

# A Randomized Double-Masked Phase 2a Trial to Evaluate Activity and Safety of Topical Ocular Reproxalap, a Novel RASP Inhibitor, in Dry Eye Disease

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## Abstract

**Purpose:** To determine whether reproxalap, a novel reactive aldehyde species (RASP) inhibitor, is safe and effective for the treatment of the signs and symptoms of dry eye disease (DED).

**Methods:** In a randomized double-masked parallel-group Phase 2a trial of 3 topical ocular reproxalap formulations (0.1% ophthalmic solution, 0.5% ophthalmic solution, and 0.5% lipid ophthalmic solution), 51 patients with DED were randomly assigned 1:1:1 at a single US site. Eyes were treated bilaterally 4 times daily for 28 days, and standard DED signs and symptoms were assessed at baseline and after 7 and 28 days of dosing. Tear RASP levels were assessed at baseline and at day 28.

**Results:** The effect of treatment on DED signs and symptoms was similar across the treatment arms, and pooled data from the 28-day treatment period demonstrated significant improvement from baseline in Symptom Assessment in Dry Eye Disease score ( $P=0.003$ ), Ocular Discomfort Scale score ( $P<0.0001$ ), Ocular Discomfort Score and 4-Symptom Questionnaire overall score ( $P=0.0004$ ), Schirmer's test ( $P=0.008$ ), tear osmolarity ( $P=0.003$ ), and lissamine green total staining score ( $P=0.002$ ). Improvements in DED symptoms were evident within 1 week of therapy, and effect sizes generally approached or exceeded 0.5. No significant changes in safety measures were observed.

**Conclusion:** The results suggest that the novel RASP inhibitor reproxalap has the potential to mitigate the signs and symptoms of DED, and may represent a new, rapidly and broadly active treatment approach for DED (NCT03162783).

**Keywords:** reproxalap, RASP inhibitor, dry eye disease, inflammation

## Introduction

**D**RY EYE DISEASE (DED) affects ~6.8% of the US population, with the prevalence increasing with age.<sup>1,2</sup> Impaired vision, lost work productivity, and diminished quality of life are associated with DED.<sup>2-9</sup> Despite the availability of 3 approved drugs in the United States, patients with DED experience a higher prevalence of major depression and anxiety<sup>10,11</sup> and account for an estimated \$3.8 billion per year of health care cost.<sup>2,7,8</sup>

Reactive aldehyde species (RASP), such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), covalently bind amino and thiol groups on receptors and kinases, and thereby potentiate upstream proinflammatory signaling cascades that involve NF- $\kappa$ B, inflammasomes, scavenger receptor A, and other mediators.<sup>12-15</sup> Increased levels of RASP are found in

a variety of inflammatory ocular diseases, including Behcet's disease, Sjögren's syndrome, noninfectious uveitis, allergic conjunctivitis, and DED.<sup>16-27</sup> MDA levels in tears from patients with DED are elevated, and increased MDA levels positively correlate with DED severity.<sup>26</sup> Furthermore, in tears and conjunctival biopsies from patients with DED, levels of MDA and HNE are increased compared with those from control participants and correlate with the magnitude of symptoms.<sup>27</sup> In addition to proinflammatory signaling, RASP also bind phosphatidylethanolamine,<sup>28</sup> a critical component of the tear lipidome, which is critical for moisture retention in ocular surface tissues.<sup>29</sup> Thus, RASP represent a potentially important therapeutic target for the treatment of DED.

Reproxalap is a small molecule that rapidly and covalently binds RASP. Reproxalap has been shown to out-compete biological targets for MDA and HNE to inhibit

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both helper T cell 1 (Th1)- and Th2-mediated inflammation in a number of animal models.<sup>30,31</sup> The broad-based anti-inflammatory mechanism of reproxalap may be relevant to a variety of ocular inflammatory conditions, and clinical development of reproxalap has been initiated in patients with noninfectious anterior uveitis, allergic conjunctivitis, and DED. In DED, the activity of reproxalap is potentially 2-fold, the result of modulation of inflammation and prevention of RASP modification of tear lipids, suggesting that reproxalap may represent an important new therapeutic approach for the treatment of DED.

Given the unmet medical need in DED and the multifaceted mechanisms by which RASP are implicated in this condition, a Phase 2a trial was performed to evaluate the activity and safety of 3 topical ocular formulations of the novel RASP inhibitor reproxalap in patients with DED.

