The Novel RASP Modulator Reproxalap Rapidly Improves Signs and Symptoms of Dry Eye Disease: The TRANQUILITY Run-In Cohort

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Disclosures

- EJ Holland
- B Cavanagh reports employment with and stock ownership in Aldeyra Therapeutics.
- SG Machatha reports employment, patent interests, and stock ownership with Aldeyra Therapeutics.
- TC Brady reports employment, patent interests, and stock ownership with Aldeyra Therapeutics and stock ownership with F-star Therapeutics and Evoke Pharma.

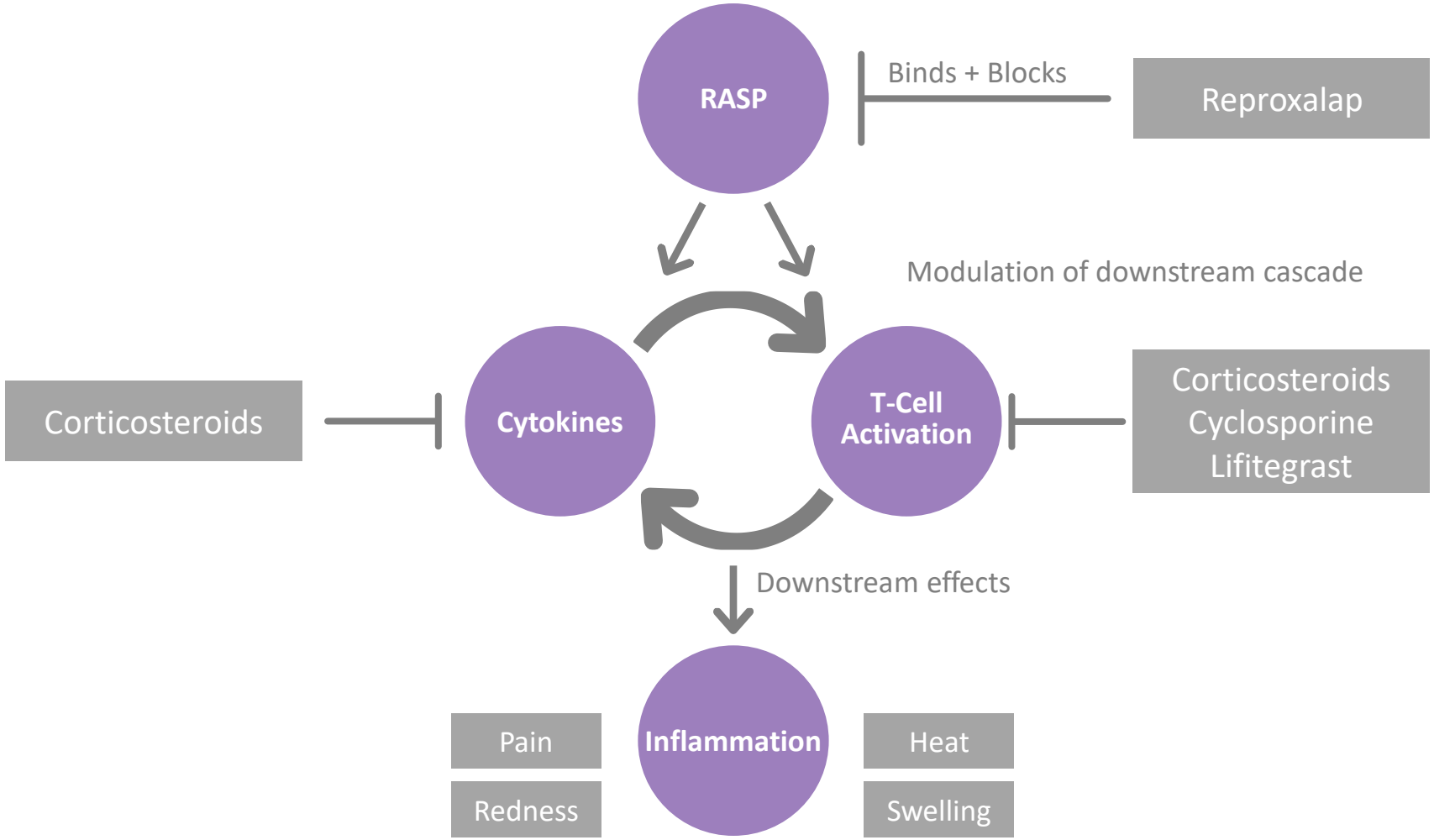
Introduction

- Dry eye disease (DED) is a chronic, progressive ocular surface disorder of multifactorial etiology.[1]
- ~15% of the adult US population (39 million) has DED[2]; however, treatments that provide fast, effective, and sustained relief are lacking.[3,4]
- The novel RASP modulator, reproxalap, has been shown to be well tolerated and effective at mitigating the symptoms of DED in Phase 2 clinical trials (NCT03404115, NCT03162783).[4,5]
- TRANQUILITY is a Phase 2/3 clinical trial (NCT04674358) to evaluate the efficacy of reproxalap vs vehicle in DED.
- Here we present results from the run-in cohort to assess the feasibility of the TRANQUILITY trial design.

RASP=reactive aldehyde species.

1. Dana R, et al. Am J Ophthalmol. 2020;216:7–17; 2. Paulsen AJ, et al. Am J Ophthalmol. 2014;157:799–806; 3. Aragona P, et al. Br J Ophthalmol. 2021;105:446–53;
4. Clark D, et al. J Ocul Pharma Ther. 2021;37:193–9; 5. Clark D, et al. Am J Ophthalmol. 2021;226:22–31.

RASP are Believed to Work at the Top of the Inflammatory Cascade



Sources: 1. Lee SJ, et al. Cardiovasc Res. 2010;88:352–9; 2. Chiarpotto E, et al. Biofactors 2005;24:229–36; 3. Natarajan K, et al. Cell Mol Biol Lett. 2015;20:647–62; 4. Raghavan S, et al. J Leukoc Biol. 2012;92:1055–67; 5. Shanmugam N, et al. Diabetes. 2008;57:879–88.

Study Design

Key eligibility criteria:

