiation	1/13/2023
GLP compliance	Yes
QA statement	Yes
Drug, lot #, and % purity	Acoltremon, lot # 2140342, purity 99.9%

Source: Study report AR15512-AS07

Abbreviations: GLP, good laboratory practice; QA, quality assurance

Key Study Findings

The administration of acoltremon via intravenous (slow push) injection to pregnant rabbits was well tolerated up to and including the highest dose tested, 400 µg/kg/day.

When the total malformations and developmental variations were evaluated on a proportional basis, no statistically significant differences from the control group were noted. Fetal malformations and developmental variations in the test-article-treated groups occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the (b) (4) historical control data ranges. Based on these data, no fetal malformations or developmental variations were attributed to the test article. Considering the lack of maternal and embryo-fetal effects, the NOAEL for maternal and embryo-fetal developmental toxicity was 400 µg/kg/day, associated with a Gestation Day 19 C₀ and AUC_{0-24hr} of 320 ng/mL and 192 hr·ng/mL, respectively.

Table 38. Methods, Rabbit Embryo-Fetal Toxicity Study

Study Method	Description
Doses	30, 100, 300 µg/kg
Frequency of dosing	Once daily during Gestation Days 7-19
Dose volume	10 mL/kg
Route of administration	Intravenously
Formulation/vehicle	(b) (4) (w/v) Cremophor EL (b) (4) Na ₂ HPO ₄ ·2H ₂ O, (b) (4) NaCl in sterile water, pH 6.8-7.2
Species/strain	Rabbit/New Zealand White
Number/sex/group	22
Satellite groups	No
Study design	See below

Study Method	Description
Deviation from study protocol	None of impact

Source: Study report AR15512-AS07

Table 39. Experimental Design, Rabbit Embryo-Fetal Toxicity Study

Group No.	Test Material	Dose Level ^a (µg/kg/day)	Dose Volume ^b (mL/kg)	Dose Concentration (µg/mL)	Number of Females
1	Vehicle	0	10	0	22
2	AR-15512	40	10	4	22
3	AR-15512	130	10	13	23 ^c
4	AR-15512	400	10	40	22

Source: Study report AR15512-AS08

^a Not corrected for salt, purity, and water content.

^b Based on the most recent body weight measurement.

^c Due to the euthanasia of female No. 3501 on Gestation Day 9, another female was added to study.

Abbreviation: AR-15512, acoltremon

Reviewer's comment: *Historical Control Data for the conducting laboratory was provided in Appendix 14 of the study report:*

- *New Zealand White rabbits*
- *Studies included: 46*
- *Multiple routes of administration*
- *Study Type: Embryo-fetal development*
- *Full Litters included: 983*
- *Fetuses included: Variable*
- *Studies between January 1, 2018, and August 8, 2022*

Results

Mortality

Female No. 3501 at 130 µg/kg/day was euthanized in extremis on Gestation Day 9 after being noted as pale with decreased activity and increased respiratory rate during dose administration. The cause of death was unknown but thought to be unrelated to treatment.

Reviewer's comment: *This reviewer agrees as it was a unique event among 88 animals.*

Clinical Signs

All animals were gravid, except Female No. 2515 at 40 µg/kg/day.

There was no test article related abnormal findings during the study.

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Body Weight and Feed Consumption

Compared to control, mean maternal body weights, body weight gains, adjusted body weights, adjusted body weight gains, and gravid uterine weights at 40, 130, and 400 µg/kg/day groups were unaffected by the test article.

Feed consumption was not affected by the test article at any dose.

Toxicokinetics

Table 40. Bioanalytical Sample Collection, Rabbit Embryo-Fetal Toxicity Study

Group No.	No. of Animals	(Time Postdose) on GD 6 and 17						
		0 hrs ^a	0.17 hrs (10 min)	0.5 hrs	2 hrs	4 hrs	8 hrs	24 hrs
1	3	-	X	-	-	-	-	-
2	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-
3	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-
4	3	X	-	X	-	X	-	X
	3	-	X	-	X	-	X	-

Source: Study report AR15512-AS08

Abbreviation: GD, gestation day

- Acoltremon was quantifiable up to 24 hours after the high dose on Days 7 and 19.
- Mean acoltremon C₀ and AUC_{0-24hr} increased approximately proportionally with increasing dose on Gestation Days 7 and 19.
- Acoltremon did not accumulate after multiple exposures.
- Mean t_{1/2} was 6 hr (Table 41).

Table 41. Summary of Toxicokinetic Parameters, Rabbit Embryo-Fetal Toxicity Study

Dose	AUC _(0-24hr) (hr•ng/mL)		C ₀ (ng/mL)		t _{last} ^a (h)		t _{1/2} (h)	
	GD 7	GD 19	GD 7	GD 19	GD 7	GD 19	GD 7	GD 19
40 µg/kg/day	13.0	13.6	27.3	21.6	8.0	8.0	NA	NA
130 µg/kg/day	49.6	41.9	107	82.8	24.0	8.0	6.04	NA
400 µg/kg/day	169	192	328	320	24.0	24.0	6.42	5.92

Source: Study report AR15512-AS08

^a Median presented.

Abbreviations: AUC, area under the concentration-time curve; C₀, _concentration at time 0_; GD, gestation day NA, not applicable; t_{last}, last measurable time point; t_{1/2}, half-life

Dosing Solution Analysis

All dose formulation concentrations were within ±10% of target at all intervals tested (Table 42).

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Table 42. Results of Concentration Analyses, Rabbit Embryo-Fetal Toxicity Study

Date of Preparation	Mean Concentration, mg/mL (% of Target)		
	Group 2 (4 mg/mL)	Group 3 (13 mg/mL)	Group 4 (40 mg/mL)
20 Jan 2023	3.64 (91.0)	12.51 (96.2)	36.46 (91.2)
02 Feb 2023	4.33 (108) ^a	14.11 (109) ^a	43.48 (109)

^a Backup samples processed.

Source: Study report AR15512-AS08

Terminal Procedures

Table 43. Terminal Procedures, Rabbit Embryo-Fetal Toxicity Study

Main Study Animals

Group No.	Scheduled Euthanasia Day	Necropsy Procedures			
		Necropsy	Tissue Collection	Ovarian and Uterine Examination	Fetal Examination
1	GD 29	X	Gross Lesions and Injection Sites	X	X
2	GD 29	X	Gross Lesions and Injection Sites	X	X
3	GD 29	X	Gross Lesions and Injection Sites	X	X
4	GD 29	X	Gross Lesions and Injection Sites	X	X
Found dead or unscheduled euthanasia	-	X	Gross Lesions and Injection Sites	X	X ^a

Source: Study report AR15512-AS08

^a External examination only.

Abbreviations: -, not applicable; GD, Gestation Day; X, procedure to be conducted

Constructed Variables

Figure 5. Constructed Variables, Rabbit Embryo-Fetal Toxicity Study

Body Weight Gains	Calculated between each scheduled interval as well as between the following intervals: GD 6-18
Food Consumption	Calculated for each corresponding body weight interval
Additional or alternative body weight or food consumption intervals may be evaluated to elucidate study results at the discretion of the Study Director.	
The following parental indices and litter calculations will be included, where applicable:	
Pre-Implantation Loss	= $\frac{\text{No. of corpora lutea} - \text{no. of implants}}{\text{No. of corpora lutea}} \times 100$
Post-Implantation Loss	= $\frac{\text{No. of implants} - \text{no. of live fetuses}}{\text{No. of implants}} \times 100$
Sex Ratio (% males)	= $\frac{\text{No. of live male fetuses}}{\text{No. of live males} + \text{No. of live females}} \times 100$
Litter % of Fetuses with Abnormalities	= $\frac{\text{No. of fetuses in litter with a given finding}}{\text{No. of fetuses in litter examined}} \times 100$

Source: Study report AR15512-AS08
Abbreviation: GD, gestation day

Necropsy

There were no test-article-related macroscopic findings at the scheduled necropsy.

Cesarean Section Data

Compared to control, there was no effect of the test article on mean litter proportions of postimplantation loss, mean number of live fetuses, mean fetal body weights, fetal sex ratios, mean numbers of corpora lutea, mean numbers of implantation sites, and mean litter proportions of preimplantation loss.

Offspring

The numbers of fetuses (litters) available for morphological evaluation were 186 (22), 186 (21), 181 (22), and 191 (22) in the control, 40, 130, and 400 µg/kg/day groups, respectively. Malformations were observed in 1 (1), 0 (0), 2 (2), and 2 (2) fetuses (litters) in these same respective dose groups and were considered spontaneous in origin. In addition, 3, 6, 2, and 1 late resorptions in the control, 40, 130, and 400 µg/kg/day groups, respectively, were found (which were excluded from group mean calculation).

External Malformations and Variations

No test-article-related external developmental variations were observed in fetuses in this study.

Visceral Malformations and Variations

No test-article-related visceral malformations were observed in fetuses in this study. Fetus No. 3509-3 in the 130 µg/kg/day group was noted with narrow ductus arteriosus, absent A-V valve, and pulmonary trunk atresia, and Fetus No. 4522-8 in the 400 µg/kg/day group was noted with a blood-filled pericardium; these malformations were not considered test-article-related since they occurred in single fetuses. Additionally, Fetus No. 1513-2 in the control group was noted with a misshapen spleen.

No test-article-related visceral developmental variations were noted.

Skeletal Malformations and Variations

No test-article-related skeletal malformations were observed in fetuses in this study. Fetus No. 3508-6 in the 130 µg/kg/day group was noted with branched rib, supernumerary rib, and supernumerary thoracic arch, and Fetus No. 4510-4 in the 400 µg/kg/day group was noted with an absent rib, fused thoracic arches and centrum, and thoracic hemivertebra; these malformations were not considered test article-related since they occurred in single fetuses.

No test-article-related skeletal developmental variations were noted.

Prenatal and Postnatal Development

Not performed based on justified waiver request.

Reproductive Study Waiver Requests

Alcon consulted with the Agency at the End of Phase 2 meeting held on January 28, 2022, about embryo-fetal toxicity studies, as per ICH M3(R2) ([January 2010](#)) and ICH S5(R3) ([May 2021](#)) guidance and what supporting data would be required for waiver requests for fertility and early embryonic development and pre- and postnatal development studies. The Agency indicated that waivers should include a thorough discussion of the risk based on the drug class, pharmacological activity, pharmacokinetics in humans and animals, genotoxicity and toxicity results, clinical safety findings, and supportive information from the literature as appropriate. The Applicant's justification for waiving the studies (submitted in Module 1.12.5 [Other Correspondence]) was that the nonclinical safety assessment program for Tryptyr (acoltremon ophthalmic solution 0.003%) did not suggest a risk for the male and/or the female reproductive system.