## Methods

### Trial design

Fifty-one patients with DED were enrolled in a Phase 2a single-center randomized double-masked trial (NCT03162783) designed to evaluate the safety, tolerability, and pharmacodynamic activity of topical ocular reproxalap. A vehicle control group was not included in the design as the planned sample size of ~15 participants per arm did not support formal powering for DED signs or symptoms. Pooling of the 3 active treatment groups was utilized as a method to allow clearer interpretation of drug activity. The trial consisted of a screening and enrollment phase (day 1), a 1-week follow-up (day 8), and a 4-week follow-up (day 29). Participants were randomly assigned in a 1:1:1 ratio to receive either reproxalap 0.5% topical ophthalmic solution, reproxalap 0.1% topical ophthalmic solution, or reproxalap 0.5% topical ophthalmic lipid solution. The lipid solution was similar to the nonlipid formulations except that 5% castor oil was added. Each participant received one drop in each eye 4 times daily (QID) for 29 days. Study participants, investigators, and the sponsor were masked to treatment assignment throughout the trial.

The trial was performed in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. In addition, the trial was performed in accordance with the protocol, the International Conference

on Harmonisation Guideline on Good Clinical Practice, and all applicable local regulatory requirements and laws. Each participant provided written consent to participate in the trial before any trial-related procedures, and the trial was carried out with approval from an Institutional Review Board.

### Study participant selection

Male and female participants at least 18 years of age with a history of DED in both eyes for at least 6 months were eligible. At screening, participants were required to have a history of use, or desire to use, eye drops for dry eye symptoms within the past 6 months and a score of  $\geq 2$  on the Ora Calibra<sup>®</sup> Ocular Discomfort and 4-Symptom Questionnaire (OD4SQ)<sup>32</sup> for at least one symptom; a Schirmer's test score of  $\leq 10$  mm and  $\geq 1$  mm; a tear film break-up time (TFBUT) of  $\leq 5$  s; a corneal fluorescein staining score of  $\geq 2$  for at least one region (eg, inferior, superior, or central); a sum corneal fluorescein staining score of  $\geq 4$ , based on the sum of the inferior, superior, and central regions; and a total lissamine green conjunctival score of  $\geq 2$ , based on the sum of the temporal and nasal regions. All objective criteria were required in at least 1 eye.

Participants were excluded for any clinically significant slit lamp findings, including active blepharitis, meibomian gland dysfunction, lid margin inflammation, or active ocular allergies that required therapeutic treatment and that may have interfered in the conduct of the trial. Participants also were excluded for ongoing ocular infection or active ocular inflammation; contact lens wear within 7 days of screening visit; or use of eye drops within 2 h of screening visit.

### Study assessments

Activity was assessed with TFBUT; fluorescein staining (Ora Calibra<sup>®</sup> scale for central, superior, inferior, temporal, and nasal regions); Ora Calibra<sup>®</sup> Ocular Discomfort Scale (ODS)<sup>33,34</sup>; OD4SQ; Ocular Surface Disease Index (OSDI)<sup>35</sup>; and the Symptoms Assessment in Dry Eye Disease (SANDE) questionnaire<sup>36</sup> on days 1, 8, and 29. On days 1 and 29, lissamine green staining (Ora Calibra<sup>®</sup> scale for inferior, superior, central, temporal, and nasal regions); unanesthetized Schirmer's test; and tear osmolarity were assessed. Adverse events (AEs), visual acuity, and slit lamp biomicroscopy were assessed on

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	<i>Reproxalap solution</i> 0.1% (n = 17)	<i>Reproxalap solution</i> 0.5% (n = 17)	<i>Reproxalap lipid</i> 0.5% (n = 17)	<i>All participants</i> (N = 51)
Age, years <sup>a</sup>	63.9 ± 11.9	67.2 ± 8.3	67.3 ± 12.6	66.1 ± 11.0
Age range, years	39–78	55–83	40–83	39–83
Female, n (%)	9 (52.9)	14 (82.4)	11 (64.7)	34 (66.7)
Hispanic or Latino, n (%)	0	2 (11.8)	0	2 (3.9)
Race, n (%)				
Asian	2 (11.8)	0	0	2 (3.9)
Black or African American	0	1 (5.9)	0	1 (2.0)
White	15 (88.2)	16 (94.1)	17 (100)	48 (94.1)
Iris color, n (%)				
Blue	2 (11.8)	7 (41.2)	5 (29.4)	14 (27.5)
Brown	13 (76.5)	6 (35.3)	6 (35.3)	25 (49.0)
Hazel	1 (5.9)	3 (17.6)	4 (23.5)	8 (15.7)
Green	1 (5.9)	1 (5.9)	2 (11.8)	4 (7.8)

<sup>a</sup>Mean ± standard deviation.

