Reproxalap Acutely Reduces Ocular Discomfort in Phase 3 Dry Eye Disease Chamber Trial

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Reproxalap is an investigational therapy that has not received FDA (or any regulatory authority) approval and has not been demonstrated safe or effective for any use.

Reproxalap is owned by Aldeyra Therapeutics and subject to option exercise pursuant to an agreement between Aldeyra Therapeutics and AbbVie.

Introduction

Objective:

This Phase 3 trial assessed patient-reported ocular discomfort using a visual analog scale (0-100) following treatment with either 0.25% reproxalap or vehicle to determine improvements in ocular discomfort in patients with dry eye disease (DED)

DED is a common ocular condition that is characterized in part by ocular discomfort

- Many current therapeutic options for DED require weeks or months of treatment to achieve noticeable levels of activity, and may lead to adverse events such as installation site pain, ocular burning, temporary blurring of vision, and dysgeusia[1]

- Reproxalap is a novel reactive aldehyde species (RASP) inhibitor that works upstream in the inflammation cascade. Reproxalap is in development for the treatment of DED and has demonstrated improvement in DED symptoms within minutes of administration, without clinically significant safety concerns

1. Jones L, et al. Am J Ophthalmol. 2025;279:289-386.
Abbreviation: DED, dry eye disease.

Methods

Trial Design: Single-center, randomized, double-masked, vehicle-controlled, parallel group, Phase 3 clinical trial that was conducted in a dry eye chamber and included 3 visits

Visit 1: Screening/ Vehicle Chamber Visit

- Medical screening and administration of vehicle treatment**.** All patients received vehicle ~ 5 minutes before and 50 minutes after entry to the dry eye chamber

Visit 2: Randomization

- Patients were randomized 1:1 to receive four doses of reproxalap or vehicle. Treatment was administered four times (QID) in office