- (1) Preclinical findings in repeated-dose toxicity studies were negative for reproductive toxicity in rats (systemic up to 28 days), rabbits (ocular up to 6 months) and dogs (ocular up to 6 months) based on anatomic pathology findings.

Reviewer's comment: Note that at the start of the 6-month studies, neither the rabbit (age of 4 to 5 months old while sexually mature at 6 months ([Macari and Machado 1978](#)) nor the dog

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(age of 5 to 7 months old while sexually mature at 6 to 12 months ([Shayne C. Gad and Chengelis 1998](#)) were fully sexually mature.

- (2) There were no findings of maternal toxicity, embryo-fetal survival, intrauterine growth, or morphological development in embryo-fetal development toxicology studies in rats and rabbits.
- (3) Following topical ocular application, the systemic exposure to the test article was considered negligible due to lack of pharmacological activity and systemic toxicity.

Reviewer's comment: This reviewer agrees with the negligible systemic exposure.

- (4) The Applicant indicated that they have reviewed the published literature related to acoltremon ophthalmic solution use in pregnant and lactating women and the effects of acoltremon ophthalmic solution on male and female fertility with no results.

So far, in the clinical development program for acoltremon, 70 female subjects (aged 15 to 44 years) have been exposed to acoltremon ophthalmic solution 0.003% and 3 female subjects (aged 15 to 44 years) were exposed to acoltremon ophthalmic solution 0.00014%.

Reviewer's comment: Based on the absence of systemic findings and negligible systemic exposure observed during preclinical development, this reviewer judged that the requirements for fertility and pre- and postnatal development studies may be waived.

Integrative Summary and Safety Evaluation

In consultation with the Agency, the Applicant has completed a nonclinical safety assessment program in support of the use of Alcon's Tryptyr (acoltremon ophthalmic solution) 0.003%. These included pharmacology, pharmacokinetics, and toxicity studies. While carcinogenicity and certain reproductive and developmental toxicity studies were waived, it was justified due to negligible systemic exposure observed after ocular administration in all GLP toxicity studies and at the therapeutic dose in the clinic, hence the RHOD of 1.8 µg/eye/day is supported by the nonclinical program.

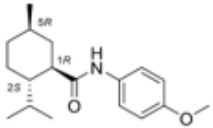
Pharm/Tox Recommendation

Tryptyr (acoltremon ophthalmic solution) 0.003% is approvable from a pharmacology and toxicology perspective.

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Table 44. S1B(R1) Rat Carcinogenicity Weight of Evidence Cover Sheet

S1B(R1) Rat Carcinogenicity Weight of Evidence (WoE) Cover Sheet/Template

Application Information – (to be completed by the reviewer)	
Reviewer:	Muriel Saulnier, D.V.M., Ph.D., D.A.B.T.
Supervisor/Director:	Kimberly Hatfield, Ph.D.
Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPTRPURM/SM)
Associated Divisions:	Division of Ophthalmology
Date Sponsor submitted WoE Assessment:	May 30, 2024
Date of WoE Meeting:	October 29, 2024
Application Number and Sponsor:	NDA 217370 Alcon Laboratories, Inc.
Product name/type:	<u>Acoltremon</u> Ophthalmic Solution, 0.003%/small molecule CAS Registry Number: 68489-09-8 Chemical Name: (1R,2S,5R)-N-(4-methoxyphenyl)-5-methyl-2-(propan-2-yl) cyclohexane-1-carboxamide Molecular Formula/Molecular Weight: C₁₈H₂₇NO₂/ 289.42 g/mol 
Clinical Indication:	Treatment of Dry Eye Disease
Pharmacology/MOA:	Transient Receptor Potential Cation Channel Subfamily M (<u>Melastatin</u>) Member 8 (TRPM8) is a calcium-permeable cation channel, i.e., the activation of TRPM8 opens the channel and allows influx of calcium ion into the cell resulting in a variety of effects such as cooling sensation and pain relief. Menthol is considered a TRPM8 agonist. <u>Acoltremon</u>, due to its structural similarity to menthol, is hypothesized to act as a TRPM8 agonist.
Secondary Pharmacology:	No secondary pharmacology study reports were submitted to the NDA. <u>Acoltremon</u> (AR-15512) was not active against other Transient Receptor Potential (TRP) channels including TRPV1, TRPV2, TRPV3, TRPV4 and TRPA1 (<u>Sherkheli</u>, 2008). Sherkheli MA, Gisselmann G, Voigt-Eisele AK, et al. 2008. Menthol derivative WS-12 selectively activates transient receptor potential melastatin-8 (TRPM8) ion channels. Pak. J. Pharm. Sci. 21(4): 370-378.

Metabolites of Concern:	No information
Summary of Sponsor's Rationale for not conducting 2-year rat study:	Rodent carcinogenicity studies were not conducted by the sponsor because the nonclinical safety assessment program for <u>Acoltremon Ophthalmic Solution 0.003%</u> does not indicate a carcinogenic risk to human subjects for <u>acoltremon (AR-15512)</u> on the basis that: • The cooling agent dl-menthol, a closely related molecule, was not shown to be carcinogenic in 104 week feeding studies in mice and rats (NTP 1979¹). ¹BIOASSAY OF dl-MENTHOL FOR POSSIBLE CARCINOGENICITY • Chronic <u>acoltremon (AR-15512)</u> exposure in rabbits and dogs did not produce histopathological findings of carcinogenic concern (e.g., hyperplastic, hypertrophic, atypical cellular alterations, or degenerative/regenerative changes). • <u>Acoltremon (AR-15512)</u> was negative for genotoxicity in the standard battery of genotoxicity studies. • Chronic <u>acoltremon (AR-15512)</u> exposure in rabbits and dogs did not produce findings consistent with perturbation of the endocrine, reproductive, or immune systems. • Following the clinically intended route of administration (topical ocular), <u>acoltremon (AR-15512)</u> plasma exposure in 6-month rabbit and dog repeated dose ocular toxicology studies was negligible given <u>acoltremon (AR-15512)</u> would not be pharmacologically active and did not produce systemic toxicity.
Division conclusion regarding human carcinogenic potential:	Likely, therefore a 2-year rat study would <u>not</u> add value. ☐ Unlikely, therefore a 2-year rat study would <u>not</u> add value. ☒ Uncertain, therefore a 2-year rat study <u>would</u> add value. ☐ Other reason why a 2-year rat study would <u>not</u> add value (<i>2-year rat study is not feasible, or residual uncertainty would not be informed by 2yr rat data (e.g., risk due to immunomodulatory activity, high</i>) ☐

	<i>confidence that the rodent toxicology findings or tumor profile is known and not human-relevant).</i>		
Division's Summary Basis:	Concern from:	Yes	No
	Target biology and drug class	☒	☐
	Secondary pharmacology	☐	☒
	Repeat dose toxicity studies	☐	☒
	Hormonal perturbation	☐	☒
	Immunotoxicity	☐	☒
	Genotoxicity	☐	☒
Division's primary basis for concurrence or non-concurrence with sponsor:	ICH S1A² indicates that pharmaceuticals administered by the ocular route may not require carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure. The Division supports the Sponsor's choice of waiving rodent carcinogenicity studies (mouse and rat) because of expected negligible (i.e., not expected to be pharmacology active and in the absence of systemic toxicity) clinical systemic exposure after ocular administration and negative carcinogenetic findings in 2-year rodent studies with a closely related molecule (dl-menthol) having a similar pharmacological mode of action. ²https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1a-need-long-term-rodent-carcinogenicity-studies-pharmaceuticals The Division considered the following factors to support its conclusion: <i>Target biology:</i> Peer reviewed literature points to a role for TRPM8 in cancer biology in humans playing important roles in cancer cells proliferation, survival, migration, invasion, and neurosecretion (Yee, 2015). Yee NS, 2015. Roles of TRPM8 Ion Channels in Cancer: Proliferation, Survival, and Invasion. Cancers (Basel). 2015 Oct 23;7(4):2134–2146. <i>Drug class effect:</i> Negative in 2-year rodent carcinogenicity studies with a closely related molecule.		

	<i>Toxicity studies:</i> No test article systemic findings in dog (ocular; 6 month; 9X* the MRHD), and rabbit (ocular; 6 months, 29X*) toxicity studies. Systemic findings were observed in rats (IV; 28 days; NOAEL 97X* the MRHD) as significant dose dependent decrease of serum calcium that is thought to be due to exaggerated pharmacological activity of the test article causing calcium mobilization. <i>Endocrine activity:</i> None suggested in toxicity studies. <i>Immune modulation:</i> None suggested in toxicity studies. <i>Pharmacological activity:</i> Taking into account the most conservative EC₅₀ of approximately 1 μM (289 pg/mL) (range 1-50 μM) observed in pharmacology studies <i>in vitro</i>, and 90% protein binding in all species tested, in the absence of systemic toxicity in GLP ocular studies for 6 months in the rabbit and the dog, this reviewer considers the systemic exposure to the test article (free C_{max}) negligible after ocular exposure and hence, does not expect on- and/or off-target activity other than locally in the ocular tissues. <i>Systemic exposure:</i> <u>In the animal</u> In ocular GLP toxicity studies in the rabbit and the dog, this reviewer considered the systemic exposure negligible based on the absence of expected pharmacological activity and the absence of systemic toxicity. <u>In the clinic</u> No measurable (LLOQ = 20 pg/mL) plasma concentrations of the test compound in most (22/25) subjects receiving <u>Acoltremon Ophthalmic Solution</u>, 0.003% at the therapeutic dose in Clinical Safety Study AR-15512-LTSS suggesting that systemic exposure after the topical ocular route could be considered negligible (<i>per Sponsor</i>). <i>This reviewer's comment: Negligible exposure will need to be confirmed by the Clinical Team.</i> <i>Genotoxicity:</i>

	Negative in a standard battery of genotoxicity studies. <i>Embryofetal toxicity:</i> Studies in the rat and the rabbit were negative for maternal and embryofetal toxicity up to the highest dose tested (maternal and fetal NOAELs of 806X* and 2151X* MRHD with the rat and the rabbit respectively) *Calculated in mg/m² equivalent.
Additional documents:	WoE review NDA217370 PT final and Sponsor risk assessment \\CDSESUB1\EVSPROD\nda217370\0001\m1\us\m1-12-5-request-for-a-waiver.pdf
ECAC+ Recommendations – (to be completed by Exec Sec. after the meeting and reviewed by ECAC+ committee members)	
ECAC+ Recommendation (include primary basis of recommendation):	
Additional Comments (optional):	

Last revised 8/4/2023

Source: [\\CDSESUB1\EVSPROD\nda217370\0001\m1\us\m1-12-5-request-for-a-waiver.pdf](#)

Abbreviations: CAS, Chemical Abstracts Service; C_{max}, maximum plasma concentration; ECAC, Executive Carcinogenicity Assessment Committee; GLP, good laboratory practice; ICH, International Council for Harmonisation; IV, intravenous; LLOQ, lower limit of quantification; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; NTP, National Toxicology Program; WoE, weight of evidence

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Report AR-15512-IPK02: In Vitro Binding of Acoltremon to Rat, Rabbit, Dog, and Human Plasma

Protein binding of acoltremon in plasma was assessed by incubating acoltremon with rat, rabbit, dog, or human plasma for 30 minutes at room temperature at concentrations of 5nM, 2.5nM, and 1.25nM. Results showed that the average percentage of acoltremon plasma binding was 93% for SD rat, 89% for New Zealand White rabbit, 95% for Beagle dog, and 94% for human. No trend was observed between acoltremon concentration and the level of acoltremon bound to proteins.