TABLE 2. EFFECT OF REPROXALAP ON DRY EYE DISEASE SIGNS AND SYMPTOMS BEFORE AND AFTER TREATMENT (POOLED RESULTS)

Endpoint mean (SD)	Pretreatment	Post-treatment (day 28)	P value
SANDE frequency score	67 (20)	54 (22)	0.0002
ODS score	2.3 (1.0)	1.5 (1.0)	0.0004
OD4SQ			
Overall score	2.6 (1.0)	2.0 (1.1)	0.0004
Dryness score	2.9 (1.0)	2.3 (1.2)	0.001
Burning score	1.6 (1.2)	1.1 (1.1)	0.007
Grittiness score	1.7 (1.5)	1.2 (1.2)	0.046
Schirmer test	5.4 (2.7)	8.3 (6.7)	0.008
Osmolarity	303 (16)	294 (13)	0.003
Lissamine green staining total score	5.4 (2.0)	4.3 (1.7)	0.018

OD4SQ, ocular discomfort and 4-symptom questionnaire; ODS, ocular discomfort scale; SANDE, symptoms assessment in dry eye disease questionnaire.

days 1, 8, and 29. In addition, undilated funduscopy examination and intraocular pressure measurements were performed on days 1 and 29. At baseline and after completion of treatment, MDA was measured by ELISA (Cell Biolabs, San Diego, CA) in tears extracted through capillary. Both eyes were pooled per patient. A standard curve was generated, and a 1:60 dilution was established as optimal using 3 µL of tears per patient.

Statistical analysis

Because the trial was exploratory, no formal *a priori* sample size calculation was employed and no primary or secondary end points were specified. The intention-to-treat (ITT) population included all randomized participants. The safety population included all randomized participants who received study drug.

For assessment of activity, analyses were performed on data from the most severe eye eligible for analysis at baseline, as measured by total corneal fluorescein staining. If total corneal staining was the same in both eyes, then the eye with the worst (higher) ODS score at

screening was deemed the most severe eye. If the total corneal staining and ocular discomfort scores were the same for both eyes, then the right eye was selected as the most severe eye.

Pairwise 2-sample *t* tests were employed to compare the observed treatment means and the changes from baseline at each visit. No imputation was performed for withdrawn participants or missing data. Pooling of the 3 treatment groups was utilized to allow for clearer interpretation of drug activity. Pooled analyses were conducted by including participants from all 3 treatment groups. For pooled average symptomatic change, percentage average improvements for all symptom scales were compared with no change (zero) using a one-way *t* test, and within-participant standard error bars were plotted as has been previously described.<sup>37</sup> Above- and below-median percentage MDA reduction subgroups were compared using 2-way *t* tests and 1-way *t* tests versus 0 (no change from baseline).

Results

Participant disposition and baseline characteristics

Sixty participants were screened, and 51 were randomized and treated between June 2017 and July 2017, resulting in 17 participants per arm. Eleven participants (1 [5.9%] in the 0.1% reproxalap group, 4 [23.5%] in the 0.5% reproxalap group, and 6 [35.3%] in the 0.5% reproxalap lipid group) discontinued the trial because of AEs, which generally consisted of transient ocular irritation. One participant in the 0.5% reproxalap group was lost to follow-up. Baseline demographic and disease severity characteristics were generally comparable across treatment groups (Table 1). Two-thirds of participants were women. All participants had a history of eye disorders, and 17 (33.3%) participants had a history of ocular surgical or medical procedures.