- ≥18 years of age
- History of DED for ≥6 months before screening
- Corneal fluorescein staining sum ≥4 in at least one eye on the Ora Calibra® Scale at Visit 1
- Increase in dryness symptom score and redness in chamber
- No artificial tear use ≤2 hours of screening, ≤24 hours of randomization, or day of chamber entry

Primary endpoint:

- Conjunctival redness* over 90 minutes in the Controlled Adverse Environment (CAE) chamber

Secondary endpoints:

- Visual Analog Scale (VAS) eye dryness score over Days 1 and 2 (except CAE®) and over 90 minutes in CAE®
- Ora Calibra® Ocular Discomfort Scale over Days 1 and 2 (except CAE®) and over 90 minutes in CAE®
- Ocular Discomfort & 4-Symptom Questionnaire over Days 1 and 2, and before and after CAE
- Schirmer's test change from baseline (screening) before and after the final dose on Day 1

TRANQUILITY Run-In Cohort Design

	Day 1	Day 2
	Environmental	Controlled Chamber
Groups:	Reproxalap 0.25% (n=12)	Reproxalap 0.25% (n=12)
	Vehicle (n=11)	Vehicle (n=11)
Dosing:	QID	• One dose within 10 min prior to chamber entry • One dose 45 min after chamber entry • One dose post-chamber exit
Measures:	Dry Eye Symptoms Schirmer's Test	Dry Eye Symptoms Ocular Redness

*Assessed by digital photography; CAE = controlled adverse environment; LASIK = laser-assisted in situ keratomileusis; MGD = meibomian gland dysfunction; QID = 4 times per day; RASP = reactive aldehyde species; VAS = visual analog scale.

Baseline Patient Characteristics

	Reproxalap (n=12)	Vehicle (n=11)
Sex, n, (%)		
Female	9 (75.0)	8 (72.7)
Male	3 (25.0)	3 (27.3)
Median age in years (range)	65 (39–81)	66 (53–78)
Age ≥65 years, n, (%)	7 (58.3)	7 (63.6)
Ethnicity, n (%)		
White	10 (83.3)	10 (90.9)
Black/African American	2 (16.7)	1 (9.1)
Not identifying as Hispanic or Latino	11 (91.7)	10 (90.9)
Eye color, n (%)		
Brown	6 (50.0)	6 (54.5)
Blue	3 (25.0)	4 (36.4)
Hazel	2 (16.7)	0
Green	1 (8.3)	1 (9.1)