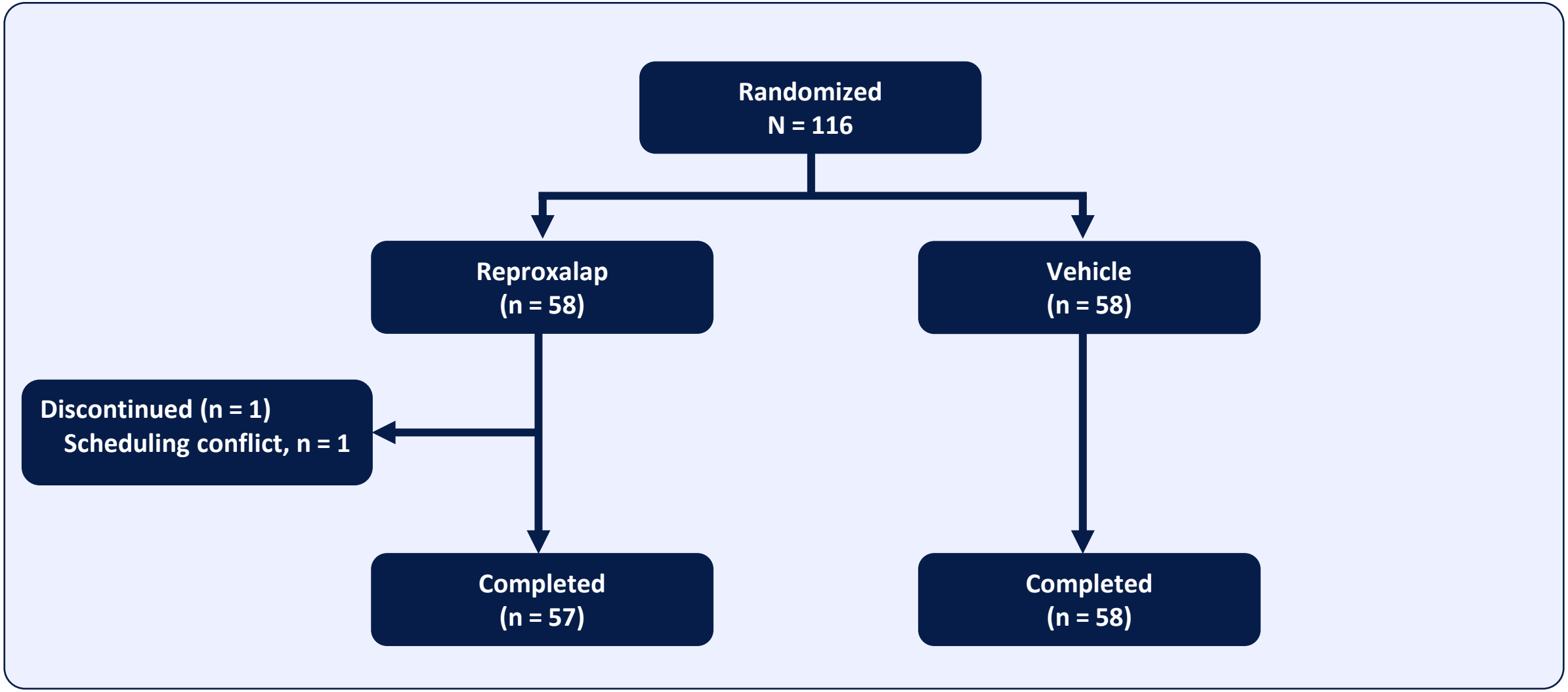
Visit 3: Treatment Chamber Visit

- The same treatment was administered the following day, during which patients received treatment ~ 5 minutes before and 50 minutes after entry to the dry eye chamber

- The **primary endpoint** of ocular discomfort symptom score (visual analogue score of 0 to 100; Treatment Chamber – Vehicle Chamber) was assessed from 80 to 100 minutes after chamber entry
- Ocular discomfort was recorded every 5 minutes after chamber entry from 10 to 100 minutes

Abbreviation: QID, quater in die.

Figure 1. Patient Disposition



Baseline characteristics were similar for both groups

Table 1. Baseline Characteristics

Outcome	Reproxalap n = 58	Vehicle n = 58
Age, mean (SD)	63.1 (12.6)	65.5 (10.9)
Age ≥ 65, n (%)	30 (51.7)	32 (55.2)
Female, n (%)	42 (72.4)	36 (62.1)
Ethnicity, n (%)		
Hispanic or Latino	4 (6.9)	1 (1.7)
Not Hispanic or Latino	54 (93.1)	57 (98.3)
Race, n (%)		
Asian	3 (5.2)	0
Black or African American	0	3 (5.2)
White	54 (93.1)	54 (93.1)
Multiple	1 (1.7)	1 (1.7)
Eye disorders other than DED, n (%)		
Cataract	21 (36.2)	19 (32.8)
Cataract nuclear	5 (8.6)	14 (24.1)
Eyelid ptosis	4 (6.9)	0
Myopia	20 (34.5)	14 (24.1)
Hypermetropia	7 (12.1)	3 (5.2)
Pinguecula	7 (12.1)	3 (5.2)
Vitreous detachment	5 (8.6)	3 (5.2)
Ocular discomfort score, mean (SD)[a]	39 (19.3)	39.6 (16.7)

[a] Ocular discomfort score ranges from 0 to 100, with lower scores indicating less severe symptoms.
Abbreviation: DED, dry eye disease.

Reproxalap-treated patients experienced significantly less ocular discomfort

Table 2. Primary Efficacy Analysis: Ocular Discomfort Symptom Score (ITT Population Observed Data Only)

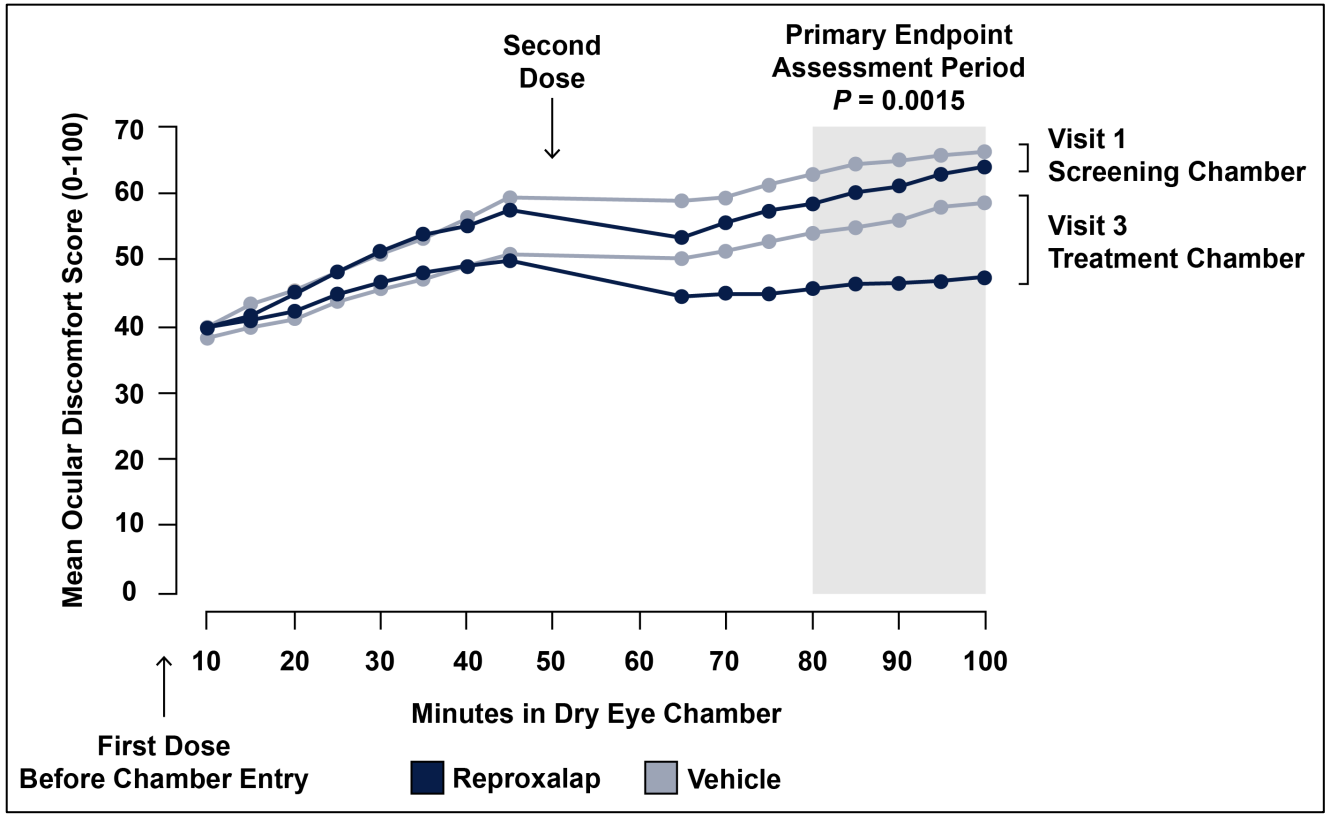
Outcome	Reproxalap n = 58	Vehicle n = 58
Overall change from Vehicle Chamber to Treatment Chamber (80 to 100 minutes)		
LS mean (95% CI)	-16.9 (-19.7, -14.0)	-10.4 (-13.2, -7.5)
LS mean (95% CI) Treatment Chamber – Vehicle Chamber	-6.5 (-10.5, -2.5)	
P Value	.0015	