Efficacy

The results from pooled data across all treatment arms over the 28-day treatment period demonstrated significant improvement from baseline in the SANDE frequency score ( $P=0.0002$ ), ODS ( $P=0.0004$ ), OD4SQ overall score ( $P=0.0004$ ), OD4SQ dryness score ( $P=0.001$ ), OD4SQ burning score ( $P=0.0007$ ), OD4SQ grittiness score ( $P=0.046$ ),

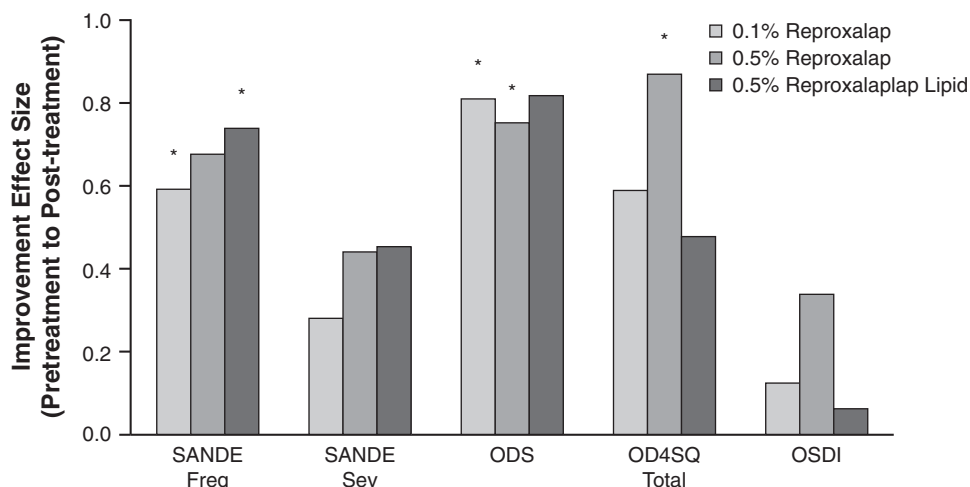
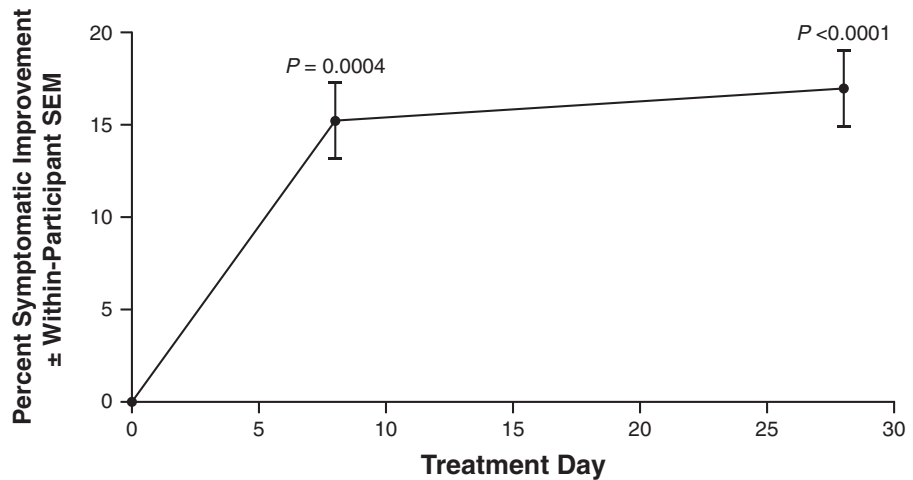


FIG. 1. Dry eye disease mean symptom effect sizes. Improvement effect size is improvement from baseline divided by standard deviation at baseline. \* $P < 0.05$ . ODS, Ocular Discomfort Scale; OD4SQ total, Ocular Discomfort and 4-Symptom Questionnaire overall score; OSDI, Ocular Surface Disease Index; SANDE Freq, Symptoms Assessment in Dry Eye Disease frequency scale; SANDE Sev, Symptoms Assessment in Dry Eye Disease severity scale.

**FIG. 2.** Within-participant symptomatic improvement of pooled reproxalap groups. Data represent within-participant average percentage improvement across all symptom scales assessed in the trial: SANDE frequency and severity scales, ODS, OD4SQ overall score, and OSDI. *P* values represent one-way tests versus no change from baseline. SEM, standard error of the mean.



unanesthetized Schirmer’s test (*P*=0.008), tear osmolarity (*P*=0.003), and lissamine green total staining score (*P*=0.018) (Table 2).

In the ITT analysis by treatment group, statistically significant (*P*<0.05) improvement from baseline to day 29 was observed for the ODS score and the SANDE frequency score in the 0.1% reproxalap group; the ODS score and the OD4SQ overall score in the 0.5% reproxalap group; and the SANDE frequency score in the 0.5% reproxalap lipid group. For symptoms in which statistically significant improvements were observed, improvement effect sizes (improvement from baseline divided by baseline standard deviation) generally approached or exceeded 0.5 (Fig. 1). Within-participant improvements of the pooled treatment groups averaged across all DED symptom scales (SANDE frequency, SANDE severity, ODS, OD4SQ overall score, and OSDI) were statistically different from no change within 1 week of therapy (Fig. 2).