Assessments at Day 1

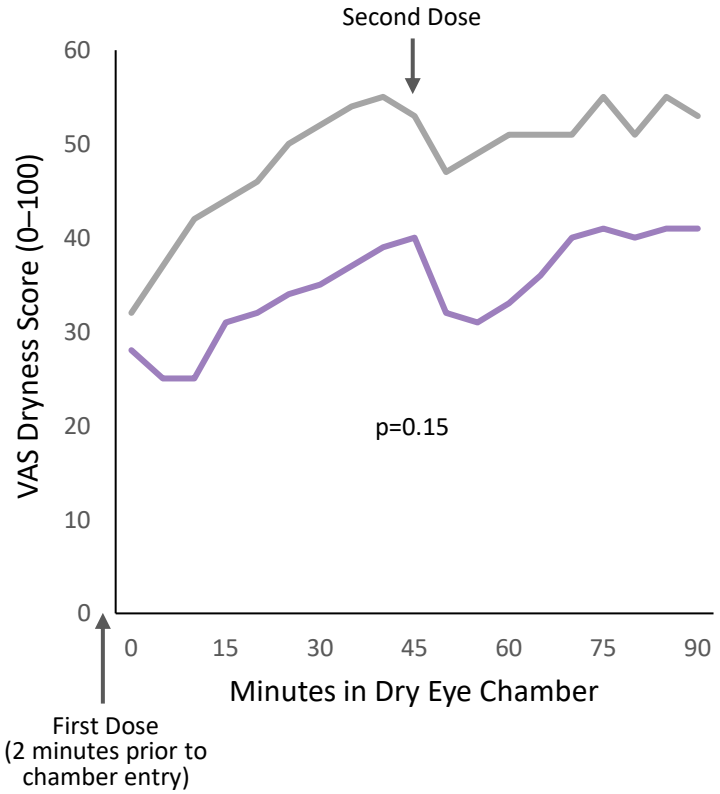
TRANQUILITY Run-In Cohort Day 1 (24 Hours) Results:*

Dry Eye Assessment (Scale) after Environmental Dosing	Change from Baseline		p value
	Reproxalap (n=12)	Vehicle (n=11)	
VAS Dryness (0–100)	-26	+2.6	0.01
OD4S: Discomfort (0–5)	-0.7	+0.4	0.01
OD4S: Dryness (0–5)	-1.2	+0.1	0.02
OD4S: Grittiness (0–5)	-1.1	+0.1	0.02
OD4S: Burn (0–5)	-0.1	+0.8	0.11
OD4S: Sting (0–5)	-0.1	+0.4	0.29
Ocular discomfort scale (0–4)	-0.4	+0.1	0.14
Schirmer's Test (mm)*	+3.2	+0.6	0.06

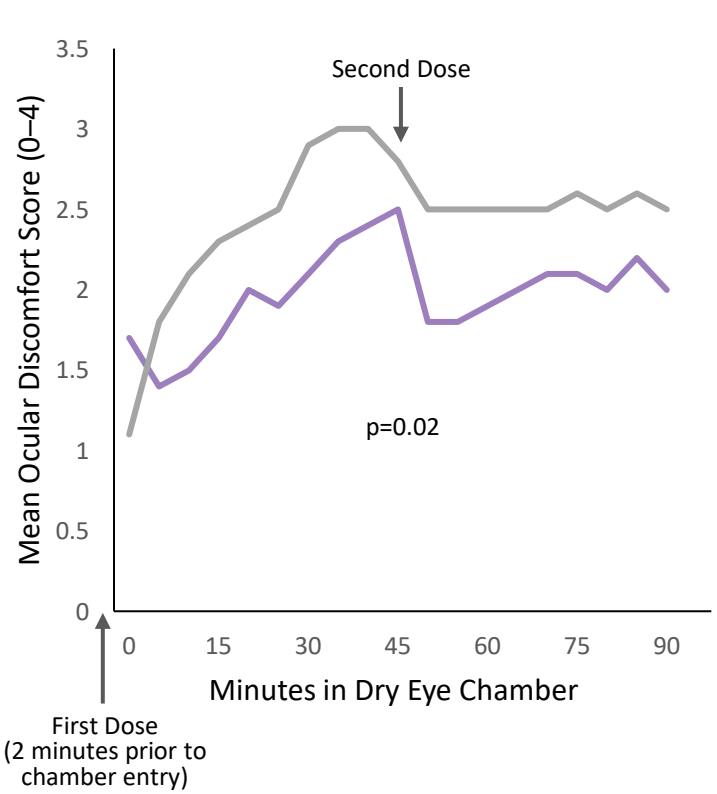
*Day 1 Schirmer's Test results based on improvement after a single dose; all other Day 1 assessments performed over 24 hours of QID dosing.
VAS = Visual Analog Scale; OD4S = Ocular Discomfort & 4-Symptom Questionnaire; QID = Four times daily.