14.1.2. Report R-01008: In Vitro S9 Metabolism of Acoltremon

Metabolism of acoltremon by liver S9 fractions was evaluated by combining acoltremon with liver S9 fraction of Sprague-Dawley rat, New Zealand White rabbit, Beagle dog, and human in a salt solution. Following the incubation at 37°C for a total of 4 hours, acoltremon was metabolized by liver S9 fractions of all species tested and was not degraded in the absence of liver S9 fraction.

14.2. In Vivo Studies

PK-Substudy of Study COMET-4

Acoltremon ophthalmic solution (0.003%) PK were evaluated in a subset of subjects with DED in the ongoing long-term safety study COMET-4, in which subjects received acoltremon ophthalmic solution (0.003%) or vehicle one drop in each eye twice daily for 12 months. Plasma samples were collected predose and postdose (15 min, 30 min, 1 hour, 4 hours, and 8 hours) on Days 1, 14 and 90 from a total of 38 subjects, including 25 subjects with acoltremon ophthalmic solution 0.003% and 13 subjects with vehicle. Acoltremon plasma concentrations were determined using a fully validated high performance liquid chromatography with tandem mass spectrometry assay with the LLOQ of 20 pg/mL.

Among the 25 subjects receiving acoltremon ophthalmic solution 0.003%, only 3 subjects had 6 plasma samples with acoltremon concentrations above LLOQ ([Table 45](#)), including 5 samples collected at baseline or predose. Since acoltremon is a common food additive with GRAS status, the possibility that the detected acoltremon in plasma is due to postprandial consumption of food items containing acoltremon could not be ruled out.

Table 45. Summary of Acoltremon Concentrations in Human Plasma in a Subset of Subjects With DED, Study COMET-4

Visit Subject	Max Concentration (Timepoint)	0.003% AR-15512 N=25	Vehicle N=13
Baseline			
(b) (6)	38.2 pg/mL (pre dose)	1 (4.0)	0 (0.0)
Day 14			
(b) (6)	53.5 pg/mL (15 min post) 24.8 pg/mL (pre dose)	2 (8.0)	0 (0.0)
Day 90			
(b) (6)	73.6 pg/mL (pre dose) 213 pg/mL (pre dose) 90.3 pg/mL (pre dose)	3 (12.0)	0 (0.0)

Source: Table 2 of Summary of Clinical Pharmacology Studies
Abbreviations: DED, dry eye disease; max, maximum

14.3. Bioanalytical Method Validation and Performance

Overall, the bioanalytical method is acceptable for determination of acoltremon concentrations in human plasma.

Acoltremon concentrations in human plasma samples have been determined using a fully validated liquid chromatography with tandem mass spectrometry assay with the LLOQ of 20 pg/mL (Report V/AR-15512/HP). The validation parameters are summarized in the table below. All plasma samples from Study COMET-4 were stored at -80°C and analyzed within 198 days, which is within the demonstrated long-term storage stability duration of 202 days at -80°C.

Table 46. Summary of Validated LC-MS/MS Method Used To Measure Acoltremon in Human Plasma (Report V/AR-15512/HP)

VALIDATION SUMMARY		
Analyte	AR-15512	
Internal standard	AR-15626	
Matrix	Human Plasma (K ₂ EDTA)	
SOP Number	SOP 5-195.0	
Analytical Method	High performance liquid chromatography with tandem mass spectrometric detection	
Detector	Sciex API 4000	
Human Plasma Volume Required	200 µL	
Standard Curve Range	20.0 to 5000 pg/mL	
QC Concentrations	60.0 pg/mL (Low QC), 1500 pg/mL (Mid QC), 4000 pg/mL (High QC)	
Regression Type	Linear (1/concentration ²)	
Quantification Method	Peak area ratio	
Inter-batch Precision and Accuracy	Precision (%)	Accuracy (%)
LLOQ QC	9.3	107.0
Low QC	8.4	111.3
Mid QC	5.4	102.7
High QC	6.6	108.0
Intra-batch Precision and Accuracy	Precision (%)	Accuracy (%)
LLOQ QC	2.1 – 13.6	102.5 – 115.5
Low QC	2.9 – 11.9	104.7 – 122.7*
Mid QC	1.8 – 7.7	99.3 – 116.7*
High QC	1.5 – 10.7	102.8 – 117.5*
Dilution Integrity	up to 20000 pg/mL with a 10-fold dilution factor using control human K ₂ EDTA plasma	
Selectivity	No interfering peaks noted in individual matrix	
Matrix Effects	No matrix effects observed	
Analyte Recovery	≥ 73.2 % (Low QC level) ≥ 68.3 % (Mid QC level) ≥ 69.0 % (High QC level)	
Internal Standard Recovery	65.7 %	
Carry-over	No carry-over observed. 1 carry-over double blank sample required after each ULOQ calibration standard.	
Stock Solution Stability	50 days in DMSO at 5°C and 23 hours in DMSO at room temperature	

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Analytical Solution Stability	49 days in DMSO at 5°C and 22 hours in DMSO at room temperature
Internal Standard Stability	Not assessed in validation – suitability of internal standard for use is assessed on an ongoing basis through the use of a single blank sample (blank matrix spiked with internal standard only) included in each analytical run.
Short Term Stability	25 hours at room temperature and 5°C
Freeze/Thaw Stability	4 cycles between -20°C and room temperature and -80°C and room temperature
Long Term Stability	202 days at -20°C and -80°C
Processed Sample Stability	120 hours at room temperature 96 hours at 5°C
Reinjection Reproducibility	76 hours at 5°C
Whole Blood Stability	4 hours at room temperature and 5°C

Source: Page 8 of (b) (4) Bioanalytical Validation Report V/AR-15512/HP

*Accuracy =122.7% for Low QC and 116.7% for Mid QC in batch 2, accuracy =117.5% for High QC in batch 7. No impact, interbatch precision meets acceptance criteria. In addition, an estimate of within run precision has been calculated in line with ICH M10 guidelines 1. Mean intrabatch accuracy for Low QC =113.3%, mean intrabatch accuracy for Mid QC =105.5 and mean intrabatch accuracy for High QC =108.8%. Acceptance met.

Abbreviations: DMSO, dimethyl sulfoxide; ICH, International Council for Harmonisation; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; SOP, standard operating procedure; QC, quality control; ULOQ, upper limit of quantification

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

Not applicable.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Study Name / Title

- COMET-2 (Study AR-15512-CS301) A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease
- COMET-3 (Study AR-15512-CS302) A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease

COMET-2 and COMET-3 had identical study designs and visit schedules.

Primary Objective

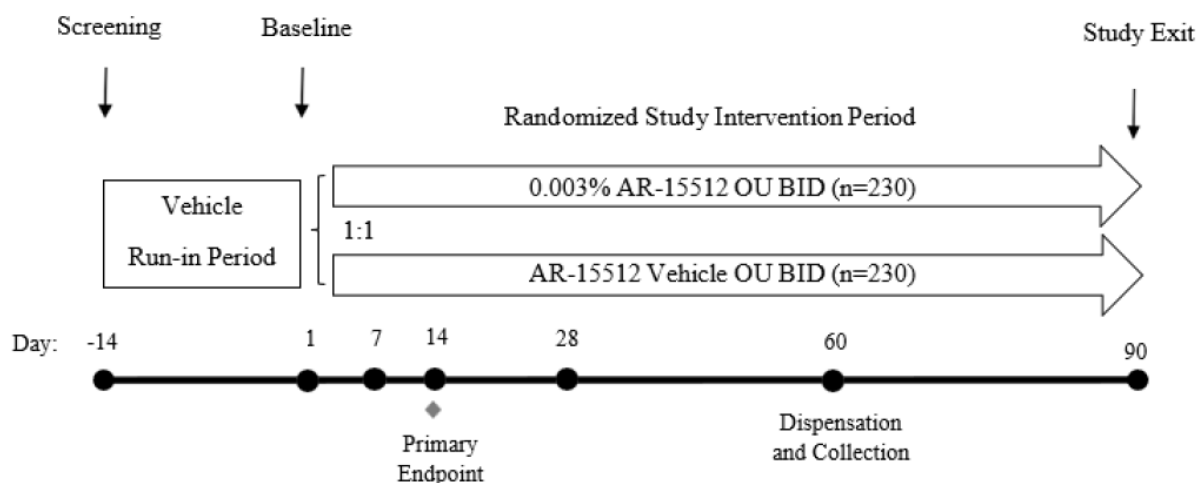
To evaluate the safety and efficacy of topical ophthalmic 0.003% acoltremon compared to its vehicle administered BID in subjects with DED.

Study Design

Study COMET-2 was a Phase 3, multicenter, vehicle-controlled, double-masked, randomized study conducted at 23 sites in the United States. The study consisted of Screening (Day -14) and Baseline (Day 1) visits, and follow-up visits on Days 7, 14, 28, and 90 (Study Exit). In addition, there was a Day 60 dispensing visit. All subjects were exposed to the CAE at the Screening visit to assess eligibility.