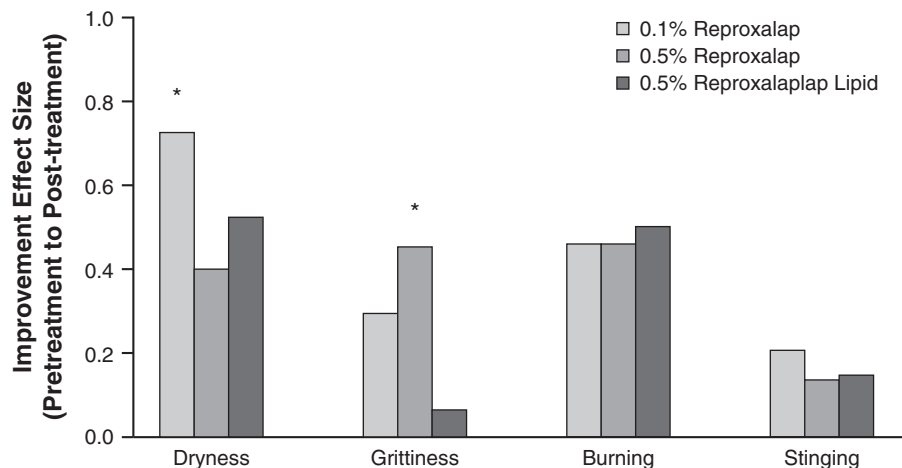
All OD4SQ subscales improved in each group over the course of treatment, and statistically significant (*P*<0.05) improvement was observed for the dryness scores in the 0.1% reproxalap group and the OS4SQ grittiness scores in the 0.5% reproxalap group (Fig. 3). Change from baseline was also statistically significant for the unanesthetized Schirmer’s test in the 0.1% reproxalap group and for tear osmolarity in the 0.5% reproxalap lipid group. No significant changes were observed in staining, TFBUT, or OSDI.

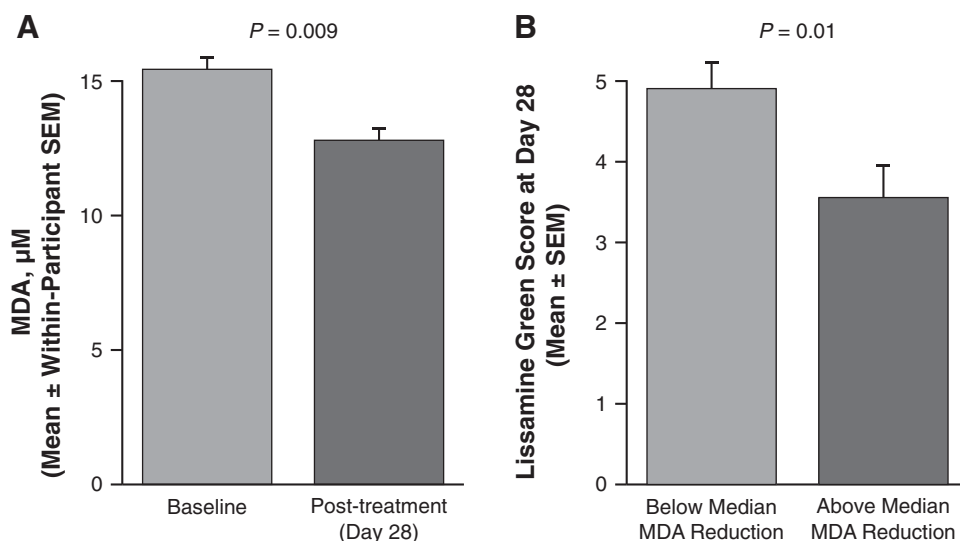
In addition, tear levels of MDA adduct were statistically lower after treatment (Fig. 4A). Participants with above-median reduction in MDA demonstrated statistically lower lissamine green staining scores than did participants with below-median reduction in MDA (Fig. 4B). Participants with above-median reduction in MDA adduct levels demonstrated statistically different tear osmolarity scores versus 0, whereas participants with below-median MDA adduct reduction were not statistically different from 0. Supportive of the relationship of MDA adducts to osmolarity, reduction in osmolarity was correlated with reduction in MDA adduct levels (Pearson *r*=0.31, *P*=0.07).