- Compared with Vehicle Chamber, patient-reported ocular discomfort was significantly lower in reproxalap-treated patients from 80 to 100 minutes after Treatment Chamber entry (LS mean difference [95% CI]: -6.5 [-10.5, -2.5]; *P* = .0015) (**Table 2**)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least squares.

Ocular discomfort remained lower in reproxalap-treated patients for the entirety of the chamber

Figure 2. Ocular Discomfort Score by Treatment and Chamber (ITT Population)



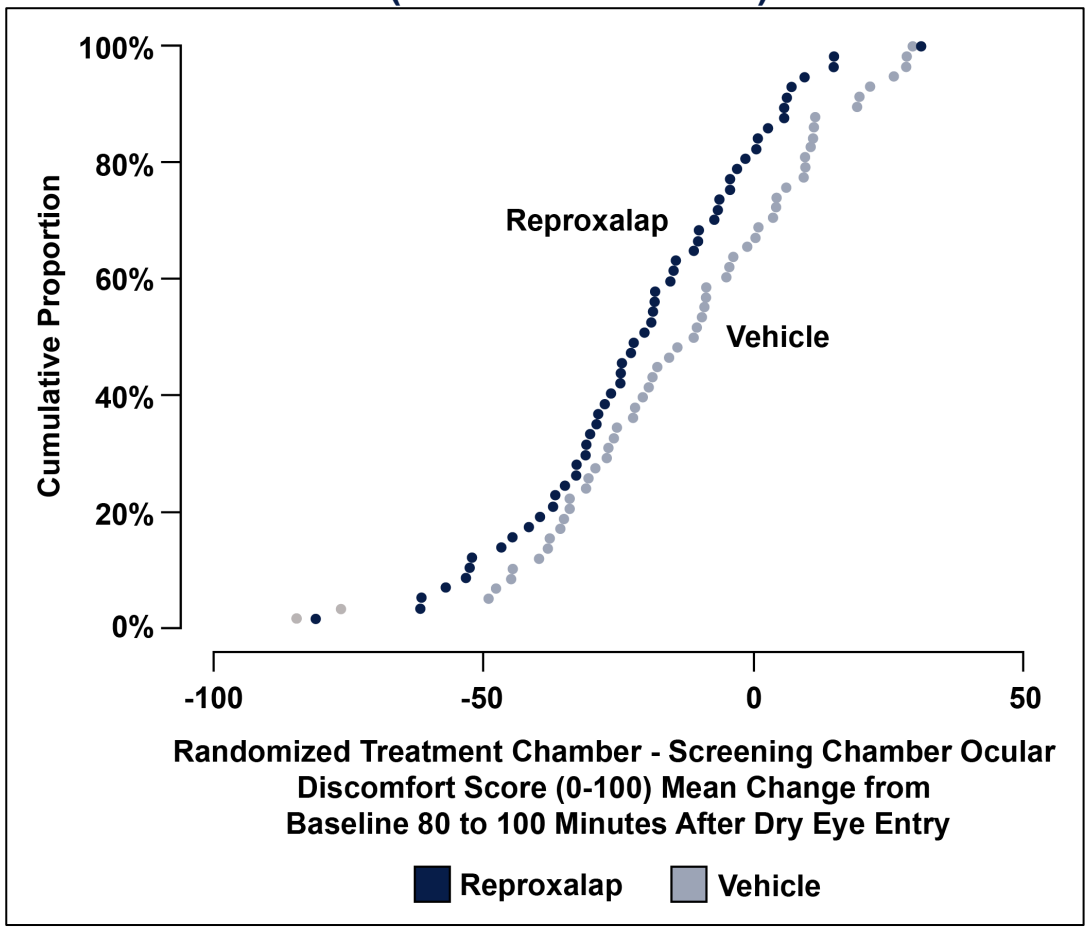
- Scores at the beginning of the Treatment Chamber (0 to 50 minutes) were not notably different across treatment groups because levels of symptomatic exacerbation were low