At the end of the Screening visit, all qualified subjects were assigned to administer vehicle BID to both eyes for 14 days (vehicle run-in period). After the vehicle run-in period, subjects were reevaluated for signs and symptoms of DED. Only subjects who requalified, based on inclusion/exclusion criteria, were enrolled in the study and randomized in a 1:1 ratio to receive 0.003% acoltremon or vehicle to be administered BID as one drop in each eye for 90 days. Efficacy was assessed at the Baseline visit and on Day 7, Day 14, Day 28, and Day 90. At the end of the Day 90 visit, subjects exited the study. Safety assessments were conducted at each study visit.

Figure 6. Study Design Diagram, Studies COMET-2 and COMET-3



Source: CSR COMET-2, Figure 9-1
 Abbreviations: BID, twice daily; OU, both eyes

Table 47. List of Investigators, Studies COMET-2 and COMET-3

Site Number	Investigator	Role	No. Subjects Enrolled
Study COMET-2			
201	Guruprasad Pattar, MD, PhD Butchertown Clinical Trials 205 North Spring St Louisville, KY 40206 USA	PI	30
202	Lance Bergstrom, MD Bergstrom Eye Research 2607 S. University Dr Fargo, ND 58103, USA	PI	11
203	Jared Peterson, MD Alpine Research Organization 1407 N 2000 W, Suite L Clinton, UT, 84015, USA	PI	14

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Site Number	Investigator	Role	No. Subjects Enrolled
204	Eva Liang, MD Center For Sight 871 Coronado Center Drive, Suite 130 Henderson, NV, 89052, USA	PI	12
205	Charles Reilly, MD Anhtuan Nguyen, MD R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX, 78229, USA	PI	14
206	Eugene McLaurin, MD Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119, USA	PI	68
207	Alex Liu, MD Premiere Practice Management 23441 Madison Street, Suite 12 Torrance, CA 90505, USA	PI	59
208	Nhu-Y Dao, MD (CT) The Eye Care Group 1201 West Main Street Waterbury, CT 06708, USA	PI	2
209	Michelle Boyce, MD Moyes Eye Center 5151 NW 88th St. Kansas City, MO 64154, USA	PI	10
210	Jay Rubin, MD Eye Clinics of South Texas 999 East Basse Rd., Suite 128-B San Antonio, TX 78209, USA	PI	6
211	William E. Whitson, MD Michael Washburn Center for Ophthalmic Research, LLC 901 E 86th St Indianapolis, IN, 46240, USA	PI	24
212	Gary Jerkins, MD Advancing Vision Research (Goodlettsville) 520 Rivergate Parkway, Suite 200 Goodlettsville, TN 37072, USA	PI	31
213	Stephen Whiteside, MD Austin Clinical Research 9707 Anderson Mill Road, Suite 100 Austin, TX 78750, USA	PI	10
214	Gary Jerkins, MD Advancing Vision Research (Smyrna) 515 Stonecrest Parkway, Suite 210 Smyrna, TN 37167, USA	PI	24
215	Albert Edwards, MD Verum Research 1011 Valley River Way, Suite 110 Eugene, OR 97401, USA	PI	5

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Tryptryr (acoltremon ophthalmic solution) 0.003%

Site Number	Investigator	Role	No. Subjects Enrolled
216	Victor Gonzalez, MD Valley Retina Institute (Harlingen) 1205 N. Ed Carey Drive Harlingen, TX 78550, USA	PI	4
217	Victor Gonzalez, MD Valley Retina Institute (McAllen) 1309 E. Ridge Road, Suite 1 McAllen, TX 78503, USA	PI	1
218	Nancy Cline, MD CORE 222 N Lafayette St Ste 23 Shelby, NC 28150, USA	PI	21
219	Erik Anderson, MD Vision Institute 320 E Fontanero St, Ste. 201 Colorado Springs, CO 80907, USA	PI	35
220	David Almeida, MD Erie Retina Research 300 State Street, Suite 201 Erie, PA 16507, USA	PI	13
221	John Lonsdale, MD Central Maine Eye 181 Russell St. Lewiston, ME 04240, USA	PI	18
222	Bruce Segal, MD Segal Drug Trials 5258 Linton BLVD SUITE #302-301A, Delray Beach, FL, 33484, USA	PI	10
223	Sherif M. El-Harazi, MD, MPH Global Research Management 1510 S Central Ave #300 Glendale, CA 91204, USA	PI	43
Study COMET-3			
301	Kenneth Kenyon, MD Andover Eye Associates - Warwick Site 171 Service Avenue, Suite 105 Warwick, RI 02886, USA	PI	14
302	Blair Boehmer, MD Pankratz Eye Institute 3135 Middle Road Columbus, IN 47203, USA	PI	24
303	Sheila Garcia Santana, MD Pure Ophthalmic Research 7014 Tutor Street, Suite C Mint Hill, NC 28227, USA	PI	16
304	David L. Wirta, MD Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663, USA	PI	90

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Tryptyr (acoltremon ophthalmic solution) 0.003%

Site Number	Investigator	Role	No. Subjects Enrolled
306	Marc Malouf, MD (initial PI) Philip Cofoid, MD (transitioned to PI) Virginia Eye Institute 400 Westhampton Station Richmond, VA 23226, USA	PI	14
308	Farrell C. Tyson, MD Argus Research Center, Inc. 4120 Del Prado Blvd. South Cape Coral, FL 33904, USA	PI	3
309	Kenneth Kenyon, MD Andover Eye Associates – Raynham Site 675 Paramount Dr., Suite 101 Raynham, MA 02767, USA	PI	20
310	Gail Torkildsen, MD Andover Eye Associates 138 Haverhill St., Suite 104 Andover, MA 01810, USA	PI	22
311	Clark Springs, MD Wilmington Eye 1176 E. Cutlar Crossing Leland, NC 28451, USA	PI	23
312	Mitchell A. Jackson, MD Jackson Eye 300 N. Milwaukee Ave., Suite L Lake Villa, IL 60046, USA	PI	0
313	James Paauw, MD Piedmont Eye Center 116 Nationwide Drive Lynchburg, VA 24502, USA	PI	90
314	Samir Melki, MD Boston Vision 200 Fortune Blvd. Milford, MA 01757, USA	PI	5
315	David Woods, MD Reeve Woods Eye Center 280 Cohasset Road Chico, CA 95926, USA	PI	2
316	Sonya Bamba, MD Wyse Eyecare 900 Skokie Blvd, Suite 150 Northbrook, IL 60062, USA	PI	27
317	Lee Katzman, MD NVision Clinical Research 160 Elmgrove Park Rochester, NY 14624, USA	PI	13
319	Matthew Swanic, MD AdvanceMed Clinical Research 9555 S. Eastern Ave., Suite 260 Las Vegas, NV 89123, USA	PI	1
320	Kyla R. Aschenbeck, MD Keystone Research 5717 Balcones Drive Austin, TX 78731, USA	PI	12

Site Number	Investigator	Role	No. Subjects Enrolled
321	Sai Chavala, MD Axis Clinicals 11615 Forest Central Dr., Unit 308 Dallas, TX 75243, USA	PI	0
322	Mitchell C. Shultz, MD Mitchell C. Shultz 18350 Roscoe Blvd., #101 Northridge, CA 91325, USA	PI	15
324	Preeya Gupta, MD Oculus Research 958 Vandora Springs Road Garner, NC 27529, USA	PI	39
325	David Almeida, MD Erie Retina Research, LLC 300 State Street, Suite 201 Erie, PA 16507, USA	PI	13
326	Jeffrey Winston, MD NVision Clinical Research, LLC 1400 N. Harbor Blvd., Suite 101 Fullerton, CA 92835, USA	PI	11
327	Alex C. Liu, MD MPH NVision Clinical Research, LLC 23441 Madison St., Suite 120 Torrance, CA 90505, USA	PI	12

Source: Module 5.3.5.1, COMET-2 and COMET-3 CSRs, Appendix 16.1.4
Abbreviations: No., number; PI, principal investigator

Diagnosis and Main Criteria for Inclusion

Key Inclusion Criteria

- Male or female, 30 years of age or older at the Screening visit
- Previous history of DED, clinician-diagnosed or patient-reported, within the previous 6 months prior to the Screening visit
- Had used and/or desired to use artificial tears for DED symptoms within 2 months prior to the Screening visit
- Both of the following in the same eye:
 - Total corneal fluorescein staining score of ≥ 2 and ≤ 15 based on the modified National Eye Institute grading scheme, with no one region scoring >3 in at least 1 eye at the Screening visit only
 - Anesthetized Schirmer test score ≥ 2 and < 10 millimeters (mm)/5 minutes in at least 1 eye and the same eye must qualify at both the Screening and Baseline visits
- Symptoms of DED based on the following:
 - A score of ≥ 50 based on ODS assessed on a VAS at both the Screening and Baseline visits
 - A score of ≥ 50 based on SANDE at both the Screening and Baseline visits

- Increase in the signs and symptoms of DED based on the CAE exposure at the Screening visit only demonstrated by:
 - ≥ 1 -point increase in inferior region corneal staining score (assessed using sodium fluorescein staining) in at least 1 eye based on the Ora Calibra[®] grading scale after the 90-minute CAE exposure
 - Ora Calibra ODS score ≥ 3 at 2 or more consecutive time points in at least 1 eye during CAE exposure within ≤ 20 minutes of entering the CAE (if a subject had an ocular discomfort rating of 3 at time 0 for an eye, the subject must have reported an ocular discomfort rating of 4 for 2 consecutive measurements for that eye within ≤ 20 minutes of entering the CAE)
- CVA equal to or better than +0.7 LogMAR (Snellen equivalent equal to or better than 20/100) as assessed by Early Treatment of Diabetic Retinopathy Study scale in both eyes at both the Screening and Baseline visits