Day 2 Symptoms and Signs in a Controlled Chamber

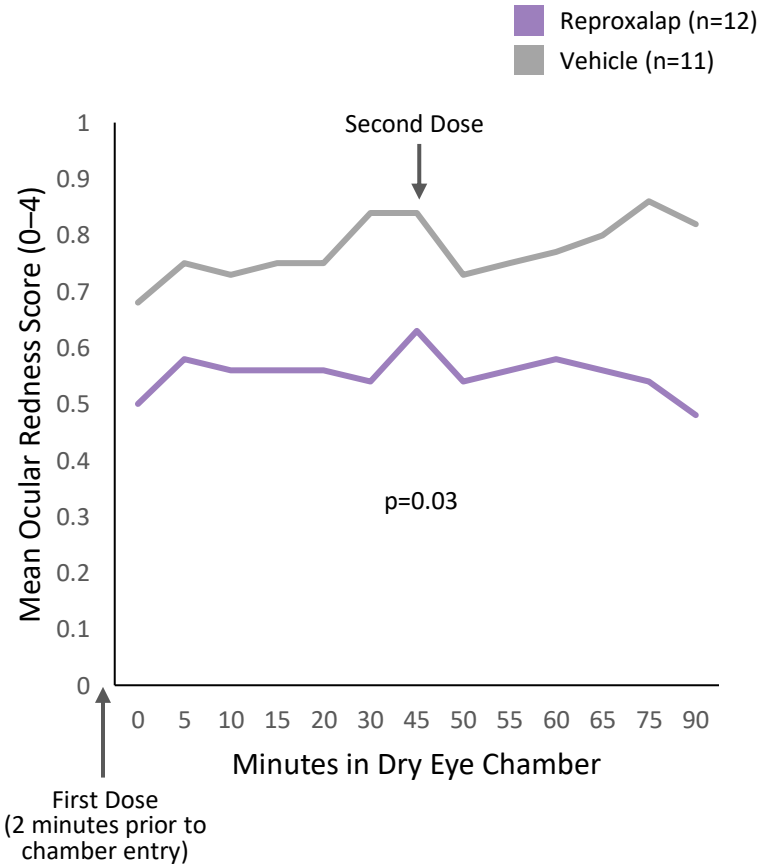
Ocular Dryness Score (VAS)



Ocular Discomfort Scale (0–4)



Ocular Redness Score (0–4)



Safety Overview from the TRANQUILITY Run-In Cohort

	Reproxalap (n=12)	Vehicle (n=11)
Installation site warmth n (%)	1 (8)	0
Installation site discomfort n (%)	7 (58)	0
Adverse events (AEs) leading to discontinuation	0	0
Serious adverse events (SAEs)	0	0

- All AEs were mild and related to instillation of reproxalap.
- Instillation-related AEs occurred in both eyes in all cases.
- Reproxalap has currently been studied in more than 1,500 patients with no significant observable safety concerns; mild instillation site irritation is the most commonly reported adverse event in clinical trials.

Summary and Conclusions

- Reproxalap reduced ocular dryness and discomfort symptom scores relative to vehicle after one day in an environmental setting.
- In the controlled chamber, reproxalap demonstrated acute and sustained improvements vs. vehicle in ocular dryness, discomfort, and redness.
- Reproxalap was not associated with any serious adverse events (SAEs) or adverse events (AEs) leading to discontinuation.
- The most commonly reported adverse event was mild instillation site irritation.
- The findings from the run-in cohort confirmed the feasibility of the primary and secondary endpoints for the Phase 3 TRANQUILITY and TRANQUILITY-2 trials.
- In follow-up to the run-in cohort findings, the Phase 3 TRANQUILITY study found that:
  - The primary endpoint of ocular redness was missed, possibly due to unexpectedly low baseline redness scores.
  - The secondary endpoint of Schirmer's test was achieved (p=0.0001).
- As a result of these findings, the primary endpoint of the ongoing TRANQUILITY-2 trial was modified to be met if either redness or Schirmer's test is achieved.