- The difference in ocular discomfort score between reproxalap and vehicle at the end of the Screening Chamber was -2.4 compared with -11.3 at the end of the Treatment Chamber

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least squares.

Ocular discomfort scores were lower for a greater proportion of reproxalap-treated patients

Figure 3. Distribution Function of Change From Baseline in Ocular Discomfort Dry Eye Chamber Score (Treatment Chamber - Vehicle Chamber) Averaged Across Eyes and Primary Endpoint Contrast Timepoints (80 to 100 Minutes)



- The cumulative distribution function of change from baseline in ocular discomfort score (Treatment Chamber – Vehicle Chamber), averaged across both eyes and all prespecified contrast timepoints (80 to 100 minutes after chamber entry), indicated that reproxalap was superior to vehicle at every level of response

- From 80 to 100 minutes after chamber entry, ocular discomfort scores of approximately 80% of patients in the reproxalap treatment arm were lower in Treatment Chamber than in Vehicle Chamber vs approximately 60% in the vehicle treatment arm

Most ocular TEAEs were mild or moderate for reproxalap-treated patients

Table 3. All Treatment and Ocular Treatment-Emergent Adverse Events (Safety Population)

TEAEs	Reproxalap n = 58 n (%)	Vehicle n = 58 n (%)
≥ 1 TEAE	41 (70.7%)	2 (3.4)
≥ 1 ocular TEAE	40 (69.0)	2 (3.4)
≥ 1 nonocular TEAE	2 (3.4)	0
≥ 1 TEAE by maximum severity Mild Moderate Severe	 41 (70.7) 0 0	 2 (3.4) 0 0
Any TEAE related to study procedure	40 (60.9)	2 (3.4)
Any severe TEAE	0	0
Any serious TEAE	0	0
Any TEAE leading to death	0	0
Any TEAE leading to early discontinuation	0	0
Any ocular TEAE	40 (69.0)	2 (3.4)
Eye disorders Vision blurred	1 (1.7) 1 (1.7)	0 0
General disorders and administration site conditions Instillation site irritation Instillation site pruritus	40 (60.9) 40 (60.9) 0	2 (3.4) 1 (1.7) 1 (1.7)

- 41 (70.7%) of patients in the reproxalap group experienced ≥ 1 TEAE compared with 2 (3.4%) of patients in the vehicle group
- All were considered related to the test article
  - All TEAEs (reproxalap: n = 41 [70.7%]; vehicle: n = 2 [3.4%]) were mild in severity; no serious or severe TEAEs were reported, and no TEAE led to early discontinuation or death
- Ocular TEAEs occurred in 40 (69.0%) patients who received reproxalap and 2 (3.4%) who received vehicle
- The most common ocular TEAE in both treatment groups was instillation site irritation (reproxalap: n = 40 [60.9%]; vehicle: n = 2 [1.7%]), which were mild and most commonly lasted < 1 minute

Abbreviation: TEAE, treatment-emergent adverse event.

Limitations

- Interpretation of this study is limited by several factors including:
  - Single-center design
  - Small number of patients included
  - Long-term effects not assessed

Conclusions

Patient-reported ocular discomfort scores from Vehicle Chamber to Treatment Chamber for 80 to 100 minutes after dry eye chamber entry were significantly lower in reproxalap-treated patients compared with vehicle-treated patients

The primary endpoint of ocular discomfort symptom score was achieved, indicating the rapid activity of reproxalap in reducing ocular discomfort associated with DED in a challenge model designed to mimic dry eye flare, the most disturbing aspect of DED for most patients

No patients discontinued from the trial due to adverse events, nor were there any serious adverse events, consistent with previous clinical trials

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