Key Exclusion Criteria

- History or presence of any ocular disorder or condition (other than DED) in either eye that would, in the opinion of the investigator, interfere with the interpretation of the study results or subject safety, such as: significant corneal or conjunctival scarring; pterygium or nodular pinguecula; conjunctivitis, or inflammation not associated with DED; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; evidence of keratoconus; etc. Note: Blepharitis and/or Meibomian gland disease not requiring treatment were allowed
- Current evidence of other significant ophthalmic disease requiring topical medication (e.g., glaucoma, ocular hypertension) which may have interfered with vision (e.g., cataract, macular degeneration) or other disease which the investigator believed may interfere with study findings or interpretation
- History of ocular surgery within 1 year prior to the Screening visit, including punctal cauterization, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision)
- Corneal transplant in either or both eyes
- Use of contact lenses in either eye within 7 days prior to the Screening visit or planned use during the study
- Punctal or intracanalicular plug present in either eyelid within 14 days prior to the Screening visit or anticipated plug insertion or occlusion at any time during the study
- Regular use of lid hygiene within 14 days prior to the Screening visit or any planned use during the study
- Use of lid heating therapy (i.e., LipiFlow[®], iLUX[®], TearCare[®]) or Meibomian gland probing/therapeutic expression within 1 year prior to the Screening visit or anticipated during the study

- Use of artificial tears within 2 hours prior to the Screening visit or anticipated use during the study
- Use of any topical ocular anti-inflammatory medication within 30 days prior to the Screening visit or anticipated use during the study (e.g., ocular cyclosporine [Restasis[®], Cequa[™]], lifitegrast [Xiidra[®]], or any other prescription ophthalmic product for DED, topical ocular corticosteroid or nonsteroidal anti-inflammatory agents, or autologous serum)
- Use of any topical ocular glaucoma medication within 30 days prior to the Screening visit or anticipated use during the study
- Regular use of any other topical ocular medication within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine[®], Lumify[®]], topical ocular antibiotics, topical ocular antihistamines, mast cell stabilizers, age-related blurry near vision [presbyopia] drops [Vuity[™]], or other OTC, herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications was permitted provided that no drops were used within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit
- Use of Tyrvaya[™] (varenicline solution, nasal spray 0.03 milligrams [mg]) within 30 days prior to the Screening visit or anticipated use during the study
- Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days prior to the Screening visit or anticipated use during the study
- Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) less than 14 days prior to the Screening visit or a change in dosage was anticipated during the study. Note: Occasional short-term use of medications such as systemic antihistamines was permitted provided that use was not within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit
- Initiation, discontinuation, or change in dose of a systemic corticosteroid less than 60 days prior to the Screening visit or a change in dosage was anticipated during the study. Note: Nonocular topically applied corticosteroids (including topical creams, nasal sprays, and inhalers) were permitted during the study and the dose was not required to be stable
- Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) less than 60 days prior to the Screening visit or a change in dosage was anticipated during the study

Identity of Investigational Product(s)

Study Drug

Acoltremon is the active pharmaceutical ingredient in Tryptyr (acoltremon ophthalmic solution) 0.003%. Tryptyr is a sterile, preservative-free, isotonic, (b) (4) aqueous solution containing acoltremon (0.003%), hypromellose, polyoxyl 35 castor oil, sodium dihydrogen phosphate dihydrate, and sodium chloride (b) (4) purified water (b) (4) The

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Tryptyr (acoltremon ophthalmic solution) 0.003%

product formulation was adjusted to a pH of approximately 7 with sodium hydroxide and was packaged in (b) (4) polyethylene.

Vehicle (Placebo) or Control Drug

Acoltremon ophthalmic solution vehicle is a sterile, preservative-free, isotonic, (b) (4) aqueous solution containing hypromellose, polyoxyl 35 castor oil, sodium dihydrogen phosphate dihydrate, and sodium chloride (b) (4) purified water (b) (4). The product formulation was adjusted to a pH of approximately 7 with sodium hydroxide and was packaged in (b) (4) polyethylene.

Method of Assigning Subjects to Treatment Groups

All subjects were centrally assigned to randomized study treatment using an interactive response technology (IRT). Before the study was initiated, the login information and directions for the IRT were provided to qualified personnel at each site. All qualified subjects were assigned to receive acoltremon vehicle BID to both eyes for 14 days (vehicle run-in period).

Following the run-in period, all subjects who requalified at the Baseline visit were randomized in a 1:1 ratio, within each site, to receive:

- 0.003% acoltremon
- Acoltremon vehicle

The IRT provided the site with the specific kit number(s) for each randomized subject at the time of randomization. Sites dispensed the study treatment according to the IRT instructions and the Schedule of Visits and Assessments.

Rescue Medication

Disallowed medications and treatments were listed in the Exclusion Criteria. All medications and treatments that were not allowed prior to the study were not allowed during the study, except that occasional short-term use of topical ocular medications (specified above) was permitted provided that no drops were used within 24 hours of the Screening visit or anticipated use within 24 hours of any study visit.

Prior and Concomitant Therapy

Medical treatment(s) taken by the subject upon study entry were maintained throughout the study. Treatments prohibited during the course of the study included:

- Artificial tears (2-hour washout required prior to the Screening visit)
- Use of any of topical ocular anti-inflammatory medication (e.g., ocular cyclosporine [Restasis, Cequa], lifitegrast [Xiidra]), any other prescription ophthalmic product for DED, topical ocular corticosteroid or nonsteroidal anti-inflammatory agents, autologous serum, and topical glaucoma or ocular IOP-lowering medications (30-day washout required prior to the Screening visit)

- Use of Tyrvaya (varenicline solution, nasal spray 0.03 mg; 30-day washout required prior to the Screening visit)
- Regular use of any other topical ocular medication (i.e., medications not excluded by exclusion criterion #11 or #12) within 14 days prior to the Screening visit or anticipated use during the study (e.g., eye whitening products [Visine, Lumify], topical ocular antibiotics, topical ocular antihistamines, mast cell stabilizers, age-related blurry near vision [presbyopia] drops [Vuity], or other OTC, herbal, prescription, or nutritional supplements). Note: Occasional short-term use of these topical ocular medications was permitted provided that no drops were used within 24 hours of any study visit
- Medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids (30-day washout required prior to the Screening visit)
- Any investigational product or device (30-day washout required prior to the Screening visit)
- Lid-heating therapy, Meibomian gland probing, or therapeutic Meibomian gland expression (1-year washout required prior to the Screening visit)
- Regular use of lid hygiene (14-day washout required prior to the Screening visit)
- Removal of punctal or intracanalicular plugs (14-day washout required prior to the Screening visit)
- Contact lenses (7-day washout required prior to the Screening visit)

Details on the required washout periods prior to the Screening visit and the prior and concomitant therapies requiring stability, are located in Sections 4.6.1 and 4.6.1.2 of the clinical study protocol.

Criteria for Evaluation

Primary Efficacy Endpoint

- Proportion of subjects with ≥ 10 -mm increase (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14

Secondary Efficacy Endpoints

- Change from baseline in global SANDE score on Day 28
- Change from baseline (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14
- Proportion of subjects with ≥ 10 -mm increase (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1
- Change from baseline (postdrop on Day 1 versus predrop at baseline) in unanesthetized Schirmer score on Day 1
- Proportion of subjects with ≥ 10 -mm increase (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90

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- Change from baseline (postdrop on Day 90 versus predrop at baseline) in unanesthetized Schirmer score on Day 90
- Change from baseline in global SANDE score on Day 90
- Change from baseline in SANDE frequency score on Day 90
- Change from baseline in SANDE severity score on Day 90
- Change from baseline in eye dryness score – VAS on Day 90
- Change from baseline in ODS – VAS on Day 90

Exploratory Efficacy Endpoints

For brevity, details of the of exploratory endpoints included in this study can be found in Section 6.2.2.1 of the study protocol.

Table 48. Schedule of Visits and Procedures, Studies COMET-2 and COMET-3

Visit ^a	Start of 2-Week Run-In (Vehicle)	Randomized Study Intervention Period (BID-OU, 1:1 Randomization 0.003% Acoltremon: Vehicle)						
	Screening (Day -14)	Baseline (Day 1)	Day 7	Day 14	Day 28	Day 60 ^b	Day 90 (Study Exit)	Early Termination
Visit Window (Days)	+3 ^c	N/A	±2	±2	±2	±5	-2/+5	N/A
Informed consent	X							
Demographics	X							
Collection of used / unused study intervention		X		X	X	X	X	X
Medical, ophthalmic, and surgical history	X							
Prior or concomitant medication review	X	X	X	X	X		X	X
AE review	X	X	X	X	X		X	X
Vital signs (heart rate and blood pressure)	X	X					X	X
Urine pregnancy test (WOCBP only)	X	X					X	X
Symptom questionnaire (VAS) (Ocular Discomfort, Eye Dryness and Ocular Pain)	X	X	X	X	X		X	
SANDE questionnaire (VAS)	X	X	X	X	X		X	
Activities of Daily Living questionnaire		X	X	X	X		X	
Quality of Life questionnaire		X	X	X	X		X	
Drop tolerability questionnaire							X	
Corrected visual acuity	X	X	X	X	X		X	X
Slit-lamp biomicroscopy	X	X	X	X	X		X	X
Ora Calibra conjunctival redness scale		X	X	X	X		X	
At least 5 min rest period	X	X						
Anesthetized Schirmer test	X	X						
At least 10-minute rest period	X	X	X	X	X		X	
Tear film break-up time	X	X	X	X	X		X	
Fluorescein staining of cornea (modified NEI grading scale)	X	X	X	X	X		X	
Fluorescein staining of cornea (Ora Calibra scale) performed prior to CAE exposure	X							
Lissamine green staining of conjunctiva (modified NEI grading scale)	X	X	X	X	X		X	

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Visit ^a	Start of 2-Week Run-In (Vehicle)		Randomized Study Intervention Period (BID-OU, 1:1 Randomization 0.003% Acoltremon: Vehicle)					Day 90 (Study Exit)	Early Termination
	Screening (Day -14)	Baseline (Day 1)	Day 7	Day 14	Day 28	Day 60 ^b			
CAE exposure	X								
Ora Calibra ODS	X ^d								
Fluorescein staining of cornea (Ora Calibra scale) performed post CAE exposure	X								
Inclusion and exclusion criteria	X	X							
Randomization		X							
Dispensing of study intervention ^e	X	X		X	X	X			
At least 30 and up to 45-minute rest period		X	X	X	X		X		
Predrop unanesthetized Schirmer test		X	X	X	X		X		
At least 15- and up to 20-minute rest period		X	X	X	X		X		
In office administration of study intervention ^f	X	X	X	X	X		X		
Postdrop unanesthetized Schirmer test		X	X	X	X		X		
Hematology, chemistry, and urinalysis		X					X	X	
Intraocular pressure	X	X					X	X	
Dilated fundus exam	X	X					X	X	
Study exit							X	X	