**Safety and tolerability**

No serious AEs were observed. Of the total ocular treatment-emergent AEs (*n*=47), 42 involved ocular discomfort or pain upon instillation, which was transient and self-limiting in all cases, and was observed in all participants (*n*=17) in the 0.5% reproxalap treatment groups and 8 of 17 (47%) of participants in the 0.1% reproxalap group. The additional ocular treatment-emergent AEs were blurry vision in 2 subjects (1 subject in each of the 0.5% reproxalap and 0.5% reproxalap lipid groups) and eyelid margin crusting in 1 subject (0.5% reproxalap lipid group). No clinically significant changes from baseline were observed

**FIG. 3.** Ocular Discomfort and 4-Symptom Questionnaire subscale mean effect sizes. Improvement effect size is improvement from baseline divided by standard deviation at baseline. \**P*<0.05.





**FIG. 4.** MDA concentration in tears of pooled reproxalap groups. **(A)** Within-participant tear MDA adduct levels before treatment were compared with tear MDA adduct levels after treatment. **(B)** Total lissamine green staining scores at day 28 in participants with below-median MDA adduct reduction after treatment were compared with those of participants with above-median MDA adduct reduction after treatment. MDA, malondialdehyde.

for any of the 3 active treatment groups with respect to slit lamp biomicroscopy, undilated funduscopy, visual acuity, or intraocular pressure.

## Discussion

DED remains inadequately addressed by currently available therapies, and there is, therefore, considerable demand for drugs with novel mechanisms of action. The pooled reproxalap groups in this trial demonstrated statistically significant improvements from baseline across numerous ocular signs and symptoms characteristic of DED, a surprising finding given the small number of patients per arm and a treatment duration that was shorter than most dry eye trials. Improvements in symptoms were noted as early as 1 week after initiation of therapy. Supportive of the activity of reproxalap, symptomatic improvement generally approached or exceeded an effect size (change from baseline divided by baseline standard deviation) of 0.5, a commonly used threshold for clinical relevance.<sup>38</sup> Given the potential effects of vehicle in DED, the results merit further study against a vehicle comparator.

Results from the pooled reproxalap groups indicated that levels of MDA, a RASP previously described to be elevated in the tears of patients with DED,<sup>26,27</sup> were statistically lower after 28 days of therapy than at baseline. Consistent with the clinical relevance of RASP as a proinflammatory mediator, reduction in MDA levels correlated with improvements in tear osmolarity and lissamine green staining. RASP are upstream pre-cytokine potentiators of the innate immune response, including activation of NF- $\kappa$ B, inflammasomes, and scavenger receptor A, which may broadly exacerbate anterior segment inflammatory disease.<sup>12–15</sup> Thus, RASP inhibition could explain the multifaceted activity of reproxalap observed across several signs and symptoms of DED. To our knowledge, the MDA findings represent the first direct clinical measurement of drug mechanism of action for any DED drug.

The frequency of transient ocular discomfort with the reproxalap 0.5% formulations is not unexpected in patients with DED, who are typically sensitive to ocular drop comfort, but the number of discontinuations may limit the interpretability of the results in the 0.5% groups,

especially in the absence of a vehicle control. The discontinuation rate of >20% with the reproxalap 0.5% formulations, although from a single-center trial, indicates that lower concentrations of reproxalap should be advanced to future DED clinical trials. Accordingly, the 0.1% reproxalap formulation has been advanced to subsequent clinical testing. Overall, the results suggest the potential of reproxalap as a rapidly and broadly acting novel agent for the treatment of DED. Vehicle-controlled clinical testing of reproxalap over longer treatment periods in DED is warranted.

## Author Disclosure Statement

D.C. reports employment and stock ownership in Aldeyra Therapeutics; J.S. reports financial support from Allergan, Bausch & Lomb, EyeGate, Kala, Sun Pharmaceuticals, Tear Solutions, Inc.; consulting for and honoraria from Aldeyra Therapeutics, Allergan, Alcon, Bausch & Lomb, Clementia, Kala, Novartis, Noveome Biotherapeutics, EyeDetec, EyePoint Pharmaceuticals, EyeGate, Ocular Therapeutix, Quidel, Sun Pharmaceuticals, Tear Science, Tear Solutions, and Topivert; T.C.B. reports employment, patent interests, and stock ownership for Aldeyra Therapeutics and stock ownership in F-star Therapeutics and Evoke Pharma.

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