Source: Module 5.3.5.1 CSRs for COMET-2 and COMET-3, Appendix 16.1.1 Protocol, Schedule of Assessments Appendix 1

^a All office visits must be arranged at approximately the same time of day $\pm$ 1 hour

^b Dispensing and collection visit only

^c The Baseline visit should be scheduled between 11 and 14 days after the Screening visit. If absolutely necessary, the Baseline visit may be delayed up to 7 days (extending the run-in period to a maximum of 21 days)

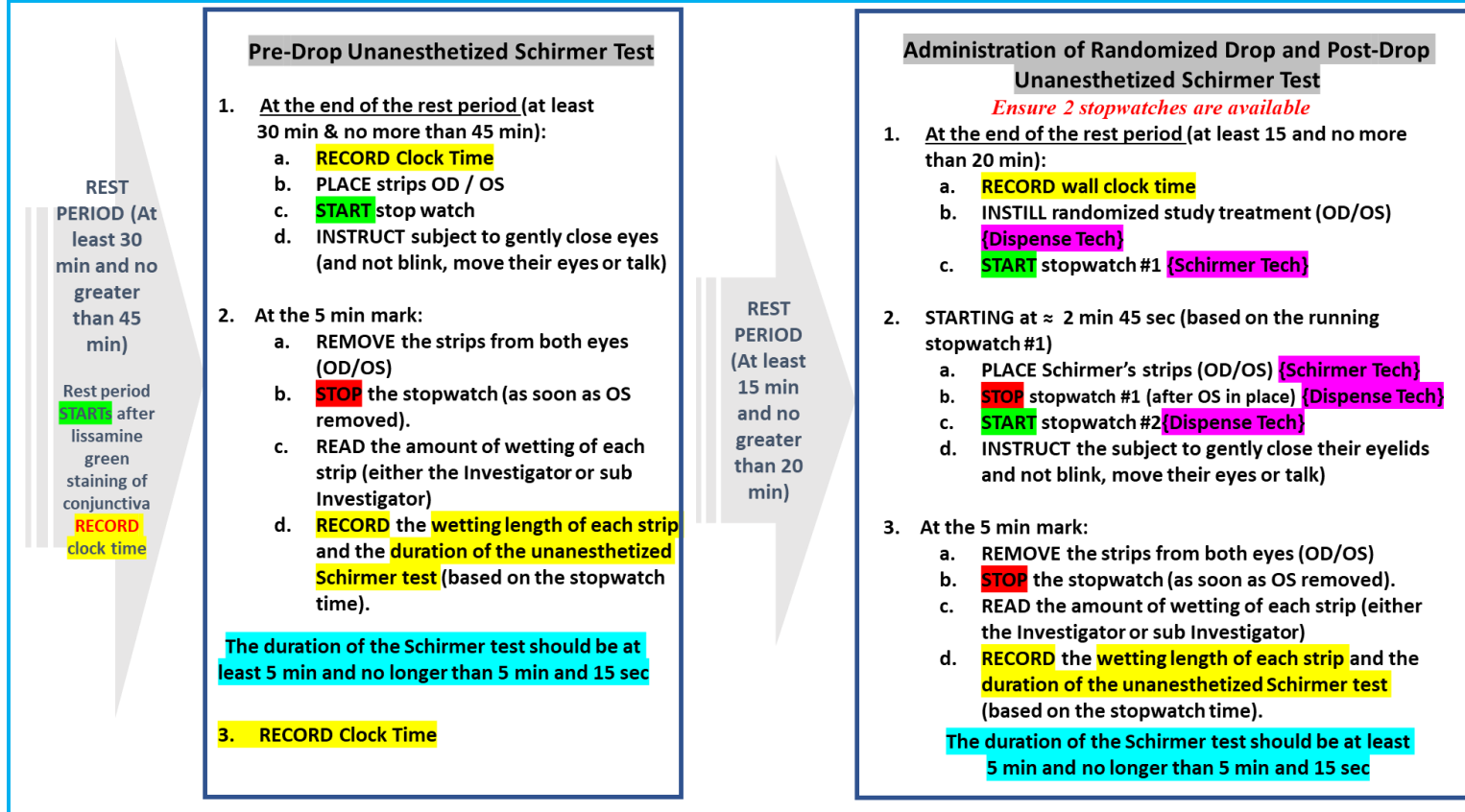
^d Administered every 5 minutes while in the CAE

^e Day 7 randomized intervention kit is not to be dispensed home to the subject. A single vial is used at the day seven visit and then return to the kit. These single used vial as well as remaining 4 unused vials are to be retained for accountability

^f Study intervention must be removed from the refrigerator at least 30 minutes before use

Abbreviations: BID, twice daily; CAE, controlled adverse environment; NEI, National Eye Institute; ODS, ocular discomfort score; OU, both eyes; SANDE, Symptoms Assessment in Dry Eye; VAS, visual analog scale; WOCBP, women of childbearing potential

Figure 7. Flow Scheme of Unanesthetized Schirmer Tests



Source: COMET-3 Manual of Procedures, Version 1.0, Appendix 2
 Abbreviations: OD, right eye; OS, left eye

Planned Statistical Analysis Methods

Sample Size Determination

Two hundred and two subjects per treatment group yields 99% power to conclude superiority of 0.003% acoltremon over vehicle in the proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14, assuming a true difference of proportions (acoltremon versus vehicle) of 80% versus 30% and a two-sided alpha =0.05.

Additionally, 202 subjects per treatment group yields 99% power to conclude superiority of 0.003% acoltremon over vehicle in the mean change from baseline in SANDE score on Day 28 assuming a true difference (acoltremon minus vehicle) of -7.9, a common standard deviation of 17.72, and a two-sided alpha =0.05.

Accounting for subject discontinuations, approximately 460 total subjects (230 per treatment arm) were planned to be randomized assuming a dropout rate of 10%.

Analysis of Primary Endpoint

The primary comparison in this study was between 0.003% acoltremon and vehicle in the ITT population using Estimand 1.

Analysis of primary efficacy was based on the difference of proportions using Pearson's Chi-square test. Available data only were used if the discontinuation rate was <5% in each arm; otherwise, an estimand based on multiple imputations was used for the primary analysis. Inference across multiple imputed datasets was obtained by pooling Chi-square distributed statistics as proposed by Ratitch (2013), Rubin (1987), and Li (1991) ([Rubin D.B. 1987](#); [Li 1991](#); [Ratitch et al. 2013](#)).

The primary endpoint was tested as follows:

- H_{01} : The difference between study eyes treated with 0.003% acoltremon and study eyes treated with vehicle, in the proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14=0.
- H_{11} : The difference between study eyes treated with 0.003% acoltremon and study eyes treated with vehicle, in the proportion of subjects with ≥ 10 -mm increase in unanesthetized Schirmer score on Day 14 $\neq 0$.

The primary estimand (Estimand 1) was based on the ITT population targeting the treatment effect attributable to the randomly assigned treatment, regardless of compliance to study treatment and assuming subjects who discontinued due to lack of efficacy, AEs, or disallowed concurrent treatments followed the behavior of subjects in the reference arm for the duration of the study and subjects who discontinued for other reasons (outside of lack of efficacy, AEs, or use of disallowed treatment) would follow the behavior of subjects who were still in the study under same randomly assigned treatment. For further details on Estimands 1, 2, and 3 refer to Statistical Analysis Plan.

Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints were analyzed using the ITT population and repeated using the PP population.

Analysis of secondary efficacy was conducted as described for the primary efficacy endpoints, using the difference of proportions tests, or ANCOVA for difference of change from baseline means. Available data only was used if the discontinuation rate was <5% in each arm and multiple imputation otherwise. For details on Estimands 1, 2, and 3 as applicable to secondary efficacy endpoints refer to Section 9.7.1.6.2.

Two-sample t-tests comparing treatment groups were performed as sensitivity analyses. Wilcoxon rank sum tests were also performed as sensitivity analyses. The secondary dichotomous efficacy endpoints were analyzed similarly to the primary endpoint.

To ensure Type 1 error rate was controlled at the 5% significance level (2-sided) over all set of study hypotheses, a fixed-sequence hierarchical strategy was employed, requiring all preceding endpoints in the testing hierarchy to be statistically significant at the 5% level before an endpoint could be evaluated for statistical significance. For example, the primary endpoint must have shown statistical significance at the 5% significance level before the first (key) secondary endpoint could be evaluated for statistical significance and so on.

Safety

All safety analyses were carried out using the Safety population and included the study eye and fellow eye separately, where applicable.

The assessment of safety was evaluated by:

- Adverse events
- Clinical laboratory (hematology, clinical chemistry, and urinalysis)
- Vital signs (heart rate and blood pressure)
- CVA
- Slit lamp biomicroscopy
- IOP
- Dilated fundus exam

All safety variables were descriptively summarized by treatment group at each assessment time and for relevant changes from baseline, where applicable.

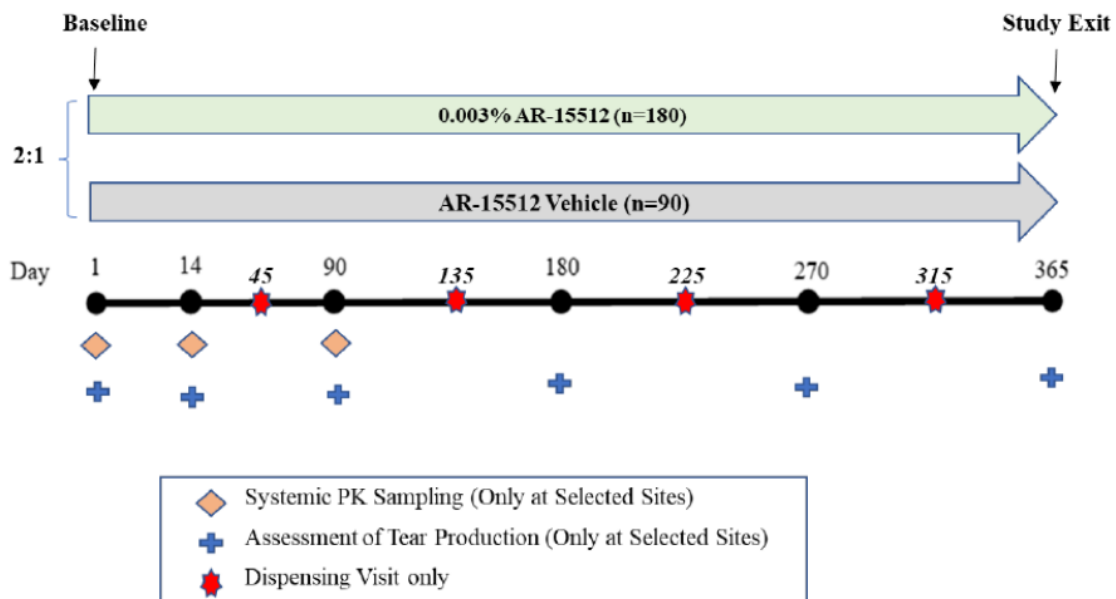
16. Efficacy

Refer to Section [6](#).

17. Clinical Safety

A general description of the long-term safety study COMET-4 is within this review section. Study results as well as pooled safety results are in Section 7.

Figure 8. Schematic of Study Design, Study COMET-4



Source: Module 5.3.5.4 Appendix 1 Protocol AR-15512-LTSS, Figure 1
Abbreviation: PK, pharmacokinetics

Table 49. Schedule of Visits and Procedures, Study COMET-4

Visit	Baseline (Day 1)	Day 14	Day 45	Day 90	Day 135	Day 180	Day 225	Day 270	Day 315	Day 365 (Study Exit)	Early Termination
Visit Window (Days)	N/A	±2	±5	±5	±7	±7	±7	±7	±7	±7	N/A
Visit Type											
C = Clinic											
D = Dispensing	C	C	D	C	D	C	D	C	D	C	C
Informed consent	X										
Demographics	X										
Collection of unused study intervention		X	X	X	X	X	X	X	X	X	X
Medical, ophthalmic, and surgical history	X										
Prior or concomitant medication review	X	X		X		X		X		X	X
AE review ^a	X	X		X		X		X		X	X
Vital signs (heart rate and blood pressure)	X	X		X		X		X		X	X
Urine pregnancy test (WOCBP only)	X									X	X
Corrected visual acuity	X	X		X		X		X		X	X
Best corrected visual acuity	X									X	X
Slit-lamp biomicroscopy	X	X		X		X		X		X	X
At least 5 min rest	X	X		X		X		X		X	
Total ocular staining (fluorescein staining of cornea and lissamine green staining of conjunctiva; Oxford grading scheme)	X	X		X		X		X		X	
At least 10 min rest	X									X	
Specular microscopy to assess corneal endothelial cell counts	X									X	X
Inclusion and exclusion criteria review ^b	X										
Randomization	X										
Hematology, chemistry, and urinalysis	X					X				X	X
Pre-dose Blood Draw for PK Samples (selected sites only) ^c	X	X		X							
Dispensing of study intervention	X	X	X	X	X	X	X	X	X		
At least 30 and up to 45-minute rest period (at selected sites only) ^c	X	X		X		X		X		X	

Visit	Baseline (Day 1)	Day 14	Day 45	Day 90	Day 135	Day 180	Day 225	Day 270	Day 315	Day 365 (Study Exit)	Early Termination
Visit Window (Days)	N/A	±2	±5	±5	±7	±7	±7	±7	±7	±7	N/A
Visit Type											
C = Clinic											
D = Dispensing	C	C	D	C	D	C	D	C	D	C	C
Predrop unanesthetized Schirmer test (at selected sites only) ^c	X	X		X		X		X		X	
At least 15 and up to 20-minute rest period (at selected sites only) ^c	X	X		X		X		X		X	
In-office administration of study intervention	X	X		X		X		X		X	
Postdrop unanesthetized Schirmer test (at selected sites only) ^d	X	X		X		X		X		X	
Postdose blood draws for PK samples (selected sites only) ^c	X	X		X							
Drop attribute and acceptability questionnaire	X	X				X				X	
Activities of daily living questionnaire	X	X		X		X		X		X	
Quality of life questionnaire	X	X		X		X		X		X	
Intraocular pressure	X	X		X		X		X		X	X
Dilated fundus exam	X	X		X		X		X		X	X
Study exit										X	X

Source: Appendix 1 of the clinical study protocol in Appendix 16.1.1.

^a A drop tolerability questionnaire will be completed by subjects who report burning or stinging as an AE. Complete instructions are described in the Manual of Procedures.

^b Pertaining to inclusion criteria #4, if a documented Schirmer test score does not exist, a Schirmer test (either with or without topical anesthesia), can be performed at the Baseline visit and a score ≥ 2 and < 10 mm/5 min in at least 1 eye is required. This test should be performed approximately 15 minutes after total ocular staining followed by the start of the rest period (at least 10 min) prior to specular microscopy.

^c Pharmacokinetic evaluation will only be performed in a subset of subjects (n=35) at selected sites on visit Days 1, 14, and 90. Six plasma samples will be drawn at each of these visits as follows: predose, and postdose at 15 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours.

^d Two unanesthetized Schirmer tests will be performed at selected sites only with required rest periods prior to test starts as specified. Complete instructions are described in the Manual of Procedures

Abbreviations: AE, adverse event; PK, pharmacokinetics; WOCBP, women of childbearing potential

17.1. List of Investigators

A list of the principal investigators who participated in this study is provided below.

Table 50. List of Investigators, Study COMET-4

Site Number	Investigator	Role	No. Subjects Enrolled
401	David Wirta, MD Eye Research Foundation 520 Superior Ave #235 Newport Beach, CA 92663, USA	PI	42
402	Mitchell C Shultz, MD Shultz Vision 18350 Roscoe Blvd #101 Northridge, CA 91325, USA	PI	47
403	James Paauw, MD Piedmont Eye Center 116 Nationwide Dr Lynchburg, VA 24502, USA	PI	70
404	Sherif El-Harazi, MD Global Research Management, Inc. 1510 S Central Ave #300 Glendale, CA 91204, USA	PI	46
405	Jonathan Macy, MD Macy Eye Center 8635 W 3rd St, Ste 360W Los Angeles, CA 90048, USA	PI	9
406	Kenneth Olander, MD University Eye Specialists 622 Smithview Dr Maryville, TN 37803, USA	PI	4
407	Laura Periman, MD Periman Eye Institute 100 W Harrison St, NORTH Tower, Ste 360 Seattle, WA 98119, USA	PI	4
408	Michael Deppenbusch, MD Arizona Eye Center 1500 W Ray Rd Chandler, AZ 85225, USA	PI	29
409	Brad Kligman, MD Sight MD, 133 Plandome Rd Manhasset, NY 11030, USA	PI	13
410	Emilio Justo, MD Arizona Eye Institute 10701 W Bell Rd Sun City, AZ 85351, USA	PI	11

Source: Module 5.3.5.1, CSR AR15512-LTSS, Appendix 16.1.4
Abbreviations: No., number; PI, principal investigator

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Overall Assessment of Findings and Recommendations

Clinical data from Protocols AR-15512-CS301 and AR-15512-CS302 were submitted to the Agency in support of NDA 217370 for the use of Tryptyr (acoltremon) for the treatment of signs and symptoms of dry eye disease. Drs. Liu, Anderson, Springs, and Bamba were inspected in support of this NDA.

Based on the results of these inspections, Protocols AR-15512-CS301 and AR-15512-CS302 appear to have been conducted adequately and the data generated by these sites and submitted by the Applicant appear acceptable in support of the respective indication.

Background

The Applicant submitted this NDA to support the use Tryptyr (acoltremon), a receptor (TRPM8) agonist, for the treatment of signs and symptoms of dry eye disease.

Inspections were requested of the following protocols in support of this application:

Protocol Numbers and Titles

- Protocol AR-15512-CS301: “A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-2)”
- Protocol AR-15512-CS302: “A Phase 3 Study Evaluating the Safety and Efficacy of AR-15512, a Cold Thermoreceptor Modulator, for the Treatment of Dry Eye Disease (COMET-3)”

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Protocols AR-15512-CS301 and AR-15512-CS302

These protocols were very similar in design with both studies being designed to assess the safety, efficacy, and tolerability of Tryptyr (acoltremon) in the treatment of signs and symptoms of dry eye disease over a 15-week study period.

Both studies shared the same efficacy objectives, treatment schedules, and subject qualification criteria. These protocols were multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trials whose primary objectives were to evaluate the safety, efficacy, and tolerability of Tryptyr (acoltremon) compared to placebo for approximately 13 weeks in the treatment of signs and symptoms of dry eye disease.

The study consisted of six clinic visits over a period of 15 weeks. Eligible subjects were randomized in a 1:1 ratio to receive Tryptyr (acoltremon) or vehicle (placebo) once daily for 13 weeks. Clinical assessments of efficacy were conducted at the baseline visit and on Day 7, Day 14, Day 28, and Day 90.

The primary efficacy endpoint of the study was the increase (postdrop on Day 14 versus predrop at baseline) in unanesthetized Schirmer score on Day 14.

Each protocol was conducted at 23 sites in the United States. For Protocol AR-15512-CS301, there were 465 randomized subjects with the first subject being enrolled on May 23, 2022, and the last subject completing the study on July 24, 2023. For Protocol AR-15512-CS302, there were 467 randomized subjects with the first subject being enrolled on August 1, 2022, and the last subject completing on October 17, 2023.

1. Alex Liu, M.D.

East West Eye Institute
23441 Madison St., Suite 120
Torrance, CA 90505

Site: 207
Protocol: AR-15512-CS301
Inspection Dates: October 7-11, 2024

Dr. Liu was inspected for the conduct of Protocol AR-15512-CS301. This was the first inspection of Dr. Liu. At this site, 75 subjects were screened, 58 subjects were enrolled, and 53 subjects completed the study.

The study files of the 53 subjects completing the study were reviewed, including the verification of the primary and secondary efficacy endpoints and the reporting of adverse events. Subject records reviewed included study eligibility, informed consent, randomization, protocol deviations, discontinuations, and concomitant medications.

Study-related documents reviewed included the Form 1572, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, investigational product (IP) receipt, storage, accountability, and administration records, electronic records including access controls and audit trails, and financial disclosures.

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The inspection compared the source documents with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

2. Erik Anderson, M.D.

Vision Institute
320 E. Fontanero St., Ste. 201
Colorado Springs, CO 80907

Site: 219
Protocol: AR-15512-CS301
Inspection Dates: December 17-19, 2024

Dr. Anderson was inspected for the conduct of Protocol AR-15512-CS301. This was the first inspection of Dr. Anderson. At this site, 104 subjects were screened, 35 subjects were enrolled, and 27 subjects completed the study.

The study files of 29 of the 35 subjects were reviewed for verification of the primary efficacy endpoint. Of the 27 subjects completing the study, the complete source data was reviewed for 23 subjects, in addition to the verification of the primary efficacy endpoint and safety data for the remaining four subjects completing the study. Subject records reviewed included study eligibility, informed consent, and protocol deviations.

Study related documents reviewed included the Form 1572, IRB and monitor correspondence, training documentation, delegation logs, IP receipt, dispensation, and storage records, and financial disclosures.

The inspection compared the source documents with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

3. Clark Springs, M.D.

Wilmington Eye
1176 E. Cutlar Crossing
Leland, NC 28451

Site: 311
Protocol: AR-15512-CS302
Inspection Dates: November 18-21, 2024

Dr. Springs was inspected for the conduct of Protocol AR-15512-CS302. This was the first inspection of Dr. Springs. At this site, 109 subjects were screened, 86 subjects were screen failures, 23 subjects were enrolled and randomized to the study, 20 subjects completed the study, and three subjects withdrew from the study.

The study files of all 23 randomized subjects were reviewed, including the verification of the primary efficacy endpoint and the reporting of adverse events. Subject records reviewed included

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study eligibility, informed consent, randomization, protocol deviations, and concomitant medications.

Study related documents reviewed included the Form 1572, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, IP receipt, storage, accountability, dispensation, and return records, electronic records including access controls and audit trails, and financial disclosures.

The inspection compared the source documents and electronic case report forms with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

4. Sonya Bamba, M.D.

Wyse Eyecare
900 Skokie Blvd, Suite 150
Northbrook, IL 60062

Site: 316
Protocol: AR-15512-CS302
Inspection Dates: 14-20 Nov 2024

Dr. Bamba was inspected for the conduct of Protocol AR-15512-CS302. This was the first inspection of Dr. Bamba. At this site, 132 subjects were screened, 27 subjects were enrolled and randomized, and one subject withdrew from the study.

The study files of all 27 randomized subjects were reviewed, including the verification of the primary efficacy endpoint and the reporting of adverse events. Subject records reviewed included study eligibility, informed consent, randomization, protocol deviations, discontinuations, and concomitant medications.

Study related documents reviewed included the Form 1572, IRB, sponsor, and monitor correspondence, training documentation, delegation logs, IP receipt, storage, accountability, and dispensation records, electronic records including access controls and audit trails, and financial disclosures.

The inspection compared the source documents with the data listings, and no significant discrepancies were observed. Adherence to the regulations and the investigational plan appeared adequate.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 51](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 51. Key Labeling Changes and Considerations

Full PI Sections^a	Rationale for Major Changes to Finalized PI^b Compared to Applicant's Draft PI
BOXED WARNING	None
1 INDICATIONS AND USAGE	None
2 DOSAGE AND ADMINISTRATION	None
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	Inclusion of 5.2 Use with Contact Lenses
6 ADVERSE REACTIONS	None
7 DRUG INTERACTIONS	Not applicable
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	None
9 DRUG ABUSE AND DEPENDENCE	Not applicable
10 OVERDOSAGE	Not applicable
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of action revised for clarity
13 NONCLINICAL TOXICOLOGY	None
14 CLINICAL STUDIES	Revised to be consistent with other products with similar study design.
17 PATIENT COUNSELING INFORMATION	None.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	None

Source: Approved labeling

^a Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

^b For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application the following labeling documents will be FDA-approved:

Draft Carton and Container Labels

[Table 52](#) lists the NDC number for the sample and trade configurations of Tryptyr (acoltremon ophthalmic solution) 0.003% for the draft cartons, pouch, vial labels and package insert (full Prescribing Information and Instructions for Use).

Table 52. Draft Labeling Components for Tryptyr (Acoltremon Ophthalmic Solution) 0.003%

Configuration	Draft Component
15 Count - Professional Sample NDC No. 0065-8595-01	Sample Carton
	Sample Pouch
60 Count- Trade NDC No. 0065-8595-02	Trade Carton
	Trade Pouch
	Trade Vial

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Configuration	Draft Component
15 Count - Professional Sample NDC No. 0065-8595-01	Package Insert
60 Count- Trade NDC No. 0065-8595-02	
Source: Module 1.14.1.1 Abbreviation: NDC, national drug code	

24. Postmarketing Requirements and Commitments

Not applicable.

25. Financial Disclosure

Table 53. Covered Clinical Studies: COMET-1, COMET-2, COMET-3, and COMET-4

Was a list of clinical investigators provided:		Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 1306		
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
	If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	N/A	Yes ☐	No ☐ (Request information from Applicant)
	Number of investigators with certification of due diligence (Form FDA 3454, box 3): N/A		
Is an attachment provided with the reason:		Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

The Applicant provided Form 3454 attesting to the following:

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed

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clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)

NAME Mr. George Baklayan	TITLE Sr. Director, Global Regulatory Affairs
FIRM/ORGANIZATION Alcon Laboratories, Inc.	
SIGNATURE George Baklayan Digitally signed by George Baklayan DN: cn=George Baklayan, o=Alcon, ou=Regulatory Affairs, email=george.baklayan@alcon.com, c=US Date: 2024.05.08 13:36:16 -0700	DATE (mm/dd/yyyy) 05/08/2024

The list of primary investigators and subinvestigators and attestation were provided in section 1.3.4 FINANCIAL DISCLOSURE INFORMATION.

26. References

Literature

European Food Safety Authority, 2014, Scientific Opinion on Flavouring Group Evaluation 304, Revision 1 (FGE.304Rev1): Four carboxamides from Chemical Groups 30, EFSA Journal, 12(7)

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Guidance for Industry

FDA guidance for industry *Q3B(R) Impurities in New Drug Products (Revision 3)* (August 2006)

FDA guidance for industry *Quality Considerations for Topical Ophthalmic Drug Products* (December 2023)

FDA guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)

FDA guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020)

FDA guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023)

FDA guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008)

FDA guidance for industry *S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996)

FDA guidance for industry *Certain Ophthalmic Products: Policy Regarding Compliance With 21 CFR Part 4* (March 2022)

FDA guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021)

27. Review Team

Table 54. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Michael Puglisi
Nonclinical reviewer	Muriel Saulnier
Nonclinical team leader	Muriel Saulnier, Kim Hatfield
OCP reviewer(s)	Lei He
OCP team leader(s)	Ping Ji
Clinical reviewer	David Summer
Clinical team leader	Rhea Lloyd
Biometrics reviewer	Epiphanie Nyirabahizi
Biometrics team leader	Guoxing Soon
Cross-discipline team leader	Rhea Lloyd
Division director (pharm/tox)	Kim Hatfield
Division director (OCP)	Chandahas Sahajwalla
Division director (OB)	Thamban Valappil
Division director (clinical)	William Boyd
Office director (or designated signatory authority)	Charles Ganley

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 55. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	DS- Milton Sloan DP- Fardokht Abulwerdi OPMA- Wenchun Feng ATL- Chunchun Zhang
Microbiology	David Quan
OPDP	Not applicable.
OSI	Roy Blay
OSE/DEPI	Not applicable
OSE/DMEPA	Sofanit Getahun/ Valerie Vaughn
OSE/DRISK	Not applicable
Other	RPM – Shazma Aftab

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-56 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Rhea Lloyd OSM DO	Sections: Labeling	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rhea Lloyd Digitally signed by Rhea Lloyd Date: 5/27/2025 3:20 PM EDT GUID: 2025527192057				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Rhea Lloyd OSM DO	Sections: Clinical	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rhea Lloyd Digitally signed by Rhea Lloyd Date: 5/27/2025 3:21 PM EDT GUID: 2025527192128				

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Chunchun Zhang OPQAll DPQAIX	Sections: NDA 217370 is recommended Approval from Product Quality perspective.	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	NDA 217370 is recommended Approval from Product Quality perspective. Refer to OPQ IQA #1 and Addendum #1.
Signature: Chunchun Zhang Digitally signed by Chunchun Zhang Date: 5/27/2025 3:35 PM EDT GUID: 2025527193531				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Epiphane Nyrabahizi OB DBIV	Sections: 6	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Epiphane Nyrabahizi Digitally signed by Epiphane Nyrabahizi Date: 5/27/2025 3:59 PM EDT GUID: 2025527195931				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Lei He OCP DIIP	Sections: 5.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lei He Digitally signed by Lei He Date: 5/27/2025 4:41 PM EDT GUID: 2025527204119				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Medication Error Reviewer Discipline Secondary Reviewer	Valerie Vaughan OMEPRM DMEPAI	Sections: n/a	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Valerie Vaughan Digitally signed by Valerie Vaughan Date: 5/28/2025 7:36 AM EDT GUID: 2025528113629				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Medication Error Reviewer Discipline Primary Reviewer	Sofanit Getahun OMEPRM DMEPAI	Sections: DMEPA Label Labeling Review and Memo uploaded to DARRTS	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sofanit Getahun Digitally signed by Sofanit Getahun Date: 5/28/2025 9:03 AM EDT GUID: 20255281332				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Regulatory Project Manager Discipline Secondary Reviewer	Shazma Aftab OPRO DRBPMI	Sections: OPQ Sections	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shazma Aftab Digitally signed by Shazma Aftab Date: 5/28/2025 9:12 AM EDT GUID: 2025528131221				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Product Quality Regulatory Project Manager Discipline Primary Reviewer	Shazma Aftab OPRO DRBPMI	Sections: OPQ	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shazma Aftab Digitally signed by Shazma Aftab Date: 5/28/2025 9:12 AM EDT GUID: 2025528131249				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Primary Reviewer	Muriel Saulnier ORDPURM DPTRDPURM	Sections: 5.1, 7.1, 8.4, 13.1, 13.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Muriel Saulnier Digitally signed by Muriel Saulnier Date: 5/28/2025 10:23 AM EDT GUID: 2025528142356				

NDA 217370
 Tryptyr (acoltremon ophthalmic solution) 0.003%

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Tertiary Reviewer	Rhea Lloyd OSM DO	Sections: Modules 1 through 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rhea Lloyd			Digitally signed by Rhea Lloyd Sign on behalf of Rhea Lloyd signing as proxy for William Boyd. Date: 5/28/2025 12:41 PM EDT GUID: 2025528164159	

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/

RHEA A LLOYD
05/27/2025 03:28:50 PM

CHARLES J GANLEY
05/28/2025 01:06:35 PM